(a control group to compare for effects specifically related to the switch from IVIG to SCIG); prior therapy for 1 patient was not stated.

Methods. Patients received weekly SCIG infusions at home over a period of 10 months (43 infusions). Questionnaires were administered at baseline and at 6 and 10 months. For assessment of HRQOL in children, parents completed the Child Health Questionnaire-Parental Form 50; adults used the Short Form 36. For assessment of treatment satisfaction, the authors adapted a Life Quality Index instrument previously developed in a study of antibody-deficient patients receiving IVIG.

Results. On the Child Health Questionnaire-Parental Form 50, the children demonstrated significant improvement in 6 of 14 concepts analyzed: “role/social-emotional, behavioral,” “general health perceptions,” “parental impact-emotional,” “parental impact-time,” “family activities,” and “global health.” On the Short Form 36, adults had improvements in vitality, mental health, and social functioning. These differences were found only in those adults who switched from IVIG to SCIG, not in those who were already receiving SCIG, suggesting that the improvement resulted from the change in therapy. Both children and adults had significant improvements in Life Quality Index. Again, in the adults, no change was seen in the group that was already receiving SCIG at enrollment. At study end, all children/parents, the 10 adults on SCIG at enrollment, and 73% of the adults who switched preferred to continue SCIG at home. Two expressed a preference for SCIG regardless of setting, 1 expressed a preference for home regardless of method, 1 expressed no preference for anything, and 1 only expressed a preference for IVIG in the hospital.

Conclusions. Home therapy with SCIG in children and adults with antibody deficiency is generally self-perceived as superior to in-hospital therapy with IVIG with respect to several validated measures of HRQOL.

Reviewer’s Comments. IVIG has been a major mode of therapy for immunodeficiency for 30 years. Many primary care providers have 1 or a few patients who receive this therapy. Less widely recognized, SCIG has also been used with safety and efficacy equivalent to IVIG and has been the major mode of immunoglobulin delivery in some countries (although this is an off-label use in the United States). For a variety of reasons, SCIG is gaining in popularity and may replace IVIG for many patients with immunodeficiency diseases.

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HUMAN IMMUNODEFICIENCY VIRUS

PERFORMANCE CHARACTERISTICS OF HIV-1 CULTURE AND HIV-1 DNA AND RNA AMPLIFICATION ASSAYS FOR EARLY DIAGNOSIS OF PERINATAL HIV-1 INFECTION


Purpose of the Study. The diagnosis of HIV infection in a newborn exposed to HIV in utero is a challenge. In the early years of the epidemic, HIV clinicians monitored the decline of HIV antibody levels for up to 2 years after birth to confirm that a child was not HIV-infected. HIV infection in infants is now typically made by the detection of viral DNA sequences in peripheral blood mononuclear cells by means of a DNA polymerase chain reaction (PCR). Plasma HIV-RNA measurements with PCR may also be valuable but has the theoretic limitation of false-negative reactions resulting from early treatment of the mother and infant. The purpose of this study was to evaluate the performance of HIV DNA PCR, HIV RNA PCR, and HIV culture to identify infected infants exposed to the virus in utero.

Study Population. Infants participating in the Pediatric AIDS Clinical Trials Group protocol 185.

Methods. Specimens from the infants (24 infected and 100 uninfected) obtained prospectively were studied with standard nucleic acid-amplification assays and peripheral blood mononuclear cell microroutines. The sensitivities, specificities, and positive and negative predictive values were calculated for each of the 3 assay systems.

Results. At birth the sensitivity of culture, DNA PCR, and RNA PCR were 21%, 11%, and 27%, respectively. By 6 weeks, the sensitivity had improved to 90%, 83%, and 95%. The specificity was 99% to 100% for all assays at all times.

Conclusions. The authors concluded that the diagnostic performance of the RNA PCR assay matched or exceeded that of culture and DNA PCR. Because RNA assays require less blood volume and often can be performed more quickly at reference laboratories, it is suggested that RNA assays may be used for early diagnosis of HIV infection in infants.

Reviewer’s Comments. This study demonstrates that RNA PCR assays are effective for the diagnosis of HIV infection. However, it must be noted that cryopreserved specimens were used for these PCR assays and may have impacted the sensitivity of the DNA PCR. Additionally, we have had 3 false-positive RNA PCR assays in 2 newborns and 1 adolescent exposed to HIV. A negative RNA PCR at or after 6 weeks of age strongly indicates that an infant is not infected.

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GROWTH HORMONE IN T-LYMPHOCYTE THYMIC AND POSTTHYMIC DEVELOPMENT: A STUDY IN HIV-INFECTED CHILDREN


Purpose of the Study. Growth hormone (GH) plays a role in thymic function, and decreased hormone secretion has been reported in HIV-infected children. Highly active antiretroviral therapy suppresses HIV replication and results in increases in CD4+ T cells in HIV-infected patients. The aim of this study was to determine if the level of immune reconstitution associated with antiretroviral therapy is influenced by the status of the GH insulin-like growth factor 1 axis.

Study Population. HIV-infected children (n = 26) were studied. Half of them had GH deficiency as defined by a reduced peak GH response to GH-releasing hormone and arginine-stimulation test. These patients were matched to 13 patients of similar age, pubertal status, and clinical findings but with normal GH-response tests.

Methods. Thymic volume was measured with magnetic resonance imaging. Peripheral blood lymphocyte subsets were evaluated with standard monoclonal antibody techniques. Serum interleukin 7 levels were measured with an enzyme-linked immunosorbent assay.

