CRISPR HIV Gene Therapy Disappoints in Early Study

EBT-101 recipients who stopped antiretrovirals experienced HIV viral rebound, but similar therapies may hold more promise for herpes and hepatitis B.

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EBT-101, a CRISPR-based gene-editing therapy from Excision BioTherapeutics, was safe and well tolerated in a Phase I/II study, but it did not prevent viral rebound in the first three participants who stopped antiretroviral treatment, according to a presentation last week at the American Society of Gene & Cell Therapy (ASGCT) annual meeting.

Excision put a positive spin on the findings, noting that favorable safety data is a necessary step on the path to developing therapies for latent viral infections. The company also touted promising early results from studies of CRISPR-based therapies for herpes simplex virus and hepatitis B. But the HIV rebound news is disappointing, and it underscores the importance of remaining wary of exaggerated claims from industry and the mainstream press about the state of HIV cure research.

“Initial data from the EBT-101-001 trial provides important clinical evidence that a gene editing treatment modality can be safely delivered for targeting the HIV DNA reservoirs in human cells,” study investigator Rachel Presti, MD, PhD, of Washington University St. Louis School of Medicine, said in a news release. “This study provides researchers with invaluable insights for how CRISPR technology can be applied for addressing infectious disease and was an important first step towards additional programs designed to optimize this treatment modality for treating the millions of individuals who are impacted by HIV and other infectious disease.”

Antiretroviral therapy can keep HIV replication suppressed indefinitely, but the virus inserts its genetic blueprints into the DNA of human cells and establishes a long-lasting reservoir that the drugs can’t reach. This integrated HIV DNA lies dormant in resting T cells during treatment, but it can start churning out new virus when antiretrovirals are stopped, making a cure nearly impossible. The only way to tell whether an intervention leads to long-term remission is to discontinue antiretroviral therapy with careful monitoring, known as an analytic treatment interruption.

Kamel Khalili, PhD, of Temple University, and colleagues have been studying gene therapy to cure HIV for more than a decade. Their work employs CRISPR-Cas9, a technology that combines guide RNAs that home in on specific segments of DNA and a nuclease enzyme that cuts the genetic

material at the desired site. In 2014, they reported that a CRISPR-Cas9 tool could cut out a segment of integrated HIV DNA necessary for viral replication in a laboratory study. Another study published in 2019 showed that this approach could remove integrated HIV genes and clear latent viral reservoirs in mice.

This led to the development of EBT-101, a CRISPR-based therapy delivered by an adeno-associated virus that uses dual guide RNAs to target three sites on the integrated HIV genome. Making cuts at these locations prevents the production of intact virus. Last August, researchers reported that a single dose of a simian version of the therapy safely and effectively removed an HIV-like virus from viral reservoirs in monkeys on antiretroviral therapy, but this study did not include a treatment interruption.

The first human clinical trial of EBT-101 (NCT05144386) started in 2022, enrolling people on antiretroviral therapy with a stable undetectable viral load. The study protocol called for participants who maintained viral suppression at 12 weeks after receiving the gene therapy to undergo an analytic treatment interruption.

At the European Society of Gene & Cell Therapy annual meeting last October, Presti reported that EBT-101 was detectable in the blood of the first three treated participants after a single IV infusion at the initial dose level. EBT-101 was well tolerated with only mild temporary side effects. She did not present treatment interruption outcomes, but that didn't stop the Daily Mail from proclaiming that a cure for HIV "could be months away."

Presti gave an update last week, and the news generally wasn't good. Of the five participants who have so far received the initial dose of EBT-101, three stopped antiretroviral therapy. Unfortunately, all three experienced viral rebound and had to restart their antiretrovirals. This likely occurred because the gene therapy did not reach all cells harboring latent HIV, and even a very small number of cells containing residual HIV DNA is enough to reignite viral replication.

But the news was not all bad. One EBT-101 recipient was able to maintain viral suppression for four months after treatment discontinuation—considerably longer than it typically takes for the virus to rebound after stopping antiretrovirals. This suggests that EBT-101 or similar CRISPR therapies might play a role in a combination functional cure strategy.

"We know that many people were hopeful that a first trial could provide evidence of a possible cure for HIV because the field has been waiting over 20 years for a cure," Excision senior vice president William Kennedy, MD, said in a news release. "However, it was essential that this clinical trial establish safety for EBT-101 as a gene therapy product as well as safety related to the use of CRISPR for the field."

Excision is now testing a higher dose of EBT-101 in a second cohort and is exploring new CRISPR delivery methods that might be more efficient than the adeno-associated virus vector. One possibility is lipid nanoparticles like the ones used to deliver messenger RNA (mRNA) in COVID-19 vaccines.

The company is also exploring CRISPR-based approaches for other latent viral infections. Herpes simplex virus (HSV) persists in nerve cells, and it can reactivate to cause cold sores, genital herpes or eye inflammation (keratitis). Hepatitis B virus (HBV) establishes chronic infection in the liver, where it can potentially lead to cirrhosis and liver cancer. Unlike HIV and other retroviruses, however, HSV and HBV do not integrate their genetic blueprints into the chromosomes of human cells, so they may be easier to remove.

In other presentations at the ASGCT meeting, researchers reported preclinical results for another experimental CRISPR therapy dubbed EBT-104, showing that a single dose reduced HSV DNA by more than 99% in laboratory cell cultures. What's more, it eliminated viral shedding in 11 of 12 rabbits with herpes keratitis, according to the news release.

In other preclinical research, a single dose of EBT-107—a CRISPR compound delivered by lipid nanoparticles—reduced HBV DNA, hepatitis B surface antigen and hepatitis B e antigen by 98%, 97% and 92%, respectively, in a mouse model of hepatitis B. Unlike CRISPR delivered by viral vectors, EBT-107 in nanoparticles and could potentially be given as multiple doses to reach more latent virus.

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