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 antiretroviral 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 a 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-
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Pediatrics 2006;118;S51
DOI: 10.1542/peds.2006-0900FFFF
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