by using a lentiviral vector (LV) to introduce a functional WAS gene into hematopoietic stem and progenitor cells (HSPCs) for autologous transplantation.

STUDY POPULATION. Three patients who had WAS with a severe clinical condition or severe mutation/absent WAS protein expression without a suitable matched donor for allogeneic transplant or ineligible for HSPC transplantation were enrolled.

METHODS. Patients were pretreated with a reduced-intensity myeloablative regimen. Afterward, they received autologous HSPCs that were transduced with an optimized LV carrying the WAS gene. Patients were monitored for up to 2.5 years after gene therapy, and the genomic distribution of LV integration sites in bone marrow and peripheral blood lineages was investigated.

RESULTS. Researchers were able to administer autologous HSPCs transduced with LV with high efficiency (>90%). This technique resulted in robust (25%–50%) and long-term engraftment in bone marrow, as well as detection of WAS protein expression in peripheral blood. All 3 patients experienced improved platelet counts, protection from bleeding and severe infections, and resolution of eczema. Analysis of LV integration resulted in highly polyclonal multilineage hematopoietic reconstitution with no in vivo selection of clones carrying integrations near oncogenes, as had been seen with previous γ-retroviral gene therapy.

CONCLUSIONS. The authors concluded that gene therapy using lentiviral HSPCs results in hematopoietic reconstitution and restoration of WAS expression to near physiologic levels in patients with resultant clinical benefit. There was no increased risk of malignant transformation as seen with γ-retroviral gene therapy in the same disease setting.

REVIEWER COMMENTS. Infusion of autologous HSPCs that have been genetically corrected ex vivo is an alternative therapeutic strategy for patients with WAS for whom a fully matched allogeneic donor is unavailable. Previous gene therapy in WAS patients using the γ-retroviral vector showed initial clinical benefit but was later associated with development of leukemia or myelodysplasia. This study addresses a potentially safer alternative with the use of the LV carrying the WAS gene under the control of its endogenous promoter to ensure that the transgene is expressed in a physiologic manner. Because there is currently no curative treatment of WAS other than a fully matched allogeneic HSPC transplant, LV gene therapy could be an attractive treatment option for patients. It would be of particular interest because of its safety profile compared with previous therapies because WAS patients are already innately prone to developing malignancies. Future studies with the use of a larger patient population will likely provide information about indications for LV gene therapy as an alternative to traditional stem cell transplantation.


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Absence of Detectible HIV-1 Viremia After Treatment Cessation in an Infant

PURPOSE OF THE STUDY. Until very recently, the only patient “cured” of HIV was the “Berlin patient,” an adult male treated for HIV-associated acute myeloid leukemia with stem cell transplantation from a donor who was intrinsically resistant to HIV. The donor carried homozygous mutations (delta32) in the chemokine receptor 5 gene, which is an essential co-receptor for HIV entry into most target cells. The present study reports on an infant who also may be cured with early, highly active antiretroviral therapy (ART) after documented perinatal infection.

STUDY POPULATION. A 35-week gestational age infant was born by normal vaginal delivery to an HIV-infected woman who received no prenatal care and who was not taking ART. ART was initiated in the infant at 30 hours of age with zidovudine, lamivudine, and nevirapine. At 1 week of age, this regimen was adjusted to zidovudine, lamivudine, and ritonavir-boosted lopinavir. The infant remained on ART for 18 months and was then lost to follow-up until 23 months of age. ART has been discontinued and, because of results from subsequent studies, has not been restarted.

METHODS. Standard HIV polymerase chain reaction (PCR) assays and HIV antibody testing were used to diagnose and monitor the HIV-exposed infant. Peripheral blood mononuclear cell cultures were analyzed with PCR for virus DNA and with co-culture techniques for replication-competent virus. Lymphocyte subset analysis was conducted with standard flow cytometry, and HIV-specific T-cell responses were evaluated with intracellular cytokine generation assays.

RESULTS. During the first month of life and while receiving ART, the infant had elevated quantitative HIV RNA PCR measurements that declined to undetectable levels and remained there. Subsequently, although proviral DNA was detected at the limits of the assay at 26 months of age, plasma viral RNA was undetectable, and replication-competent virus could not be cultured at age 24 months. HIV antibody assays were not detected in the infant at or after 24 months of age, when maternal antibody would not confound the assays, and HIV-specific T-cell responses
were not detected at age 28 months. CD4+ T-cell counts remain normal throughout the study.

