Immune Responses to HIV Vaccines and Potential Impact on Control of Acute HIV-1 Infection

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Unanticipated results from 2 recent candidate human immunodeficiency virus type 1 (HIV-1) vaccine regimens in large-scale international trials highlight the importance of understanding the optimal earliest immune defense against HIV-1 infection. Presented here are key findings in these vaccine studies with relevance to the development of future vaccines to control acute HIV-1 infection.

Although the marked success of combination antiretroviral therapy in controlling human immunodeficiency virus type 1 (HIV-1) infection offers hope for longer and better quality of life for millions of infected people, full deployment of treatment in regions where HIV-1 has hit hardest is unlikely to eradicate the virus and its disease sequelae. Unquestionably, a safe and efficacious HIV-1 vaccine is crucial to halt the epidemic of HIV-1 infection. Of the 150 vaccine regimens entering clinical trials over the past 2 decades, only 4 have undergone evaluation in larger-scale, test-of-concept (phase IIb) or efficacy (phase III) trials. The unanticipated outcomes of the 2 most recent expanded trials, the Step Study [1] and the Thai trial [2], underscore the importance of understanding how the immune system responds to early events in HIV-1 infection in order to better guide vaccine development.

STEP STUDY

The multicenter Step Study evaluated a Merck adenovirus serotype 5 (Ad5) HIV trivalent subtype B vaccine in HIV-1–uninfected persons reporting high-risk activities and residing in regions where HIV-1 subtype B predominates. No significant reduction in the vaccine group, compared with the placebo group, was observed in HIV-1 acquisition rates [1]. In fact, the initial analyses revealed an increased infection rate in uncircumcised male vaccine recipients with preexisting Ad5 neutralizing antibodies [1], but detailed regression analyses with additional data indicate that circumcision status in the vaccinees was the significant baseline risk factor associated with higher infection rates (S. Buchbinder, unpublished findings). Moreover, while the T cell–based vaccine regimen was assumed to have a greater impact on control of viremia after infection than on prevention of infection, the vaccine failed to lower set-point viremia despite eliciting remarkably high HIV-specific CD8+ T cell response rates [3].

A wide range of investigations ensued in an attempt to explain the lack of vaccine efficacy, and a few key issues have emerged as relevant to control of acute viremia. A chief consideration has been the incorporation of the appropriate HIV-1 genes or proteins into the vaccine candidate. The selection of vaccine antigens for HIV-1 has been largely empirical, but common approaches include expression of HIV-1 structural genes, particularly gag for those vaccines intended to induce primarily CD8+ T cells and env for those intended to induce neutralizing antibodies. The MRKAd5 HIV trivalent vaccine, intended to induce a T cell response, encoded HIV-1 Gag, Pol, and Nef but did not encode Env because of its high variability and the desire to exclude functional antibodies in this test-of-concept study. Although HIV-specific CD8+ T cells are able to
CD8+ T cell responses after vaccination compared with matched case patients mounted similar frequencies of Gag-specific responses important in generating effective vaccine-induced protection [10], the range and specificities of these responses may be im-
tively) [3]. Some case patients mounted vaccine-induced CD8+ controls who did not acquire infection (40% vs 42%, respec-

An additional consideration is the understanding of the epitope specificities that are important to elicit in a protective HIV-1 vaccine. Detailed studies of immune responses in acute HIV-1 infection have revealed the emergence of circulating HIV-1–specific CD8+ T cells as viremia peaks, and rapid viral escape mutations can occur within or upstream of the targeted epitopes [6–9]. Thus, viral epitopes first recognized in acute infection are unlikely to represent those commonly seen in chronic infection. Advances in the early diagnosis of HIV infection and implementation of these screening tests into large-scale vaccine trials will permit better understanding of whether a vaccine is exerting pressure on incoming virus or whether escape is occurring very early within the epitopes originally recognized. Furthermore, although Gag-specific CD8+ T cells have been associated with lower levels of plasma HIV-1 RNA [10], the range and specificities of these responses may be important in generating effective vaccine-induced protection.

In the Step Study, participants who acquired HIV-1 infection (case patients) mounted similar frequencies of Gag-specific CD8+ T cell responses after vaccination compared with matched controls who did not acquire infection (40% vs 42%, respectively) [3]. Some case patients mounted vaccine-induced CD8+ T cells recognizing as many as 6 Gag epitopes, but on average only 1 Gag epitope was recognized, and the recognized epitopes were located within both variable and conserved regions of the protein (McElrath, unpublished findings). Although no vaccine effect on postinfection viral load was demonstrated, viral sequence analysis suggests that immune pressure was exerted by the vaccine on the early founder viruses [11]. Taken together, these findings suggest that T cell–inducing vaccines will need to either elicit broader responses or target certain antigen specificities associated with conserved or functional sequences in order to contain early bursts of viremia and rapid viral escape mutation. In this regard, new vaccine designs employing conserved sequences and antigenic mosaic sequences may have utility, because they have the potential to induce T cell responses to high-frequency viral strains, and they have more epitopes and more variants within a given epitope [12–14]. Clinical trials will soon evaluate these approaches.

