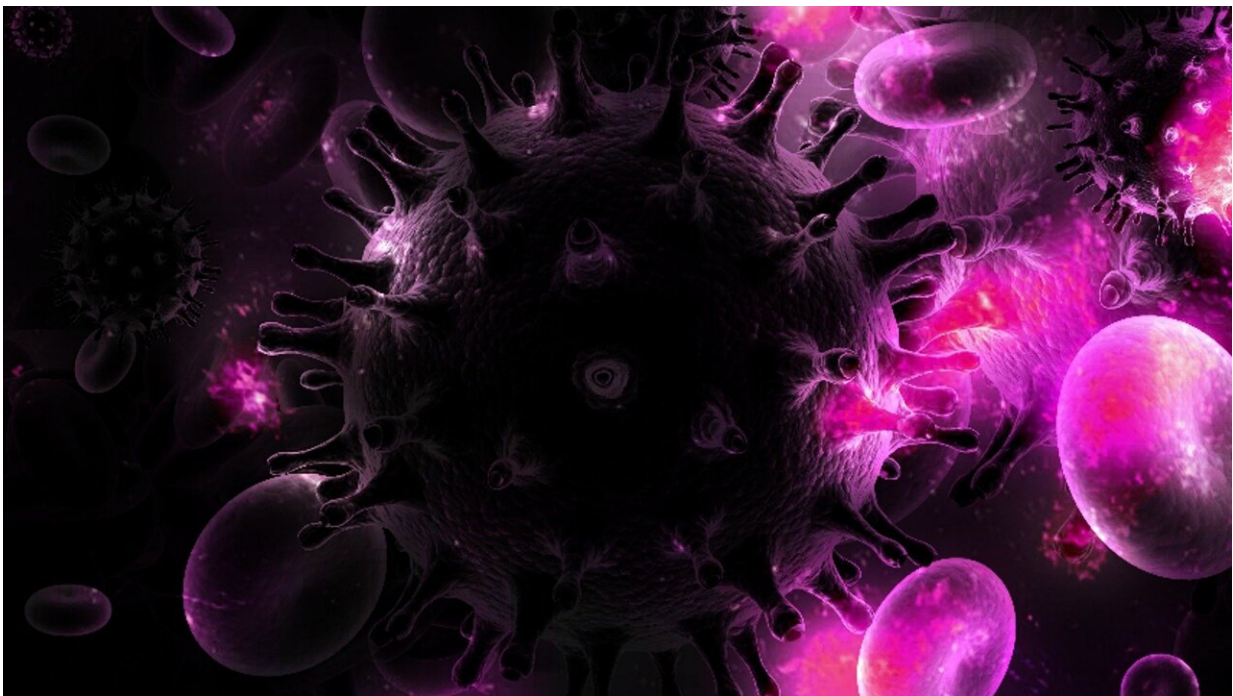


HIV in cell culture can be completely eliminated using CRISPR-Cas gene editing technology, increasing hopes of cure

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New research presented early ahead of this year's [European Congress of](#)

[Clinical Microbiology and Infectious Diseases](#) (ECCMID 2024, Barcelona, 27-30 April) from a team of researchers in the Netherlands shows how the latest CRISPR-Cas gene editing technology can be used to eliminate all traces of the HIV virus from infected cells in the laboratory, raising hopes of a cure.

The studies, led by Dr. Elena Herrera-Carrillo and part of her team (Yuanling Bao, Zhenghao Yu and Pascal Kroon) at Amsterdam UMC, Netherlands, present a significant breakthrough in the search for an HIV cure.

CRISPR-Cas gene editing technology is a groundbreaking method in [molecular biology](#) that allows for precise alterations to the genomes of living organisms. This revolutionary technique, which brought its inventors, Jennifer Doudna and Emmanuelle Charpentier, the Nobel Prize in Chemistry in 2020, enables scientists to accurately target and modify specific segments of an organism's DNA (genetic code).

Functioning like molecular scissors with the guidance of guide RNA (gRNA), CRISPR-Cas can cut the DNA at designated spots. This action facilitates either the deletion of unwanted genes or the introduction of new genetic material into an organism's cells, paving the way for advanced therapies.

One of the significant challenges in HIV treatment is the virus's ability to integrate its genome into the host's DNA, making it extremely difficult to eliminate. Numerous potent antiviral drugs are currently in use for treating HIV infection. Despite their efficacy, lifelong antiviral therapy is essential, as HIV can rebound from established reservoirs when treatment is halted. The authors explain that the CRISPR-Cas genome editing tool provides a new means to target HIV DNA.

They say, "Our aim is to develop a robust and safe combinatorial CRISPR-Cas regimen, striving for an inclusive 'HIV cure for all' that can inactivate diverse HIV strains across various cellular contexts." HIV can infect different types of cells and tissues in the body, each with its own unique environment and characteristics. The researchers are thus searching for a way to target HIV in all of these situations.

In this research, the authors used molecular scissors (CRISPR-Cas) and two gRNAs against "conserved" HIV sequences, meaning they focused on parts of the virus genome that stay the same across all known HIV strains, and achieved cure of HIV-infected T cells. By focusing on these conserved sections, the approach aims to provide a broad-spectrum therapy capable of combating multiple HIV variants effectively.

However, they explain that the size of the vehicle (known as "vector"), used to transport the cassette encoding the therapeutic CRISPR-Cas reagents into the cells, presents logistical challenges, as it is too large. Thus, the authors trialed various techniques to reduce the size of the cassette—and therefore the vector system itself.

In simpler terms, they're attempting to pack oversized luggage into a compact car for a journey to the infected cell, leading them to find ways to downsize the "luggage" (cassette) for easier transport. Another issue the authors wanted to overcome was reaching the HIV reservoir cells that "rebound" when HIV antiretroviral treatment is stopped.

The authors further evaluated various CRISPR-Cas systems from different bacteria to determine their effectiveness and safety in treating CD4⁺ T cells infected with HIV. They shared results from two systems, saCas9 and cjCas. SaCas9 showed outstanding antiviral performance, managing to completely inactivate HIV with a single guide RNA (gRNA) and excise (cut out) the viral DNA with two gRNAs.

The strategy of minimizing the vector size was successful, enhancing its delivery to HIV-infected cells. Moreover, they were able to target "hidden" HIV reservoir cells by focusing on specific proteins found on the surfaces of these cells (CD4⁺ and CD32a+).

The authors say, "We have developed an efficient combinatorial CRISPR-attack on the HIV virus in various cells and the locations where it can be hidden in reservoirs, and demonstrated that therapeutics can be specifically delivered to the cells of interest. These findings represent a pivotal advancement towards designing a cure strategy."

The authors emphasize that their work represents proof of concept, and will not become a cure for HIV tomorrow. They say, "Our next steps involve optimizing the delivery route to target the majority of the HIV reservoir cells. We will combine the CRISPR therapeutics and receptor-targeting reagents and move to preclinical models to study in detail the efficacy and safety aspects of a combined cure strategy. This will be instrumental to achieve preferential CRISPR-Cas delivery to the reservoir cells and avoiding delivery into non-reservoir cells.

"This strategy is to make this system as safe as possible for future clinical applications. We hope to achieve the right balance between efficacy and safety of this CURE strategy. Only then can we consider clinical trials of 'cure' in humans to disable the HIV reservoir. While these preliminary findings are very encouraging, it is premature to declare that there is a functional HIV [cure](#) on the horizon."

Provided by European Society of Clinical Microbiology and Infectious Diseases

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