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Treatment of infants coinfectd with HIV-1 and cytomegalovirus with combination antiretrovirals and ganciclovir

To the Editor:

Infants coinfectd with HIV-1 and cytomegalovirus (CMV) experience rapidly progressive disease, leading to immunologic deterioration and poor survival.¹ As for adults, treatment of infants with highly active antiretroviral therapy (HAART) has been successful, leading to a significant decrease in mortality and delayed disease progression. In association with a decrease in plasma HIV-1 RNA, there is a restoration of CD4⁺ lymphocytes, which could lead to better immune control for various viral infections, including CMV and HIV-1.

Ganciclovir has been reported to be effective for the treatment of CMV-induced diseases in the immunocompromised host. However, little information is available regarding the efficacy of ganciclovir for congenital CMV infection. Phase II-III studies of ganciclovir for symptomatic congenital CMV have shown a decreased incidence of hearing loss in infants treated with ganciclovir, suggesting that preemptive therapy might prevent the recurrence of disease and neurologic damage in infants infected with CMV.^{2,3} We hypothesized that the addition of ganciclovir therapy to HAART early in life in infants coinfectd with

HIV-1 and CMV could lead to better preservation of viral-specific immunity and thus improve overall survival and disease outcome related to both viruses.

Three infants were given diagnoses of CMV and HIV-1 infections between 1 and 6 months of age. The dose of ganciclovir used in these patients was 5 mg/kg per dose every 12 hours intravenously for 2 weeks as induction therapy, followed by either 5 mg/kg per dose every 24 hours intravenously or 30 mg/kg/day every 8 hours orally as maintenance therapy. HAART was also initiated after the identification of HIV infection. Sustained plasma HIV-1 RNA of less than 400 copies/mL and normal CD4⁺ lymphocyte counts and percentages were achieved in each of the 3 study patients.

Patient 1 (Fig 1, A). A 6-month-old girl was hospitalized with a 2-month-history of persistent cough and cyanosis. Her weight, height, and head circumference were less than the fifth percentile for age. Chest roentgenography showed diffuse bilateral pulmonary infiltrates. The diagnosis of CMV-induced pneumonitis was made by means of positive viral culture from the lung tissue obtained by open lung biopsy. Head computed tomography showed intracranial calcifications consistent with congenital CMV infection. Her initial plasma HIV-1 RNA was 931,000 copies/mL, and her CD4⁺ lymphocyte count was 550/ μ L (20%) (normal range, 1800-4000/ μ L [35% to 56%]).⁴ Brainstem auditory evoked responses showed bilateral sensorineural hearing loss. Six weeks after discontinuation of ganciclovir treatment, her plasma CMV DNA PCR result became positive, and an additional 8-week course of ganciclovir was instituted. Since that time, she has achieved sustained suppression of both CMV and HIV-1. Although she has made developmental progress, she remains developmentally and physically delayed at 3 years of age.

Patient 2 (Fig 1, B). A 3-month-old girl was given a diagnosis of CMV-induced hepatitis and HIV-1 infection. On physical examination, her weight, height, and head circumference were less than the fifth percentile. Generalized lymphadenopathy and hepatosplenomegaly were noted. The aspartate aminotransferase level was 390 U/L, and the alanine aminotransferase level was 347 U/L. Her plasma HIV-1 RNA was 518,000 copies/mL, and her CD4⁺ lymphocyte count was 2337/ μ L (41%) (normal range, 1600-4000/ μ L [35% to 64%]).⁴ After the initiation of HAART and ganciclovir therapy, the plasma CMV DNA PCR result became negative, and the patient's plasma HIV-1 RNA levels became less than 400 copies/mL. Results of a hearing test were normal at 12 months of age. A head magnetic resonance imaging scan showed increased signal in the bilateral periventricular white matter consistent with congenital CMV infection. She has shown continued developmental progress but has required speech therapy for her language delay.

