Cutting Edge: Unusual NK Cell Responses to HIV-1 Peptides Are Associated With Protection Against Maternal-Infant Transmission of HIV-1


PURPOSE OF THE STUDY. To investigate the role of specific T cell responses in maternal-fetal HIV-1 transmission.

METHODS. CD3− cell responses to HIV-1 peptide were measured in HIV-infected mothers and their infants at birth and at 6 to 10 weeks after delivery. Samples from the mother-child cohort were stimulated with HIV-1 synthetic peptides in pools representing Gag, Pol, Nef, envelope, and regulatory protein regions. A positive peptide-induced CD3− response was defined as >3% of cells expressing cytokine at a level at least twofold above background levels. Additional HIV-infected women were recruited to determine whether CD3− HIV-responding cells expressed markers for B cells, monocytes, T cells, or natural killer (NK) cells.

RESULTS. In the cohort of infected mothers, 54% and 22% had CD3− responses to envelope and regulatory peptides, respectively. These same regions were targeted to a lesser degree in their infants (21% and 5% had CD3− responses to envelope and regulatory peptides, respectively). Twenty-eight (57%) of 49 nontransmitting mothers and 13 (30%) of 44 exposed uninfected infants had detectable, HIV-specific, CD3− responses. In comparison, 1 (7%) of 15 transmitting mothers and 1 (6%) of 18 infected infants had these responses. When both the mother and the infant had HIV-specific CD3− responses, none of the infants became infected. One of the 22 responder mothers with a nonresponder infant transmitted HIV to her infant, and 2 of the nonresponder mothers with responder infants transmitted HIV to their infants. HIV-specific CD3− cells were identified as NK cells on the basis of cell surface markers.

CONCLUSIONS. Mothers and infants who have CD3− NK cells that respond to HIV-1 peptides are substantially less likely to transmit and to acquire infection, respectively. CD3− NK cells respond with high specificity and strength to HIV-1 peptides from envelope and regulatory protein regions. This finding highlights the importance of innate immunity in preventing maternal-fetal transmission of HIV-1.

REVIEWERS COMMENTS. Significant research has been conducted to find ways to reduce the risk of maternal-fetal transmission of HIV-1 infection. These interventions have been very successful, with transmission rates as low as 5% in developed countries. This article describes the immune responses seen in HIV-positive mothers and HIV-exposed infants and offers a possible marker for transmission risk. Although future studies need to be conducted, it is possible not only that this robust immune response to specific HIV-1 proteins may serve as a predictor of possible vertical transmission but also that a decrease in these cell numbers may serve as a marker of disease progression. In addition, the HIV-1-specific CD3− cell population may serve as a possible target for future immunotherapy for HIV infection.

T Cell-Specific siRNA Delivery Suppresses HIV-1 Infection in Humanized Mice


PURPOSE OF THE STUDY. Since the discovery of RNA interference within mammalian cells in 2001, RNA interference has become a significant bench research tool and presents a new therapeutic modality against viral infections and cancer. The purpose of this study was to determine whether a novel method for delivery of small interfering RNAs (siRNAs) to T cells can suppress HIV viral infection.

STUDY POPULATION. A humanized mouse model of AIDS was used to demonstrate in vivo effects.

METHODS. A CD7-specific antibody conjugated to a peptide was used to deliver siRNA to target cells in mice reconstituted with human lymphocytes or CD34+ stem cells. Anti–chemokine receptor 5 (viral coreceptor) complexed with antiviral siRNAs was also used in HIV-infected mice.

RESULTS. Treatment controlled viral replication, prevented disease-associated CD4+ T cell loss, suppressed endogenous virus, and restored CD4+ T cell counts. In addition, it was demonstrated that antiviral siRNAs could be delivered to naïve T cells and effectively suppress viremia.

CONCLUSIONS. siRNA therapy for HIV infection seems to be feasible in a preclinical animal model.

