EDITORIAL

Baby Steps on the Road to HIV Eradication

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The durable suppression of plasma human immunodeficiency virus type 1 (HIV-1) RNA that is conferred by potent antiretroviral therapy (ART) has been associated with dramatic improvements in immunologic and clinical well-being and reductions in morbidity and mortality from opportunistic complications. It has also brought the restoration of normal life expectancies within our grasp, has effectively eliminated the vertical transmission of HIV in resource-unconstrained settings in women who receive antenatal care, and can substantially reduce horizontal transmission.[1]

Concomitantly, the ability to drive plasma HIV-1 RNA to levels below the limits of quantification of sensitive clinical assays has unveiled the limitations of our current knowledge and therapies. Residual viremia, defined as less than 20 copies of plasma HIV-1 RNA per milliliter, can be detected in most persons receiving effective therapy, and replication-competent virus can be isolated from peripheral-blood CD4+ T cells cultured ex vivo from such patients. The best-described cellular reservoir is the resting, memory CD4+ T cell, but other cell types probably contribute.[2] The persistence of the virus in cell reservoirs is thought to feed the residual viremia by means of intermittent release of infectious virus rather than by rounds of ongoing viral replication, although this point is still debated.[2] The persistence of HIV in reservoirs has at least two major implications: it may be responsible for the ongoing immune activation and inflammatory state seen in virologically suppressed persons, which, in turn, may be linked to the non-opportunistic complications of cardiovascular, renal, hepatic, and malignant disease; and, with integrated HIV proviral DNA, this reservoir presents the biggest challenge to achieving the complete eradication of replication-competent HIV-1 from an infected person.

There has been one well-documented case of an adult in whom the eradication of replication-competent HIV-1 (i.e., a cure) has been achieved.[3] This person required a hematopoietic stem-cell transplant for acute myelogenous leukemia, with the donor being homozygous for the 32-base-pair deletion in the chemokine (C-C motif) receptor 5 gene (*CCR5* delta32), making the patient's engrafted lymphocytes resistant to infection with the R5 (CCR5-tropic) HIV-1 strain. Bone marrow ablation and graft-versus-host disease also probably contributed to the cure in this patient, which has now been documented for more than 5 years.[4] Other reports of reductions of the viral reservoir after hematopoietic stem-cell transplantation for the treatment of lymphoma or early ART have subsequently appeared that support the hypothesis that the HIV reservoir is a viable therapeutic target.[5-7]

Persaud and colleagues[8] now describe in the *Journal* a case of a child who was born at 35 weeks of gestation to an HIV-infected mother who had not received prenatal care and thus was not receiving ART at the time of delivery. The child began receiving combination ART 30 hours after birth, and the subsequent early course was notable for the decreasing but detectable viremia through 19 days of age. After a 5-month absence from care, during which ART was not administered, viral rebound was not detected when the child presented again at 23 months of age.

Challenging questions have been raised by this case. Was infection established in the infant? Are the early virologic findings a result of maternal–fetal circulatory exchange? Could this be a case of postexposure prophylaxis? The positive

HIV-1 DNA polymerase chain reaction drawn at 30 hours and the plasma HIV-1 RNA level of 19,812 copies per milliliter drawn separately at 31 hours taken together meet the criteria for neonatal infection, and the early test positivity is compatible with in utero, rather than intrapartum, infection. The transfer of maternal cells and virions would probably not result in an HIV-1 RNA level that was eight times as high in the neonate as it was in the mother (maternal viral load at 24 hours, 2423 copies per milliliter), nor would it result in 19 days of viremia. These data, along with the classic trajectory of viremic decline during ART, support the authors' perspective that the infant was truly infected.

The big question, of course, is, "Is the child cured of HIV infection?" The best answer at this moment is a definitive "maybe." This uncertainty is due to the need for long-term follow-up while the child is not receiving ART and the imprecision with which the viral reservoir can be measured. Assays for proviral DNA in the child at 24 and 26 months of age were inconclusive, but the failure to isolate replication-competent HIV-1 from resting CD4+ T cells and the absence of rebound viremia months after ART was discontinued are compelling.

The eradication of HIV-1 is now the goal of a formidable research effort. One line of investigation is focused on reducing, destabilizing, or eliminating the latent cell reservoir. Drugs such as the histone deacetylase inhibitors (e.g., vorinostat) can disrupt the epigenetic control of integrated provirus, resulting in viral RNA transcription.[9] However, this may not result in reliable killing of the cell, which suggests that the addition of an immune effector mechanism may be necessary to ensure the death of these cells.[10] Destabilization of the viral reservoir can also be achieved by engaging the programmed death 1 receptor on the surface of latently infected CD4+ T cells. Another line of investigation being pursued is gene therapy directed at interrupting the expression of CCR5 coreceptors.[11]

The child described by Persaud et al. may be unique, and thus we have to exercise caution before inferring general principles from this case report. This said, we are at the stage at which individual case reports can provide proofs of principle, stimulate hypotheses, and lead to carefully designed experimental therapeutic studies involving both adults and children that, we hope, will lead us down the road to the reduction or eradication of the HIV-1 reservoir. To paraphrase the Chinese philosopher, Lao-tzu, "A journey of a thousand miles begins with a single step." In the case of HIV infection, this may turn out to be a baby step.

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