Researchers find potential map to more effective HIV vaccine

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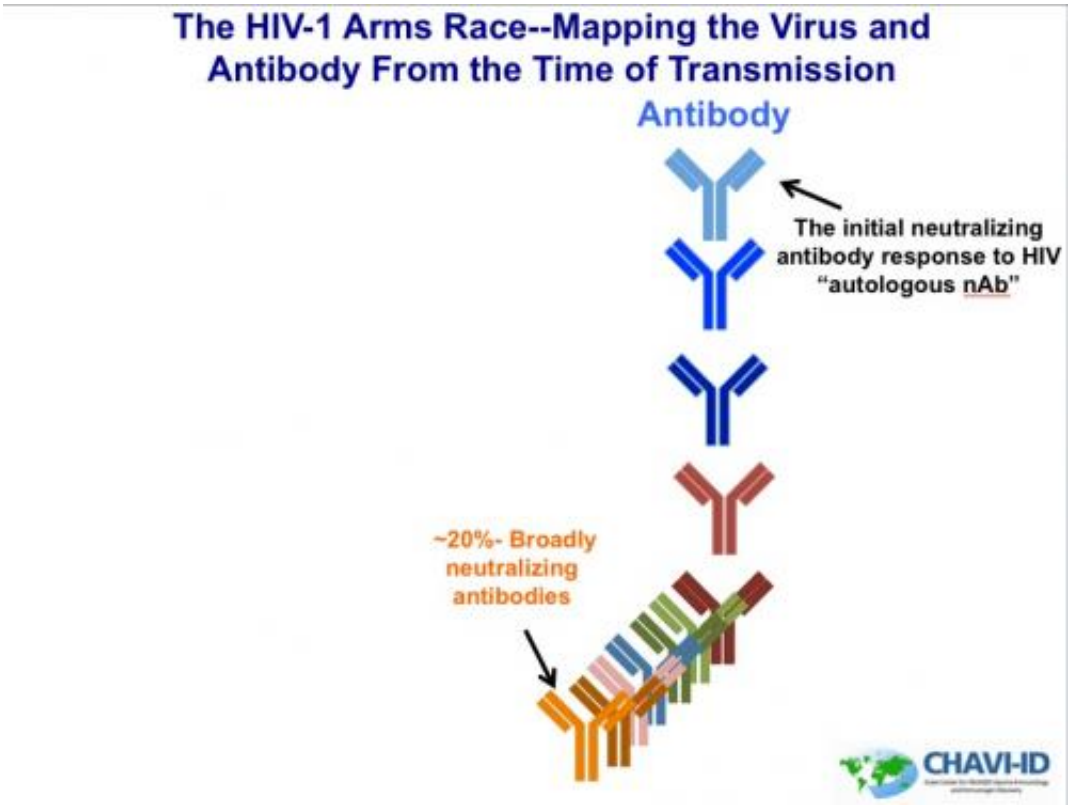


In a paper published Apr. 3, 2013, in the journal *Nature*, researchers for the first time mapped the simultaneous evolution of the HIV virus and the broadly neutralizing antibodies. Credit: CHAVI-ID

By tracking the very earliest days of one person's robust immune response to HIV, researchers have charted a new route for developing a long-sought vaccine that could boost the body's ability to neutralize the

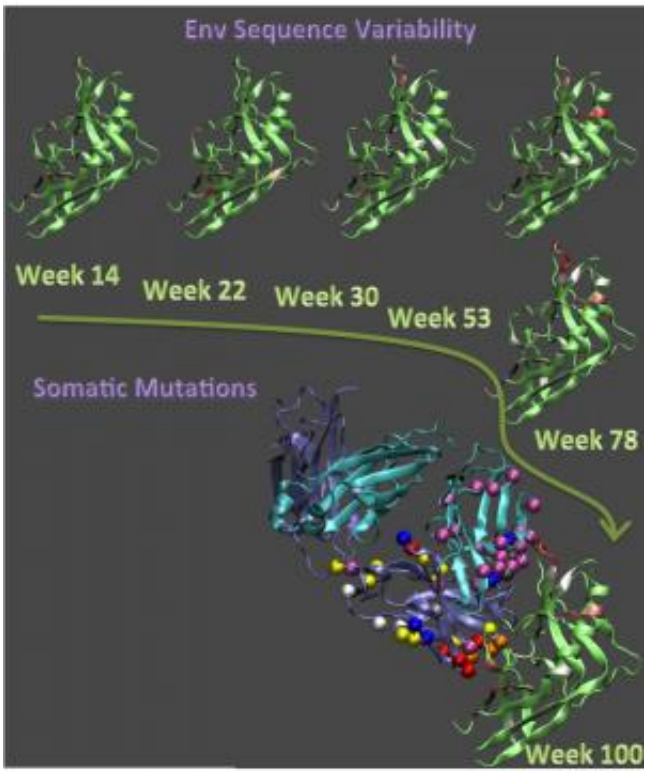
virus.

