nodeficiency (SCID-X1) in patients without an HLA-matched donor for bone marrow transplant.

STUDY POPULATION. All 4 children with SCID-X1 resulting from a γ-c chain mutation and without an HLA-identical sibling referred to Great Ormond Street Hospital (London, United Kingdom) between July 2001 and December 2002 were offered and consented to receive gene therapy.

METHODS. The complete coding region of human γ-c was cloned into a pMFG gammaretroviral vector and transfected into bone marrow $CD34^+$ stem cells for reinfusion into the patients. T-cell function was assessed by responses to mitogens, *Candida* antigen, and mixed lymphocyte reactions. T-cell receptor (TCR) repertoires were assessed by direct immunofluorescence with fluorochrome-conjugated antibodies to TCRV-β. Somatic hypermutation was expressed as the fraction of κ light-chain polymerase chain reaction product with mutations preventing cleavage by *Fnu*4HI.

RESULTS. At reinfusion, 27% to 58% of cells were CD34-positive and γ-c–positive. In all patients, natural killer cells appeared 2 to 4 weeks postinfusion and remained at low-normal levels. Naive $CD45RO^-$, $CD27^+$ T cells appeared at 10 to 30 weeks. Two patients developed normal numbers of CD3, CD4, and CD8 cells, allowing discontinuation of prophylactic medications. One of these patients developed a maculopapular rash on the palms and soles after CD4 T-cell recovery. Another patient had gastrointestinal bleeding resulting from rejection of engrafted maternal cells. The eldest patient, who received gene therapy at 33 months of age, had slower lymphocyte recovery. All patients developed normal T-cell–proliferative responses to mitogens, antigens, and mixed lymphocyte reactions. One year after treatment, all patients showed normal TCRV-β usage and polyclonality within individual V-β families. Two patients maintained normal immunoglobulin levels after discontinuing replacement, and normal serologic responses to vaccines were documented in 1 patient. Somatic mutation demonstrated by mutated V-κ A27 transcripts increased from <2.0% to 5.3% to 23.3% by 1 to 2 years after gene therapy. No pathologic clonal expansions or insertions near the T-cell protooncogene LMO-2 were detected.

CONCLUSION. After somatic gene therapy, all 4 patients with SCID-X1 had significant improvement in clinical and immunologic function without serious adverse events.

REVIEWER COMMENTS. Morbidity and mortality are high in patients with SCID-X1 for whom an HLA-matched family donor is not available. This small study suggests that substantial, prolonged immunologic recovery is possible with somatic gene therapy; however, recovery of thymopoiesis may be compromised in older patients. Previous studies have shown more serious adverse events, including enhancer-mediated activation of the T-cell protooncogene LMO-2. Additional longitudinal studies will help to determine the duration of reconstitution and quantify the risk of adverse events.

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Pediatric Hypereosinophilic Syndrome (HES) Differs From Adult HES

Katz HT, Haque SJ, Hsieh FH. *J Pediatr.* 2005;146:134–136

PURPOSE OF THE STUDY. To highlight specific differences between pediatric and adult patients with hypereosinophilic syndrome (HES).

STUDY POPULATION. The case report involved a 15-year-old male who presented with abdominal pain, diarrhea, and a 10-lb weight loss. Colonoscopy revealed colitis. A nonproductive cough, night sweats, and a diffuse pruritic, papular rash developed. His initial absolute eosinophil count was 1890/mm³ (reference: <400/mm³), which increased to 52 000/mm³. Additional laboratory studies included: immunoglobulin E, 8561 U/mL (7–110 U/mL); alkaline phosphatase, 1149 U/mL (reference: 50–280 U/mL); γ-glutamyl transpeptidase, 193 (reference: 0–50 U/mL); and serum tryptase, 4.7 μg/L (reference: 1.9–13.5 μg/L). Ultrasound of the liver revealed an abnormal parenchymal pattern with dilated bile ducts. Molecular analysis of the patient's peripheral blood for the Fip1-like-1 platelet-derived growth factor receptor α chain (FIP1L1-PDGFRA) fusion tyrosine kinase associated with HES in adults was negative. Open lung biopsy revealed patchy interstitial and intra-alveolar inflammation with a predominance of eosinophils. A skin biopsy showed acute neutrophilic folliculitis with perivascular dermatitis with eosinophils. Bone marrow biopsy demonstrated a hypercellular marrow with predominantly eosinophils, which is consistent with idiopathic HES.

METHODS. The investigators compared this case report of pediatric HES and additional published cases of pediatric and adult patients with HES.