Patient 3 (Fig 1, C). A 2-month-old girl was hospitalized with the diagnosis of HIV-1 infection and CMV-induced hepatitis. The aspartate aminotransferase level was 116 U/L, and the alanine aminotransferase level was 347 U/L. A urine viral culture result was positive for CMV

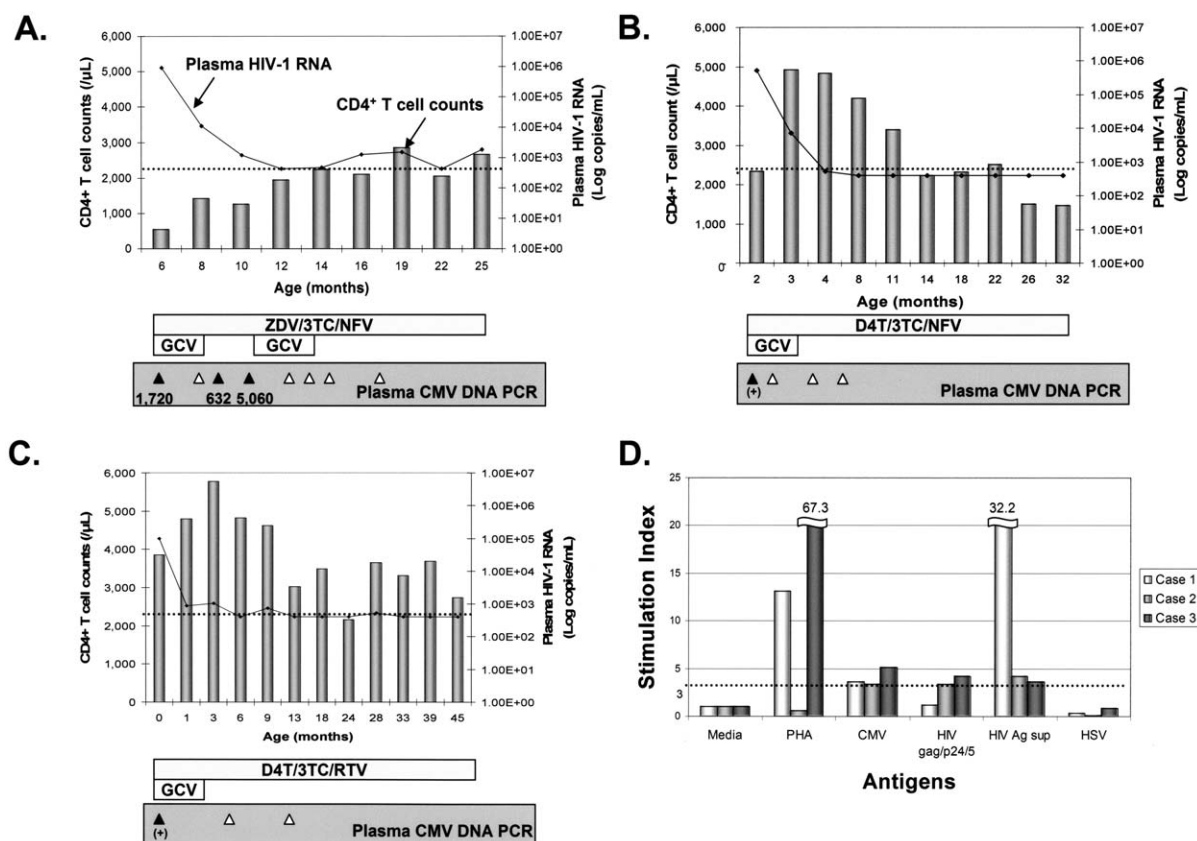


FIG 1. Clinical courses (A-C) and LPAs (D) in 3 infants coinfectd with CMV and HIV-1. **A**, Patient 1. **B**, Patient 2. **C**, Patient 3. Filled triangles indicate detectable plasma CMV DNA PCR results, and the numbers below are copy numbers (copies per milliliter). Open triangles indicate negative plasma CMV DNA PCR results. Dotted horizontal lines indicate undetectable plasma HIV-1 RNA of less than 400 copies/mL. ZDV, Zidovudine; 3TC, lamivudine; NFV, nelfinavir; D4T, stavudine; RTV, ritonavir. **D**, Simulation index (SI) of media was 1. Dotted horizontal line, SI of 3. An SI of greater than 3 was considered positive. HIV gag/p24/5, HIV p24 reagent; HIV Ag sup, HIV antigen supernatant; HSV, herpes simplex virus.

on the first day of life, and her plasma HIV-1 RNA was 98,000 copies/mL. Her CD4⁺ lymphocyte count was 3849/μL (28%) (normal range, 1600-4000/μL [35% to 64%]).⁴ Intravenous ganciclovir therapy was given for 2 weeks, followed by oral ganciclovir for 4 weeks, after which time her plasma CMV DNA PCR result and plasma HIV-1 RNA level were undetectable. The results of audiography, ophthalmic examination, and a head magnetic resonance imaging scan were normal. She has been developing well, except for a language delay requiring speech therapy.

