Vaccine Efficacy Trials for Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome Are Feasible in the United States: A Commentary on the HIVNET Vaccine Preparedness Study

Sten H. Vermund1,2

The Human Immunodeficiency Virus (HIV) Network for Prevention Trials (HIVNET) was established in 1994 to mount HIV/acquired immunodeficiency syndrome (AIDS) vaccine trials (at best) and to prepare for such trials in the future (at least) at both US and international sites (1, 2). HIVNET has now spawned two new and larger activities sponsored by the National Institutes of Health (NIH): the HIV Vaccine Trials Network and the HIV Prevention Trials Network. The sponsor of HIVNET, the National Institute of Allergy and Infectious Diseases (NIAID), chose not to initiate an efficacy trial during the 5-year life of HIVNET, but the intended site preparedness studies were completed.

The research study presented in this issue of the Journal by Seage et al. (3) is a national effort by investigators representing a veritable “who’s who” of HIV epidemiologists in the United States and was sponsored by HIVNET. In nine US cities, about 4,900 HIV-uninfected persons at high risk for HIV because of sexual risk or injection drug use were recruited and were followed for at least 18 months. Efforts were made to educate cohort members to reduce their personal risk behaviors, and these efforts were repeated at follow-up visits. Seroconversions were measured, and factors associated with HIV acquisition were assessed. The investigators answer a key question regarding HIV vaccine trials in the United States, namely, whether they are feasible in groups at risk for HIV that have more than one HIV seroconversion per 100 person-years of follow-up. Furthermore, selection of subjects on the basis of their reported risk at baseline (e.g., receptive anal intercourse or crack use) identified those subjects at highest risk, with double the overall rate of seroconversion. I was convinced by Seage et al. that while any HIV/AIDS vaccine trials present tremendous challenges, ethical efficacy trials are feasible and high-risk cohorts can be assembled and followed without an unusually high loss-to-follow-up rate by investigators willing to engage communities in HIV research.

Two HIV vaccines are currently being tested in large-scale, community-based, phase III clinical trials to determine their efficacy and safety in the United States and in Thailand. Both trials are spearheaded by a small, private company, VaxGen (Brisbane, California) using bivalent rgp120 subunit products (4, 5). VaxGen was formed largely because large pharmaceutical firms and government agencies, the more traditional funding agents for such trials, have not deemed available first-generation HIV vaccine candidates worthy enough to merit the considerable investment needed to test them in thousands of at-risk persons. VaxGen founders and investors disagreed, formed the company, raised the tens of millions of dollars needed, and initiated the trials. Early accounts of the VaxGen trials report adequate patient accrual and high retention, with no major social harms noted (6). However, in official convocations of NIH advisory groups in 1994 (AIDS Research Advisory Committee) and again in 2000 (Office of AIDS Research Advisory Committee), government advisors expressed serious doubts as to whether large-scale trials are truly feasible, particularly if vaccines used in the first trials prove to be ineffective. Even if one large trial can be mounted successfully, will it be possible to mount a subsequent trial, or will we have exhausted the pool of willing volunteers?

In the future, I hope that the HIVNET investigators can calculate and publish the costs of their cohort studies. VaxGen costs, if they are made public, are not likely to represent the true costs of the trials, because their sites have been heavily subsidized by NIAID HIVNET and AIDS Vaccine Evaluation Group infrastructure and training. The Centers for Disease Control and Prevention has provided direct funding support for six field sites as well as for behavioral science studies within these historic HIV phase III vaccine efficacy trials. Costs are not easy to calculate because the preparedness studies are not the same as vaccine trials, but some estimate of cost per subject per year of follow-up would be a valuable adjunct to the investigators’ seroincidence data and risk profiles of seroconverters (3). Also useful would be identifying the extent to which year 2000 VaxGen clinical trials overlap with the HIVNET vaccine cohort preparedness sites. This information would be helpful for four reasons. First, at the sites currently enrolling patients in the VaxGen trial in the United States, it should be possible to assess the degree of success in recruitment and

Received for publication October 9, 2000, and accepted for publication December 1, 2000.

Abbreviations: AIDS, acquired immunodeficiency syndrome; CTL, cytotoxic T lymphocytes; HIV, human immunodeficiency virus; HIVNET, HIV Network for Prevention Trials; NIAID, National Institute of Allergy and Infectious Diseases; NIH, National Institutes of Health.

