

HIV May Establish More Than One Viral Reservoir

Latent HIV may hide in a distinct reservoir in the brain and spinal cord.

February 8, 2023 By [Liz Highleyman](#)

HIV may lie dormant in a distinct viral reservoir in the central nervous system (CNS), or brain and spinal cord, which could present an additional barrier to a cure, according to a recent report in [Nature Microbiology](#).

“Our analysis of rebound virus suggests latently infected T cells in the CNS are separate from the latent reservoir in the blood,” senior study author Ron Swanstrom, PhD, of the University of North Carolina School of Medicine said in a [press release](#). “Our analysis allows us to infer the presence of a distinct pool of latently infected cells in the CNS waiting to reinitiate infection once antiretroviral therapy is interrupted.”

While [antiretroviral therapy](#) can keep HIV replication under control as long as treatment continues, the virus inserts its genetic blueprints into the chromosomes of human cells and establishes a [long-lasting viral reservoir](#) that is unreachable by antiretrovirals and invisible to the immune system. These latent HIV proviruses can lie dormant indefinitely in resting CD4 cells in the blood and lymph tissue in the presence of antiretrovirals, but they usually start churning out new virus soon after the drugs are discontinued.

Now, researchers have found that HIV may actually establish multiple reservoirs, which could make achieving a functional cure, or long-term remission, even more difficult.

Swanson, Laura Kincer and colleagues asked whether there might be a distinct HIV reservoir in the CNS. During antiretroviral treatment interruption, HIV can be detected in the cerebrospinal fluid (CSF) surrounding the brain and spinal cord, they noted as background.

The researchers compared genetic sequences of rebounding virus soon after treatment interruption in the blood and CSF of people living with HIV to determine whether they were part of a common latent viral reservoir.

The analysis included eight men at the University of California San Francisco (UCSF) and two men and one woman at the University of Gothenburg in Sweden. Ages ranged from 39 to 56. All but one of the UCSF participants had been living with HIV for more than a decade, while the Gothenburg

participants were diagnosed between one and five years prior. At UCSF, five participants had experienced treatment failure and had a detectable blood viral load. Most stopped treatment in 1998 or 1999, when combination antiretroviral treatment was not as effective or well tolerated. The other three were initially on suppressive therapy and undertook a treatment interruption as part of a study in 2000 or 2001. The Gothenburg participants stopped antivirals in 2001, 2006 and 2016.

Rebound DNA sequences from the blood (red) and the CSF (blue)UNC Health

The researchers found that high rebound viral load in the CSF was associated with the transient entry of white blood cells into the CNS—known as pleocytosis—which occurred in about half of the participants after treatment interruption. In some people, viral sequences were not the same in the blood and CSF, suggesting they arose from different populations of latently infected cells.

The authors observed that clonally amplified viral lineages, or virus that originates from cells with a common ancestor, were disproportionately present in the CSF compared with the blood in these

individuals (a phenomenon dubbed compartmentalization), suggesting a local source of virus within the central nervous system.

Differences in rebound virus populations in the CSF and blood during treatment interruption “suggests that there may be CNS-resident CD4+ T cells that can release virus during treatment interruption to create a population that is in part distinct from that in the blood,” [according to Kincer and Swanson](#).

In contrast, in participants who did not experience pleocytosis after treatment interruption, the resurgent virus in the CSF and the blood were similar. “In the absence of pleocytosis, the rebound virus in the CSF closely resembles the virus in the blood, whereas the influx of cells into the CSF strongly influences the composition of the viral population by providing cells that can be infected to amplify the virus through replication,” they wrote.

The researchers did not see any evidence that rebounding virus in the CSF had evolved to preferentially infect macrophages or microglia in the brain rather than CD4 T cells. This virus required a high density of CD4 surface receptors to enter cells efficiently, which is a characteristic of CD4 T cells but not macrophages. One participant initially had macrophage-tropic virus in the CSF prior to starting antiretrovirals but it was no longer present in the rebound virus population after treatment interruption.

The study authors noted that examination of brain tissue samples collected during autopsies of HIV-positive people would offer more direct evidence about the nature of viral reservoirs in the CNS. A larger study of people living with HIV would be challenging due to the need for lumbar punctures (spinal taps), which can be a painful procedure.

The researchers proposed a model in which R5 T cell-tropic virus—that is, HIV that preferentially infects CD4 cells using CCR5 receptors—is released from infected T cells that either enter the CNS from the blood or are already present in the CNS during treatment. These T cells then multiply when antiretrovirals are interrupted, leading to viral replication in the brain.

“We found that the majority of the viral populations that rebounds in the CSF during treatment interruption represents clonally amplified virus with a T cell-tropic entry phenotype,” they concluded. “This suggests that the main rebounding populations in the blood and CNS compartments are probably produced from T cell reservoirs.”

These findings suggest that strategies to cure HIV may need to reach a latent viral reservoir in the brain as well as dormant virus residing in T cells in the blood and lymph system.

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