Spanish Woman Is in Remission 15 Years After Stopping HIV Treatment

A new case may provide clues to help researchers develop strategies for a functional cure.

August 10, 2022 By Liz Highleyman

A Barcelona woman has maintained an undetectable HIV viral load for more than 15 years after stopping antiretroviral treatment, according to a case report presented last week at the 24th International AIDS Conference in Montreal.

The woman's HIV is not completely eradicated—so she can't be considered cured in the strictest sense—but her long-term remission may provide clues to help researchers develop strategies for a "functional cure," meaning viral control without antiretrovirals.

"The presented case is exceptional, not just because there are so few people with long-term post-treatment control but also because of the HIV-control mechanism, which is different than that described in elite controllers and other cases documented to date," study coinvestigator Josep Mallolas, MD, PhD, of Hospital Clinic-IDIBAPS at the University of Barcelona said in a press release.

Although antiretroviral therapy can keep HIV replication suppressed as long as treatment continues, the virus integrates its genetic blueprint (known as a provirus) into the DNA of human cells, establishing a viral reservoir that is unreachable by antiretrovirals and usually invisible to the immune system. These proviruses can lie dormant in resting immune cells indefinitely, but they usually start churning out new virus when treatment is stopped.

The handful of people thought to be truly cured of HIV—a fifth such case was reported at the conference—received stem cell transplants from donors with a rare mutation, known as CCR5-delta32, that blocks HIV from entering cells. But a larger group of people have been able to keep the virus under control without treatment, either since they acquired HIV (like Loreen Willenberg, dubbed the San Francisco Patient) or after stopping antiretroviral therapy (post-treatment controllers).

The new case, presented by Núria Climent, PhD, of Hospital Clinic-IDIBAPS, involves a woman (researchers are calling her the Barcelona Patient) who was diagnosed with HIV during acute infection at age 59. People with very early infection have a smaller viral reservoir, which may improve their chances of achieving a functional cure. At baseline, her viral load was about 70,000 copies—showing that she isn't a natural controller like Willenberg—and she still had a high CD4

count (about 800).

The woman joined a small clinical trial testing various immune-modulating therapies (NCT00979706). She first received a standard antiretroviral regimen of lopinavir/ritonavir (Kaletra), tenofovir disoproxil fumarate and lamivudine for nine months plus a short course of cyclosporine A (an immunosuppressive drug).

At that point, she underwent a brief planned treatment interruption, during which she received granulocyte-macrophage colony-stimulating factor (an agent that promotes production of white blood cells) and interferon-alpha (a cytokine that regulates innate, or non-specific, immune activity). She then restarted antiretrovirals plus a short course of interleukin-2 (a cytokine that activates T cells and natural killer cells).

Eight weeks later, with her viral load suppressed, she started another analytic treatment interruption, but her HIV did not rebound as expected after stopping antiretrovirals. Her plasma HIV RNA viral load remained undetectable, and she also experienced a "pronounced and progressive" reduction of the viral reservoir, as indicated by dramatic declines in total HIV DNA and integrated proviral DNA in CD4 cells. However, using a sensitive viral outgrowth assay, the researchers were able to isolate a small amount of virus capable of replication.

To shed more light on the woman's unusual response, the researchers performed a genetic analysis, finding that "she had no classical genetic factors" associated with natural viral control, including the CCR5-delta32 mutation, Climent reported. The woman also did not have defective virus, which has been found in some people who naturally control HIV. In fact, her virus was able to replicate normally and her T cells were susceptible to HIV entry in laboratory studies.

Looking more closely at the woman's immune responses, the researchers found that natural killer cells and CD8 killer T-cells played key roles in controlling HIV. What's more, she had higher levels of specific types of natural killer cells (NKG2C+ memory-like NK cells) and killer T cells (gamma-delta CD8 T-cells) than usually seen in untreated people with typical HIV progression. These cell types have been shown to have "potent cytotoxic activity against HIV-infected CD4 T cells," Climent said.

Although Climent did not present detailed outcomes for the other 19 people in the small trial, the woman "was the only one that was able to control [HIV] during the long term," she told reporters at an AIDS 2022 media briefing. Of note, this exceptional controller was reportedly the only woman in the study; other research suggests women may have an advantage over men when it comes to controlling HIV.

The question now is whether researchers can use information gained from this case and others like it to develop treatment strategies that could enable the millions of people with typical progressive HIV to keep their virus in check without ongoing antiretroviral treatment. Indeed, advocates say, cases like this are more relevant for the vast majority people living with HIV than the rare cures after a stem cell transplant, and they should get more media attention.

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