1 School of Public Health, University of Alabama at Birmingham, Birmingham, AL.

2 University of Alabama School of Medicine, Birmingham, AL.

Correspondence to Dr. Sten H. Vermund, School of Public Health, University of Alabama at Birmingham, BBRB 203, 845 19th Street South, Birmingham, AL 35294-2170 (e-mail: sten@uab.edu).
follow-up in the context of the trial compared with their results in the epidemiologic “preparedness” studies. Second, HIV seroconversion rates in the trial can be compared with those measured earlier at the HIVNET sites. Third, it may be possible to estimate whether enough subjects who (unfortunately) continue to engage in high-risk activities are available to make a second trial possible at these same sites, even after hundreds of high-risk persons have been enrolled in a prior vaccine study. Fourth, it would be helpful to judge how the community liaison work within the HIVNET or the AIDS Vaccine Evaluation Group helped sites with their efficacy trial recruitment, retention, and educational efforts.

The lower-than-expected HIV seroincidence among injection drug users, as reported by Seage et al. (3), is most intriguing. Might this be a transient phenomenon, or is it likely to be a sustained consequence of risk-reduction activities among drug users? All of us hope that the latter is true, even though it makes study of injection drug users in such US cohorts perhaps unaffordable in HIV vaccine studies. Because we surely want to learn about any vaccine efficacy against a parenteral route of transmission, other parts of the world, such as sites in eastern Europe and the Far East, may need to be considered for trials that include injection drug users.

If HIV vaccine trials now being promulgated are successful, and if the Seage et al. (3) data convince the scientific community that additional trials are feasible, then the often-raised argument that such trials are not feasible appears to be invalid. This leaves us with the merits of the early HIV vaccine products as the main source of dispute. Some scientists are convinced that current vaccine candidates will not be successful in preventing or modulating HIV disease; hence, efficacy trials are a waste of resources. Others believe that only efficacy trials can answer this question and that they should be conducted expeditiously. In fact, few scientific issues in recent years have been as contentious within the community of investigators themselves as the 1994 decision not to go forward with phase III vaccine efficacy trials using one or both of two recombinant gp120 subunit products prepared by Genentech (San Francisco, California) and by Chiron Biocine (Emeryville, California) in the early 1990s.

In April 1994, NIAID convened a vaccine working group. This working group, of which I was a member, recommended overwhelmingly to proceed with such trials in April 1994 on the basis that optimized primate protection studies within the NIH-sponsored system, could mount such a trial. The debate did not hinge on whether the products were likely to work well; few thought that they would be highly efficacious given their poor ability to generate CTL and cross-neutralization responses, especially given the synergy between the cellular and humoral arms of the immune system in responding to acute human HIV infection or simian immunodeficiency virus in rhesus macaques. The argument favoring early trials, rather, was that the potential public health utility of a suboptimal, but partially effective vaccine could be substantial when combined with other effective public health strategies, including behavior change, promotion of the use of latex barriers, effective use of antiretroviral therapies for HIV-infected persons, and control of sexually transmitted infections (10).

While NIAID declined to support efficacy trials of subunit HIV vaccines in 1994, some government assistance has gone to the VaxGen trials nonetheless in support of sites, behavioral studies, and a specimen repository. It is likely that these efficacy trial arguments will rage again in 2001 at the NIH, its advisory committees, and among the HIV Vaccine Trials Network–sponsored investigators when the canarypox vector vaccines emerging from NIAID-sponsored phase II trials theoretically are ready for larger phase II or full-scale phase III efficacy studies. There is no doubt that the US sites participating in the study described by Seage et al. (3), with other Western Hemisphere sites that have been nurtured within the NIH-sponsored system, could mount such a trial focused on B clade viruses. The only question at hand is how promising a potential vaccine candidate has to be before enough consensus emerges at NIH and its advisory groups to permit a trial.

To enable readers to more fully understand the viewpoints of scientists both opposed to and supportive of early empirical human efficacy trial testing of available HIV vaccine candidates, I have sought to express their arguments below. The “do not test” view is given first, followed by the “test now” perspective.

