Clues from the Thai HIV vaccine trial continue to emerge

July 21, 2014

ND Weber

The monumental outcome of the Thai HIV-1 vaccine trial (RV144), aside from stirring contentious debate about its design and conclusions, has prompted a plethora of additional research dedicated to analyzing the study findings and following-up on its conclusions. The primary finding was that the vaccine was partially effective at preventing HIV acquisition compared to placebo. Much effort has been dedicated to understanding the mechanism of this protection, and in particular why it was only partially protective. A recent immunologic and genetic comparison of vaccinated versus placebo-treated study participants who contracted HIV during the study was carried out by a large consortium of researchers including many members of the Vaccine and Infectious Disease Division. Their findings were recently published in the *Journal of Virology*.

Results from the Thai trial, first announced in 2009, showed 31% protection in vaccinated trial participants compared to placebo-treated participants (n=51 vs. n=74, respectively; p=0.04). Following these findings, much research has been carried out on differences between those participants who became infected and those who did not. One study (Haynes, et al., 2012) identified immunglobulin G antibodies that bind to the V1/V2 region of HIV's envelope protein as a correlate of protection in vaccinated participants. Later studies also pointed to the importance of immune recognition of the HIV envelope V1/V2 region.

The current study led by Fred Hutchinson Cancer Research Center investigators focused on the effect of vaccine-primed T cells on recognition of peptides from the V1/V2 region. By analyzing viral sequences from vaccinated participants who became infected, researchers identified several viral peptide epitopes that possibly escaped binding by human leukocyte antigen (HLA) proteins. HLAs are responsible for recognizing and binding foreign peptide antigens and presenting them to T cells, allowing the immune system to recognize the antigen and mount a response. HLA-expressing alleles are highly variable from one individual to the next.

The viral peptide analysis implicated two HLA alleles in particular: HLA A*02 and A*11. Upon sequencing and comparing the HLA alleles of infected to uninfected study participants, it was evident that the vaccine may have provided better protection to participants expressing an A*02

allele. The vaccine efficacy for recipients with A*02 was 54%, compared to 31% for the entire cohort and 3% for A*02 negative participants ($A*02^{+/-}$ interaction-p = 0.05) (see figure). This finding led to the hypothesis that study participants possessing HLA A*02 were more likely to be protected from infection following vaccination.

Lead author of the study, Dr. Andrew Gartland explained, "Though the study cannot provide conclusive evidence of differential vaccine efficacy, it emphasizes the importance of considering host-genetics in future vaccine trials." Indeed, the identification of differences in vaccine efficacy according to host HLA alleles is an important follow-up finding to the original study. Additional research is still underway to further understand the RV144 outcomes and what they mean to the greater HIV vaccine research community.

According to Dr. Gartland, "The entire HIV vaccine community has been engaged in follow-up studies of RV144 samples, and great strides have been made in understanding how the vaccine may have conferred partial protection. However, all of the hypotheses generated by this work will need to be tested and validated in future efficacy trials. The planning for these trials is currently underway."

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See also: Haynes BF, Gilbert PB, McElrath MJ, Zolla-Pazner S, Tomaras GD, Alam SM, Evans DT, Montefiori DC, Karnasuta C, Sutthent R, Liao HX, DeVico AL, Lewis GK, Williams C, Pinter A, Fong Y, Janes H, DeCamp A, Huang Y, Rao M, Billings E, Karasavvas N, Robb ML, Ngauy V, de Souza MS, Paris R, Ferrari G, Bailer RT, Soderberg KA, Andrews C, Berman PW, Frahm N, De Rosa SC, Alpert MD, Yates NL, Shen X, Koup RA, Pitisuttithum P, Kaewkungwal J, Nitayaphan S, Rerks-Ngarm S, Michael NL, Kim JH. 2012. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. *N Engl J Med*. 366: 1275-86.

