New approach for delivery of anti-HIV antibody therapy shows promise in phase I clinical trial

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Since the first reports of HIV infection in the early 1980s, multiple clinical trials have tested potential vaccines against the virus, but unfortunately, HIV has numerous defense mechanisms that prevent a person's immune system from mounting an effective response following HIV vaccination. An alternative anti-HIV strategy called Vectored ImmunoProphylaxis (VIP) designed by researchers at the Ragon Institute of MGH, MIT and Harvard and Massachusetts General Hospital (MGH) involves an adeno-associated viral (AAV) vector to deliver instructions to muscle cells to pump out antibodies that block the virus. The strategy recently generated promising results in a phase I clinical trial that was conducted by the National Institutes of Health and is published in *Nature Medicine*.

AAV vectors can be safely used in humans to deliver DNA to cells, and two AAV-based gene therapies are currently FDA approved. In this clinical trial, the AAV vector designed by MGH investigators carries the genetic sequence for what is called a broadly neutralizing HIV-1 antibody that blocks HIV's ability to bind to CD4, an immune cell's receptor that HIV targets before infecting the cell. When injected into a patient, the AAV therapy (called AAV8-VRC07) enters muscle cells, where the genetic sequence is read and translated to produce large quantities of the broadly neutralizing antibody (called VRC07) that are pumped out of the cells and travel through the blood to seek out their target. The result is that numerous antibodies circulate to block any interaction between HIV and the CD4 receptor on immune cells, essentially shutting the door on HIV's entry into the cells.

The phase I clinical trial enrolled eight adults with HIV who were on stable antiretroviral therapy for at least three months. Investigators found that intramuscular injection of AAV8-VRC07 was safe and well tolerated. All eight individuals produced measurable amounts of VRC07 in the blood, with maximal VRC07 concentrations in three individuals. In six individuals, these amounts remained stable and near maximal

concentration for up to three years of follow-up. (The trial is ongoing, and some participants have not been followed as long as others.) Three of the eight participants showed signs of an anti-drug antibody response directed against a portion of VRC07, and this response appeared to decrease the production of VRC07 in two of the participants.

"This work represents the first successful AAV-based production of a monoclonal antibody of any kind in people," says co-author Alejandro B. Balazs, Ph.D., who created the vector used in the trial and is a principal investigator at the Ragon Institute of MGH, MIT and Harvard, where his laboratory is continuing to develop this technology. "It's also the first time we've had an approach capable of yielding broadly neutralizing antibodies against HIV in humans," he says.

Balazs notes that the results have wide-ranging clinical implications for potentially preventing or treating HIV and other infections. "The findings prove that the platform we designed is capable of producing long-lived expression of an antibody from a single injection. Given our ability to encode any desired antibody into these vectors, we may be able to produce effective preventive treatments against a wide range of infectious diseases from malaria to COVID-19," he says. "This technology also has the potential to be applied to the delivery of other biologic drugs to treat a wide range of conditions from autoimmunity to cancer."

The technology was initially developed at the California Institute of Technology in the laboratory of Nobel laureate David Baltimore, Ph.D., by Balazs when he was a postdoctoral fellow. The Vaccine Research Center of the NIH supported the clinical study, which was conducted at the National Institutes of Health Clinical Center.

More information: Joseph P. Casazza et al, Safety and tolerability of AAV8 delivery of a broadly neutralizing antibody in adults living with

HIV: a phase 1, dose-escalation trial, *Nature Medicine* (2022). DOI: 10.1038/s41591-022-01762-x