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Interferon decreases HIV-1 levels, controls virus after stopping antiretroviral therapy

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A multi-institutional team of researchers, led by The Wistar Institute, has announced the results of a clinical trial that shows how the immune system can engage in fighting HIV infection if given the right boost. In their study, HIV-infected volunteers suspended their daily antiretroviral therapy to receive weekly doses of interferon-alpha, an antiviral chemical produced by the human immune system. The study provides the first clinical evidence for a means of reducing the persistent amount of HIV in patients and the ability to control HIV without continued antiretroviral therapy.

Wistar's Luis J. Montaner, D.V.M., D.Phil., today presents their findings of the first clinical strategy able to harness host control and decrease HIV reservoir measures, at the 2012 Conference on Retroviruses and Opportunistic Infections in Seattle, Washington. HIV reservoirs are populations of cells that harbor HIV-1, enabling the virus to persist as a chronic infection.

"Our data shows that our human immune response can be made to control HIV in persons who have otherwise lost that ability and, if sustained by natural interferon production, it establishes proof-of-concept that a functional cure is theoretically possible," said Montaner, a professor at Wistar and director of the Institute's HIV-1 Immunopathogenesis Laboratory. "And while we still have much to pursue with this early clinical finding, I firmly believe this gives us hope that one day we can control—and eventually eradicate—HIV in absence of antiretroviral therapy."

The trial showed that interferon-alpha when used as a drug (Peg-IFN-α2A) sustained control of HIV in 9 of 20 patients while also decreasing measures of HIV reservoirs in patients otherwise dependent on antiretroviral therapy (ART). No other clinical strategy to date has shown an impact on decreasing integrated HIV DNA levels in HIV-infected humans.

"While our data may not immediately change clinical practice, it identifies the first strategy that shows a clinical response where both viral replication and HIV reservoir indicators are observed to be reduced in absence of current chemotherapy," Montaner said. "This is the type of response HIV cure research aims to achieve."

The study analyzed 20 patients over a period of 24 weeks. Remarkably, 45 percent of these patients were able to sustain viral control under 400 copies per mililiter and a similar frequency showed more than 50 percent reduction in circulating HIV reservoirs, as measured by the laboratory of Una O'Doherty, M.D., at the University of Pennsylvania. According to the researchers, these results show that our immune system , which is targeted by the HIV-1 virus, can mount a defense to HIV infection, if given the right stimulation.

"In previous studies, we have seen that when people suspend ART, their viral loads begin to creep upward while their white blood cell count gradually drops," Montaner said. "We expected to see the same thing during this trial, but we were, frankly, surprised to see patients maintain the gains made through ART using only interferon that modulates our body's response rather than acting directly against HIV as all current HIV drugs do."

"When someone is first infected with HIV-1, the immune system is overwhelmed, and the natural release of interferon into the bloodstream is ineffective as cells that produce it are quickly impaired," Montaner

said. "But in our study, conducted at a later stage of chronic infection in an individual, we saw that adding interferon to a recovered immune system can have a dramatic effect in directing responses against HIV-1 to both control and reduce its detection within places we know it can hide."

Patients were recruited in partnership with local HIV/AIDS clinical treatment programs, including the University of Pennsylvania, Drexel University, and the Philadelphia Field-initiating Group for HIV Trials Philadelphia (FIGHT). The trial followed the progress of 20 men and women of various ethnicities as they started on either of two different doses of interferon on ART, discontinued ART, and maintained interferon treatment for up to 24 weeks. The trial lasted either 24 weeks or until either their HIV-1 levels rose or CD4 T cell counts dropped to a pre-determined level, at which point they would resume ART. Surprisingly, at midpoint (12 weeks), 45 percent (9 out of 20) of the patients still controled viral replication, and those that dropped out still compared favorably to the controls. Eight patients remained in the trial during the entire 24 weeks. Both dosage arms achieved similar results.

"It is exciting to show control against HIV-1 can be regained by way of stimulating natural mechanisms," Montaner said. "Our findings also open the way to determine if we can move this clinical research strategy towards a cure based on the decrease in HIV reservoirs we observed."

Interferon-alpha is a chemical naturally manufactured by the human immune system to "interfere" with the ability of viruses to replicate within cells. Since human interferon does not persist long enough in the body to serve as a useful antiviral drug, pharmaceutical researchers modified it by adding polyethelyne glycol (PEG) to the interferon molecule, making it last longer in the bloodstream with less toxicity. This "pegylated" form of interferon was approved in 2008 to treat hepatitis B and C infections.

Provided by The Wistar Institute