REVIEWERS COMMENTS. The annual rate of new HIV infections around the globe was 2.7 million in 2007, with 14% of these cases (370 000 cases) occurring in children <15 years of age (1013 cases per day). RNA interference holds considerable potential for antiviral therapy, but delivering effective quantities of siRNAs into the right target cells in vivo represents a considerable challenge. Several small clinical trials using siRNAs are currently underway. This study represents a significant advance for 2 reasons: (1) the findings heighten the prospect of a new HIV-1/AIDS therapy and (2) this study provides a
Timing of HAART Defines the Integrity of Memory B Cells and the Longevity of Humoral Responses in HIV-1 Vertically-Infected Children


PURPOSE OF THE STUDY. HIV infection induces a progressive decline in immune function that affects not only T-cell but also B-cell activities, including the progressive decline in memory B cells, markedly elevated serum immunoglobulin levels, impaired responsiveness to routine immunizations, and loss of specific antibodies previously generated. Treatment of adults with highly active antiretroviral therapy (HAART) reduces immunoglobulin levels and increases B-cell numbers. However, several studies indicate that the B-cell compartment does not recover completely and patients maintain impaired antibody responses to immunizations. The purpose of this study was to determine whether the timing of HAART initiation affected pediatric patients’ ability to generate and to maintain protective levels of antibodies to routine immunizations.

STUDY POPULATION. Seventy children perinatally infected with HIV were studied with 50 healthy control subjects.

METHODS. Patients and control subjects received childhood immunizations according to the national (Italian) vaccine protocol. Patients who started HAART within the first year of life were categorized as “early treated”; children treated after the first year of life were considered “late treated,” and this group was subdivided into individuals with controlled virus and those who developed virological failure. Peripheral blood cells were evaluated with standard flow cytometry for B-cell subsets, including memory B cells. Antigen-specific B-cell functions were measured with an enzyme-linked immunosorbent spot assay. Plasma antibody titers against measles, tetanus, and pneumococcal antigens were assayed with enzyme-linked immunosorbent assays.

RESULTS. Early-treated patients maintained high percentages of memory B cells, compared with levels observed in healthy control subjects; patients who started HAART later showed lower percentages. Patients treated early maintained the capacity to generate antigen-specific memory B cells, and early HAART resulted in maintenance of multiple antibody levels above protective thresholds in HIV-infected children. Of concern, 25% of patients treated late failed to generate protective levels of antibodies to measles, and this number increased to >40% among those who experienced failure of antiretroviral therapy. In addition, >60% of subjects who received late HAART failed to maintain protective levels of antibodies to antigens including measles and tetanus; similar findings were noted in antibody responses to pneumococcal antigens.

CONCLUSIONS. Early HAART is essential for maintenance of normal B-cell functions in perinatally HIV-infected children. Regardless of T-cell numbers and/or clinical status, the results of this study strongly indicate that newborns infected with HIV should be treated as early as possible to preserve immune functions.

REVIEWER COMMENTS. Although T cells are critical for generating normal antibody responses, unique subsets of B lymphocytes are also essential in this regard. Specifically, marginal-zone B cells are required for the ability to generate polysaccharide-specific, “T-cell independent” antibodies. Infants <2 years of age are deficient in this subset of B lymphocytes. This study provides strong confirmation of many clinicians’ impressions that children who begin HAART at <1 year of age and who maintain viral suppression have normal immune functions by all measures that are clinically applied to the evaluation of this population. When to initiate HAART has been a long-term question among practitioners treating adults. Increasingly, earlier treatment (ie, at CD4+ cell counts of <500 cells per μL in adult patients) is being considered. The results of this study suggest that HAART should begin as soon as a diagnosis of HIV infection is made in perinatally exposed children.

Maraviroc for Previously Treated Patients With R5 HIV-1 Infection


PURPOSE OF THE STUDY. Although there are now >20 anti-HIV medications, new agents are still needed. HIV drug resistance is highly prevalent and 15% of newly infected patients in the United States have drug-resistant virus. In addition, enhanced safety and tolerability and improved convenience would enhance adherence to antiretroviral regimens. HIV uses 1 of 2 chemokine receptors, in addition to CD4, to gain entry into a cell, chemokine receptor 5 (CCR5) and α-chemokine receptor 4 (CXCR4). HIV that uses CCR5 is the primary type of virus that is transmitted through sexual or perinatal exposure. CCR5 antagonists are a new class of anti-
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Pediatrics 2009;124;S156
DOI: 10.1542/peds.2009-1870

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*Pediatrics* 2009;124;S156

DOI: 10.1542/peds.2009-1870CCC

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