# Netherlands Man in Remission 23 Years After Stopping HIV Treatment

While not cured, the man has maintained viral suppression for more than two decades after stopping antiretroviral therapy.

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A man in the Netherlands who started HIV treatment very soon after infection has maintained viral suppression for 23 years after stoppingantiretroviral therapy, according to a case report described in the journal AIDS.

The man still has detectable latent virus, so he is not fully cured, but this report adds further evidence that having a small viral reservoir at the time of treatment initiation may be key to posttreatment control. A strong CD8 T-cell response also plays an important role in this case.

Antiretroviral therapy can keep HIV replication suppressed as long as treatment continues, but the virus inserts its genetic blueprints (known as a provirus) into the DNA of human cells, establishing a long-lasting reservoir that is unreachable by antiretrovirals and usually invisible to the immune system. These proviruses lie dormant in resting immune cells indefinitely, but they usually start churning out new virus when treatment is stopped, making a cure nearly impossible.

A handful of people have been cured of HIV after stem cell transplants from donors with a mutation (CCR5-delta-32) that prevents HIV from entering CD4 T-cells. In addition, a few people—known as elite controllers—appear to control the virus naturally, while a somewhat larger group of posttreatment controllers remain in remission after stopping antiretrovirals. For example, at the 2022 International AIDS Conference, researchers presented the case of a Spanish woman who maintained an undetectable viral load for more than 15 years after stopping treatment.

Pien van Paassen, a PhD candidate at the University of Amsterdam, and colleagues recently described another such case.

The man, then age 49, was diagnosed with HIV during acute infection in 1998. He started antiretroviral therapy two weeks after diagnosis using an intensive five-drug regimen consisting of stavudine (d4T), lamivudine (3TC), abacavir (Ziagen), the NNRTI nevirapine (Viramune) and the protease inhibitor indinavir (Crixivan).

The man achieved viral suppression seven months after starting treatment. After making a couple

of regimen changes, he discontinued antiretrovirals at his own request after being on treatment for 26 months. But he agreed to join a study and underwent extensive ongoing testing, including viral load measurement using ultrasensitive assays, tests for latent virus in peripheral blood cells, CD4 and CD8 T-cell tests and measurement of HIV antibodies.

At diagnosis, the man had a viral load of 2.7 million copies, indicating rampant viral replication. He does not have the CCR5-delta-32 mutation that prevents HIV from entering cells. He also lacks protective HLA variants, except for one that appears to promote strong CD8 responses against HIV. These findings mean the man is probably not a natural elite controller.

For more than two decades, the man maintained an undetectable plasma viral load using standard tests, with the exception of a single 400-copy "blip" seven months after stopping treatment. However, plasma HIV RNA was detectable at very low levels (less than 5 copies) using ultrasensitive tests.

During follow-up, the man has continued to test positive for HIV antibodies targeting the viral envelope protein during follow-up, but they lack neutralizing activity—that is, they are not the type of broadly neutralizing antibodies associated with HIV control.

The man had a CD4 count of about 440 at the time of diagnosis, which rose to above 700 after starting treatment and remained stable thereafter. What's more, he has shown no clinical signs of HIV-associated disease during follow-up.

Testing performed at 18 years after treatment interruption showed that the man had detectable HIV DNA proviruses in CD4 cells at levels comparable to those seen in people with typical chronic infection. However, the researchers could not isolate replication-competent virus. In general, the man showed low levels of CD4 and CD8 cell activation, exhaustion and senescence, which are often apparent in untreated people with HIV.

Over 25 years of follow-up, the man continued to have CD8 cell responses against HIV proteins, which suggests ongoing exposure to the virus. He shows a particularly strong proliferative CD8 cell response targeting HIV's gag protein, which is necessary for assembly of new viral particles; this was already present two months after infection. In addition, the researchers noted that his HIV has a gag mutation associated with decreased viral replication.

This "exceptional" case of posttreatment control was "likely associated with sustained potent gag-specific CD8 T-cell responses in combination with a replication-attenuating escape mutation in gag," the study authors concluded, adding, "Understanding the initiation and preservation of the HIV-specific T-cell responses could guide the development of strategies to induce HIV control."

"A small viral reservoir due to early treatment initiation appears to be one of several prerequisites for posttreatment control, confirming the importance of early diagnosis of HIV infection and starting antiretroviral therapy during acute HIV infection," they wrote. "Nevertheless, modeling of the viral reservoir dynamics has shown that a large reduction of the viral reservoir is needed to

delay viral rebound only by a few weeks, which indicates that additional induction of the HIV-specific immune responses is necessary to achieve posttreatment control. This posttreatment control case, together with earlier case reports, shows that different components of the immune system—for example, natural killer cells and CD8 T-cell responses individually contribute to posttreatment control."

While this man's HIV has not been completely eradicated—so he can't be considered cured in the strictest sense—this case of long-term remission after stopping treatment provides clues to help researchers develop strategies for a functional cure.

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