Published in final edited form as:

Science. 2014 April 4; 344(6179): 49–51. doi:10.1126/science.1250672.

Immune Activation with HIV Vaccines: Implications of the Adenovirus Vector Experience

Anthony S. Fauci^{1,*}, Mary A. Marovich¹, Carl W. Dieffenbach¹, Eric Hunter², and Susan P. Buchbinder³

¹National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland ²Department of Pathology and Laboratory Medicine, Emory Vaccine Center at Yerkes National Primate Research Center, Emory University, Atlanta, Georgia ³San Francisco Department of Public Health, Department of Medicine, University of California, San Francisco, San Francisco, California

The development of a safe and effective HIV vaccine is perhaps the most significant and challenging goal remaining in HIV/AIDS research. Recent progress using a poxvirus vector prime and envelope protein boost strategy demonstrated a modest but significant level of efficacy and for the first time established the concept that a vaccine could prevent HIV infection (1). Because protection waned over time, approaches to boost durability and efficacy are currently in the planning stages (2).

In addition, alternative approaches, particularly those using adenovirus vectors with various HIV gene inserts have been evaluated. In this regard, between 2005 and 2013 two vaccine concepts based on recombinant Adenovirus serotype-5 (rAd5) were evaluated in three efficacy studies (3–5). The first study (Step) using 3 doses of the Merck rAd5-gag/pol/nef vaccine was stopped for futility; of note, a trend toward increased HIV infections in vaccine recipients was observed (3). Once the entire Step dataset accumulated from 18 months of blinded follow-up was analyzed, this trend became statistically significant (6). The Step study showed an overall increased risk of acquisition (HR 1.4, $p < 0.03$); however, the group at highest risk was uncircumcised men who both had sex with men (MSM) and had high levels of pre-existing Ad5 antibodies (HR 4.2, $p = 0.02$) (6).

Following the release of the Step findings, the Phambili trial of the same Merck Ad5 vaccine platform conducted in South Africa, was closed and unblinded early during the enrollment period. Few Phambili participants received the planned three doses of vaccine. Primary analysis of the Phambili follow up data showed no increased risk of HIV infection (5). However, data from the long term unblinded follow-up of Phambili participants suggested an increased risk of infection in vaccinated men compared to unvaccinated controls (7).

*Corresponding Author: Anthony S. Fauci, M.D., ¹National Institute of Allergy and Infectious Diseases, 9000 Rockville Pike, Building 31, 7A03, Bethesda, Maryland 20892, Phone: (301) 496-2263, afauci@niaid.nih.gov.

In 2009, a different rAd5 vaccine platform advanced to efficacy testing in the HIV Vaccine Trial Network (HVTN) 505 trial. The vaccine contained 3 doses of a DNA prime followed by a single rAd5 boost with inserts expressing HIV envelope and viral structural antigens. As a safety precaution, this study restricted enrollment to circumcised MSM who lacked pre-existing Ad5 antibodies, since no level of increased risk had been seen in this group in the Step Trial (6). The HVTN 505 trial was halted prematurely because it met futility criteria; however, there was no evidence of increased risk of acquisition in the vaccinated subjects (8).

Based upon this information, the National Institute of Allergy and Infectious Diseases (NIAID) convened the Mini-Summit on Adenovirus Platforms for HIV Vaccines on September 19, 2013 (9) to investigate: 1) if rAd5 vectors are associated with increased risk of HIV infection; and 2) whether these problems extend to some or all of the other recombinant adenovirus vectors currently in development. Additional goals were to evaluate possible mechanisms by which rAd vectors could increase susceptibility to infection. In addition, the question was raised whether increased susceptibility might be seen with any HIV vaccine that activates the immune system rendering activated CD4+ T cells more susceptible to HIV infection, while at the same time inducing little or no protective effect against HIV acquisition (9).

