and in ~40% of the cases, it has been associated with acute leukemia. As opposed to the vast majority of adult HES cases, no pediatric case with the FIP1L1-PDGFRα fusion gene has been reported.

CONCLUSION. There are several distinct features of pediatric, compared with adult, HES.

REVIEWER COMMENTS. Most of the published information on the HES has focused on adult patients. This report compares a pediatric case report of HES and a review of published pediatric cases of this condition to adult patients with this syndrome. This is an insightful clinical report that should be useful in the overall workup of pediatric patients who present with dramatic eosinophilia (>1500/mm³) for >6 months' duration without other known causes of eosinophilia and who have evidence of organ involvement that might be attributable to HES.

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HUMAN IMMUNODEFICIENCY VIRUS

HIV-Infected Individuals Receiving Effective Antiviral Therapy for Extended Periods of Time Continually Replenish Their Viral Reservoir


PURPOSE OF THE STUDY. Latently infected, resting CD4⁺ T cells provide a reservoir for HIV, and the persistence of these cells prevents the eradication of HIV even in patients who have received highly active antiretroviral therapy (HAART) for prolonged periods. The purpose of this study was to examine the underlying mechanisms by which HIV persists in CD4⁺ T cells in individuals treated effectively for up to 9 years.

METHODS. Eleven HIV-infected subjects were studied. These individuals had received effective therapy for an average of 8 years (range: 7.16–9.1 years). None of the patients had experienced detectable plasma viremia after initial suppression. Peripheral blood cells were obtained sequentially on all individuals and studied for the presence of replication-competent virus.

RESULTS. All infected subjects carried replication-competent HIV in their CD4⁺ T cells despite having received prolonged, effectively suppressive antiviral therapy. Contrary to current thinking, substantial higher levels of HIV proviral DNA were found in circulating activated CD4⁺ T cells when compared with the resting subset. Sequence analysis revealed evidence for cross infection between the resting and activated T-cell compartments, indicating that ongoing reactivation of latently infected, resting CD4⁺ T cells may occur in these patients.

CONCLUSIONS. Continual replenishment of the CD4⁺ T-cell reservoir occurs despite prolonged periods of plasma aviremia.

REVIEWER COMMENTS. It is only with the elimination of viral reservoirs that HIV infection can be “cured.” Resting T cells harboring proviral DNA do not live forever. However, the rate of viral replenishment in this cell compartment at least equals the natural decline in their numbers. Eliminating this cell reservoir will be a daunting task.

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Emergence of Drug Resistant HIV-1 After Intrapartum Administration of Single-Dose Nevirapine Is Substantially Underestimated


PURPOSE OF THE STUDY. An inexpensive, effective regimen to prevent perinatal HIV transmission in the developing world is highly desirable. Nevirapine, a nonnucleoside reverse transcriptase inhibitor, seems to provide such an intervention. However, drug-resistance mutations have been identified in up to 40% of women shortly after they received a single intrapartum nevirapine dose as part of a transmission-prevention strategy. This study was undertaken to reexamine the incidence of drug-resistant HIV-1 after single-dose nevirapine.

STUDY POPULATION. Fifty South African women infected with HIV subtype C.

METHODS. Sensitive, real-time polymerase chain reaction assays were sequentially performed for nonnucleoside reverse transcriptase inhibitor–resistance mutation, K103N and Y181C.

RESULTS. Resistance mutations emerged in 65% of women after a single dose of nevirapine.

CONCLUSIONS. Single-dose nevirapine as used in the developing world for prevention of perinatal HIV transmission results in the development of resistance mutations in a very high percentage of women who receive this intervention.

