Pathway to a Cure: Cancer Drug Helps Purge HIV From Resting Cells

March 9, 2012 By Tim Horn

Researchers have shown for the first time that it is possible to target and interrupt the mechanism by which HIV remains hidden and unreachable by antiretroviral (ARV) drugs, according to highly anticipated study results presented Thursday, March 8, at the 19th Conference on Retroviruses and Opportunistic Infections in Seattle. Though no people living with HIV participating in the study saw their virus eradicated as result of the experiment, the findings paint an optimistic picture for scientists in pursuit of a cure for HIV.

After protease inhibitors were approved in the mid-1990s, researchers hoped that the advent of combination ARV therapy would be potent enough to burn out HIV infection over time. It soon became apparent, however, that no matter how strong the drugs are and how long a person's virus level remains undetectable, HIV can still hide out inside dormant cells and bring the infection flaring back to life once ARV meds are stopped.

Therapies initially studied to reawaken these cells succeeded in forcing them to purge their HIV payload, but the therapies caused too much immune system inflammation. In other words, while they "turned on" the dormant cells, they also created so many susceptible uninfected CD4 cells that the ARV drugs couldn't protect them.

What was needed, scientists argued, was a drug that could force out the HIV hiding within these cells without activating immune system cells at the same time. One such approach that has gained a lot of attention in recent years is the inhibition of histone deacetylase (HDAC), an enzyme believed to play a key role in maintaining HIV inside long-lived resting cells.

An early experiment with an HDAC inhibitor called Depakote (valproic acid), conducted by David Margolis, MD, of the University of North Carolina and Chapel Hill and his colleagues, proved promising. But another round of studies, reported a few years later in 2005, failed to show that valproic acid significantly affected the recalcitrant reservoirs of dormant HIV-infected cells.

Margolis and his team then set their eyes on another HDAC inhibitor, Zolinza (vorinostat), a cancer chemotherapeutic that in 2009 was found to awaken dormant HIV-infected cells, both in laboratory cell cultures and in blood taken from people on ARV therapy. A year later, Margolis's group announced their plans for a clinical trial involving people living with HIV.

The clinical trial enrolled six HIV-positive men averaging 45 years old. All study volunteers had been on therapy for an average of four years, had undetectable viral loads and had stable CD4 cell counts in excess of 500.

The study’s first step was to harvest resting CD4 cells from the patients, which was needed to test HIV-RNA levels—a marker of viral activity—inside the cells. From there, the cells were exposed to Zolinza, which confirmed that the HDAC inhibitor had the ability to increase HIV-RNA levels.

The second step was to explore whether or not the Zolinza dose selected for the study—400 milligrams (mg)—had an effect on histone acetylation, the cellular process needed to turn on HIV expression in the dormant cells. Margolis reported that there was a more than twofold increase in this activity within eight hours of receiving a single dose of Zolinza.

The final step was to check Zolinza’s ability to increase HIV-RNA levels in the pools of resting CD4 cells obtained after vorinostat, compared with pre-treatment measurements. Margolis reported that there was an average 4.8 increase in all six patients, which ranged from a 1.5-fold increase in one patient to a 10-fold increase in another.

The researchers also failed to find a statistically significant increase in blood-based HIV-RNA levels, suggesting that while Zolinza succeeded at turning on HIV expression in the cells, it did not have an unfavorable effect of increasing viral load.

Margolis also noted that any adverse effects reported during the study were mild and that none appeared to be related to Zolinza treatment.

“This study provides first proof of concept, demonstrating disruption of latency, a significant step toward eradication,” Margolis concluded. “The effort to fully understand the potential of such approaches to influence both the natural history and clinical management of HIV infection deserves urgent and accelerated investigation.”

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