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 <20/copy 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.


Joseph A. Church, MD
Los Angeles, CA

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. Subsequent 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.


Joseph A. Church, MD
Los Angeles, CA

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
vaccine clinical trials have failed to illicit protective immunity to infection. Furthermore, pre-exposure and postexposure prophylaxis regimens have had limited success, primarily due to nonadherence to the prescribed regimens. Protection with currently available vaccines to mucosal infections, such as human papilloma virus and influenza virus, correlate with systemic neutralizing antibodies. The purpose of this study was to evaluate a new strategy for prevention of HIV transmission, “vected immunoprophylaxis,” a specific form of gene transfer therapy in which the gene for a modified broadly neutralizing antibody is directed into muscle cells via an adeno-associated virus vector. This technique results in an episomally replicating construct that produces the neutralizing antibody that enters the systemic circulation.

STUDY POPULATION. Genetic immunodeficient mice that had been reconstituted with a human immune system, BLT (bone marrow-liver-thymus) mice, were used to study mucosal HIV infection. These mice exhibit extensive engraftment of immune cells in mucosal tissues.

METHODS. BLT mice were administered adeno-associated virus vectors containing genes either for a control protein or for a broadly neutralizing monoclonal immunoglobulin (Ig)G antibody. These mice were then challenged intravenously with infectious HIV. In addition, mice were challenged weekly with low-dose, nonabrasive vaginal HIV challenge to mimic mucosal exposure.

RESULTS. The initial antibody tested, VRC01, was shown to reduce HIV transmission of a diverse range of HIV strains. This antibody also reduced vaginal transmission of HIV. All control animals were infected after a mean of 4.25 vaginal challenges; 2 VRC01-expressing mice became infected after 13 and 15 challenges, respectively. A second antibody, VRC07G54W, was selected for additional study with the repetitive challenge model. None of the mice expressing VRC07G54W exhibited detectible virus in the plasma despite 21 consecutive weekly challenges.

CONCLUSIONS. Providing broadly neutralizing monoclonal antibody with vector immunoprophylaxis protects humanized mice against mucosal HIV challenge.

REVIEWER COMMENTS. “Protective” immunologic responses to virus infection differ when considering prevention of new infection versus control of chronic infection. Neutralizing antibody seems to be necessary and sufficient for the former, CD8+ cytotoxic T cells for the later. Early HIV vaccines were designed to enhance CD8+ T-cell responses and were ineffective in preventing new HIV infection. Even for viruses transmitted through mucosal surfaces, neutralizing antibody levels provide the best surrogate marker for protection in humans. Importantly, the view that the dominant antibody in vaginal secretions is of the IgA isotype is incorrect; IgG that is actively transported across vaginal epithelium via Fc receptors is the predominant antibody isotype in this location. This at least in part explains the efficacy of systemic immunizations against human papillomavirus. Unfortunately, the generation of broadly neutralizing antibodies against HIV occurs naturally only in the context of chronic infection and with selection of effective antibodies only after many cycles of B-cell affinity maturation. Creating an immunogen that replicates this process will be exceptionally challenging. Vectored immunoprophylaxis uses gene transfer technology to generate a systemic monoclonal antibody that provides the desired neutralizing response. Although it will require additional studies in higher animal models, vectored immunoprophylaxis may offer an alternative to standard immunizing techniques.

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Joseph A. Church, MD
Los Angeles, CA
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