Results of a Meta-Analysis

To better understand the impact of rAd5 vaccination on HIV acquisition, a meta-analysis of the Step, Phambili and HVTN 505 trials was performed by a group of statisticians from the HVTN Statistics and Data Management Center and from NIAID. Combining data from the three studies, the statisticians determined there was an overall hazard ratio of 1.33 ($p < 0.01$) associated with vaccination. However, almost all of the increased risk of HIV acquisition was driven by the Merck vaccine (Step and Phambili: HR = 1.41, $p = 0.005$) with the Step trial contributing most infection endpoints. HVTN 505 considered alone did not show any trend toward infection risk (9–10). It could not be determined by this analysis whether the lack of increased susceptibility in the latter trial was due to population or regimen (inclusion of env, DNA prime, single rAd5 boost with differences in vector backbone).

Other Ad-Based Vaccines

HIV acquisition risk following vaccination with other Ad-based vaccines was also investigated. Alternative Ad vectors for use in tuberculosis or malaria vaccines have not been evaluated in trials in sufficient numbers of adults at risk for HIV infection to provide useful information about possible interactions with HIV. However, active duty U. S. Army recruits have been vaccinated with Ad4/7 to prevent highly contagious respiratory illnesses in close quarters during training (11). During the time window of 1999–2011, the U.S. Army interrupted and then resumed vaccination with Ad4/7, creating three separate cohorts for comparison. The serologic data for incidence of HIV infection was reviewed retrospectively for these three cohorts by Dr. A.M. Cost and no changes in HIV incidence was detectable (9).

Potential Mechanisms for rAd5 effects

In 2008, NIAID held an HIV Vaccine Summit to reassess research directions following the lack of efficacy of the Step trial that had been reported that year. That summit fostered studies to understand the possible mechanisms of the effects seen in the Step study (12). At the 2013 NIAID Mini-Summit, Dr. M. Betts, presenting on behalf of collaborative work with Dr. G. Silvestri, summarized results from non-human primate (NHP) studies of the Merck rAd5-gag/pol/nef vaccine constructs that were used in the Step and Phambili studies. The data revealed an increase in activated CD4+ T cells in the gastrointestinal mucosa after rAd vaccination; and increased SIV acquisition following rAd-SIV vaccination, although immunization with the empty rAd vector did not increase SIV acquisition (13). In this regard, Dr. J. McElrath reported that the human gut biopsies of individuals vaccinated with the DNA prime and rAd5 boost as part of HVTN 204 (low risk) and HVTN 505 (high risk) revealed high levels of activated Ad-specific CD4+ T-cells, with an increase in CCR5 expression, but no HIV specific cells in multiple samples from the rectum and colon (9). Furthermore, the activated T cells were concentrated in unevenly distributed foci making extensive sampling a necessity (14). Although there is no current evidence of increased risk of HIV acquisition for other Ad vectors, the presence of rAd5-activated T-cells in tissue and the known degree of shared T cell epitopes between Ad serotypes needs to be considered as a possible area of concern. Ad serotype cross reactivity can be attributed, in part, to extensive CD4+ and CD8+ T cell recognition of highly conserved hexon regions across most human and primate Ad species (15–17). Therefore, this issue must at least be considered in the risk/benefit analysis of potential HIV vaccine trials using alternate Ad vectors. However, according to Dr. Dan Barouch in a Phase 1 study using a single rAd26-HIV env vaccination, a limited set of rectal biopsies showed no evidence for increased Ad-specific T cell activation in low risk volunteers and a different host gene activation signature from that in Ad5 vaccinated individuals (9). Nonetheless, we feel that a description of the rAd5 experience should be included in informed consents associated with HIV vaccine trials using alternate Ad vectors.