CONCLUSIONS. Very early ART therapy in infants born at risk may abort HIV infection.

REVIEWER COMMENTS. In patients with established HIV infection, effective ART drives the virus to “undetectable” levels, usually defined as <20copies of viral RNA/mL of plasma. However, viremia persists in such patients at very low levels and as DNA-pro-virus in peripheral blood mononuclear cells. Was this infant cured of HIV? According to the Centers for Disease Control and Prevention definition, the infant was “infected”: 2 positive PCR test results on at least 2 different blood specimens. The data presented demonstrated that after unintended discontinuation of therapy, the infant remained free of replication-competent HIV from at least 12 months of age. As the authors conclude, “very early ART in infants may alter the establishment and long term persistence of HIV-infection.” But why might this happen in a newborn when it has not been demonstrated in older patients except under the unique circumstances of the Berlin patient? HIV persistence depends on the establishment of a reservoir of infected cells. Recent studies suggest that this condition involves a specific population of “central memory T cells.” Perhaps very early therapy aborts or inhibits establishment of this reservoir or perhaps these cells have not fully matured to be infected in newborns. In any case, the present report suggests that very early therapy may prevent establishment of HIV in high-risk infants, and certainly this possibility is being studied intensively.

Cell Death by Pyroptosis Drives CD4 T-Cell Depletion in HIV-1 Infection

PURPOSE OF THE STUDY. HIV-induced disease is characterized by progressive CD4+ T-cell depletion. A long-standing question has been: what drives this depletion? Earlier reports suggested that caspase-3-driven apoptosis was a primary form of HIV-induced T-cell depletion. The focus of the present study was to examine an alternative mechanism of T-cell loss induced by HIV.

METHODS. Human lymphoid aggregate culture formed with human tonsillar and splenic cells were used to study how CD4+ T cells die in a “natural and preserved lymphoid environment” in the absence of artificial cell activation. In situ immunostaining of fresh lymph node tissue obtained for HIV-infected, untreated adults was also studied.

RESULTS. HIV infection of human lymphoid aggregate culture produced extensive loss of CD4+ T cells, but >95% of dying cells were abortively infected, and only 5% were productively infected. Abortively infective T cells were noted to specifically contain activated caspase-1, a mediator of the proinflammatory programmed cell death pathway, pyroptosis. Only productively infected cells activated caspase-3 and died by apoptosis. Normal resting CD4+ T cells constitutively express pro-IL1β and caspase-1 activation, and abortively infected T cells resulted in IL1β secretion from these cells. Immunostaining of lymph nodes from HIV-infected subjects provided in vivo evidence of HIV-mediated pyroptosis. As the authors conclude, “This death pathway thus links two signature events in HIV-infection—CD4 T-cell depletion and chronic inflammation—and creates a pathogenic vicious cycle in which dying CD4+ T-cell release inflammatory signals that attract more cells to die.” Finally, VX-765, a caspase-1 inhibitor currently in clinical trials, blocked IL1β secretion by CD4+ T cells in vitro.

CONCLUSIONS. Caspase-1-mediated pyroptosis accounts for 95% of CD4+ T-cell deaths and is triggered by abortive HIV infection. This highly pro-inflammatory form of programmed cell death may explain 2 characteristics of HIV pathogenesis: progressive loss of CD4+ T cells and persistent inflammation.

REVIEWER COMMENTS. Programmed cell death describes host defense mechanisms whereby specific enzymatic cascades result in morphologically and physiologically variable forms of cell suicide. Such host defense is initiated when danger-associated molecular patterns are engaged by cytoplasmic pattern recognition receptors (PRRs). Cytoplasmic danger-associated molecular patterns, in the present article represented by incompletely transcribed HIV DNA, are engaged by a PRR that triggers inflammation. Activation of caspase-1 results in cell death by pyroptosis and the release of proinflammatory IL1β. In a companion paper (Monroe KM, Yang Z, Johnson JR, et al. IFI16 DNA sensor is required for death of lymphoid CD4 T cells abortively infected with HIV. Science. 2014;343[6169]:428–432), the PRR for incompletely transcribed HIV DNA was identified as IFI16. These findings raise the possibility of a new form of HIV therapy that would target a host process, pyroptosis, rather than HIV directly.

Vectored Immunoprophylaxis Protects Humanized Mice From Mucosal HIV Transmission

PURPOSE OF THE STUDY. A large majority of new HIV infection results from transmission across mucosal barriers. HIV
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