POLICY FORUM

PUBLIC HEALTH

A Sound Rationale Needed for Phase III HIV-1 Vaccine Trials

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The need for a human immunodeficiency virus–1 (HIV-1) vaccine is unquestioned, and we strongly support its development as the highest AIDS research priority. We have a concern about the wisdom of the U.S. government's sponsoring a recently initiated phase III trial in Thailand of a vaccine made from the live-replicating canarypox vector ALVAC (from Aventis Pasteur) with a boost of monomeric gp120 (from VaxGen) (*1*). The original aim of this trial was to determine whether a combination of immunogens designed to induce cellular immunity (ALVAC) and humoral immunity (gp120) could prevent infection and/or lead to the immune control of HIV-1 replication postinfection. These remain questions fundamentally worth addressing, but we doubt whether these immunogens have any prospect of stimulating immune responses anywhere near adequate for these purposes.

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A phase III trial of similar design was scheduled to be conducted in the U.S.A. by the HIV Vaccine Trials Network (HVTN), the world's largest consortium of AIDS vaccine scientists and clinicians. However, the trial was canceled last year. Multiple phase I and II clinical trials have revealed that the ALVAC vector is poorly immunogenic (*2*). The gp120 component has now been proven in phase III trials in the United States and Thailand to be completely incapable of preventing or ameliorating HIV-1 infection (*1*, *3*). There are no persuasive data to suggest that the combination of ALVAC and gp120 could induce better cellular [$CD8^+$ cytotoxic T lymphocyte (CTL)] or humoral (neutralizing antibody) responses than either component can alone. Instead, the rationale for the Thai trial is reported to have now shifted toward an exploration of the hypothesis that the combination ALVAC + gp120 vaccine might induce an improved $CD4^+$ T helper (T_H) cell response that would enhance host defenses (*1*). The evidence underlying this hypothesis is derived from phase I/II trials of the same or very similar vaccines and is, in our opinion, extremely weak (*4*–*6*). Moreover, the same data were available to the HVTN. We concur with the HVTN's decision not to proceed with a phase III trial of the ALVAC + gp120 vaccine (*2*). What scientific reasons mandate a different decision for the Thai trial? We also take issue with the scientific rationale for the revised hypothesis underlying the trial (*1*). Merely trying to answer a question about the protective role of the T_H response does not seem to justify an experiment on this scale. Whether induction of T_H responses by the gp120 component could enhance the breadth or magnitude of CTL responses to the ALVAC vector sufficiently could be answered rapidly by a small trial using methodology that was not available at the time of the earlier studies (*4*–*6*).

The cost of the phase III trial in Thailand is reported to be $119m, with at least $3m for the purchase of the gp120 component from its commercial manufacturer, itself a controversial point based on past precedent (*7*). The trial will involve 16,000 volunteers. Approval was obtained from several committees, including one from the World Health Organization. But the latter committee's recommendation to proceed was made over a year before the results of the gp120 efficacy trial in Thailand were available, and it was made irrespective of the outcome of that trial (*1*). Our opinion is that the overall approval process lacked input from independent immunologists and virologists who could have judged whether the trial was scientifically meritorious. The U.S. National Institutes of Health (NIH) investment in basic and applied immunology research has been massive and appropriate over the past 15 years; the cumulative expertise gained should be used when important strategic decisions are made.

Society expects the scientific community to develop a vaccine to counter the AIDS pandemic, but there are adverse consequences to conducting large-scale trials of inadequate HIV-1 vaccines. We have recently seen two large phase III trials of immunogens that, all too predictably, failed to generate protective immunity (*1*, *2*). We seriously question whether it is sensible now to conduct a third trial that, in our opinion, is no more likely to generate a meaningful level of protection against infection or disease. One price for repetitive failure could be crucial erosion of confidence by the public and politicians in our capability of developing an effective AIDS vaccine collectively. This seems to us to be another readily predictable scenario that is best prevented.

Phase III trials are, ultimately, the only way to judge HIV-1 vaccine efficacy, but sometimes a formal end point is not needed. Applying judgment about the value of existing data is an essential part of the scientific process when determining whether or not to move ahead with any experiment. The failure of the gp120-only vaccine was, for example, fully predicted by phase II trial data (*8*). For a phase III trial to be justifiable, there should be a reasonable prospect that the vaccine will benefit the study population, i.e., that it will protect at least some of the participants from HIV-1 infection or its consequences. The decision about whether or not to proceed with mounting a phase III HIV-1 vaccine trial needs to take into account the likelihood of success and the consequences of failure, the value of what can realistically be learned, and the human and financial costs involved. As a whole, the scientific community must do a better job of bringing truly promising vaccine candidates to this stage of development and beyond. More highly immunogenic HIV-1 vaccines that offer a greater hope of success than the ALVAC-gp120 combination are, in fact, now in early-phase clinical trials.

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References

1. J. Cohen, *Science* **302**, 1309 (2003).
2. J. Cohen, *Science* **299**, 1290 (2003).
3. J. Cohen, *Science* **295**, 1616 (2002).
4. M. L. Clements-Mann *et al.*, *J. Infect. Dis.* **177**, 1230 (1998).
5. G. J. Gorse *et al.*, *Vaccine* **19**, 1806 (2001).
6. S. Ratto-Kim *et al.*, *J. Acquir. Immune Defic. Syndr.* **32**, 9 (2003).
7. J. Cohen, *Shots in the Dark: The Wayward Search for an AIDS Vaccine* (Norton, New York, 2001).
8. R. I. Connor *et al.*, *J. Virol.* **72**, 1552 (1998).