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The Ethical Design of an AIDS Vaccine Trial in Africa

by Nicholas A. Christakis

Proper conduct of an AIDS vaccine trial in Africa must be informed not only by the epidemiology and biology of HIV infection in African settings, but also by the ethical norms and cultural constraints prevailing in African settings.

On March 19, 1987, a group of French and Zairian scientists published a report in *Nature* stating that one of the investigators, Dr. Daniel Zagury of the Pierre and Marie Curie University in Paris, had immunized himself with an investigational AIDS vaccine.¹ With "the full support of the Zairian Ethics Committee," the investigators also immunized "a small group of Zairians, all of whom were HIV-seronegative volunteers and immunologically normal."

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The fact that this first trial of an AIDS vaccine took place in Africa leads to a variety of concerns. Most troubling is the possibility that Africans might serve as "guinea pigs" for clinical trials that would not be allowed in the U.S. or Europe, particularly in view of past cases of disregard for the rights of human subjects of research in Third World countries. Africans, feeling that "Western science often comes to Africa with dirty hands," have been concerned that Western investigators, unchecked by foreign or local supervision, might conduct "savage experiments."² Indeed, an unidentified source close to the Zagury group informed a *New York Times* reporter that a major reason they conducted the trial in Zaire was that "It was easier to get official permission [in Zaire] than in France."³

Differences in permissibility of trials in developed versus developing countries, however, are not supposed to occur. According to the guidelines for human subjects research established jointly by the World Health Organization (WHO) and the Council for International Organizations of Medical Sciences (CIOMS), when research is conducted by investigators of one country on subjects of another, "the research protocol should be submitted to ethical review by the initiating agency. The ethical standards applied should be no less exacting than they would be for research carried out within the initiating country."⁴ Yet the great complexity, varied presentation, and wide distribution of HIV infection challenge this stance. When the epidemiologic and scientific aspects of HIV infection and vaccination are coupled with the cultural differences throughout areas of the world where AIDS is prevalent and AIDS research is conducted, the uniform application of ethical principles in the conduct of an AIDS vaccine trial becomes considerably more complicated.

To some extent, the CIOMS guidelines anticipate this. Their stated purpose is to amend the principles of the Declaration of Helsinki "to suggest how [these principles] may be applied in the special circumstances of many technologically developing countries."⁵ There is a tension in the guidelines, however, between the desire for culturally relevant application of ethical principles on the one hand and the belief that "the ethical implications of research involving human subjects are identical in principle wherever the work is undertaken" on the other. If trials of HIV vaccines are to take place worldwide, this tension must be resolved. Are there justifiable differences in research ethics in different sociocultural settings? How are ethical concerns to be met in the face of a pandemic? Is it possible to distinguish "medical imperialism" from legitimate reasons for conducting an AIDS vaccine trial in Africa?

Design of an AIDS Vaccine Trial

Though several types of AIDS vaccines are being considered, investigation has been largely directed towards using recombinant DNA technology to produce HIV proteins or insert portions of the HIV genome into other viruses (such as the vaccinia virus used by the Zagury group).⁶ A protocol for evaluating candidate vaccines would involve: 1) preparing the vaccine in sufficient quantity and purity; 2) testing in animals to see if it results in antibodies able to neutralize HIV *in vitro*; 3) testing in nonhuman primates to establish the ability of the vaccine to protect against subsequent challenge with HIV; 4) testing in a small group of humans (members of AIDS risk groups or others) to evaluate short-term safety and immunogenicity (a phase I trial); 5) determining ideal dose and spacing of the vaccine through larger safety and immunogenicity trials (phase II); and 6) determining protection against HIV infection through large scale efficacy trials involving as many as 1,000 to 2,000 subjects (phase III).⁷ A phase III trial would be of the randomized, double-blind, controlled type.

The epidemiology of HIV in Africa will raise special considerations in the scientific design of a trial that will, in turn, affect its ethical design. The ethical design of an AIDS vaccine trial in Africa, that is, must be informed by the scientific parameters of the research and of the study population in the familiar interaction between science and ethics.

