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A Step Forward for HIV Vaccines

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The development of a safe and effective HIV vaccine will likely be essential to achieve a durable end to the HIV pandemic[1, 2]. However, only four HIV vaccine concepts (six trials) have been tested for clinical efficacy in the 35 year history of the HIV epidemic. The main challenges facing the development of an HIV vaccine are scientific and are unprecedented in the history of vaccinology, including the need to protect against globally diverse virus strains and the unclear immune correlates of protection. In this issue of *The Lancet HIV*, Bekker et al. report an important next chapter in the quest to develop an HIV vaccine.

In 2009, the RV144 study demonstrated the first, and to date only, positive results from an HIV vaccine efficacy trial in humans[3]. This vaccine included priming with canaypox ALVAC vectors and boosting with alum-adjuvanted Env gp120 proteins, and it provided 31% efficacy in a low risk population in Thailand. Although not sufficient for licensure, these data catalyzed a wave of enthusiasm to understand the immune correlates of protection in an effort to try to improve this vaccine. An immune correlates analysis demonstrated that antibodies against Env V1V2 correlated inversely with infection risk[4], and a sieve analysis concordantly demonstrated evidence for vaccine-induced immune pressure on Env V1V2[5]. These data led to a hypothesis that vaccine-elicited binding antibodies against V1V2 may have been responsible for the protection observed in RV144. Additional potential correlates of protection that emerged from RV144 include IgG3 responses and CD4+ T cell responses.

A validated and predictive immune correlate of protection would be a major advance for the HIV vaccine field. Thus, a key priority has been to test this potential V1V2 immune correlate prospectively in another study. To adapt this vaccine concept to the clade C epidemic in South Africa, new ALVAC vectors (vCP2438 expressing clade C *env gp120* and clade B *env gp41*/*gag*/*pro*) and bivalent clade C Env gp120 proteins (TV1/1086) were manufactured.

Bekker et al. now report the safety and immunogenicity of this vaccine in a placebo-controlled, randomized, double-blinded phase 1/2a trial in South Africa called HVTN100. The authors used a more potent squalene-based adjuvant MF59 in place of alum and also added a late boost at 12 months (for a 0, 1, 3, 6, 12 month vaccine schedule). Thus, multiple parameters were different between RV144 and HVTN100. Higher magnitude binding antibody responses and higher frequency cellular immune responses were observed in

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HVTN100 compared with RV144, but V1V2-specific antibody responses were lower in HVTN100 compared with RV144. The reasons for these differences are not entirely clear but may be related to the specific Env strains selected for the vaccines and the more potent adjuvant used in HVTN100.

HVTN100 is important because it achieved pre-determined go/no-go criteria and led to the initiation of the phase 2b/3 efficacy trial HVTN702, which will determine the capacity of this vaccine to protect against HIV acquisition in South Africa. HVTN702 will also prospectively test whether vaccine-elicited V1V2-binding antibodies correlate with protection. Validation of this immune correlate would be immensely useful, as it could then be used as a surrogate biomarker that would greatly accelerate HIV vaccine development moving forward.

As the field eagerly awaits the efficacy results from HVTN702, potentially in 2021, additional HIV vaccine candidates are also being pursued. These include adenovirus vectors expressing mosaic immunogens with an Env gp140 protein boost, cytomegalovirus vectors that induce persistent T cell responses, native-like Env trimers, and sequential Env immunization approaches that aim to induce broadly neutralizing antibodies. One lesson from RV144/HVTN100/HVTN702 is that the time and resources required to bring a vaccine candidate into efficacy trials are substantial. However, only well powered clinical efficacy trials can determine if a vaccine candidate actually protects humans. Moreover, efficacy data in humans helps to refine preclinical models and immunologic assays. We therefore need to increase the numbers of efficacy trials to test a diversity of scientifically meritorious vaccine concepts. We need more “shots on goal” if we are to achieve the ultimate objective of developing an HIV vaccine and ending the HIV pandemic.

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