siRNA delivery system that might be adapted to target various receptors and thus other cell types.

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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.

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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-
retroviral agents. The purpose of this study was to evaluate a CCR5 antagonist, maraviroc, in the treatment of HIV-infected adults.

STUDY POPULATION. Two double-blind, placebo-controlled studies were conducted. More than 1000 patients were randomly assigned to receive either maraviroc or placebo in combination with investigator-chosen optimized background therapy. Most patients were resistant to multiple classes of antiretroviral agents; mean baseline viral loads were >72,000 copies per mL, and median CD4+ cell counts were 169 cells per mm3.

METHODS. Subjects were assigned to receive maraviroc or placebo in addition to optimized background therapy based on treatment history and drug resistance testing. Safety and efficacy were assessed after 48 weeks.

RESULTS. The demographic and baseline characteristics of patients were similar between the 2 study groups (placebo and active drug). A significantly greater proportion of individuals receiving placebo discontinued treatment, primarily because of lack of efficacy. The primary end point of the study, mean change in plasma levels of HIV RNA, was substantially greater for maraviroc-treated patients than placebo-treated patients (-1.82 log10 copies per mL in the maraviroc-treated group, compared with -1.079 log10 copies per mL in the placebo-treated group). Secondary end points included the proportion of subjects who achieved undetectable viral loads (<50 copies per mL of plasma) at 48 weeks. Forty-seven percent of individuals receiving maraviroc twice daily achieved viral suppression, compared with ~18% of placebo-treated patients. Finally, the improvement in circulating CD4+ T-cell counts was substantially greater in the maraviroc-treated patients (~122 cells per mm3 gained), compared with the placebo-treated subjects (69 cells per mm3 gained). Maraviroc was well tolerated. Rates of discontinuation because of adverse events related to study treatment were the same in the placebo and maraviroc groups. Rates of serious adverse events were similar among the treatment groups (~18%–20%), and rates of laboratory abnormalities were similar among the study groups.

CONCLUSIONS. Maraviroc was well tolerated, and adverse events were no greater than in the placebo group. Maraviroc treatment resulted in greater suppression of HIV, greater increases in CD4+ cell counts, and a greater proportion of individuals who achieved HIV RNA levels of <50 copies per mL.

REVIEWER COMMENTS. This study and its companion article (Fätkenheuer G, Nelson M, Lazzarin A, et al. N Engl J Med. 2008;359[14]:1442–1455) demonstrated that maraviroc is an effective antiretroviral agent. It achieved remarkable success in a very heavily pretreated population. Of particular importance was the need for at least 1 and preferably 2 effective agents in the optimized background regimen to maximize the effect of maraviroc. In addition, in the secondary analysis of the results, pre-existing CXCR4-using HIV essentially eliminated any benefit of maraviroc. The development of CXCR4-using HIV after primary infection with CCR5-using virus is a matter of time and chance. Approximately 50% of heavily pretreated, long-term HIV-infected adults have CXCR4-using virus and thus would be completely resistant to maraviroc therapy. Currently, maraviroc is approved for patients who are known to be resistant to multiple other drugs. Perhaps maraviroc and similar chemokine receptor blockers would best be used before the likely development of CXCR4-using virus. Studies are underway to evaluate the use of this novel agent in patients naive to antiretroviral therapy.

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Raltegravir With Optimized Background Therapy for Resistant HIV-1 Infection

PURPOSE OF THE STUDY. As described above, there are compelling reasons for expanding the anti-HIV armamentarium. Raltegravir is an inhibitor of HIV integrase, an enzyme essential in the cycle of HIV replication. Because it belongs to a novel class of antiretroviral agents, the drug should be effective against HIV that is resistant to other antiretroviral drugs. The purpose of this study was to evaluate the safety and effectiveness of raltegravir in adults with multidrug-resistant virus.

STUDY POPULATION. HIV-infected patients ≥16 years of age were eligible if they had plasma HIV RNA levels of >1000 copies per mL and documented resistance to ≥1 drug in each of the 3 classes of antiretroviral drugs (ie, nucleoside transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors).

METHODS. Two identical trials in different geographic regions were conducted to evaluate raltegravir versus placebo in combination with optimized background anti-HIV therapy. Patients were randomly assigned to receive raltegravir or placebo, in a 2:1 ratio. Clinical status was assessed regularly during the trial, and protocol-mandated laboratory studies were performed at a central laboratory. The primary end point of the study was the proportion of patients achieving HIV RNA levels of <400 copies per mL after 16 weeks of study therapy.

RESULTS. Subjects (N = 699) were enrolled in studies in the different geographic locations. Because results were very consistent between the 2 substudies, combined re-
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