

The Road to an Effective HIV Vaccine

Lindsey R. Baden, M.D., and Raphael Dolin, M.D.

During the 30 years since the discovery of HIV as the cause of AIDS, efforts to develop a vaccine have faced immense challenges. First, naturally acquired immunity to protect against infection that results in disease, found with virtually all other known infectious agents, may not exist for HIV. Second, the best available experimental animal model for AIDS, the nonhuman primate, provides potentially important information but also has substantial limitations. Therefore, advancement in the field has put an extraordinarily high premium on data from human studies. Yet only three candidate HIV vaccines have completed clinical efficacy trials. The first of these was a recombinant protein of the HIV-1 envelope (AIDSVAX),^{1,2} and the second was a nonreplicating adenovirus serotype 5 vector expressing an internal HIV-1 protein (gag).^{3,4} Both of these candidate vaccines failed efficacy trials, although important information was gathered about human immune responses to HIV-1 and about the methods for conducting complicated trials of vaccines.

However, the third candidate vaccine to reach a field trial (RV144) did show some efficacy in preventing acquisition of HIV-1 infection.⁵ This vaccine was a combination of a canarypox vector expressing HIV-1 immunogens (ALVAC) and the previously studied recombinant HIV-1 envelope protein (AIDSVAX). Although its efficacy was modest (31.2%) and perhaps short-lived, there clearly was an efficacy signal. This permitted an opportunity to search for a correlate of protection provided by a vaccine.

The results of this search for correlates of protection reported by Haynes and colleagues in this issue of the *Journal*⁶ was conducted by a consortium with broad-based skills in immunologic investigation and statistical analyses. Working within limitations of sample availability, laboratory assay requirements, and relatively small numbers of vaccine recipients who became HIV-infected after completion of the four-dose vaccination series, the consortium conducted a case-control study that focused on the relationship of six primary immune-response variables to the risk of HIV-1 infection. The findings indicated that IgG antibody binding to variable regions 1 and 2

(V1V2) of the HIV-1 envelope (Env) glycoprotein 120 was associated with a lower risk of infection. This observation has biologic plausibility, since this region is associated with important functions such as CD4-receptor and chemokine-receptor binding. In addition, a complex relationship to risk was observed with levels of monomeric plasma IgA antibodies, which were not associated with an overall increased risk of infection as compared with placebo, but which did appear to mitigate the protective effect of IgG antibodies to V1V2. These IgA responses also appeared to modulate, in a similar fashion, a suggestion of possible protective responses associated with other immune responses such as the avidity of IgG antibodies, antibody-dependent cellular cytotoxicity, neutralizing antibodies, and CD4+ T-cell responses.

The mechanism for the apparent effect of IgA in inhibition of the protective effect observed with anti-V1V2 IgG antibody against HIV-1 infection is unclear, but inhibition of IgG activity by IgA has been noted in certain other bacterial (e.g., meningococcus) and viral (e.g., Epstein-Barr virus) infections. However, the only samples available for IgA measurements were from peripheral blood, so the responses in key compartments such as the mucosa remain unknown. Interpretation of the significance of these immunologic responses is limited by the restriction in sample availability and assay requirements and by remaining uncertainty regarding correlation with other possible protective responses that could not be measured. Since this extensive search for potential correlates of protection is generating hypotheses, it is important to carefully evaluate these and other possible protective immune responses in future studies.

Because of the efficacy observed in the trial, new hypotheses to advance the investigation of HIV candidate vaccines can now be generated, as the authors suggest. These hypotheses should be tested in an iterative manner both in the experimental nonhuman primate model and in clinical trials. Many intriguing questions emerge. How do we better understand the protective response — or, more likely, the interplay of im-

mune responses — that affords protection? Do the immune responses in peripheral blood correlate with responses in important compartments such as the mucosa? Which components of the vaccine regimen are responsible for the protection observed? The findings of correlates reported by Haynes and colleagues suggest that certain antibody responses may be responsible for the protective effect and, thus, that the envelope protein may be central to that effect. Can the protective effect be enhanced or prolonged by the administration of booster doses of the vaccine? Can immunogens be designed to stimulate antibody responses to the V1V2 region without inducing potentially interfering Env-specific IgA responses?

The findings from the RV144 trial also raise questions regarding its applicability to other populations. The first efficacy trials were conducted in populations at high risk for HIV acquisition, whereas RV144 was conducted in a population at low-to-moderate risk for heterosexual acquisition of HIV-1 infection. Recent data suggest that transmission of infection between low-risk persons may involve fewer numbers of founder viruses and thus may be more amenable to interruption by vaccine-induced effects.⁷ It is important that follow-up trials be initiated promptly to confirm and better understand the findings of RV144.

The studies of correlates of infection described here, as well as the clinical trials from which

they emerge, are daunting. They are expensive and difficult to perform. But if properly designed and conducted, they may play an indispensable, iterative role on the road toward the development of an effective vaccine to control the HIV pandemic. If this approach works, it may shortcut the road to a clinically viable vaccine.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Division of Infectious Diseases, Department of Medicine, Brigham and Women's Hospital (L.R.B.); and the Division of Viral Pathogenesis and the Division of Vaccine Research, Department of Medicine, Beth Israel Deaconess Medical Center (R.D.) — both in Boston.

1. Flynn NM, Forthal DN, Harro CD, Judson FN, Mayer KH, Para MF. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. *J Infect Dis* 2005;191:654-65.
2. Pitisuttithum P, Gilbert P, Gurwith M, et al. Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand. *J Infect Dis* 2006;194:1661-71.
3. Buchbinder SP, Mehrotra DV, Duerr A, 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;372:1881-93.
4. McElrath MJ, De Rosa SC, Moodie Z, et al. HIV-1 vaccine-induced immunity in the test-of-concept Step Study: a case-cohort analysis. *Lancet* 2008;372:1894-905.
5. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 2009;361:2209-20.
6. Haynes BF, Gilbert PB, McElrath MJ, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. *N Engl J Med* 2012;366:1275-86.
7. Li H, Bar KJ, Wang S, et al. High multiplicity infection by HIV-1 in men who have sex with men. *PLoS Pathog* 2010;6(5):e1000890.

Copyright © 2012 Massachusetts Medical Society.

NEJM 200TH ANNIVERSARY AND SOCIAL MEDIA

Follow NEJMTeam on Twitter and click "Like" on the *New England Journal of Medicine* page on Facebook for links to the latest articles, stories, and multimedia available at the NEJM 200th Anniversary website, <http://NEJM200.NEJM.org>.

Tweets incorporating the hashtag #NEJM200 also appear in a Twitter feed at the anniversary website.