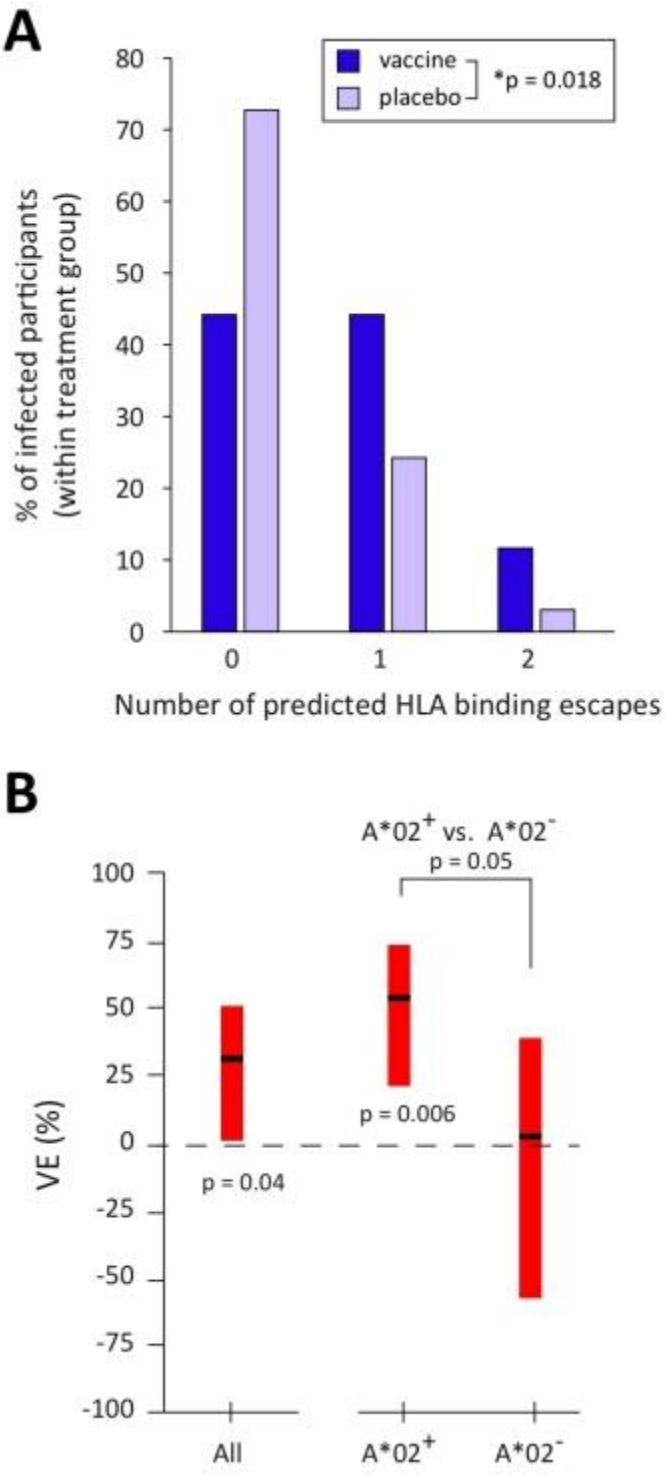

Image provided by Dr. Andrew Gartland.

T-cell based sieve analysis and vaccine efficacy in the RV144 HIV vaccine trial. (A.) A T-cell based sieve analysis of breakthrough HIV infections in RV144 participants suggests that there was a greater number of HLA binding escapes in the V2 region of Env protein. The finding was based on computationally predicted T-cell epitopes restricted by class I HLA alleles A*02 and A*11. (B.) Though it was hypothesized that the sieve effect was the result of post-acquisition viral selection by T-cells, it was found that the efficacy of the vaccine to prevent infection was greater in participants expressing an A*02 allele. This suggested that HLA A*02 played a role in the vaccine efficacy observed in the RV144 trial and emphasized the importance of considering host immune genetics in the evaluation of future vaccine candidates.