HIV May Reproduce in Cells Other Than CD4s, Which Might Explain Brain-Related Problems

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For the first time, researchers have shown that HIV can actively reproduce in a cell type other than CD4 cells, according to a new paper published October 6 by the online journal *PLoS Pathogens*. These findings, the authors explain, may help explain why antiretroviral therapy may not offer complete protection against HIV-associated neurological problems.

According to the paper authored by Ronald Swanstrom, PhD, and his colleagues at the University of North Carolina Center for AIDS Research in Chapel Hill, some people diagnosed with HIV-associated dementia have two genetically distinct HIV types in their cerebrospinal fluid (CSF), the clear fluid found in the spaces around and inside the brain and spinal cord.

These variants, the authors point out, are not detected in HIV circulating in the blood, and one of them could be present years before the onset of dementia and potentially contribute to mild forms of neurologic disease, including HIV-associated neurocognitive disorder (HAND). The detection of these viruses in the CSF, Swanstrom and his colleagues point out in an accompanying press release, is evidence that they are growing in the central nervous system.

One of the two HIV variants found in CSF reproduces in CD4 cells, as does the virus growing in the blood. But the other type does not. It infects and replicates in macrophages, another white immune cell that engulfs and digests foreign material, including bacteria.

“This is the first time that anyone has demonstrated active replication of HIV virus in a cell type other than [CD4] cells,” Swanstrom said in the press release.

Researchers have known for many years that macrophages trap HIV—macrophage means “big eaters”; their role is to engulf harmful pathogens and diseased cells in tissues of the body. Once a macrophage encases a pathogen like HIV, the macrophage displays pieces of the virus on its membranes and produces chemicals, known as cytokines, to alert other cells of the immune system to the presence of the pathogen in bodily tissues.

CD4s are among the immune system cells to respond to the macrophage’s plea for help. For years, researchers believed that the only way HIV can escape the macrophages is by being passed

on to the CD4 cells, where the virus can begin replicating. The new research by Swanstrom's group suggests that HIV can reproduce in macrophages without any help from CD4 cells.

Swanstrom's group had been collecting blood and CSF samples from patients who had either HIV-associated dementia or other severe neurological defects.

"After the start of therapy, we looked at the rate at which the virus disappeared," Swanstrom said. "We know that HIV in the blood disappears quickly when you go on therapy, and that's because the virus is growing in [CD4] cells, which have a very short half-life," referring to the period of time it takes for a substance undergoing decay to decrease by half. "Infected [CD4] cells decay by half every one to two days."

But for half of the patients in the new study, HIV growing in the cerebrospinal fluid decayed very slowly, several weeks to one month. "This is evidence the virus is actually being produced by a cell with a longer half-life, and not a [CD4] cell," Swanstrom said.
The researchers also found that the slow-decaying HIV had a particular attraction, or "tropism," to macrophages and were able to infect them.

"Those viruses are known to exist in autopsy brain studies. It has been known for 10 years that a subset of HIV-infected patients have slow decay of the virus in the CSF, and it's also been known for a long time that you can find macrophage-tropic virus in the brain," Swanstrom said. "But no one has ever brought the two together in a way that makes sense and could give you a tool to evaluate what's going on the brain by looking at cerebrospinal fluid."

The study also found HIV-infected macrophages present in a CSF sample two years before the patient was diagnosed with dementia. Swanstrom said this tells us there's information in the CSF that potentially could predict disease progression. "Is it bad to have these viruses around even if you don't get a diagnosis of dementia? And are they potentially causing cognitive damage that can be reversed with HAART?"

To explore these and other questions, Swanstrom's University of North Carolina group will continue collaborating with researchers and the University of California at San Francisco to expand the research in HIV patients who don't have dementia and are starting therapy. A new study will look for biomarkers in the CSF in the form of HIV variants or other immune protein information that may predict improvement, stability or decrease in cognitive capacity during therapy.

People living with HIV sometimes delay going on antiretroviral therapy, Swanstrom said. "Our research will help further understand what's going on in the central nervous system of patients who are still alive and in tissue that's accessible in the clinical setting, i.e. CSF. If these individuals knew there was an AIDS virus replicating independently in their [central nervous system], it might affect their decision when to start treatment with [antiretrovirals]."
