evaluations to determine if vaccination has altered the way the immune system attempts to control the new viral infection.

The study team does not want people to increase their risk for acquiring HIV based on the mistaken assumption that the vaccine has conferred protection.[12] Other areas of concern include the risk of social harm and possible stigmatization.[13,14] For instance, detectable HIV antibodies may not reflect HIV infection and instead reflect vaccine administration. Testing positive for HIV due to vaccine administration could cause harm in terms of obtaining health insurance, travel, or military service. In addition, because participation in a vaccine study is predicated on high-risk behavior, study identification alone carries the risk for stigmatization. Nevertheless, many people at high-risk state that contributing to ending the AIDS epidemic and desires to help others are key factors for participating in a vaccine study.[14-16] Assuming that patients are protected from harm, this study is a failure only if it has to be repeated. The vaccine may not protect against infection. However, the questions of concern that remain are: what happens after infection and can disease progression be reduced?[17] Only long-term follow-up will address these key questions. Ultimately, we all hope that this vaccine or another vaccine candidate will provide an inexpensive and reliable treatment to end the HIV epidemic.

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What about the ethics?

Leslie E Wolf
Bernard Lo

Center for AIDS Prevention Studies and the Program in Medical Ethics
University of California San Francisco, CA 94143

Correspondence to:
Ms Wolf
lwolf@medicine.ucsf.edu

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INTRODUCTION

Clinical trials will be essential to develop an effective HIV vaccine and to stem the devastation of the HIV epidemic. Ethical concerns about research on human subjects have recently been highlighted because of incidents at two academic medical centers.[1-3] Such incidents remind physicians and the public alike of the need for clinical trials to be conducted in an ethically sound manner. As phase 3 trials of HIV candidate vaccines begin, it is appropriate to reflect on the ethical concerns raised by such research. While many of the issues are pertinent to all clinical research, the special characteristics of HIV raise additional ethical concerns.

STUDY DESIGN

The researchers' first ethical obligation is in the design of the research study. The study must be designed to provide valuable information, and the researcher must have reason to believe that the vaccine under trial may work. If these conditions are not met, it is unethical to expose subjects to the risks of participating in the trial.[4] Human trials typically require support from laboratory and animal research. HIV presents some difficulties because a good animal model does not exist, HIV is highly variable and undergoes rapid mutation, and we know little about HIV immunity.[5] Furthermore, it is likely that a vaccine will confer only partial immunity. Because of the gravity of the HIV

epidemic, however, it is ethically appropriate to begin vaccine trials without fully understanding the correlates of viral immunity. Meeting these ethical obligations requires an adequate study size and, because of the relatively low incidence rates of HIV infection, close follow-up.

Researchers must recognize and address the inherent conflict between their obligations to carry out sound research and their obligations to protect their subjects. Trial participants may mistakenly believe that they will receive protection from the vaccine and, therefore, may increase risky behaviors.[6] The study endpoints should, therefore, include not just new infections but also information on risk behaviors. Researchers' obligation to protect their subjects requires that they provide high quality counseling to reduce risk and emphasize the uncertainty about the effectiveness of the candidate vaccine. If counseling were fully effective in reducing risk, however, none of the participants in the trial would seroconvert and there could be no efficacy evaluation. To address the conflict, it may be necessary to have separate counseling and vaccine staff and specific protocols regarding counseling.

THE RESEARCH PARTICIPANT

Informed consent in an HIV vaccine trial presents several difficulties. First, ensuring that consent is truly informed is complicated because participants frequently misunderstand or exaggerate the likelihood that they will receive clinical benefit from the intervention.[6] Second, HIV vaccine trials pose unique risks to participants. Participants may be prevented from participating in future vaccine trials, and vaccines that are developed later may be less effective for them. In addition, because participants may react positively to certain HIV antibody tests, they may also be denied certain governmental jobs (for example, Peace Corps, Foreign Service, military) even if their seroconversion does not represent true infection.[5] Participants in the trial may also face stigmatization from family or friends to whom they disclose information. Because the mere participation in a phase 3 trial will identify the subject as someone at high risk of contracting HIV, it may be impossible to eliminate these risks. While researchers always have an obligation to protect the confidentiality of the information they collect, this duty is particularly important in HIV vaccine trials because of the high risks to participants if confidentiality is breached.

Researchers also must consider their obligations to participants in the trial to provide access to medical care and to any successful vaccine. Some participants will become infected during the vaccine trial. Researchers have an obligation to provide these individuals with medical care, and yet, there has been considerable dispute over whether researchers are obligated to provide state-of-the-art care and, particularly, for international studies, which standard of care should govern.[7-9] Researchers also have an ethical obligation to provide the vaccine to participants in the control group if it is shown to be efficacious. Because the control group has taken on the risk and inconvenience of the trial, it is fair to give them first priority to the benefits of an effective vaccine.

THE COMMUNITY

The interventions in the vaccine trial must be relevant to affected populations. For example, the vaccine candidate should be expected to work against the HIV subtype common to the trial community. Researchers also have an obligation to inform the community about the trial, to respond to misconceptions about the trial, and to ensure that cautionary information is emphasized in any publicity about the trial, to avoid a false sense of security.

CONCLUSIONS

Development of an effective HIV vaccine may be the best chance at stemming the epidemic around the world and in very high-risk groups in the United States. Achieving this goal is likely to require testing of multiple vaccines and, accordingly, the participation of many thousands of research volunteers. This effort cannot be sustained without the support of the affected communities and must be conducted at the highest ethical and scientific levels.

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