

A New Gene Editing Approach Shields the Immune System From HIV

Genetically editing T cells or stem cells to create the delta32 mutation might potentially lead to a functional cure.

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More than 40 million people worldwide are living with HIV, and, while antiretroviral therapy has transformed the disease from a death sentence into a manageable condition, it requires lifelong daily medication. The cost and commitment of treatment remain enormous barriers to successfully controlling the disease, particularly for people living with HIV in low- and middle-income countries (LMICs) where the burden of HIV is highest.

A small number of patients have achieved what appears to be a functional cure through bone marrow transplantation from donors carrying a rare natural mutation in the *CCR5* gene that renders their immune cells resistant to HIV infection. But that approach is impractical on a large scale. It is expensive, invasive, and dependent on a rare transplant-donor match.

A new study published in [Molecular Therapy](#) imagines if the immune system could be safeguarded against HIV in another way. Led by Anna K Anderson and Dr. Chang Li in the Lieber Lab at the University of Washington along with Fred Hutch colleagues, researchers developed a gene editing strategy that aims to recreate that same protective mutation through a single intravenous injection.

CCR5 encodes a protein expressed on the surface of immune cells and serves as one of the two doorways HIV uses to enter and permanently infect them. CD4 is that major “doorway” for HIV entry but *CCR5* as a co-receptor is also required. A naturally occurring 32 base pair deletion (delta32) creates a frameshift mutation in the *CCR5* gene, truncating the protein and preventing it from reaching the cell surface. Carriers of the mutation are highly resistant to HIV infection.

The handful of patients cured of HIV to date—including the [Berlin patient](#), the [London patient](#), and others—received hematopoietic stem cell (HSC) transplants from donors carrying this mutation, replacing their entire immune system with HIV-resistant cells. Another approach being tested is removing a patients’ T cells or HSCs, genetically editing them to create the delta32 mutation, and reimplanting these cells in the patient. The results from these trials are promising so far, but these approaches still suffer from high costs and technical complexity.

The Lieber Lab researchers developed a delivery system using a modified adenoviral vector that can be injected intravenously and infect HSCs through HSC surface receptors. The vector carries a precision gene editing tool called a [base editor](#), which create A>G or C>T conversions. The team tested the efficacy of different base editors and targeting various positions on the gene (start codon, splice sites, stop codon). They found two base editors effective at reducing CCR5 expression: one eliminated the start codon and another created an early stop codon in *CCR5*, causing the cells to abandon production of CCR5 protein. In this context, base editors may have an advantage over other gene editing systems such as CRISPR-Cas9, which cuts DNA and can sometimes cause unintended large deletions or trigger stress responses in stem cells.

Working first in cell lines and then in primary human stem cells, the team demonstrated efficient *CCR5* knockout and substantial protection against HIV infection in laboratory models: HIV infection was inhibited by 70% to 84% in T cells derived from the edited primary human stem cells. The team then moved to testing their method in a humanized mouse model. In this model, the researchers transplanted human fetal liver CD34+ cells (enriched for HSCs) into irradiated immunodeficient mice, allowed for engraftment, mobilized the injected HSCs using G-CSF and AMD3100 (both mobilizers approved for clinical applications), and delivered the base editing vector via a single IV injection. Following a chemical selection step to enrich for successfully edited cells, approximately half of the bone marrow stem cells carried the desired edit. CCR5 expression was reduced by up to half in bulk blood cells.

When these mice were subsequently challenged with HIV, they showed dramatically lower viral loads than unedited controls, up to 12-fold lower in plasma. The base editor treatment led to significantly better survival after HIV challenge: while 40% of control mice survived infection, in two treated cohorts, 62.5% and 100% of mice survived. Importantly, researchers found no significant off-target editing at top-scored sites in the genome, and no signs of toxicity or adverse effects in treated animals.

Dr. Li explains: “The significant contribution is the first proof-of-concept for systemic, in vivo base editing of CCR5 in hematopoietic stem cells for HIV gene therapy. Targeting HSCs enables continuous generation of all types of HIV-resistant progeny (T cells, macrophages, dendritic cells) across all major reservoir tissues. Unlike ex vivo approaches that require mobilization, apheresis, purification, editing, expansion, and reinfusion, this in vivo method uses a single intravenous injection of an all-in-one adenoviral vector (HDA5/35) for precision CCR5 targeting. Our approach offers technical simplicity and scalability, which are key for broad applications, particularly in LMICs where more than 90% of HIV infections occur.”

The vector’s practical advantages are also notable: unlike many gene therapy platforms, it can be stored at refrigerator temperature and potentially lyophilized for room-temperature shipping, an important consideration for global deployment to LMICs.

The study stops short of a clinical therapy and acknowledges that editing efficiency will need to improve further without inducing toxicity before it can achieve the threshold predicted by mathematical models for full viral control. The team is already working on vectors with improved

safety and methods to increase targeting efficiency including dosing schemes, optimized editors and alternative in vivo selection strategies. They are also testing their strategy in combination with other anti-HIV treatments such as an eCD4-Ig decoy receptor and HIV fusion inhibitors.

Questions remain: Will CCR5 editing alone prevent viral escape (e.g. with CXCR4-tropic or mutant CCR5 viruses)? Why is there variation of editing among different patient specimens? Will the results translate beyond mice? But as a proof of concept for affordable, scalable, in vivo gene therapy for HIV, it represents a meaningful and exciting step forward.

Fred Hutch/University of Washington/Seattle Children's Cancer Consortium Members Drs. Hans Peter Kiem and André Lieber contributed to this research.

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