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, Flys 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.

**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.

**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-
nounced CD4+ T-cell decline, and plasma levels of didanosine correlated with the extent of T-cell loss.

CONCLUSIONS. Although patients receiving tenofovir + didanosine–based combinations generally achieved excellent viral suppression, their CD4+ T cells often paradoxically declined. This effect generally progressed over time. It is hypothesized that the use of these 2 agents together results in a condition that metabolically resembles purine nucleoside phosphorylase deficiency, a rare but well-described primary immunodeficiency syndrome.

REVIEWER COMMENTS. Tenofovir and didanosine frequently are the only nucleoside analog agents available to patients with drug-resistant virus. This combination with either a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor is often effective in suppressing virus in patients with limited options. However, the paradoxical decline in T-cell numbers is of great concern. Patients on this regimen must be monitored carefully for this potential complication.

Massive Infection and Loss of Memory CD4+ T Cells in Multiple Tissues During Acute SIV Infection


PURPOSE OF THE STUDY. It was recently established that both acute HIV and its simian counterpart, simian immunodeficiency virus (SIV), are accompanied by dramatic and selective loss of memory CD4+ T cells. This loss has been shown to primarily occur in mucosal tissues. The extent and mechanisms underlying this depletion have not been defined. The purpose of this study was to investigate these questions in a simian model.

METHODS. Eight rhesus macaque monkeys were infected with a pathogenic strain of SIV. Plasma and tissue samples were collected at various time points by biopsy and necropsy. Lymphocyte subsets were analyzed with standard flow cytometry, and T-cell–associated viral DNA was measured by a highly sensitive quantitative polymerase chain reaction assay.

RESULTS. This study demonstrated that in this monkey model, memory CD4+ T cells are depleted in multiple tissues during acute SIV infection. In addition, the loss of these cells is explained by a massive infection of these cells by the virus. Specifically, ~50% of these cells throughout the body are infected by SIV at the peak of infection, and most of the infected cells disappear within several days. Alternative mechanisms are not required. This depletion occurs to a similar extent in all tissues.

CONCLUSIONS. Acute immunodeficiency virus infection results in the loss of ~50% of all memory T cells within days of infection. This and other studies strongly suggest that this loss, at least in adult animals and humans, is irreversible.

REVIEWER COMMENTS. This study confirms and extends previous findings demonstrating massive memory T-cell loss during acute HIV or SIV infection. The extent to which this loss is recoverable is likely to be very limited. Most interesting is that these authors also noted that naive T cells are highly resistant to SIV infection. These observations are particularly important for infants infected with HIV. Young infants have fewer memory CD4+ T cells, and, therefore, their loss may not be as critical in newborns. In addition, the thymus in young children may be more capable of reconstituting memory T-cell functions if HIV is completely suppressed early. Similar studies should be performed on infant laboratory animals to determine the extent to which recovery is likely in infected children.

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