

Novel mRNA Technology Coaxes HIV Out of Hiding

Forcing inactive virus in CD4 cells to reveal itself could facilitate a functional cure.

June 25, 2025 By [Liz Highleyman](#)

Researchers have found a way to deliver messenger RNA (mRNA) to latently infected CD4 T cells in the laboratory and coax inactive HIV out of hiding, an approach that could potentially be used for functional cure therapies, according to study results reported in [Nature Communications](#).

“As HIV cure researchers, our goal has been to reach the virus where it hides,” said lead study author Paula Cevaál, PhD, of the Peter Doherty Institute for Infection and Immunity at the University of Melbourne, in a [news release](#). “We were excited to see that a new lipid nanoparticle, essentially a tiny fat bubble, could carry mRNA into HIV-infected cells successfully. It forced the virus out of hiding, which is exactly what we need to start clearing it from the body.”

Antiretroviral therapy can keep HIV suppressed indefinitely, but the virus inserts its genetic blueprints into host cells and establishes a long-lasting reservoir that has been nearly impossible to eradicate. This inactive HIV in resting CD4 cells is invisible to the immune system and not susceptible to antiretrovirals, but it can start churning out new virus as soon as the drugs are stopped. HIV cure researchers have [tried many different strategies](#), including “kick and kill,” or latency reversal, which aims to reactivate resting cells and flush the virus out of hiding, as well as the opposite approach, “block and lock,” which aims to keep latent virus permanently asleep.

The Australian researchers employed [mRNA technology](#) similar to that used for the Moderna and Pfizer/BioNTech COVID-19 vaccines and experimental [cancer vaccines](#). mRNA vaccines encode genetic instructions for making proteins—such as the SARS-CoV-2 spike protein in the COVID vaccines or abnormal proteins expressed by cancer cells—that trigger an immune response.

The researchers hypothesized that mRNA encoding proteins that reverse HIV latency could help flush out the virus, but getting mRNA into resting CD4 cells without harming them has proved difficult. To overcome this challenge, they developed a novel type of lipid nanoparticle—dubbed LNP X—that could successfully deliver mRNA genetic blueprints into CD4 cells collected from people with HIV.

“Back in 2020, my lab started looking at mRNA to deliver a new treatment for COVID-19. That work sparked a lot of new ideas for HIV, despite the two being very different viruses,” said Sharon

Lewin, MD, PhD, who oversaw the research with Michael Roche, PhD. “Over the last five years, we’ve built this whole new program of work to use mRNA and designed lipid nanoparticles to get to the HIV reservoir and eliminate persistent virus.”

Specifically, LNP X was used to deliver mRNA that encodes instructions for Tat, an HIV protein that initiates transcription, or copying viral genetic material to produce new virus. Once inside infected cells in the laboratory, LNP X enhanced HIV transcription and exposed the dormant virus. The treatment had no apparent toxicity and did not trigger immune cell activation, which has doomed some previous latency reversal approaches.

The researchers also found that the novel nanoparticles can be used to deliver CRISPR, a gene editing tool. Other scientists have explored CRISPR cure approaches, such as [excising HIV DNA from infected cells](#) and knocking out CCR5 receptors the virus uses to enter cells, mimicking the [handful of people who have been cured](#) after receiving stem cell transplants from donors with a rare mutation.

The Doherty team is now preparing for preclinical testing in animals, with the goal of moving toward human clinical trials, a process that could take years. Most experts think latency reversal would likely need to be part of a combination cure strategy that also includes, for example, agents that enhance immune response.

“We programmed mRNA to tell infected cells to ‘give up’ the virus and make it visible,” Cevaal said. “This is the first time this strategy has been shown to work so well in HIV-infected cells. Our hope is that this new nanoparticle design could be a new pathway to an HIV cure.”

What’s more, the novel nanoparticle approach could have broader implications beyond HIV, Roche noted. “The white blood cells where HIV hides are also involved in other diseases, including some cancers and autoimmune conditions,” he said. “The ability to safely deliver mRNA into these cells opens new possibilities for treating a range of illnesses.”

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