

First Woman May Be Cured of HIV Without a Bone Marrow Transplant

Loreen Willenberg is part of a group of elite controllers whose HIV appears to be locked away where it can't produce new virus.

August 28, 2020 By [Liz Highleyman](#)

A California woman may be the first person to be cured of HIV without a bone marrow transplant, according to a [recent report in Nature](#). More than 60 other so-called elite controllers, who have unusually potent immune responses to HIV, were found to have their virus sequestered in parts of their genome where it is unable to replicate.

The unusual case involves Loreen Willenberg, who acquired HIV in 1992. Her immune system has maintained control of the virus for decades without the use of antiretroviral treatment, and researchers have been unable to find any intact virus in more than 1.5 billion of her cells. Elite controllers are thought to make up less than half a percent of all people living with HIV.

"I believe Loreen might indeed meet anyone's definition of a cure," study coauthor Steven Deeks, MD, of the University of California at San Francisco, told POZ. "Despite heroic efforts, we just could not find any virus that is able to replicate. Her immune system seems completely normal. Even her HIV antibody levels are low, which is unprecedented in an untreated person."

Although antiretroviral therapy can keep HIV replication suppressed, the virus inserts its genetic material into the chromosomes of human cells, making it very difficult to eradicate. HIV can lie dormant in a reservoir of resting immune cells indefinitely, but when antiretrovirals are stopped and the cells become activated, they can start churning out new virus.

Previously, only two people were known to have been cured of HIV: Timothy Ray Brown, [formerly known as the Berlin Patient](#), and [a man in London](#). Both received bone marrow stem cell transplants from a donor with a rare genetic mutation that makes cells resistant to HIV entry. But this procedure is far too dangerous for people who don't need it to treat advanced cancer.

The new research suggests that Willenberg and some five dozen other people with long-term untreated HIV have their virus hidden away in their cell's genomes in such a way that the viral genetic blueprint (known as a provirus) can't be used to produce new viral particles that can go on to infect other cells.

Xu Yu, MD, of the Ragon Institute of Massachusetts General Hospital, MIT and Harvard analyzed integrated HIV in millions of cells from 64 elite controllers and 41 typical HIV-positive people on antiretroviral therapy recruited at Mass General and San Francisco General Hospital.

In both groups, about 20% were women, the average age was approximately 56 and they had been living with HIV for an average of 17 years and had undetectable virus according to standard tests for nine years. Overall, the elite controllers had a higher average CD4 count (about 900 versus 70, respectively).

The researchers used next-generation gene sequencing to characterize the participants' viral blueprints, including where they were inserted into human chromosomes. They found that the elite controllers had fewer integrated proviruses, but a larger proportion of them were intact, or potentially capable of replicating. The virus in these individuals was highly consistent, without the wide variety of mutations seen in most people with HIV.

What's more, their proviruses were integrated at distinct sites in the human genome, farther away from elements that enable viral replication. Specifically, the integrated DNA was not located near sites that switch on transcription or close to accessible chromatin, which contains histone proteins that package long DNA strands into a more compact form. The DNA must then be unwound from these proteins before it can be used to produce new virus.

"These data suggest that a distinct configuration of the proviral reservoir represents a structural correlate of natural viral control and that the quality, rather than the quantity, of viral reservoirs can be an important distinguishing feature for a functional cure of HIV-1 infection," Yu and colleagues wrote.

In a [commentary accompanying the report](#), Nicolas Chomont, PhD, of the University of Montreal, characterized the proviruses in these elite controllers as being in a state of "deep sleep" compared with latent virus in typical people with HIV. This has only now become apparent because researchers have more sophisticated tools to pinpoint the location of proviruses within the genome.

It is unclear why this "block and lock" phenomenon happens in only a small proportion of people with HIV. It's possible that the virus ends up sequestered in these locations by chance. But the researchers think it's more likely that the integrated proviruses at these sites are evolutionarily selected over time as the ones in locations more conducive to viral replication are eliminated by the immune system.

In Willenberg's case, the research team analyzed more than 1.5 billion of her peripheral blood immune cells, including samples from gut tissue, where the virus often hides. They could not find any intact proviruses that could be used to produce new HIV. Given her lack of intact proviruses, the researchers were unable to determine whether she ever fit the pattern of having latent HIV locked away in inaccessible locations.

Another 11 people, dubbed exceptional controllers, only had detectable proviruses at remote sites

in the genome where it could not replicate. Since this study, the researchers have discovered a couple more elite controllers who may qualify as additional cures, [according to The New York Times](#).

This raises the possibility that a sterilizing cure of HIV—meaning complete eradication—“may be feasible in rare instances,” the study authors suggested. A similar but less complete process may be at play in the subset of about 10% of people with HIV who maintain viral suppression after stopping antiretroviral therapy but who still have detectable proviruses (known as post-treatment controllers).

This research was first presented at the International AIDS Society Conference on HIV Science last summer, where Willenberg was referred to as “the San Francisco Patient.” Willenberg later [went public with her status](#), and she and Yu discussed the study findings during a webinar with HIV cure advocates last November.

“I broke out in tears when I saw Dr. Yu’s final slide,” said Willenberg, who over the years has participated in more than a dozen studies. “I can only hope and pray that with continued dedication we can figure out how I have dumped the virus into the DNA junkyard.”

The question now is whether it’s possible to develop treatments that could enable the millions of typical people with progressive HIV to become elite controllers like Willenberg. Chomont suggested that immune-based therapies—including CAR-T cells—might be able to shrink the viral reservoir until it consists only of deeply latent proviruses that are unable to replicate.

“The key question is, ‘How did her immune system achieve this remarkable state?’” Deeks said. “We do not know. We need to find more people who are ‘exceptional controllers’ like Loreen and get to work on figuring out the mechanism.”

In this video from amfAR, the Foundation for AIDS Research, Loreen Willenberg talks about living as an elite controller of HIV.

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