Possible clues found to why HIV vaccine showed modest protection

April 4 2012

Insights into how the first vaccine ever reported to modestly prevent HIV infection in people might have worked were published online today in the *New England Journal of Medicine.* Scientists have found that among adults who received the experimental HIV vaccine during the landmark RV144 clinical trial, those who produced relatively high levels of a specific antibody after vaccination were less likely to get infected with the virus than those who did not. The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, co-funded the research.

"This analysis has produced some intriguing hints about what types of human immune responses a preventive HIV vaccine may need to induce," said NIAID Director Anthony S. Fauci, M.D. "With further exploration, this new knowledge may bring us a step closer to developing a broadly protective HIV vaccine."

In the RV144 clinical trial, which involved more than 16,000 adult volunteers in Thailand, the group that received the vaccine had a 31 percent lower chance of becoming infected with HIV than the group that received a placebo. Since the study results were reported in 2009, a consortium of more than 100 scientists from 25 institutions has been searching for molecular clues to explain why the vaccine showed a modest protective effect.

The new report describes the researchers' analyses of blood samples taken from a representative subset of study participants: 41 who were

vaccinated and later became infected with HIV and 205 vaccinated participants who remained uninfected. The participants who made relatively high levels of one antibody to HIV were significantly less likely to become infected than those who did not. This particular binding antibody attaches to a part of the outer coat of the virus called the first and second variable regions, or V1V2, which may play an important role in HIV infection of human cells. The antibody belongs to a family called immunoglobulin G, or IgG.

Vaccinated study participants who had relatively high levels of a different type of HIV binding antibody, however, appeared to have less protection from the virus than vaccinated participants who had low levels of this protein. The antibody attaches to a part of the virus's outer coat called the first constant region, or C1, and belongs to a family called immunoglobulin A, or IgA. The study team hypothesizes that the C1 IgA antibody either was associated with less benefit from HIV vaccination or directly reduced the benefit of vaccination.

"The remarkable international collaboration to understand the RV144 study results has generated important hypotheses for scientists to investigate," said Barton F. Haynes, M.D., the leader of the new analysis and the director of the NIAID-funded Center for HIV/AIDS Vaccine Immunology based at Duke University in Durham, N.C.

Researchers plan to further evaluate the new findings in studies to be conducted in non-human primates using the RV144 vaccine regimen and other vaccines. Scientists must conduct more tests to determine whether high levels of V1V2 antibodies directly caused the modest protective effect seen in the RV144 study or simply were linked to other, still unidentified factors responsible for the trial's encouraging outcome. Such testing also will determine whether the V1V2 antibody response is merely a marker of HIV exposure or decreased susceptibility to HIV infection.

The study authors note that different vaccine candidates may protect against HIV in different ways. Therefore, more research is needed to understand whether these new findings will be relevant to other types of HIV vaccines or to similar vaccines tested against HIV strains from other regions or against different routes of exposure to the virus, according to the authors.

More information: BF Haynes et al. Immune correlates analysis of the ALVAC-AIDSVAX HIV-1 vaccine efficacy trial. *NEJM* DOI:10.1056/NEJMoa1113425 (2012).

S Rerks-Ngarm et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *NEJM* DOI:10.1056/NEJMoa0908492 (2009).

Provided by National Institutes of Health