Medical Xpress

HIV active in tissues of patients who were treated, study shows

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While successful treatment of HIV with antiretroviral medications leads to undetectable levels of virus in the blood, controls the disease and leads to much longer lifespans, scientists know that HIV continues to reside in tissues. Now, UCSF researchers have found in autopsy tissue samples of patients treated with antiretrovirals that the virus evolved and migrated among tissues similar to the way it did in patients who had never received antiretroviral treatment, despite the fact that the treated patients had undetectable levels of virus in their blood.

The new study, the researchers said, supports the likelihood that the virus may at least be contributing to the development of non-AIDS-defined diseases, such as cancer and cardiovascular disease.

"Looking in tissues of treated HIV patients, we found that HIV in some tissues did not appear to be affected by antiretrovirals. Notably we saw no evidence of drug resistance, which we would have seen if the virus had been exposed to medications. While this is expected in untreated patients, it was a surprise to see this in virally suppressed patients. Our results suggest that HIV in varied tissue compartments can be untouched by the medications," said study senior author, Michael S. McGrath, MD, PhD, UCSF professor of laboratory medicine at the AIDS and Cancer Specimen Resource.

The research is published in the October 2016 issue of *The Journal of Virology* and was selected by the editors as a "Spotlight" article of significant interest.

The tissues examined by the research team came from the National Cancer Institute-supported AIDS and Cancer Specimen Resource at UCSF, which contains samples collected from patients beginning in 1984.

"Our findings suggest the spectrum of "non-AIDS defining" diseases such as cancers and cardiovascular disease that are increasingly the cause of death for virally suppressed patients are likely driven to some degree by the presence of active, untreated virus in tissues," said McGrath. "In addition, our findings suggest that strategies to "cure" HIV infection, which are centered on treatment of blood, must consider targeting tissue based sites of HIV."

In these studies, the team examined mutations in HIV genetic sequences from patient's tissues. HIV that continues to replicate and spread shows genetic changes in viral sequences that can only occur if the virus is replication competent and capable of spreading. In patients without antiretroviral treatment, this analysis can reveal if and how much the virus is evolving, a phenomenon typically observed in HIV infection without treatment. HIV replication and evolution is inhibited by antiretroviral therapy, and genetic sequencing of HIV from virally suppressed patients reflects the inhibitory effects of therapy.

In the current study, researchers looked at HIV from tissues taken from five HIV-infected patients who had been treated with antiretroviral therapy, had no detectable virus in the blood and who had died from cancer, and compared it to HIV sequence changes taken from patients who had never received therapy and also had died from cancer.

"The evolution of HIV derived from both treated and untreated patients' tissues, which showed no evidence for an antiretroviral effect, stood in sharp contrast to other researchers' findings from blood studies of patients treated with antiretrovirals showing dramatic drops in both the

number of HIV particles and evolution of the virus, confirming a predominant blood effect of antiretroviral therapy unappreciated prior to the current study," added McGrath.

The research team found evolving "wild type" HIV, that is virus unaffected by antiretroviral therapy, in the cerebellum, lymph nodes, lungs, colons, and spleens amongst others tissues.

The team also pointed to a role for HIV-infected macrophages, a long-lived tissue-based immune cell that engulfs and destroys cellular debris, foreign substances, microbes, and cancer cells, in disease progression. "Tissue macrophages, activated due to HIV infection, can turn on or contribute to disease processes, such as cardiovascular disease and neurological disease," said McGrath.

More information: Susanna L. Lamers et al. HIV DNA Is Frequently Present within Pathologic Tissues Evaluated at Autopsy from Combined Antiretroviral Therapy-Treated Patients with Undetectable Viral Loads, *Journal of Virology* (2016). DOI: 10.1128/jvi.00674-16

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