It is conceivable that increased risk of acquisition could be associated with any vaccination strategy that activates T cells, especially at mucosal surfaces. A vaccine must engage the immune system in order to induce a response. If the balance between the induction of protective anti-HIV responses versus Ad-specific responses that activate CD4+ T cells leans towards an anti-HIV response, then protection might be seen despite the presence of susceptible activated CD4+ T cell targets. However, increased susceptibility to infection may be seen if: the anti-HIV response is weak and does not counterbalance the increased susceptibility of activated CD4+ T cells; if the anti-HIV response wanes faster than the CD4+ T cell activation; or if the Ad-induced response is maintained and boosted by re-exposure to alternative Adenoviruses. Furthermore, cellular immune responses against Ad5, regardless of Ad serostatus, have been shown to diminish anti-HIV responses to rAd5-HIV vaccination in Step (15). In summary, the efficacy or not of an HIV vaccine may reflect a balance of two competing activities—protection driven by anti-HIV responses versus a risk of increased acquisition driven by cellular activation induced by anti-vector or any other immune activating response.

Considerations for the future

Given the increased risk together with the lack of efficacy in trials using rAd5, further HIV vaccine studies testing rAd5 vectors are not appropriate. When considering HIV vaccines that are designed to elicit a component of T-cell immunity, a risk/benefit analysis should consider the balance between anti-HIV responses and vector-directed responses that activate CD4+ T cells, thus rendering them more susceptible to HIV infection, and the potential for re-exposure to vector-related antigens in the environment with subsequent restimulation of the vector response. This is particularly important when evaluating viral vectors, including alternative Ad vectors. Future clinical testing of Ad-based vaccines should evaluate the levels and distribution of both vector and insert responses in target tissues where HIV acquisition is known to occur.

There are a number of research activities that could be pursued to help understand the roles of anti-vector responses in overall HIV vaccine efficacy. First, NHP studies using empty vectors or vectors with non-HIV inserts as placebo controls could define the levels of anti-vector immunity and evaluate the effect on virus acquisition of this vector-related activation of CD4+ T cells independent of an anti-HIV response. Second, the field could benefit from additional NHP studies. For example, the identification of biomarkers in primates that indicate increased risk of acquisition (18) could be valuable to monitor for risk in early phase human studies.

Third, a better understanding of mucosal immune responses to HIV vaccination is needed. The timing, location and number of mucosal biopsies that define the vaccine-induced gut immune responses need clarification. Importantly, understanding the influence of the mucosal microbiome on vaccination (19) and the impact specifically of the virome will be important. Particularly for Ad-based vectors, understanding components of risk related to the level of Ad exposure and persistence will be essential.

For non-HIV vaccine trials using vectors that induce strong T-cell immunity that are conducted in regions with high HIV incidence, it may be important to monitor for HIV acquisition, depending on the target population. In such studies where the population may be at risk of HIV exposure, HIV incidence should be monitored at the end of the study and for an appropriate follow-up period.

In summary, the experience with rAd5-based HIV vaccines has taught us that vaccine-induced protection against acquisition of HIV infection likely reflects the balance between beneficial anti-HIV responses and deleterious effects of immune activation that increases the susceptibility of CD4+ T cells to infection (Figure 1). Among the spectrum of existing or planned vaccines, this phenomenon is likely unique for an HIV vaccine since the activated CD4+ T cell is the very target for the virus. These observations should be taken into serious consideration in future HIV vaccine research endeavors and underscores the importance of maximizing the specific anti-HIV responses of such candidates.