Understanding correlates of protection with T cell–inducing vaccines may require more extensive analysis of the antiviral functional properties of the T cells elicited. In recent years, extensive efforts to standardize and validate immunogenicity measurements have been undertaken to clearly define response rates, magnitude, and antigen specificity of the responding T cells [15, 16]. These assays are robust, highly sensitive, and reliable when applied in early trials to screen vaccine candidates and compare vaccine regimens, and they have utility for bridging immunogenicity results from the previous phase I or II studies to the larger trials. However, they may not be sufficient as the benchmark for predicting vaccine efficacy. Additional approaches to be incorporated into future studies, alone or in combination, include analyses of T cell suppression of viral replication, proliferation, and cytolytic and broader immunologic functions at the transcriptional and proteomic levels [3, 17–19]. Key factors in moving these platforms forward will be scaling them for performance in small numbers of specimens, making them cost-effective, and building the capacity to manipulate the resulting large databases for timely comparative analyses.

**THAI TRIAL**

The ALVAC vCP1531 (4 doses) in combination with AIDSVAX B/E (2 boosts concurrent with doses 3 and 4 of ALVAC vCP1531) showed low-level efficacy in reducing HIV-1 acquisition in a community-randomized trial in Thailand of subjects at relatively low risk of HIV-1 infection [2]. Although serious efforts are underway to discover how this vaccine may have elicited low-level protection, the prototypic high-titer broadly reactive neutralizing antibodies and class I major histocompatibility complex–restricted cytotoxic T cell responses commonly thought to provide vaccine-induced protection are unlikely to be major contributors in this trial. In fact, in previous studies with this and similar regimens, and in analysis of a subset of Thai trial subjects, the most consistent immune responses have been CD4+ T cell lymphoproliferation, antibody-directed cell-mediated cytotoxicity (ADCC), antibodies binding to HIV-1 gp120, and low-titer neutralizing antibody activities [2, 20–22].

The Thai trial findings indicate that preexisting, circulating CD4+ T cells induced by vaccination do not necessarily enhance HIV-1 infection and suggest that the vector prime may be important in inducing B cell help for antibody production. It remains an unanswered question whether the functional properties of memory CD4+ T and B cells induced by the prime-boost regimen are distinct from those induced by subunit Env protein alone and thus more likely to elicit protective immunity. In addition, induction of low-titer Env-specific antibodies with properties such as HIV-1 binding, ADCC or interference with
HIV-1 spread may be more easily generated than broadly-reactive neutralizing activities with current vaccine strategies, and these activities should be fully characterized. They may afford more protection than previously recognized at mucosal surfaces after HIV-1 exposure, as has been suggested in retrovirus challenge studies in antibody-treated macaques [23].

The study results also raise the possibility that immune activities, both innate and acquired, may be more successful in eliminating initial infection than in controlling viremia after acute infection. In acute HIV-1 infection, most often a single founder virus establishes mucosal infection [24]. In the vaginal mucosa, HIV-1 can rapidly enter CD4+ cells by fusion or Langerhans cells by receptor-mediated endocytosis, suggesting that effective vaccine strategies are needed for both entry pathways [25]. Selective activation of innate immunity with specific viral vectors, cytokines, and adjuvants may be advantageous in increasing antigen presentation and adaptive immune effector responses. However, the benefit may be outweighed by the inflammatory response, which can result in greater virus replication from activated target cells. Furthermore, natural killer (NK) cells have not been shown to mediate immunologic memory after vaccination, but NK functions in acute infection have been identified in association with control of viremia [26]. Whether vaccination can elicit NK cells with heightened antiviral activities, particularly mediating cytosis and ADCC, will need further examination.

CONCLUSION

Results from recent large-scale HIV vaccine studies underscore the need to better understand many aspects of the immune response in acute infection that can guide HIV vaccine development. Foremost is gaining knowledge of the distinct repertoire of innate and adaptive mucosal immune responses providing the first wave of attack after HIV-1 transmission. Detailed studies in the macaque model after mucosal exposure to simian immunodeficiency virus can also guide these efforts, particularly in identifying vaccine formulations that can effectively induce desired mucosal immune responses. Early detection of infection will permit better elucidation of a vaccine’s effect during acute infection, particularly in identifying T cell epitope specificities and functional properties that control viremia. Identifying cofactors such as risk activities, circumcision status, coinfections, and nonvaccine prevention modalities (eg, microbicides, preexposure prophylaxis) that can modify vaccine effects and determining the mechanism for these activities will be important in the design of future trials. Finally, building on the modest success of the recent Thai trial will require further understanding of the diverse roles that antibodies can play in preventing acute infection, and efforts to optimize these activities at mucosal surfaces will be the next step to explore.

References