As we shall see, however, attention must be focused on the specific ethical and cultural constraints prevailing in settings where AIDS research is conducted. Even if the epidemiological and scientific parameters of HIV infection were the same in research settings throughout the world, the proper ethical design of AIDS vaccine trials would still vary with the ethical and cultural parameters of the research populations.

Assembling a Suitable Study Group

Participants in a phase III trial would have to be followed and assessed for HIV infection through serial testing and examination. Such follow-up is time-consuming and expensive because of the variable expression and long latency period of HIV infection. Proper evaluation of a vaccine will require a large number of subjects drawn from a suitable population. The ease of assembling the requisite number of appropriate subjects and the relatively low cost of conducting a trial in Africa (because of typically low wages) have been explicitly identified by some investigators as benefits of conducting AIDS research in Africa.⁸

Africa has also been offered as a vaccine test site on the basis of certain scientific considerations. Specifically, subjects in a phase III trial would have to meet two important technical requirements: they would have to be free of HIV infection at the beginning of the trial, and they would nevertheless have to be *at risk* for HIV infection.

Subjects must initially be free of HIV infection to assess the vaccine's ability to prevent subsequent infection; a person already infected with HIV who received the vaccine would falsely be identified as a vaccine "failure," that is, as someone in whom the vaccine was ineffective. In addition, absence of HIV infection is necessary to avoid the possibility of serious complications that might arise if an HIV-infected individual were given a recombinant viral vaccine. An individual infected with HIV and suffering from subtle immunocompromise could develop a serious infection with the non-HIV virus used in the vaccine (such as generalized vaccinia).

At present, determining freedom from HIV infection would be accomplished through testing for HIV antibodies. But freedom from infection is not guaranteed by a single test showing absence of HIV antibodies: the test result may simply be inaccurate—scientific tests are not infallible and there will be false negative results—or the research subject may, in fact, be infected with HIV, but have not yet developed antibodies.⁹ Most people infected with HIV develop antibodies within six to twelve months if they are to develop them at all. Research subjects would thus have to be retested at a six to twelve-month interval to assure lack of prior exposure. Of course, during this interval, the study population would ideally need to avoid further exposure to HIV, which could lead to infection that might escape detection at the second testing.

The second requirement, being at risk for HIV infection, is necessary to assess the vaccine's ability to prevent HIV infection: a study population at no risk of infection whatsoever would not permit evaluation of vaccine efficacy since no one at all, in either the vaccine or control groups, would become infected.

Two aspects of the epidemiology of HIV infection in Africa facilitate meeting this requirement. First, the predominant mode of transmission of HIV in Africa is thought to be via heterosexual sex; the identified risk factors include having a large number of sexual partners, having sex with prostitutes, being a prostitute, or being a sexual partner of an infected person.¹⁰ Second, estimates of HIV antibody seroprevalence for various sub-Saharan countries range from 0.5 percent to 8.8 percent for healthy controls and 14.6 percent to 55.6 percent for risk groups such as prostitutes.¹¹ This high prevalence

implies a high risk of infection for uninfected members of the society that would allow a trial to detect a difference between the vaccinated and unvaccinated (control) study groups with greater ease in less time. Moreover, the substantial prevalence of HIV infection in the general heterosexual population further facilitates assembling an appropriately large study group.

Thus, the benefit of conducting a phase III AIDS vaccine trial in Africa (because of the high risk) would be at least partially offset by the likely increase in adverse effects attributable to vaccination (because of the high prevalence and consequent increase in the number of falsely negative individuals included in the trial).

Of course, the benefit here is to the conduct of the investigation in the form of a speedier, more accurate trial, and hence to the investigators and society-at-large. The cost, however, is borne by the research subjects. This problem could be minimized—but not eliminated—by a scrupulous testing policy aimed at excluding HIV-seropositive individuals from the study. However, achieving this objective would require a certain degree of intrusion upon the privacy of study subjects to ensure that they abstain from risky behaviors in the six-month interval between the two required HIV tests. Moreover, a degree of accuracy in testing beyond that traditionally seen in laboratories in the developing world would have to be assured.