Results. The 2 patient populations did not differ in age, weight, height, body mass index, pubertal status, clinical or immunologic stage of disease, or number and percentage of CD4+ T cells before beginning antiretroviral therapy. After antiretroviral therapy, children with GH deficiency had reduced CD4+ T-cell numbers and percentages, reduced interleukin 7 concentrations, and reduced thymic
HUMAN IMMUNODEFICIENCY VIRUS-DRIVEN EXPANSION OF CD4+CD25+ REGULATORY T CELLS, WHICH SUPPRESS HIV-SPECIFIC CD4+ T-CELL RESPONSES IN HIV-INFECTED PATIENTS


Purpose of the Study. HIV infection is associated with a progressive decline in CD4+ T-cell numbers. However, multiple mechanisms of HIV-associated T-cell dysfunction have been described, including reduced HIV-specific lymphoproliferative and cytotoxic T-cell responses and failure to generate proinflammatory cytokines. A CD4+ T-cell subset with regulatory properties has been characterized. These cells, regulatory T cells (Tregs), express CD25 and inhibit the proliferation of T lymphocytes both in vitro and in vivo. This suppression may be antigen specific and cytokine mediated.

Methods. Peripheral blood T cells were obtained from clinically stable, antiretroviral-treated HIV-infected individuals with CD4+ T cells >500/μm³ and plasma HIV RNA <50 copies per mL. These cells were used for extensive flow-cytometric analysis, proliferation and suppression assays, and expression of FOXP3, a transcription factor in Tregs.

Results. HIV-infected individuals had increased numbers of CD4+CD25+ T cells with the phenotypic, molecular, and functional characteristics of Tregs. This expanded population persisted despite long-term viral control. Patient Tregs suppressed CD4+ T-cell proliferation to recall antigens and specific HIV proteins. The proliferative capacity of T cells to recall and p24 antigens significantly increased after the depletion of Tregs. Additionally, these T cells responded specifically to p24 antigen with expression of transforming growth factor β and interleukin 10. It is interesting to note that the suppressive activity by the cell population did not depend on secretion of transforming growth factor β or interleukin 10.

Conclusions. HIV derives expansion of CD4+CD25 regulatory T cells. This regulatory T-cell subset in turn suppresses HIV-specific CD4+ T-cell responses in HIV-infected patients.

Reviewer’s Comments. HIV induces an immunodeficiency by depleting CD4+ T cells. However, demonstrable immunodeficiency occurs before the onset of severe peripheral T-cell depletion. A variety of mechanisms have been invoked to explain this process. The present study demonstrates an additional potential mechanism by which HIV subverts immune responses to both HIV-specific antigens and to those of other infectious agents. The expansion of HIV-induced Tregs suggests a mechanism by which HIV induces partial tolerance to its own antigens. Therapeutic strategies aimed at reducing HIV-specific Tregs might allow more effective control of HIV replication. Alternatively, species-specific simian immunodeficiency viruses seem to induce little disease caused by immune silence. Perhaps enhancement of HIV-specific Tregs rather than suppression of them might result in similar tolerance and lack of disease progression in HIV-infected humans.

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CD4+ T CELL DEPLETION DURING ALL STAGES OF HIV DISEASE OCCURS PREDOMINANTLY IN THE GASTROINTESTINAL TRACT


Purpose of the Study. Mechanisms underlying T-cell depletion in HIV infection are not well understood. This depletion has been studied primarily in the peripheral blood and, to some extent, in peripheral lymphoid tissue. However, a large fraction of CD4+ T cells resides in the gastrointestinal tract. The purpose of this study was to identify the effects of HIV infection on activation and depletion of T cells in the peripheral blood, gastrointestinal tract, and lymph nodes.

Study Population. A total of 14 antiretroviral therapy-naive HIV-infected individuals and 7 HIV-uninfected individuals were recruited.

Methods. Peripheral blood mononuclear cells were obtained from venous blood, ileal Peyer’s patches and lamina propria samples were acquired by endoscopy and biopsy, and inguinal lymph nodes were obtained by percutaneous biopsy. Flow-cytometric analysis was conducted on specimens with standard techniques. HIV-specific T cells were analyzed for phenotypic markers. Additional studies were performed for HIV-specific CD8+ T cells and levels of collagen deposition within lymph nodes.

Results. During primary HIV infection, preferential depletion of mucosal CD4+ T cells occurs compared with peripheral blood and lymph nodes. At all stages of HIV disease, most CD4+ T-cell depletion occurs in the gastrointestinal tract. The primary targets for depletion are activated CD4+CCR5+ T cells. Finally, T-cell activation in lymph nodes is associated with abnormal collagen deposition.

Conclusions. These findings define the nature and extent of CD4+ T-cell depletion in lymphoid tissue, particularly that of the gastrointestinal tract. Most CD4+ T-cells in the effector sites of the gastrointestinal tract are activated and express CCR5. This circumstance creates a particularly attractive medium for HIV infection and replication, which occurs most efficiently in activated CCR5+CD4+ T cells. Additionally, it was shown that therapeutic suppression of HIV permits recovery of circulating CD4+ T cells but did not restore CD4+ T cells in the gastrointestinal tract.

Reviewer’s Comments. Intestinal CD4+ T cells are depleted selectively and rapidly in HIV-infected patients. These findings reflect earlier studies in simian immunodeficiency virus–infected macaque monkeys (Science. 1998; 280:142–431). All of these studies together demonstrate that HIV induces severe, organ-specific T-cell depletion in a much briefer time frame than previously identified. Although clinical immunodeficiency may not be apparent for
Growth Hormone in T-Lymphocyte Thymic and Postthymic Development: A Study in HIV-Infected Children

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