Lessons from Failure—Preparing for Future HIV-1 Vaccine Efficacy Trials

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(See the article by the rgp120 HIV Vaccine Study Group, on pages 654–65, and the article by Gilbert et al., on pages 666–77.)

Two articles [1, 2] in the current issue of the Journal of Infectious Diseases report the analysis of the first phase 3 efficacy trial of a candidate HIV-1 vaccine. The trial was successfully conducted and showed that the vaccine did not prevent HIV-1 infection. This vaccine, which was composed of recombinant gp120 (rgp120) in alum, was the culmination of testing >1 dozen monomeric envelope glycoprotein subunit constructs that represented the first generation of HIV-1 candidate vaccines. In the mid-1980s, fresh from the success of the recombinant subunit surface-protein vaccine for hepatitis B virus, it was thought that production of a recombinant construct of the HIV-1 envelope glycoprotein would result in an effective HIV-1 vaccine. The rgp120 used in the vaccine tested in the first phase 3 trial was made in mammalian cells, was properly glycosylated, and was the most immunogenic of its era. However, by the time the efficacy trial started, it was known that this type of envelope immunogen induced a type-specific immune response, meaning that the antibody elicited could only neutralize strains of virus that were very similar to the one from which the envelope sequence was originally derived.

It was also discovered that most transmitted viruses use the CCR5 coreceptor (R5) for entry into CD4+ T cells. In contrast, early HIV-1 strains, when propagated in laboratory cell lines that did not express CCR5, adapted to use the CXCRI coreceptor (X4). The vaccine used in the phase 3 trial combined an rgp120 from a typical laboratory-adapted X4 virus (HIV-1MN) with an rgp120 from an R5 virus derived from a primary HIV-1 isolate (HIV-1GNE8). Nevertheless, because HIV-1 exhibits extreme genetic and antigenic variability, particularly in envelope, it seemed unlikely that 2 monomeric gp120 antigens could induce a response that would prevent infection with the large variety of commonly transmitted strains of HIV-1 [3]. In addition, a number of structural and functional features of the native trimeric HIV-1 envelope glycoprotein were better understood when the trial began in 1998.

At the time, many scientists predicted that the vaccine would not work, because it did not elicit antibody that neutralized circulating virus strains. In fact, in 1994, the US Government–funded Clinical Trials Networks decided not to conduct an efficacy trial for MN rgp120. HIV-1 isolated from a single passage in human T cells (i.e., a primary isolate) is difficult to neutralize, even with serum from HIV-1–infected persons, and none of the vaccines evaluated during the past 2 decades has induced antibody that could neutralize a majority of primary HIV-1 isolates. The correlate of protection for virtually all successful viral vaccines, when known, has been neutralizing antibody.

Does this mean that no HIV-1 vaccines should be advanced to higher-phase clinical trials until products that can induce broadly neutralizing antibody exist? Approximately 14,000 new HIV-1 infections occur every day, and the pandemic is destroying the social fabric of many cultures throughout the world. The magnitude of the pandemic requires a dramatic call to action for governments, scientists, and all people of good will. Education on risk reduction and the current available public-health measures have not managed to dampen the pandemic. Despite the existence of multiple inexpensive diagnostic tools and the development of 20 approved antiretroviral drugs, neither diagnosis of nor specific treatment for HIV-1 infection has penetrated the developing world sufficiently to affect the pandemic. Many believe that the development of a vaccine will ultimately be necessary to control the pandemic. However, because the preclinical and early-phase testing of new vaccine concepts takes several years, by the time a candidate vaccine enters the efficacy-testing phase, the concept may appear to be...
outdated relative to current basic research. Another deterrent is the large price tag associated with efficacy evaluation. Should the urgent need for a vaccine affect decisions to advance candidate vaccines to efficacy trials when they are so expensive and when the vaccines are thought to have only a small chance of working?

The vaccine development process needs to combine empiricism with finding answers to hypothesis-driven questions. It will require both public and private investment. Importantly, it will benefit from greater cooperation and understanding among scientists and from a more informed public who can become a true partner in vaccine development. Vaccine evaluation through efficacy testing takes many years, and, for HIV-1, it is a high-risk investment, with success being measured decades later as a gradual downturn in the incidence and prevalence of HIV-1 infection. Positively affecting the prevention of HIV-1 infection through the creation of an effective HIV-1 vaccine is particularly important to developing countries, where the work of distribution will be harder and where there will be negligible opportunity for financial profit. These realities are shifting the classic paradigm of how vaccine development is accomplished. For public-health problems such as AIDS, it is inevitable that governments and nonprofit organizations will play a larger role in the future.