References

1. Rerks-Ngarm S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med*. 2009; 361:2209–2220. [PubMed: 19843557]
2. Robb ML, et al. Risk behaviour and time as covariates for efficacy of the HIV vaccine regimen ALVAC-HIV (vCP1521) and AIDSVAX B/E: a post-hoc analysis of the Thai phase 3 efficacy trial RV 144. *Lancet Infect Dis*. 2012; 12(7):531–7. [PubMed: 22652344]
3. Buchbinder S, et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet*. 2008; 372:1881. [PubMed: 19012954]
4. McElrath J, et al. HIV-1 vaccine-induced immunity in the test-of-concept Step Study: a case-cohort analysis. *Lancet*. 2008; 372:1894. [PubMed: 19012957]
5. Gray GE, et al. Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, placebo-controlled test-of-concept phase 2b study. *Lancet Infect Dis*. 2011; 11(7):507–15. [PubMed: 21570355]
6. Duerr A, et al. Extended follow-up confirms early vaccine-enhanced risk of HIV acquisition and demonstrates waning effect over time among participants in a randomized trial of recombinant adenovirus HIV vaccine (Step Study). *J Infect Dis*. 2012; 206(2):258–66. [PubMed: 22561365]
7. Gray GE, et al. Long term follow up of the HVTN503/Phambili Study, a phase 2b HIV vaccine trial, investigating an Ad5 HIV-1 gag/pol/nef vaccine in South Africa. *N Engl J Med*. Dec.2013 submitted.
8. Hammer SH, et al. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *N Engl J Med*. 2013; 369(22):2083–92. [PubMed: 24099601]
9. National Institute of Allergy and Infectious Diseases Mini-Summit on Adenovirus Platforms for HIV Vaccines. Sep 19. 2013 webcast available at: <http://www.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/Pages/adenovirusPlatforms.aspx>
10. Hammer S, et al. paper presented at AIDS Vaccine Meeting Barcelona, Spain, 2013. *AIDS Research and Human Retroviruses*. Nov; 2013 29(11):A-1–A-208.
11. Hoke CH Jr, Snyder CE Jr. History of the restoration of adenovirus type 4 and type 7 vaccine, live oral (Adenovirus Vaccine) in the context of the Department of Defense acquisition system. *Vaccine*. 2013; 31(12):1623–32. [PubMed: 23291475]
12. Fauci AS, et al. HIV Vaccine Research: The Way Forward. *Science*. 2008; 321:530–532. [PubMed: 18653883]
13. Qureshi H, et al. Low-dose penile SIVmac251 exposure of rhesus macaques infected with adenovirus type 5 (Ad5) and then immunized with a replication-defective Ad5-based SIV gag/pol/nef vaccine recapitulates the results of the phase IIb step trial of a similar HIV-1 vaccine. *J Virol*. 2012; 86(4):2239–50. [PubMed: 22156519]
14. McElrath, J. paper presented at The Collaboration for AIDs Vaccine Discovery Meeting; Seattle, WA. December. 2013 Sponsored by the Bill and Melinda Gates Foundation
15. Frahm N, et al. Human adenovirus-specific T cells modulate HIV-specific T cell responses to an Ad5-vectored HIV-1 vaccine. *J Clin Invest*. 2012; 122(1):359–67. [PubMed: 22201684]
16. Hutnick NA, et al. Adenovirus-specific human T cells are pervasive, polyfunctional, and cross-reactive. *Vaccine*. 2010; 28(8):1932–41. [PubMed: 20188249]
17. Heemskerk B, et al. Extensive cross-reactivity of CD4+ adenovirus-specific T cells: implications for immunotherapy and gene therapy. *J Virol*. 2003; 77(11):6562–6. [PubMed: 12743315]
18. Martinelli E, et al. The frequency of $\alpha 4\beta 7$ (high) memory CD4⁺ T cells correlates with susceptibility to rectal simian immunodeficiency virus infection. *J Acquir Immune Defic Syndr*. 2013; 64(4):325–31. [PubMed: 23797688]
19. Williams WB, et al. paper presented at AIDS Vaccine Meeting Barcelona, Spain, 2013. *AIDS Research and Human Retroviruses*. 2013; 29(11):A-1–A-208.

HIV-Vaccine Induced Immune Response Interactions

Figure 1. HIV-Vaccine Induced Immune Response Interactions

Immune activation associated with HIV vaccination theoretically can lead to increased infection due to the activation of CD4⁺ T cells during the immune response. The level of protection seen with a vaccine can be viewed as the balance between the responses to the vaccine that lead to susceptibility to infection counterbalanced by the responses that favor protection.