

Most Cases of HIV Persistence in Blood Following Treatment Explained by Defective Copies of the Virus

Around 95% of detectable virus was defective due to mutations or deletions in the 5'-leader region of HIV-1 RNA that prevented the generation of infectious virus.

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Antiretroviral drugs for HIV infection have enabled most people living with the virus to live long and healthy lives. However, a small portion of people experience detectable — and worrisome — traces of the virus that causes AIDS despite strict adherence to long-term treatment regimens and the absence of symptoms.

New findings published in [Nature Communications](#) suggest that most cases of this phenomenon, which is called non-suppressible viremia, are explained by defective and noninfectious copies of the virus. The research was partially supported by grants from the National Institutes of Health (NIH).

The study, which involved more than 50 people, found that while traces of HIV-1 RNA can persist in blood after optimal therapy, cases of non-suppressible viremia are driven by HIV-1 RNA with defects in a piece of the RNA known as 5'-leader.

“From a clinical perspective, this is important because people with HIV are taught that the absolute goal of their medication is to achieve undetectable viral load and they worry,” says [Francesco R. Simonetti, MBChBD, PhD](#), the senior study author and an assistant professor of medicine in the [Division of Infectious Diseases](#) at Johns Hopkins University School of Medicine. The new findings, says Simonetti and his team, should provide relief to many people living with HIV who fear a viral rebound or who are concerned about transmitting the virus to partners despite taking effective treatment.

For the study, the investigators examined blood samples from 52 people living with HIV who had detectable loads of the virus despite taking long-term antiretroviral drug therapy.

These samples, which were assessed from 32 people and compared to an additional 20 samples, were collected between 2021 and 2025. The majority of participants were white men, between ages 58 and 68, and received care in the U.S., Canada and Denmark. The researchers found that

most detectable forms of the virus, around 95%, were due to defective copies, and most defects were due to mutations or deletions in the 5'-leader region of HIV-1 RNA. This region is known to orchestrate the production of copies of the virus, but in this case the defects prevented the generation of infectious virus.

Modern antiretroviral therapies, which date back to 1996, prevent HIV from infecting new populations of immune system cells, but aren't able to retroactively prevent previously infected cells from releasing HIV viral particles. Since those cells usually represent a small portion of infected cells after a person is on stable therapy, most people who take antiretroviral therapies are able to bring their viral loads to clinically undetectable levels in their blood.

However, in some cases, which are [estimated](#) to occur less than 1% of the time, people may experience clinically detectable levels after taking long-term antiretroviral drug therapy. This could happen years later, or, in less frequent cases, they may have never achieved undetectable levels.

This new study offers evidence that clinicians can now study the virus in blood plasma and confirm if clinically detectable levels are due to defective copies released from one or a few T-cell clones, says Simonetti. If so, he adds, this could eliminate the need for extra medications and could prevent related complications. It could also help people living with HIV have access to surgeries or other procedures, such as hip or knee replacements or organ transplants, and participate in clinical studies if they know they have HIV under control.

The assay, or test, the researchers created and used to confirm the defective copies of the virus for this study is cost-effective and can be broadly used in HIV clinics and research settings. Similar to using a liquid biopsy to detect cancer mutations in DNA, the assay, which is called CLAWS (Capturing 5' Leader Anomalies Without Sequencing), uses advanced technology to identify detectable viral loads that are due to defective copies.

"We know that these defective proviruses cannot infect new cells, but they are still clinically relevant," says Simonetti. "Think of how many extra visits, extra drugs, extra costs and tests they've been causing."

"It's also clear from the new study that, over time on treatment, intact proviruses that make virus are pruned away, while defective ones escape the immune system," he says. "Now we want to understand these differences in immune recognition to uncover HIV's vulnerabilities."

Additional study authors include Julia R. Box, Angelica Camilo-Contreras, Filippo Dragoni, Feng Yun Yue, Vitaliy Matveev, Jackson Foley, Jianwei Zhang, Yan Wei Mok, Marlene DeSousa, Jun

Lai, Zachary Mulcare, Zachary Bakewell, Sebastien Poulin, Frederic Chano, Claude Fortin, Cecile Tremblay, Joel N. Blankson, Sonya Krishnan, Ethel D. Weld, Christie Basseth, Matthew M. Hamill, Christopher J. Hoffmann, Eileen P. Scully, Joyce L. Jones, Andrea L. Cox, Wissam El Atrouni, Beverly Sha, Janet D. Siliciano, Robert F. Siliciano, Robert Reinhard, Jesper D. Gunst, Mario Ostrowski, Frank Maldarelli and Colin Kovacs.

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Simonetti reports receiving honoraria from Gilead Sciences for participating in scientific conferences.

To learn about HIV, visit hopkinsmedicine.org/health/conditions-and-diseases/hiv-and-aids.

To learn about the Viral Immunity and Pathogenesis Center, visit vipc.jhmi.edu.

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