The initial results of the first phase 3 efficacy trial of an HIV-1 candidate vaccine were reported in the media on 24 February 2003, with dramatically contradictory headlines that ranged from proclaiming success to announcing failure. This raises the question of how scientists should interface with the media. On issues of public health, a better-educated media translates into a better-educated public. Discussions of public crises, such as the growing AIDS pandemic, are best conducted with candor and rigor, not fear and hyperbole. There is a tendency to spin the results of scientific experiments. This can create the impression that new discoveries will translate into meaningful clinical value within a rapid and predictable time frame. With regard to vaccine development, the process of generating public excitement over research findings often deemphasizes the entirely separate and lengthy process of product development. The distinction between these processes is not well understood by many scientists and most journalists, and even fewer among the general public comprehend it. The long and arduous process of HIV-1 vaccine development will require a solid partnership between scientists and the community at large, and, as we move forward together, it will be critical that the media distribute to the public accurate messages that are educational and realistic—not overly optimistic or pessimistic.

In the article by the rgp120 HIV Vaccine Study Group [1], aside from the demonstration that the vaccine candidate did not reduce the incidence of HIV-1 infection, an interesting trend was noted in the analysis of study subgroups. When only the nonwhite volunteers (~14% of the total study population) or the volunteers in the highest behavioral risk group (~5% of the total study population) were considered, it appeared that the vaccine conferred a slight benefit. However, after adjustment for multiple analyses, this effect was not significant and remains unexplained. A subsequent trial in Thailand, in which a similar product was used, showed 0% efficacy in a cohort of injection drug users, with no apparent benefit for ethnicity—but the different route of transmission confounds the conclusion on ethnicity. Therefore, the major implication of these findings is that diverse ethnic groups, as well as persons from various risk groups, should participate in vaccine clinical trials. Otherwise, subtle differences in immune responses or efficacy between subpopulations and differing routes of transmission may be missed. These findings also highlight the need to expand our understanding of the genetic determinants of the immune response.

In the article by Gilbert et al. [2], the major finding was that the uninfected vaccinees had generally higher antibody responses than did the infected vaccinees. The relative risk (RR) of HIV-1 infection was lower in volunteers with the highest levels of HIV-1MN neutralizing antibody and of antibody that blocked the binding of MN gp120 to soluble CD4, compared with that in the volunteers with the lowest antibody responses. The evaluation of HIV-1 incidence by quartiles of antibody responses within the group of vaccinees suggested that there was a significant inverse correlation. However, when judged against the placebo group, a high antibody response did not appear to have a benefit—this is because, in the vaccinees with low antibody responses, the RR of infection was slightly higher than that in the placebo recipients. As Gilbert et al. noted, this finding raises the following question: Do rgp120 vaccine recipients with low antibody responses have a slightly greater chance of becoming infected if they subsequently come into contact with the virus? It is known that this type of vaccine induces antibody and HIV-1–specific CD4+ T cell responses but does not induce the CD8+ T cell responses that are associated with the clearance of virus-infected cells. One hypothetical concern is that, in the absence of neutralizing antibody or a relevant CD8+ cytotoxic T cell response, infection rates could be enhanced by the presence of susceptible HIV-1–specific CD4+ T cells [4]; another is that nonneutralizing antibody may facilitate HIV-1 entry through complement or Fc receptors [5]. Table 1 in the rgp120 HIV Vaccine Study Group article shows that the vaccinees with low blocking activity against the binding of MN gp120 to soluble CD4 had an RR of infection of 1.78, compared with the placebo recipients. Among white volunteers, the RRs for those with low blocking activity and HIV-1MN neutralization were 2.20 and 2.11, respectively. In the small group of nonwhite volunteers, the lack of antibody with these functional properties did not appear to influence the RRs. These data are not sufficient to draw
solid conclusions on the association between specific antibody responses and the risk of infection, and therefore it cannot be said whether the higher vaccine-induced antibody responses were truly associated with a lower risk of infection or whether the lower vaccine-induced antibody responses were truly associated with a higher risk of infection. Also, because the higher antibody responses were associated only with causing the RR of infection to fall closer to 1.0, it is difficult to ascribe a biological effect to the vaccine-induced antibody response, and the results suggest that the phenomenon may be associated with another immune response that is not being measured.

In summary, the articles by the rgp120 HIV Vaccine Study Group and Gilbert et al. report the results of the first phase 3 efficacy trial of an HIV-1 candidate vaccine and represent the beginning of an empirical iterative process that is necessary to define the efficacy of subsequent generations of HIV-1 vaccine candidates. We need to be keenly attuned to the scientific, clinical, and operational lessons that can be learned and use each study as a stepping stone to achieve better immunogens, trial designs, measurements of immunological end points, and analyses of correlates of protection. Future studies need to evaluate biologically plausible and testable hypotheses, enroll diverse populations (with respect to ethnicity, sex, and routes of transmission), and create mechanisms for the public disclosure of knowledge that are acceptable to the scientific community and that provide information that is understandable by the general population.

References