Drugs fail to reawaken dormant HIV infection

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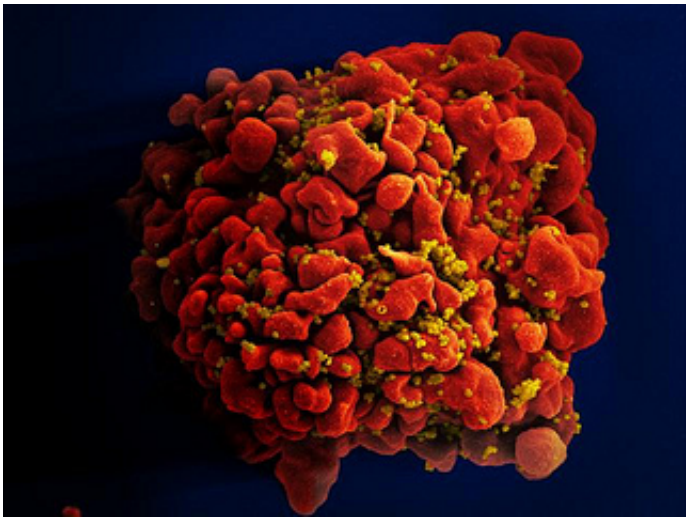

Scanning electron micrograph of an HIV-infected H9 T cell. Credit: NIAID

Scientists at Johns Hopkins report that compounds they hoped would "wake up" dormant reservoirs of HIV inside immune system T cells—a strategy designed to reverse latency and make the cells vulnerable to destruction—have failed to do so in laboratory tests of such white blood cells taken directly from patients infected with HIV.

"Despite our high hopes, none of the compounds we tested in HIV-infected cells taken directly from patients activated the latent virus," says Robert F. Siliciano, M.D., Ph.D., a professor of medicine at the Johns Hopkins University School of Medicine and a Howard Hughes Medical

Institute investigator.

Siliciano is senior author of a report on the disappointing results published online March 23 in *Nature Medicine*.

The failure challenges the idea that a single so-called latency-reversing agent can uncover the HIV hiding out in the cells of patients whose viral load is essentially undetectable with blood tests.

While inactive, the dormant HIV lurks in the cells but does not replicate in the amounts needed to produce proteins that can be recognized by the immune system. Without that recognition, the immune system cannot eliminate the last remaining HIV from the body. Current treatment with antiretroviral drug regimens known as HAART (highly active antiretroviral therapy) does not target the dormant HIV.

Studies have long demonstrated that these tiny reservoirs can be rekindled if a patient stops taking medication, a phenomenon that has proven to be the major barrier to a cure.

Laboratory models of latent HIV-infected cells suggested that certain compounds, mostly a group of drugs called HDAC inhibitors, might reverse the latency and awaken the infected cells just enough to make them vulnerable to eradication, Siliciano says. These inhibitors affect the genetic operation of viruses and have also been used in drugs that treat cancer and some neurological disorders.

The strategy depends on reactivating the very few remaining HIV reservoirs while HAART is in use, so that the infected cells will be eliminated while HAART prevents any new cells from becoming infected. The dormant virus is found in roughly one of every million white blood cells in someone with HIV. If all of the cells with latent HIV can be eliminated, Siliciano says, drug therapy can be safely stopped and

the infection essentially cured.

Because cells with latent HIV are so rare and difficult to retrieve from infected people, researchers have used engineered latent HIV cell models to test HDAC inhibitors in the past, says study co-author Janet D. Siliciano, Ph.D., an associate professor of medicine at the Johns Hopkins University School of Medicine. Typical models have used white blood cells infected with HIV in a test tube that are then cultured until the virus becomes latent. Studies with HDAC inhibitors in these models worked very well.

For their new study, the Johns Hopkins team used a process called leukapheresis, in which a patient with HIV is hooked to a machine that removes blood and separates out the red and white blood cells, returning only the red blood cells to the body. By this method, the team collected a large enough sample of lymphocytes with latent HIV reservoirs to test the HDAC inhibitors on actual cells.

The goal of the new study was to compare various latency-reversing agents against one another on these patient-derived cells to see which one was best at turning on the virus, says Greg Laird, a Ph.D. candidate at Johns Hopkins and also a study co-author. "The surprise was that none of them actually worked," he says.

HDAC inhibitors were the major class of the latency-reversing agents studied by the Johns Hopkins team. HDAC proteins repress the production of RNA, a key step in taking the DNA's blueprint and using it to create, in this case, the viral protein that comprises the business end of the virus and spurs its growth.

Despite the failure of HDAC inhibitors and other compounds in their study, Laird and another principal author, Korin Bullen, also a Johns Hopkins Ph.D. candidate, say the experiments led them to develop more

sensitive assays to test for reactivation of the virus.

They also created a yardstick by which to judge future successes with perhaps other compounds or combinations of therapies: If a T cell is activated in an HIV-infected person, that cell produces virus at the maximum level, essentially the equivalent of a 100-fold increase in viral RNA production. Most of the drugs studied created a one- or two-fold increase; one resulted in a six- to 10-fold increase.

The next step, the researchers say, is to study some of the drugs in combination using patient-derived cells, in hopes that the sum is greater than the parts.

More information: New ex vivo approaches distinguish effective and ineffective single agents for reversing HIV-1 latency in vivo, DOI: 10.1038/nm.3489

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