REVIEWER COMMENTS. Although single-dose nevirapine has been successfully implemented as a strategy to prevent perinatal HIV transmission, it is increasingly apparent that the women who are treated with this regimen more often than not develop resistance mutations to nevirapine. The clinical implications are clear: Will nevirapine...
work for future perinatal interventions for individual women with drug-resistance mutations? Will women with these drug-resistance mutations fail to respond to nevirapine as part of a highly active retroviral therapy intervention when they need treatment for their own HIV disease? In the same issue of *The Journal of Infectious Diseases*, Flies et al (J Infect Dis. 2005;192:24–29) demonstrated that drug-resistance variants of HIV may persist for >1 year in this situation. In addition, Lee et al (J Infect Dis. 2005;192:1260–1264) showed that women who developed drug-resistant HIV after exposure to single-dose nevirapine shed drug-resistant HIV in their breast milk. This increases the risk of transmission of resistant virus to uninfected infants. Together, these studies demonstrate that single-dose nevirapine, although an effective strategy for reducing maternal-child transmission of HIV, also predisposes treated women to the development of drug-resistant virus as well as the potential for transmitting drug-resistant virus to their infants via breastfeeding.

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**Depletion of Latent HIV-1 Infection in Vivo: A Proof-of-Concept Study**

**PURPOSE OF THE STUDY.** Resting CD4\(^+\) T cells are a primary reservoir for HIV. In these cells the HIV is in a latent form and not a target of current antiviral agents. The chromatin-remodeling enzyme histone deacetylase 1 (HDAC1) maintains latency of integrated HIV. This study tested the hypothesis that an inhibitor of HDAC1, valproic acid, would result in depletion of latently infected resting CD4\(^+\) T cells.

**STUDY POPULATION.** Four human volunteers with HIV receiving highly active antiretroviral therapy.

**METHODS.** The individual subjects’ antiretroviral therapies were intensified with enfuvirtide, a fusion inhibitor, to minimize the spread of HIV during potential release from latency. The subjects then were treated with oral valproic acid, 500 to 750 mg twice daily, in addition to their antiretroviral therapy, and they were followed for 3 months. Latently infected resting T cells were quantified before and after augmentation of treatment with limiting-dilution culture of resting cells after ex vivo activation.

**RESULTS.** The frequency of resting CD4\(^+\) T-cell infection was stable before the addition of enfuvirtide and valproic acid but declined thereafter. This decline was significant in 3 or 4 patients, with a mean reduction of 75% in circulating HIV-infected resting CD4\(^+\) T cells. There were no complications of the additional treatments except for the expected injection-site reactions to enfuvirtide.

**CONCLUSIONS.** Combination therapy with an HDAC inhibitor and very potent antiretroviral therapy accelerated the reduction in HIV-infected resting T cells. This suggests a new approach to the management of HIV that eventually may result in clearance of HIV from infected individuals.

**REVIEWER COMMENTS.** This study received a fair amount of media coverage at the time it was published. It begs the question, can HIV be cured? A 75% reduction in the resting T-cell reservoir seems impressive. However, this was a very short-term study, and the kinetics and degree to which the resting T-cell reservoir was replenished after discontinuation of valproic acid was not reported. In addition, valproic acid, a widely used anticonvulsant, is potentially highly toxic and has “black-box” warnings for hepatotoxicity, teratogenicity, and pancreatitis. Despite the authors’ optimistic conclusions, “this finding, though not definitive, suggests that new approaches will allow the cure of HIV in the future,” use of the “C word” is likely premature.

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**Paradoxical CD4\(^+\) T-Cell Decline in HIV-Infected Patients With Complete Virus Suppression Taking Tenofovir and Didanosine**

**PURPOSE OF THE STUDY.** Tenofovir and didanosine are adenosine analogs commonly used in highly active antiretroviral therapy combinations. Although virologically effective, this combination is theoretically associated with pharmacokinetic interactions and increased risks of pancreatitis and hyperglycemia. The study examined the CD4\(^+\) T-cell effects of the use of these 2 drugs as part of a highly active antiretroviral therapy regimen.

**METHODS.** Data from 570 individuals were analyzed retrospectively according to the nucleoside analog “backbone” of protease inhibitor–containing regimens: tenofovir + didanosine in 298 subjects, didanosine in 88, tenofovir in 44, and neither didanosine nor tenofovir in 140.

**RESULTS.** Significant CD4\(^+\) T-cell declines were noted in patients taking the combination of tenofovir + didanosine relative to all other nucleoside analog combinations including didanosine or tenofovir only. Patients exposed to higher didanosine doses showed a more pro-
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