A Possible Sterilizing Cure of HIV-1 Infection Without Stem Cell Transplantation

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Background: A sterilizing cure of HIV-1 infection has been reported in 2 persons living with HIV-1 who underwent allogeneic hematopoietic stem cell transplantations from donors who were homozygous for the CCR5Δ32 gene polymorphism. However, this has been considered elusive during natural infection.

Objective: To evaluate persistent HIV-1 reservoir cells in an elite controller with undetectable HIV-1 viremia for more than 8 years in the absence of antiretroviral therapy.

Design: Detailed investigation of virologic and immunologic characteristics.

Setting: Tertiary care centers in Buenos Aires, Argentina, and Boston, Massachusetts.

Patient: A patient with HIV-1 infection and durable drug-free suppression of HIV-1 replication.

Measurements: Analysis of genome-intact and replication-competent HIV-1 using near-full-length individual proviral sequencing and viral outgrowth assays, respectively; analysis of HIV-1 plasma RNA by ultrasensitive HIV-1 viral load testing.

Results: No genome-intact HIV-1 proviruses were detected in analysis of a total of 1.188 billion peripheral blood mononuclear cells and 503 million mononuclear cells from placental tissues. Seven defective proviruses, some of them derived from clonally expanded cells, were detected. A viral outgrowth assay failed to retrieve replication-competent HIV-1 from 150 million resting CD4+ T cells. No HIV-1 RNA was detected in 4.5 mL of plasma.

Limitations: Absence of evidence for intact HIV-1 proviruses

in large numbers of cells is not evidence of absence of intact HIV-1 proviruses. A sterilizing cure of HIV-1 can never be empirically proved.
Conclusion: Genome-intact and replication-competent HIV-1 were not detected in an elite controller despite analysis of massive numbers of cells from blood and tissues, suggesting that this patient may have naturally achieved a sterilizing cure of HIV-1 infection. These observations raise the possibility that a sterilizing cure may be an extremely rare but possible outcome of HIV-1 infection.
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Although antiretroviral therapy (ART) can effectively suppress viral replication, HIV-1 is one of the few infectious diseases for which a sterilizing cure during natural disease is currently considered elusive. Indeed, HIV-1 is known to establish a population of latently infected CD4+ T cells that harbor chromosomally integrated proviral DNA that displays limited transcriptional activity (1). These cells persist throughout the lifespan, are not susceptible to ART, and can effectively fuel rebound viremia when ART is stopped. Attempted elimination of these cells through pharmacologic or immunologic interventions has been unsuccessful in the past, except in 2 reported patients with leukemia who underwent allogeneic hematopoietic stem cell transplants that resulted in what are widely considered to be sterilizing cures (2, 3). In a small subgroup of persons living with HIV-1 who are frequently termed “elite controllers”or “natural suppressors,”HIV-1 plasma viremia remains durably undetectable by commercial polymerase chain reaction (PCR) assays in the absence of ART. However, genome-intact proviral DNA and replication-competent viruses can readily be isolated in these persons by using in vitro laboratory assays, indicat-

ing that drug-free viral control in these persons results from host-dependent inhibition of viral replication and does not reflect elimination of all virally infected cells (4, 5). Similarly, a small proportion of persons living with HIV-1 have sustained viral control after stopping ART; such "posttreatment controllers"are also known to harbor persistent reservoirs of replication-competent HIV-1, indicating that this clinical phenotype is not associated with viral eradication (6). In this article, we describe a person

who may have achieved complete clearance of all replication-competent HIV-1 proviruses during natural infection.

METHODS

Peripheral Blood Mononuclear Cell and Placental Samples

Peripheral blood from the person described in this study was collected in October 2017, January 2018, and August

Seealso:
Editorial comment

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