Sieve Analysis Shows Partial Efficacy of an HIV-1 Vaccine Tested In Thailand

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ME Arnegard

Scientists and science policy makers agree that development of an HIV-1 vaccine is the highest priority in AIDS research. However, decisions about which vaccines to investigate in pre-clinical (animal) and clinical (human) trials, as well as the outcomes of these trials, have spurred disagreement and controversy. Only a handful of HIV-1 vaccines have ever entered the third phase of clinical testing. This level of testing is typically only permitted following successful outcomes in Phase I and II clinical studies, which are focused on evaluating vaccine safety and immune responses in tens to hundreds of low-risk individuals. In a Phase III trial, thousands of higher-risk volunteers are vaccinated and then monitored over several years to test a vaccine’s efficacy in preventing infection.

Strong evidence of the first partially effective HIV-1 vaccine regimen (RV144) was recently reported in a study jointly led by Drs. Morgane Rolland and Jerome Kim (U.S. Military HIV Research Program), Drs. Paul Edlefsen and Peter Gilbert (Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center) and Dr. James Mullins (University of Washington). Five other Hutchinson Center scientists also contributed to this report, which was published in the journal *Nature*.

Rolland and Edlefsen (co-first authors) and the other co-authors performed a new analysis of samples collected during the RV144 trial, the largest Phase III HIV vaccine trial ever conducted. Also known as the Thai trial, the RV144 trial enrolled over 16,000 volunteers in the Chon Buri and Rayong Provinces of Thailand. Half of the participants were randomly assigned to the treatment group of vaccinees, and the other half to the placebo group, in a double blind manner. Over a six-month period beginning in 2003, vaccinees received six injections of the priming vaccine ALVAC-HIV, a canarypox vector that expresses the HIV envelope (Env), protease (Pro) and structural (Gag) proteins. This combination of immunogens was designed to induce an early T cell response. The last two injections also contained a 'boost' of monomeric gp120 (an envelope protein subfragment) in a vaccine called AIDSVAX B/E, which was intended to induce lasting humoral (binding and functional antibody) responses. During the ensuing three-year monitoring period, RV144 conferred an estimated 31% reduction in HIV infections in the vaccinees compared to the placebo group. Yet,
different analyses of the data gave conflicting results, leading to a heated debate about the trial's outcome.

More recently, a comparison of infected and uninfected vaccinees in the Thai trial showed that the binding of IgG antibodies to Env variable loops 1 and 2 (V1/V2; see figure) was correlated with a lowered risk of infection, suggesting that V1/V2 antibodies may have contributed to protection against HIV-1 (Haynes et al., 2012). However, because immune responses cannot be randomized among vaccinees, immune correlates of risk are not necessarily predictive of protection. To test the causal role of RV144 in preventing certain HIV-1 variants from infecting vaccinated individuals, Rolland and Edlefsen et al. performed a 'sieve analysis', which compares breakthrough viruses between vaccinees and individuals who received the placebo, taking full advantage of the Thai trial's original randomization scheme.

Rolland and Edlefsen et al. analyzed 936 HIV-1 sequences from 110 breakthrough infections, 44 in the vaccinated group and 66 in the placebo group. HIV-1 genotypes that matched the Env protein in the vaccine at amino acid position K169 (lysine) in V2 and HIV-1 genotypes that mismatched Env at position I181 (isoleucine) in V2 were significantly less common in infected vaccinees compared to infected placebo recipients. RV144 was 48% effective at preventing (or 'sieving out') infection with viruses that matched the vaccine at K169 and 78% effective at preventing infection with mismatched viruses at I181.

It remains unclear why viruses that differed from the vaccine at position 181 were less common in the infected vaccinees, though the data showed no strong evidence that the vaccine itself promoted infection with viruses that matched I181. Instead, it is possible that genotypes at this position are somehow strongly correlated with cryptic variation elsewhere in the virion's structure, or that an I181X mutation has a large impact on infectivity or antibody binding due to steric effects and/or changes in the quaternary structure of gp120.

Despite this uncertainty, the immune-correlates study of Haynes et al. (2012) and this more recent sieve analysis help to dispel many of the earlier doubts about the Thai trial’s outcome. Together, these studies provide rather compelling evidence that RV144 was indeed partially effective at preventing HIV-1 infection. Perhaps more importantly, Rolland and Edlefsen et al. found both sites with sieve effects to reside in V2, implicating this variable loop as a key target for the development of even more effective HIV-1 vaccines in the future.


Image designed by Matt Arnegard using an open access figure downloaded from Wikimedia Commons and an adaptation of Fig. 2 in Haynes et al. (2012. Nature Biotechnology 30:423-433)

Structural portrait of the HIV-1 virion (above) and four regions of the trimeric HIV-1 envelope protein (Env) containing epitopes for which broadly neutralizing antibodies have been successfully isolated by various research groups (below). Env is a trimer of both gp41 and gp120. The current study focuses on variable loops 1 and 2 (V1/V2) in gp120.