

Gene editing strategy eliminates HIV-1 infection in live animals, researchers show

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HIV-1 Virus. Credit: J Roberto Trujillo/Wikipedia

A permanent cure for HIV infection remains elusive due to the virus's ability to hide away in latent reservoirs. But now, in new research published in print May 3 in the journal *Molecular Therapy*, scientists at the Lewis Katz School of Medicine at Temple University (LKSOM) and the University of Pittsburgh show that they can excise HIV DNA from the genomes of living animals to eliminate further infection. They are the first to perform the feat in three different animal models, including a "humanized" model in which mice were transplanted with human immune cells and infected with the virus.

The team is the first to demonstrate that HIV-1 replication can be completely shut down and the virus eliminated from [infected cells](#) in animals with a powerful gene editing technology known as CRISPR/Cas9. The work was led by Wenhui Hu, MD, PhD, currently Associate Professor in the Center for Metabolic Disease Research and the Department of Pathology (previously in the Department of Neuroscience) at LKSOM; Kamel Khalili, PhD, Laura H. Carnell Professor and Chair of the Department of Neuroscience, Director of the Center for Neurovirology, and Director of the Comprehensive NeuroAIDS Center at LKSOM; and Won-Bin Young, PhD. Dr. Young was Assistant Professor in the Department of Radiology at the University of Pittsburgh School of Medicine at the time of the research. Dr. Young recently joined LKSOM.

The new work builds on a previous proof-of-concept study that the team published in 2016, in which they used transgenic rat and mouse models with HIV-1 DNA incorporated into the genome of every tissue of the animals' bodies. They demonstrated that their strategy could delete the targeted fragments of HIV-1 from the genome in most tissues in the experimental animals.

"Our new study is more comprehensive," Dr. Hu said. "We confirmed the data from our previous work and have improved the efficiency of

our gene editing strategy. We also show that the strategy is effective in two additional mouse models, one representing acute [infection](#) in mouse [cells](#) and the other representing chronic, or latent, infection in human cells."

In the new study, the team genetically inactivated HIV-1 in transgenic mice, reducing the RNA expression of viral genes by roughly 60 to 95 percent, confirming their earlier findings. They then tested their system in mice acutely infected with EcoHIV, the mouse equivalent of human HIV-1.

"During acute infection, HIV actively replicates," Dr. Khalili explained. "With EcoHIV mice, we were able to investigate the ability of the CRISPR/Cas9 strategy to block viral replication and potentially prevent systemic infection." The excision efficiency of their strategy reached 96 percent in EcoHIV mice, providing the first evidence for HIV-1 eradication by prophylactic treatment with a CRISPR/Cas9 system.

In the third animal model, latent HIV-1 infection was recapitulated in humanized mice engrafted with [human immune cells](#), including T cells, followed by HIV-1 infection. "These animals carry latent HIV in the genomes of human T cells, where the virus can escape detection," Dr. Hu explained. Following a single treatment with CRISPR/Cas9, viral fragments were successfully excised from latently infected human cells embedded in mouse tissues and organs.

In all three animal models, the researchers utilized a recombinant adeno-associated viral (rAAV) vector delivery system based on a subtype known as AAV-DJ/8. "The AAV-DJ/8 subtype combines multiple serotypes, giving us a broader range of cell targets for the delivery of our CRISPR/Cas9 system," Dr. Hu said. They also re-engineered their previous gene editing apparatus to now carry a set of four guide RNAs, all designed to efficiently excise integrated HIV-1 DNA from the host

cell genome and avoid potential HIV-1 mutational escape.

To determine the success of the strategy, the team measured levels of HIV-1 RNA and used a novel live bioluminescence imaging system. "The imaging system, developed by Dr. Young while at the University of Pittsburgh, pinpoints the spatial and temporal location of HIV-1-infected cells in the body, allowing us to observe HIV-1 replication in real-time and to essentially see HIV-1 reservoirs in latently infected cells and tissues," Dr. Khalili explained.

The new study marks another major step forward in the pursuit of a permanent cure for HIV infection. "The next stage would be to repeat the study in primates, a more suitable animal model where HIV infection induces disease, in order to further demonstrate elimination of HIV-1 DNA in latently infected T cells and other sanctuary sites for HIV-1, including brain cells," Dr. Khalili said. "Our eventual goal is a clinical trial in human patients."

More information: Chaoran Yin et al, In Vivo Excision of HIV-1 Provirus by saCas9 and Multiplex Single-Guide RNAs in Animal Models, *Molecular Therapy* (2017). [DOI: 10.1016/j.ymthe.2017.03.012](https://doi.org/10.1016/j.ymthe.2017.03.012)

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