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HIV persists in the body despite effective antiretroviral therapy

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A team of international scientists led by Northwestern University found that HIV is still replicating in lymphoid tissue, even when it is undetectable in the blood of patients on antiretroviral drugs.

The findings provide a critical new perspective on how HIV persists in the body despite potent antiretroviral therapy.

"We now have a path to a cure," said corresponding author Dr. Steven Wolinsky, chief of infectious diseases at Northwestern University's Feinberg School of Medicine and a Northwestern Medicine physician. "The challenge is to deliver drugs at clinically effective concentrations to where the virus continues to replicate within the patient."

The paper was published January 27 in the journal *Nature*.

Combinations of potent antiretroviral drugs quickly suppress HIV to undetectable levels in the bloodstream of most patients, but HIV persists in a viral reservoir within lymphoid tissue in the body. The virus rapidly rebounds in the blood if patients stop their drugs. This suggests that long-lived latently infected cells and/or ongoing low levels of HIV replication maintain these viral reservoirs.

Up until now, most scientists believed the reservoir only contained long-lived infected cells in a resting state rather than newly infected cells for several reasons. First, no one had seen viruses with the new genetic mutations that inevitably arise when HIV completes cycles of growth. Second, most patients do not develop the drug resistance mutations which might seem likely, if HIV was growing in the presence of drugs.

The team examined viral sequences in serial samples of cells from lymph nodes and blood from three HIV-infected patients from the University of Minnesota (U of M) who had no detectable virus in their blood. Scientists found that the viral reservoir was, in fact, constantly replenished by low-level virus replication in lymphoid tissue with infected cells then moving from these protected sanctuaries into the blood.

Because infected cells in drug-sanctuaries within lymphoid tissue can still produce new viruses, infect new target cells and replenish the viral reservoir, it has not been possible to purge the body of latently infected cells and eradicate the virus.

A mathematical model tracked the amount of virus and the number of infected cells as they grew and evolved in drug sanctuaries, then moved through the body. The model explains how HIV can grow in drug sanctuaries in lymphoid tissue where antiretroviral drug concentrations are lower than in the blood, and why viruses with mutations that create high-level drug-resistance do not necessarily emerge.

The findings provide a new perspective on how HIV persists in the body despite potent antiretroviral therapy. The study also explains why the development of drug resistance is not inevitable when virus growth occurs in a place where drug concentrations are very low.

Most importantly, this new understanding highlights how important it is to deliver high concentrations of antiretroviral drugs to all locations in the body where HIV can grow. Drugs that penetrate the newly discovered sanctuaries will be a prerequisite to the elimination of the viral reservoir and, ultimately, a step towards a cure.

"The study is exciting because it really changes how we think about what is happening in treated patients," said co-author Angela McLean, professor of mathematical biology at Oxford University, who supervised the mathematical modelling. "It helps explain why some strategies that tried to clear the reservoir have failed."

Source:
Northwestern University
