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.


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**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 inflammasome activation. 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.


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**Vectored Immunophylaxis 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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