Do not test these early-candidate vaccines because the scientific rationale for their success is weak to nonexistent; research resources are more wisely invested in finding more promising products. Many prominent HIV researchers hold the viewpoint that large-scale human tests of the first-

generation recombinant envelope subunit candidates or early live vector candidates such as canarypox with genetically engineered HIV antigens would be a waste of money and might exhaust community goodwill toward candidate vaccines without adequate scientific merit. Since candidate vaccines that have been studied in phase II trials generate a relatively transient humoral response that neutralizes only laboratory-adapted strains, with CTL responses noted in a minority of vaccinees, these investigators argue that the gp120 vaccine products or canarypox vectors would not block infection in the real world because primary circulating infectious isolates would not be controlled by the vaccine-induced immunologic gauntlet. Studies have not suggested that the rgp120 products tested in phase II trials reduce the viral load and/or modulate disease progression in a vaccinee who nonetheless becomes infected (13, 14). Proponents of this viewpoint hold that scientific investments are best made in discovering and developing products that generate CTL in nearly all cases and that generate humoral responses that neutralize wild-type HIV strains. I call this viewpoint the “basic research rationale” given the advocacy of product discovery and development and of phase I or animal testing in lieu of large-scale human field trials of the early products.

The alternative viewpoint might be expressed as follows: We must test these early vaccine candidates to determine whether there is any benefit from the immune responses that they elicit; current immunologic tests may underestimate the benefits of vaccines in the real-world setting. Many scientists who have vaccine-testing experience or who come from public health research traditions have argued that large-scale vaccine trials should be conducted whenever a candidate vaccine proves safe and reasonably immunogenic. The goals of the large-scale phase II or phase III efficacy trials should be to learn 1) the extent to which available products can reduce the frequency and/or modulate the severity of infection, 2) the impact of vaccination on the dynamics of infection in a community, and 3) the extent to which vaccination might reduce the infectiousness of vaccinees who nonetheless become infected with HIV. The relatively low infectiousness of HIV per contact may favor successful control by even suboptimal vaccine products. I call this viewpoint the “empirical research rationale,” one that advocates further, larger-scale clinical testing to measure the degree of efficacy, if any, with a variety of vaccine products, including those that may not meet theoretically ideal standards.

In my view, the strongest case for the basic research rationale is that the early-candidate vaccines do not appear to elicit the very responses that are their underlying rationale for success, namely, cross-neutralizing antibodies and CTL responses in a high proportion of subjects. It is easy to see the lack of enthusiasm among scientists who have not participated in previously successful empirical vaccine testing programs. The strongest case for the empirical research rationale is that we may have a partially effective vaccine that can help to contribute to worldwide HIV prevention and control, even if laboratory assays are not promising. This would not be new in the field of vaccinology (11, 15). Policy makers who are gatekeepers for vaccine trials should not be too timid if even only a partially effective product might be identified. Given the long clinical latency period during which an infected subject may be infectious within the community, an HIV vaccine might reduce the community-level burden of HIV transmission if it succeeds in reducing viral load in vaccinees as well as possibly extending their quality and length of life (16). In addition, an HIV vaccine that reduced infection rates by a fraction, say 30 percent, among vaccinees might prove helpful, especially in communities in which other prevention interventions with 30–50 percent efficacy were being promulgated (10). Thus, partially effective HIV vaccines as a component of a more comprehensive community control scheme could play a salutory role in HIV prevention.

The many challenges that we face in developing an HIV vaccine (17–21) are beyond the scope of this commentary. These challenges include cross-clade immunity, duration of immunologic responses induced by successful immunization, field challenges in vaccine delivery and boosting, quality and breadth of vaccine-induced immune responses, suboptimal support of HIV vaccine research and development in most major pharmaceutical and biotechnology companies, the rarity of “risk taking” in the government sector where consensus-building in large committees often results in conservative decisions, and many others (22). Difficulties in conducting the trials themselves, fears of increased risk behaviors among vaccinees who are not well informed about the unknown efficacy of HIV vaccines, and community fears about serving as “guinea pigs” in trials are also concerns. Seage et al. (3) argue that the latter challenges are surmountable; indeed, HIVNET has demonstrated HIV vaccine trial feasibility, as have recruitment successes in the ongoing phase III vaccine efficacy trials in the United States and Thailand.

REFERENCES