expression in these individuals on virus-specific T cells. A panel of MHC class I tetramers were used to identify HIV-specific CD8+ T cells. PD-1 expression was then measured on tetramer-positive cells. PD-1 expression was also analyzed on cytomegalovirus-specific, Epstein-Barr virus–specific, and vaccinia virus–specific CD8+ T cells from HIV-negative controls.

RESULTS. The findings in these studies were remarkably similar. PD-1 was significantly upregulated on HIV-specific T cells, and expression correlated with impaired HIV-specific CD8+ T-cell function as well as predictors of disease progression: HIV viral load, a reduced capacity for cytokine production, and decreased proliferation of HIV-specific CD8+ T cells. Cytomegalovirus–specific CD8+ T cells from the same donors did not upregulate PD-1 and seemed to maintain functional integrity. Blockade of the PD-1/PD-1L pathway result reversed immune dysfunction.

CONCLUSIONS. The PD-1/PD-1L pathway is associated with significant HIV-specific T-cell exhaustion. The accumulation of HIV-specific dysfunctional T cells in an infected host may prevent the renewal of a functionally competent HIV-specific CD8+ T-cell response.

REVIEWER COMMENTS. HIV has proven remarkably adept at inhibiting the very system that evolved to control it. Expression of a negative regulator of activated T cells, PD-1, is markedly increased on HIV-specific CD8+ T cells when HIV engages the T-cell receptor. Such T cells have been termed “exhausted” because they fail to respond as fully activated effector cytotoxic T cells. Surprisingly, blockade of PD-1 engagement with its ligand results in a restoration of T-cell function. This observation suggests a target for enhancing the function of exhausted T cells in HIV-infected individuals. However, much has to be learned about the importance of this pathway in the control of normal T-cell activation. T-cell activation seems to be an intrinsic component of HIV pathogenesis; therefore, blocking this activation may be useful. However, it would be potentially dangerous to be unable to turn off an activated immune response to a routine infection.

Potent Antiretroviral Effect of MK-0518, a Novel HIV-1 Integrase Inhibitor, in Patients With Triple-Class Resistant Virus

PURPOSE OF THE STUDY. Although there are >20 antiretroviral agents available in developed countries, multiple factors limit the construction of combinations of drugs that are capable of effective viral suppression. New agents are clearly needed, particularly for individuals with limited options. MK-0518 is a member of a new class of antiretroviral agents, integrase inhibitors. The purpose of this study was to generate preliminary information on the potency of MK-0518 in the treatment of individuals with triple-class–resistant virus.

STUDY POPULATION AND METHODS. There were 178 HIV-infected patients enrolled and assigned to 1 of 3 doses of MK-0518 or placebo. They were followed for 24 weeks, and antiretroviral responses were evaluated.

RESULTS. MK-0518 showed remarkable potency at all doses tested. Approximately 60% of the patients who received active drug achieved <50 copies per mL of plasma HIV RNA. Strikingly, ~50% of the individuals with no active agent left in their background regimens achieved undetectable viral loads. MK-0518 was generally well tolerated at all doses, with headache being the most frequent adverse effect.

CONCLUSIONS. MK-0518 had remarkable potent antiretroviral activity in individuals with limited treatment options. The availability of this new class of antiretroviral drug will markedly enhance the options available for patients who are running out of options.

REVIEWER COMMENTS. Abstracts presented at scientific meetings are usually not appropriate for a “best-articles-published” series. However, the impact of MK-0518 will be extraordinary. With 3 additional new drugs recently or soon to be available, we will soon have the ability to “salvage” patients with multiresistant virus.

A Prospective Controlled Study of Neurodevelopment in HIV-Uninfected Children Exposed to Combination Antiretroviral Drugs in Pregnancy

PURPOSE OF THE STUDY. The effective treatment of HIV-infected women with antiretroviral agents has dramatically reduced the incidence of HIV infection in their newborn infants. However, an ongoing concern has been the potential adverse effects of the antiretroviral agents themselves on the neurodevelopment of HIV-uninfected children who were exposed to combination HIV medications. The purpose of this study was to investigate the neurodevelopment of HIV-infected children exposed to combination anti-HIV therapy in pregnancy compared with children not exposed to this therapy.
A Prospective Controlled Study of Neurodevelopment in HIV-Uninfected Children Exposed to Combination Antiretroviral Drugs in Pregnancy

Joseph A. Church

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