Scientists at Temple Health Find Potential Cure for HIV

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Affecting over 35 million people a year, the number of infected individuals continues to grow because there is currently no cure to eliminate HIV.

Two scientists at Temple Health have manipulated mouse genomes to display human immunity and the effect of two different treatments on the mice after HIV is injected into the rodents. They have found promising results in ridding the mouse cells of any traces of inducible HIV DNA, are looking to further their research in hopes of soon using human subjects.

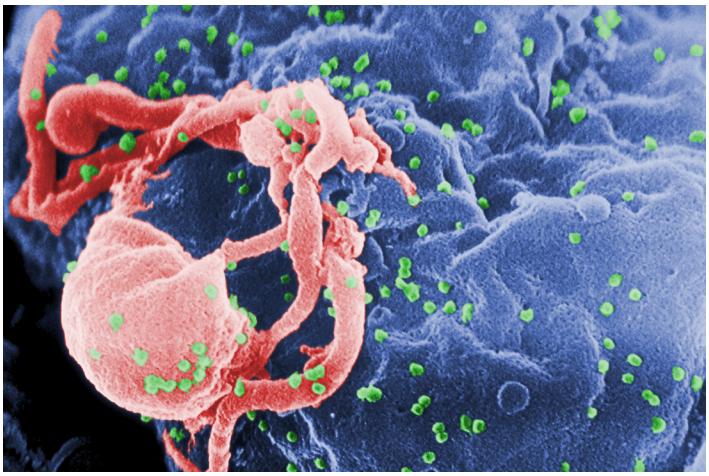
The Human Immunodeficiency Virus (HIV) is a sexually transmitted disease primarily spread by infected bodily fluids. This virus inhibits the body's ability to fight infections by targeting helper T cells, immune cells responsible for coordinating the body's response to disease. Once HIV deprives the immune system of these fighter T cells, they are not able to fight off infections and diseases that they normally would be able to without the virus. HIV fuses with the cell, converts its viral RNA to DNA, and replicating the DNA through reverse transcription. This duplicated DNA leaves itself in the host cells while the original copy leaves the host cell and moves to infect other cells.

Since HIV remains in an individual's body for life, and can switch from being dormant to active, the number of infected individuals is constantly increasing. Those who have the dormant virus could potentially not even know they contracted HIV until much later.

While HIV may seem somewhat benign, the longer the HIV-infected individual goes without treatment, the risk of obtaining Acquired Immune Deficiency Syndrome (AIDS) significantly increases. Because of low T-cell counts caused by the disease, the immune system is unable to fight off infections that a healthy person could, leading to an increased risk of opportunistic infections. For an individual diagnosed with AIDS, they could have a lower T-cell count than the baseline and have one or more of these opportunistic infections. These infections are significantly harder to control due to the established weakness of the immune system and are so malignant, they often kill patients with AIDS. It is vital, therefore, that more drugs develop to stagnate HIV in its earlier stages, to decrease the number of AIDS-related deaths worldwide.

While there is currently no cure for HIV, there are a number of medicines that can help an individual stay healthy. These medicines prevent the spread of this virus to others, limit the amount of HIV in the blood, and dramatically stagnate the progression of the disease.

One of these medicines includes pre-exposure prophylaxis, also known as PrEP, for those who don't currently have HIV but are at a significantly high risk of infection. PrEP is a pill (brand name Truvada) that is taken in combination with other medicines to help keep the virus from establishing itself for HIV prone individuals. If used properly, and combined with physician oversight, PrEP reduces the risk of contracting HIV by about 99 percent.



Regardless, it does not actively eliminate the virus from the body if the individual contracts HIV. Another defense against HIV includes Standard antiretroviral therapy (ART), a technique consisting of drugs to suppress the virus and stop the progression of the disease in the body once an individual already has already contracted the disease, while preventing its transmission to others. Despite this treatment suppressing the effects of the virus, it is unable to completely eliminate it from the body.

Researchers at Temple University, however, have been able to completely eliminate the replication-competent HIV-1 DNA from genomes of living animals. Dr. Kamel Khalili and Dr. Howard Gendelman, the two senior investigators on this study have successfully combined the use of CRISPR-Cas9 technology with Long Acting Slow Effective Release (LASER) antiretroviral therapy (ART) to eliminate HIV DNA from rat and mice cells.

At first, the researchers tested the use of only the CRISPR-Cas9 technology, which is a gene editing technology that can excise large fragments of HIV DNA from infected cells. This disrupts viral gene expression but unfortunately, similar to ART, this novel gene editor is unable to eliminate HIV on its own. However, Gendelman and his partner Dr. Edagwa had developed LASER ART, a technique that Gendelman utilized in this research to rid HIV DNA from affected cells. This technique targets viral sanctuaries to maintain lower HIV replication levels for longer periods of time. LASER ART therapy is coupled with long-lasting medications which were packed into nanocrystals and distributed meticulously to tissues still infected with dormant HIV. These nanocrys-

tals were stored in tissues for weeks, slowly releasing the drug. This combination of therapy and medication, however, was not enough in eliminating HIV either.

Gendelman and Edagwa questioned whether these two treatments could be used in parallel. Hopefully, combining the advantageous traits of each technology would create a synergistic relationship between them. They wanted to see whether LASER ART could potentially suppress the HIV DNA replication long enough for CRISPR-Cas9 technology to eliminate viral DNA from cells.

To test this theory, researchers infected special mice with HIV, genetically engineered in order to produce human T-cells that were susceptible to HIV. In order to affirm the relevance of this mouse model for studies of HIV-1 elimination from cells, the scientists accurately evaluated each of the human cell-virus model components to parallel in mice models, rather than solely injecting them with the immune cells and virus. Human immunocytes (body's fighting mechanism) in the mouse blood, injected into mice from human cord blood, were confirmed through flow cytometry. Only after a few months were mouse models injected with the virus, and the spread of the virus was confirmed through staining cells.

Following the validation of mouse models itself, the mice were split into four different groups with six mice in each group. These groups consisted of the six mice in the Control Group (left untreated), six mice in the group injected with CRISPR-Cas9 units, ten mice in the group administered LASER ART and seven mice in the group receiving both treatments. After the treatments, the animals were observed to see whether they had any evidence of HIV in their systems. All groups still had some evidence of HIV infection present, except for the last group, where two of the mice that received LASER ART with subsequent CRISPR-Cas9 had no signs of HIV in their cells. This analysis revealed that in about one-third of the HIV-infected mice, there was complete elimination of HIV. To validate this experiment, replicate experiments were performed on a different set of mice, who were all infected with a second type of HIV-1 strain, which confirmed the first experiment. This ground-breaking discovery, "confirmed the ability of LASER ART and CRISPR-Cas9 to eliminate viral rebound in a new cohort of CD34+HSC-reconstituted animals infected with HIV-1ADA HIV."

HIV, with its deadly progression to AIDS has never seen any potential traces of a cure until this experiment where researchers completely eliminated HIV viral DNA in the genomes of living animals. With this study in hand, scientists Dr. Khalili and Dr. Gendelman and their teams are ready to move to trials with non-human primates, and potentially clinical trials with humans within the year. While not 100 percent effective, the side effects were negligible in mice, and as we witness the progression of these two therapies, we could see a cure for HIV in humans after all.

SOURCES

Dash, Prasanta K., et al. 2 July 2019 "Sequential LASER ART and CRISPR Treatments Eliminate HIV-1 in a Subset of Infected Humanized Mice." *Nature News,* Nature Publishing Group, www.nature.com/articles/s41467-019-10366-y.