HVTN 505 vaccine induced antibodies nonspecific for HIV

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Credit: National Cancer Institute

A study by researchers at the National Institute of Allergy and Infectious Diseases and Duke University helps explain why the candidate vaccine used in the HVTN 505 clinical trial was not protective against HIV infection despite robustly inducing anti-HIV antibodies: the vaccine stimulated antibodies that recognized HIV as well as microbes commonly found in the intestinal tract, part of the body's microbiome. The researchers suggest that these antibodies arose because the vaccine boosted an existing antibody response to the intestinal microbiome, which may explain why the HVTN 505 vaccine candidate did not perform well. Understanding why the candidate vaccine did not protect against HIV infection will inform ongoing vaccine research efforts against HIV and other infectious diseases.

The HVTN 505 study used an investigational vaccine regimen in which volunteers were vaccinated with an initial or "prime" vaccine followed by a second, booster vaccine. In the new study, researchers examined samples from study participants who received the prime-boost vaccine and found that most vaccine-induced antibodies recognized an HIV surface protein called gp41, but these antibodies did not neutralize HIV. Instead, the antibodies were polyreactive, recognizing other proteins common to bacteria, such as *Escherichia coli*, a naturally occurring part of the body's intestinal microbiome. Polyreactivity may decrease the effectiveness of antibodies against a specific pathogen like HIV, and is one impediment that successful vaccines must overcome to adequately prevent infection in people. The study authors suggest that polyreactivity may have promoted production of ineffective antibodies that target gp41 rather than antibodies capable of neutralizing HIV.

In people with acute HIV infection, the majority of anti-HIV antibodies target gp41 but do not neutralize the virus. Prior research suggests that these naturally occurring antibodies likely originate from immune cells in the intestinal tract previously stimulated by the microbiome, leading to polyreactivity. In the current study, the researchers show that the microbiome may also influence vaccination-induced immunity. In support of this idea, the study team traced the lineage of a specific vaccine-induced antibody to a polyreactive precursor that also recognized the intestinal microbiome. More work is needed to clarify how the microbiome may affect the production and effectiveness of vaccine-induced antibodies that target HIV—an important consideration in HIV vaccine design and development. Further understanding of how the microbiome influences vaccine-induced immunity also may be leveraged to elicit the most beneficial immune response.

More information: Williams WB et al. Diversion of HIV-1 vaccine-induced immunity by gp41-microbiota cross-reactive antibodies. *Science* DOI: 10.1126/science.aab1253 (2015).

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