To evaluate the response to different antigens, including HIV-1 and CMV, lymphocyte proliferative assays (LPAs) were performed at 9 months of age in patient 1, 14 months of age in patient 2, and 26 months of age in patient 3. The assay conditions have been published previously.⁵ The CD4⁺ lymphocyte counts when LPAs were performed were 1254/μL (25%), 4349/μL (38%), and 3097/μL (35%) in patients 1, 2, and 3, respectively. All 3 patients had at least a positive and, in some cases, a consistently strong response to CMV and HIV-1 antigens but not for herpes simplex virus (Fig 1, D).

In the current study the children demonstrated a strong LPA response to CMV and HIV-1 antigens after successful ganciclovir therapy combined with effective antiretroviral therapy. In CMV- and HIV-1-coinfectd children, a higher frequency of CMV-specific CD4⁺ T-cell response was detected in subjects with suppressed plasma HIV-1 RNA of less than 50 copies/mL compared with those with greater than 50 copies/mL.⁶ In contrast, the cytotoxic T lymphocyte (CTL) response against HIV-1, which plays a central role in control of HIV-1 infection, decreases during HAART in children.^{7,8} Despite a decrease of specific CTL responses against HIV-1, HAART preserves the immune response against CMV in HIV-1-infected infants.⁸ In total, these data suggest that the early institution of HAART could be beneficial in controlling CMV infection through maintenance of normal CD4⁺ lymphocyte counts and CTL responses in HIV-1-infected children.

Ganciclovir has important adverse effects, including myelosuppression and renal impairment. The most common adverse effect is neutropenia, which has been observed in approximately two thirds of infants who

receive ganciclovir for 6 weeks.^{2,3} In our 3 patients no adverse effects were noted during the administration of ganciclovir. Different ganciclovir regimens have been reported in symptomatic infants congenitally infected with CMV to minimize the adverse effect with maximum efficacy of ganciclovir.^{2,3,9,10} The dosage of ganciclovir in infants that will optimally improve outcome without leading to adverse effects is unknown. A higher dosage⁹ or a longer duration of therapy¹⁰ might be more effective in preventing hearing loss associated with congenital CMV. Although it has not been studied in neonates, valganciclovir has been shown to be as effective as intravenous ganciclovir for CMV-induced retinitis in adult patients with AIDS. The availability of this oral medication raises the possibility of conducting a randomized controlled study in infants with perinatal CMV and HIV-1 infection.

In our 3 patients with perinatal HIV-1 and CMV infections, none are developmentally normal. Speech delay has been observed in all patients, and hearing loss and motor delay have been seen in patient 1. Although the early institution of ganciclovir therapy with antiretrovirals could be beneficial in controlling CMV infection through maintenance of strong and specific immune function in HIV-infected children, long-term improvement of neurologic outcome associated with congenital CMV infection is uncertain. A prospective study will be necessary to determine the effect of ganciclovir for the long-term neurologic outcome of infants with HIV-1 and CMV.

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Retrospective and prospective parental reports of sleep in children with asthma

To the Editor:

Interest in the daytime effects of nocturnal asthma has followed an established literature linking sleep loss to impaired daytime functioning in children.¹⁻³ However, documentation of sleep problems in most studies was primarily based on parental report, the accuracy of which has not been established. Data from the Childhood Asthma Management Program (CAMP) provide the opportunity to critically evaluate 2 methods of reporting nocturnal awakening caused by asthma, examining associations between reported sleep difficulty, asthma severity, and psychological functioning in children with mild-to-moderate asthma.

CAMP was a multicenter, randomized clinical trial initiated by the National Heart, Lung, and Blood Institute to assess the long-term effects of 3 asthma treatments on lung growth in children who were 5 to 12 years of age and demonstrated mild-to-moderate disease at the time of enrollment.^{4,5} Approval was obtained from the institutional review boards at all 8 CAMP sites before initiation of the study. During the screening period before randomization, baseline data were collected, including spirometry before and after bronchodilator, airway responsiveness to methacholine, allergy skin test results, asthma history, current asthma symptoms, and psychological functioning of the child and family. Participants completed daily asthma diary cards during the screening period while receiving only albuterol on an as-needed basis. Patients with severe asthma (ie, those with an FEV₁ of <65% of predicted value, >1 hospitalization, or ≥6 oral steroid bursts in the year before screening or intubation at any time in the past because of asthma) were excluded from participation.

Awakening because of asthma symptoms was assessed in all participants by means of 2 contrasting methods