Annals of Internal Medicine

EDITORIAL

The Esperanza Patient: More Hope for a Sterilizing HIV-1 Cure

Fewer than 1% of people living with HIV are able to control viral replication to below the limits of detection by commercial assays without antiretroviral therapy (ART). These patients are called "elite controllers" or "elite suppressors," and they represent a model of a cure for HIV-1 (1). However, it has not always been clear whether they are models of a functional cure, where replication-competent virus remains but is controlled by host factors (analogous to the control of herpes viruses), or a sterilizing cure, where the virus is eradicated by the host (analogous to the control of most viruses).

In order to distinguish between these models, one has to be able to determine whether or not replication-competent virus is present in elite controllers. It is important to specifically detect replication-competent virus because most HIV-1 DNA contains large deletions and/or mutations that render the virus replication-incompetent. The most rigorous way to do this is to culture virus from the latent reservoir, which consists primarily of rare, quiescent infected $CD4^+$ T cells that have the genome of replication-competent virus integrated into the host genome. When these cells become activated, productive viral replication is reinitiated. Studies of the latent reservoir in elite controllers have provided significant evidence that some of them harbor replication-competent virus. Indeed, the viral isolates cultured from some elite controllers can replicate robustly in vitro and cause AIDS in humanized mice (2). However, these culture assays and studies that have used elegant molecular tools to approximate the frequency of cells harboring replication-competent virus have shown that the latent reservoir is markedly smaller in elite controllers compared with patients with progressive disease who are receiving ART (3–6), and it has recently become clear that it can be challenging to detect any form of virus in some elite controllers (4, 5, 7, 8).

In their article, Turk and colleagues describe a young woman from Esperanza, Argentina, who tested positive for HIV in 2013 and has maintained undetectable viral loads since then (9). She received ART for just 6 months in 2019 and 2020 during the second and third trimesters of a pregnancy and has continued to maintain undetectable viral loads since the drugs were discontinued. In a heroic effort, the authors analyzed more than a billion of the patient's $CD4^+$ T cells and found no evidence of replication-competent virus.

Why is this exciting? It suggests that some elite controllers may have gone beyond simply controlling the virus and instead have managed to eradicate it. Viral eradication has previously been believed to have occurred only in the Berlin patient and the London patient, 2 individuals who underwent stem cell transplants with cells from donors who had a mutation of the CCR5 gene that prevents the surface expression of this HIV coreceptor (10). The authors are careful to point out that the absence of evidence of replication-competent virus is not evidence of absence of this virus. Also, it should be noted that the most rigorous way of proving a cure for HIV in patients receiving ART is to perform an analytical treatment interruption, where ART is discontinued and one determines whether the patient develops viremia. Unfortunately, treatment interruptions do not distinguish between functional and sterilizing cures and cannot be used in elite controllers because they have already controlled viral replication without ART for many years. So, there is no definitive way to prove a sterilizing cure in an elite controller. However, by screening so many cells, the authors show that the largest possible size of the latent reservoir in this patient is less than 1 infected cell per billion cells. Similar estimates were recently seen for another elite controller (5) and a patient who has maintained virologic control for 12 years after discontinuing ART (8). At such low frequencies, the likelihood that an infected cell would become activated and lead to a recrudescence of viremia is extremely low, so the line between a functional cure and a sterilizing cure becomes blurred. However, it should be noted that although a sterilizing cure is much harder to accomplish than a functional cure, there are at least 2 advantages associated with this form of cure. The complete eradication of virus means there is no possibility of the loss of control of viral replication leading to rebound viremia, as has been reported in some elite controllers (1). Some elite controllers also have higher levels of immune activation and inflammation than patients with progressive disease who are receiving ART (1). This is likely the result of the immune response to residual virus; thus, viral eradication should solve this problem.

If the Esperanza patient has indeed achieved a sterilizing cure, defining the mechanisms responsible for it becomes important. Elite controllers have potent $CD8^+$ T-cell responses that can kill productively infected $CD4^+$ T cells (1), but it seems unlikely that quiescent latently infected cells would be recognized and killed since they probably do not make viral proteins. If this is the mechanism, then how does this patient differ from many other elite controllers who control viral replication but are unable to achieve complete eradication? The authors show that her $CD4^+$ T cells could easily be infected with laboratory strains in vitro, so a unique restriction factor in this patient seems unlikely. The patient's partner eventually died of AIDS. Could it be that due to prior exposure to the virus, the patient had developed an HIV-specific immune response before becoming infected and thus was able to kill the majority of infected cells during primary infection before the reservoir was effectively seeded? It would be interesting to use her cells to develop avatars of her immune system in humanized mice to determine what happens after infection with primary HIV-1 isolates. In the meantime, it is perhaps not a coincidence that she hails from Esperanza, which translates to "hope" in English. If a spontaneous sterilizing cure of HIV is in fact possible, we may eventually be able to do more than just hope that we can replicate this phenotype on a large scale.

This article was published at Annals.org on 16 November 2021.

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Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M21-4336.

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Ann Intern Med. doi:10.7326/M21-4336

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