CRISPR HIV Gene Therapy Looks Safe—but Does It Work?

The first three people who received the experimental therapy experienced no serious adverse effects or toxicities.

November 1, 2023 By Liz Highleyman

EBT-101, a novel CRISPR-based gene-editing therapy from Excision BioTherapeutics, was not associated with any serious adverse events in the first three treated study participants, researchers reported last week at the European Society of Gene & Cell Therapy annual meeting in Brussels. But the presentation was frustratingly short on data about whether the treatment works to control HIV.

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. These so-called HIV proviruses lie dormant in resting T cells during treatment, but they start churning out new virus when antiretrovirals are stopped, making a cure nearly impossible.

Kamel Khalili, PhD, of Temple University, and colleagues have been studying gene therapy to cure HIV for more than a decade. In 2014, they reported that a CRISPR-Cas9 tool could delete a segment of integrated viral DNA necessary for viral replication. A study published in 2019 showed that it could cut out 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. This past August, the researchers reported that a single dose of a simian version of the therapy (EBT-001) safely and effectively removed an HIV-like virus from viral reservoirs in monkeys on antiretroviral therapy, but the study did not include a treatment interruption.

The first human clinical trial of EBT-101 (NCT05144386) started last year. It is enrolling people on antiretroviral therapy with a stable undetectable viral load. In September 2022, Excision announced that the first participant in the Phase I/II trial received EBT-101 in July of that year, noting that if the gene therapy appeared safe and well tolerated, he would undergo an antiretroviral treatment interruption to see whether HIV rebounds.

At the recent presentation in Brussels, Rachel Presti, MD, PhD, of Washington University St. Louis School of Medicine, reported that all three participants in the first dose cohort have received EBT-101. Initial results indicated no serious adverse events or dose-limiting toxicities. There were four mild adverse events considered definitely or possibly related to the treatment, all of which resolved. Two people experienced transient and reversible liver enzyme elevations. None of the three withdrew from the study.

EBT-101 was detectable in the blood of all participants four weeks after receiving a single IV infusion at the first dose level evaluated. There was no evidence of "horizontal transmission of gene vector shedding of EBT-101 in two tissue compartments associated with male reproductive function," suggesting that the therapy is not passed on in semen, according to Excision.

These findings support testing of a higher dose of EBT-101 in a second cohort of six people, which will happen this year. Enrollment is underway in San Francisco, St. Louis and Camden, New Jersey.

"Establishing the safety and biodistribution of EBT-101 is an important first step in the clinical program," William Kennedy, MD, Excision's senior vice president of clinical development, said in a press release. "These initial observations provide important clinical data that support the advancement of the EBT-101-001 trial to the next dosing cohort."

According to the company, study participants will be followed for 48 weeks after EBT-101 administration, and all eligible participants will be assessed for sustained viral suppression after stopping antiretrovirals in an analytical treatment interruption starting at week 12. After the initial study, they will be enrolled in a long-term follow-up study (EBT-101-002).

The first participant who received EBT-101 in the summer of 2022 is already well past the 12-week mark when the treatment interruption should have commenced, but Excision has not provided any further information about his status. The company said in its press release that additional data would be presented in 2024.

While these initial results appear promising, it is far too soon to say that a functional cure for HIV is on the horizon.

"Scientists tell me that this is going to be part of a cure some day. And I shrug my shoulders and say, 'Here we go again,'" long-term survivor and advocate Matt Sharp told the San Jose Mercury News. "Now we just have to get the research done. We've got to have hope, because the epidemic isn't over."

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