RESULTS. Pediatric HES has only a slight male predominance (55.3% male vs 44.7% female), whereas adult HES is reported to be more common among males than females, with a ratio of 9 to 1. In adults, the frequencies of symptoms found on presentation are: fatigue (26%), cough (24%), dyspnea (16%), rash (12%), and fever (12%). Fever (58.8%), arthralgias (23%), and rash (23.5%) were more common in pediatric cases. As with adults, involvement of the cardiovascular system is the major source of morbidity and mortality. Pediatric HES is commonly associated with chromosomal abnormalities,

and in ~40% of the cases, it has been associated with acute leukemia. As opposed to the vast majority of adult HES cases, no pediatric case with the FIP1L1-PDGFRA fusion gene has been reported.

CONCLUSION. There are several distinct features of pediatric, compared with adult, HES.

REVIEWER COMMENTS. Most of the published information on the HES has focused on adult patients. This report compares a pediatric case report of HES and a review of published pediatric cases of this condition to adult patients with this syndrome. This is an insightful clinical report that should be useful in the overall workup of pediatric patients who present with dramatic eosinophilia (>1500/mm^3) for >6 months' duration without other known causes of eosinophilia and who have evidence of organ involvement that might be attributable to HES.

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HUMAN IMMUNODEFICIENCY VIRUS

HIV-Infected Individuals Receiving Effective Antiviral Therapy for Extended Periods of Time Continually Replenish Their Viral Reservoir

Chun TW, Nickle DC, Justement JS, et al. *J Clin Invest.* 2005;115:3250–3255

PURPOSE OF THE STUDY. Latently infected, resting CD4$^+$ T cells provide a reservoir for HIV, and the persistence of these cells prevents the eradication of HIV even in patients who have received highly active antiretroviral therapy (HAART) for prolonged periods. The purpose of this study was to examine the underlying mechanisms by which HIV persists in CD4$^+$ T cells in individuals treated effectively for up to 9 years.

METHODS. Eleven HIV-infected subjects were studied. These individuals had received effective therapy for an average of 8 years (range: 7.16–9.1 years). None of the patients had experienced detectable plasma viremia after initial suppression. Peripheral blood cells were obtained sequentially on all individuals and studied for the presence of replication-competent virus.

RESULTS. All infected subjects carried replication-competent HIV in their CD4$^+$ T cells despite having received prolonged, effectively suppressive antiviral therapy. Contrary to current thinking, substantial higher levels of HIV proviral DNA were found in circulating activated CD4$^+$ T cells when compared with the resting subset. Sequence analysis revealed evidence for cross infection between the resting and activated T-cell compartments, indicating that ongoing reactivation of latently infected, resting CD4$^+$ T cells may occur in these patients.

CONCLUSIONS. Continual replenishment of the CD4$^+$ T-cell reservoir occurs despite prolonged periods of plasma aviremia.

REVIEWER COMMENTS. It is only with the elimination of viral reservoirs that HIV infection can be "cured." Resting T cells harboring proviral DNA do not live forever. However, the rate of viral replenishment in this cell compartment at least equals the natural decline in their numbers. Eliminating this cell reservoir will be a daunting task.

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Emergence of Drug Resistant HIV-1 After Intrapartum Administration of Single-Dose Nevirapine Is Substantially Underestimated

Johnson JA, Li JF, Morris L, et al. *J Infect Dis*. 2005; 192:16–23

PURPOSE OF THE STUDY. An inexpensive, effective regimen to prevent perinatal HIV transmission in the developing world is highly desirable. Nevirapine, a nonnucleoside reverse transcriptase inhibitor, seems to provide such an intervention. However, drug-resistance mutations have been identified in up to 40% of women shortly after they received a single intrapartum nevirapine dose as part of a transmission-prevention strategy. This study was undertaken to reexamine the incidence of drug-resistant HIV-1 after single-dose nevirapine.

STUDY POPULATION. Fifty South African women infected with HIV subtype C.

METHODS. Sensitive, real-time polymerase chain reaction assays were sequentially performed for nonnucleoside reverse transcriptase inhibitor–resistance mutation, K103N and Y181C.

RESULTS. Resistance mutations emerged in 65% of women after a single dose of nevirapine.

CONCLUSIONS. Single-dose nevirapine as used in the developing world for prevention of perinatal HIV transmission results in the development of resistance mutations in a very high percentage of women who receive this intervention.

REVIEWER COMMENTS. Although single-dose nevirapine has been successfully implemented as a strategy to prevent perinatal HIV transmission, it is increasingly apparent that the women who are treated with this regimen more often than not develop resistance mutations to nevirapine. The clinical implications are clear: Will nevirapine

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