The research team, led by Barton F. Haynes, M.D., director of the Duke Human Vaccine Institute, and John Mascola, M.D., acting director of the NIH Vaccine Research Center, have for the first time described the co-evolution of antibodies and virus in a person with HIV whose immune system mounted a broad attack against the pathogen. Findings are published April 3, 2013, in the journal *Nature*.

Most vaccines work by inducing this antibody response, but the HIV virus has proved to be a difficult vaccine target. When HIV antibodies are produced, they typically have a limited range, and the virus changes rapidly to escape harm, leading to an arms race that the virus usually wins.

The current research was aided by new technologies that can detect early infection and track the subsequent immune response and virus evolution. It fills gaps in knowledge that have impeded development of an effective vaccine for a virus that has killed more than 30 million people worldwide.

"This project could only have been carried out by a multidisciplinary team working closely together," said Haynes, who led the work as a project of the Duke Center for HIV/AIDS Vaccine Immunology-Immunogen Discovery (CHAVI-ID) consortium, which is funded by the National Institute of Allergy and Infectious Diseases. "For the first time, we have mapped not only the evolutionary pathway of the antibody, but also the evolutionary pathway of the virus, defining the sequence of events involved that induce the broadly neutralizing antibodies."



The evolution of the viral protein (green) from 14 weeks through 100 weeks post-transmission is compared to the maturation of the human antibody. Credit: Los Alamos National Laboratory

The key to this finding was a person in Africa whose HIV infection was detected so early that the virus had not yet mutated to avoid the immune assault. The individual also exhibited a fortuitous trait that occurs in only about 20 percent of people infected with HIV – an immune system that produces broadly neutralizing antibodies. These immune weapons attack vulnerable sites of the virus that are conserved despite mutations. In identifying the early viral infection, the team found the outer envelope, the viral surface glycoprotein, which triggered the start of the broadly neutralizing antibody development.

By tracking the precise virus and antibody pathways involved, the Duke CHAVI-ID and NIH teams now have a detailed road map for development of a potential vaccine, which involves immunogens with an outer envelope specifically selected to stimulate the production of broadly neutralizing antibodies.

"The next step is to use that information to make sequential viral envelopes and test them as experimental vaccines," Haynes said. "This is a process of discovery and we've come a long way with regard to understanding what the problem has been."

More information: H. Liao et al. Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus. *Nature* DOI: 10.1038/nature12053 (2013). dx.doi.org/10.1038/nature12053

In the current study, scientists identified one of the roughly 20 percent of HIV-infected individuals who naturally develop broadly neutralizing antibodies to the virus after several years of infection. This person in Africa was a volunteer in a study in which participants gave weekly blood samples beginning early in the course of infection. This individual had joined the study just 4 weeks after infection and was followed for more than 3 years. Having blood samples from such an early stage enabled researchers to pinpoint the particular "founder" virus that triggered the immune system to make an immature broadly neutralizing antibody against HIV, as well as the cell from which that antibody emerged. Analyses of the weekly samples also enabled the scientists to see the series of changes that the virus and antibody underwent over 2.5 years until the antibody matured to a form capable of potently neutralizing the virus. Scientists are now attempting to create a vaccine that harmlessly mimics the virus at key points in the observed process to generate broadly neutralizing HIV antibodies, first in uninfected animals and then in uninfected people.