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For first time, scientists show an HIV vaccine impacts the genetic makeup of the virus

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An AIDS vaccine tested in people, but found to be ineffective, influenced the genetic makeup of the virus that slipped past. The findings suggest new ideas for developing HIV vaccines.

The results were published Feb. 27 in Nature Medicine.

This is the first evidence that vaccine-induced cellular immune responses against HIV-1 infection exert selective pressure on the virus. "Selective pressure" refers to environmental demands that favor certain genetic traits over others.

The senior author of the multi-institutional study is Dr. James I. Mullins, University of Washington (UW) professor of microbiology. The research team analyzed the genome sequences in HIV-1 isolated from 68 newly infected volunteers in the STEP HIV-1 vaccine trial. Mullins and the other principal researchers who carried out this study were not involved in the STEP trial.

The STEP trial was a double-blind, Phase 2B test-of-concept of a Merck HIV-1 subtype B vaccine. The vaccine, MRKAd5, was designed to make the body produce infection-fighting white blood cells, commonly called killer T-cells, that could recognize and target specific parts of HIV-1 known as Gag, Pol and Nef.

The STEP trial was conducted at 34 North American, Caribbean, South American and Australian locations where the HIV-1 subtype B was the

predominant virus in the local HIV-infected populations. The trial enrolled 3,000 participants.

Preliminary tests indicated the vaccine was encouraging the appearance of the desired virus-attacking cells. More than 75 percent of vaccinated participants produced HIV-1 specific T cells.

Nevertheless, this response to the vaccine did not predict protection. The trial failed. Immunizations were halted, Mullins recalled, after the first interim analysis indicated that the vaccine neither prevented HIV-1 infection nor reduced the load of virus in the body.

"Even though the T-cell responses were not sufficient to prevent infection," Mullins said, "we were interested in whether the vaccine-elicited T-cells had any impact on those strains of HIV-1 that established infections in the study subjects."

The research team tested for a "sieve effect," which, Mullins explained, occurs when a vaccine successfully blocks some strains of virus and not others. The researchers wanted to know, What are the genetic characteristics of those breakthrough viruses that slipped past the immunization barrier erected by the MRKAd5 vaccine?

The research team isolated strains of HIV-1 from both vaccine and placebo recipients in the study, and compared the genetic sequences of the strains. This would help researchers to determine if any changes in the "founder virus" – the virus first detected in the infection – might have helped it evade the vaccine-induced immune response and take hold in the vaccinated individuals.

The researchers identified potential T-cell targets in the protein-producing regions of the founder virus genetic sequences and compared these to the virus protein-targets of the vaccine – Gag, Pol and Nef. The

researchers found that the distances for these viral genetic sequences were greater for the viruses taken from the vaccinated individuals, compared to those from the placebo recipients.

The most significant virus genetic site distinguishing vaccine from placebo recipients was in the region known as Gag-84, which was encompassed by several of the viral segments targeted by the vaccine.

Moreover, the researchers said that the extended divergence between the viruses from the vaccinated and the placebo groups was confined only to the sequences for the proteins targeted by the vaccine components (Gag, Pol and Nef) and was not found in other HIV-1 protein sequences. The influence of the vaccine on the virus genotype, Mullins said, was subtle.

Mullins and his team, as well as their collaborators from the STEP trials studies, are doing similar studies of the genetic impact of the Thailand vaccine RV144 on the AIDS virus. The RV144 vaccine was the first to show some probable effectiveness, but its efficacy was not great enough to put it to more general use.

The researchers added that their findings on breakthrough viruses suggest that new vaccines should be designed to put selective pressure on the virus in a controlled manner.

Such a vaccine, Mullins said, should select for genetic mutations in regions of the virus known to be associated with viral control and should avoid selecting for strains that can either escape the immune defense or act as decoys to fool the immune system.

The researchers propose a goal for new designs of vaccines aimed at inducing killer T-cell responses: corner the virus into assuming forms that debilitate it. This would make the infecting virus fitness-impaired – unable to adapt, reproduce in great numbers and cause disease

progression.

"Despite the sad results of the STEP trial," Mullins said, "it has provided clues to ways for science to go forward in the search for an HIV vaccine.

Provided by University of Washington