A final scientific concern in assembling a suitable study group regards the applicability of the findings. The pattern of infection in Africa may reflect as yet unknown biological factors in the population at risk or in the virus that may require testing a vaccine in Africa simply to evaluate vaccine efficacy in circumstances that may be unique. Since an effective vaccine would be of great utility in this continent, some trials in Africa would presumably be essential.

Risks and Consent

Eligible research subjects would have to consent to participation in the trial, which would require researchers to provide information regarding both benefits and risks. The salient personal benefit to participation in an AIDS vaccine trial is the possibility of gaining immunity to a deadly infection. An effective vaccine would be very beneficial for society-at-large, but this is not ordinarily seen as a direct benefit to the individual.

The risks involved in trial participation are significant, however. For HIV subunit or recombinant viral vaccines, possible direct adverse consequences of participation in a vaccine trial include:

1) serious infection (generalized vaccinia, for example) in the case of undetected HIV infection in recipients of a viral vaccine; 2) mild or severe systemic reactions to the vaccine (headache, severe febrile reactions, convulsions); and 3) hypersensitivity reactions. A further hazard of such research is the possible increase in risky behaviors because participants feel relatively protected. Finally, it is theoretically possible that receiving one type of an AIDS vaccine might preclude immunization with a more effective vaccine developed subsequently.

The need to test for HIV infection both at the onset and during the conduct of the trial creates a further problem peculiar to participating in an AIDS vaccine trial: that of learning one's antibody status. Some have argued that being HIV antibody positive is burdensome knowledge that should not be imposed.¹² Thus, people *excluded* from vaccine trial participation because of HIV antibody positivity might suffer through acquiring knowledge of their status. For persons *enrolled* in the trial, the necessary surveillance of HIV antibody status might also ultimately result in knowledge of HIV infection that the subject would otherwise have avoided.

Research subjects would also have to be advised that as a consequence of participation they will become HIV seropositive by conventional screening methods. Seroconversion may, in turn, lead to discrimination against the subject. This eventuality has led to some innovative measures. In a trial approved but not yet under way in the U.S., subjects will be issued both a certificate testifying to their participation in the trial and a copy of their Western blot results showing a characteristic pattern identified as being a result of participation and not infection.¹³

Beneficent Treatment of Subjects

The risks involved in the trial of an AIDS vaccine mandate beneficent treatment of participants. In the context of human subjects research, beneficence has found two complementary expressions: "(1) do not harm, and (2) maximize possible benefits and minimize possible harms."¹⁴ For the benefits to outweigh the risks in the trial of an AIDS vaccine, an individual would have to be at some risk of HIV infection. The necessity of being at risk thus has both scientific and ethical import.

But beneficent treatment of AIDS vaccine trial subjects has several aspects beyond a suitable risk/benefit ratio. Volunteers must be informed that vaccination does not provide license to engage in risky behavior, and must be counseled regarding "safe sex" practices. In Africa, counseling should at a minimum consist of strong advice to decrease

the number of sexual partners, to avoid prostitutes, and to abstain from sex with individuals known to be infected. Counseling, along with informing participants of their negative antibody status, would likely result in a decrease in risky behavior.¹⁵

In advanced trials designed to test vaccine efficacy, however, these interventions could diminish the ability of the study to detect a difference between true vaccine recipients and controls by decreasing the incidence of HIV infection in *all* participants for reasons *unrelated* to vaccine status. To circumvent this problem, a larger study group would be required to detect the relatively smaller measured influence of the vaccine. But increasing the size of the study group has attendant adverse consequences, including the increased risk of exposing more individuals to the experimental vaccine and increased cost. Thus, there will be unavoidable conflict between research design and ethics. This conflict should be resolved in favor of beneficent treatment of subjects: to minimize risk to individual research subjects, study size should be increased and all participants should be counseled to avoid risky behaviors.

Deliberately counseling all participants to avoid risky behaviors will likely also increase the time required to complete the study since researchers would have to wait longer to detect sufficient cases of HIV infection for the results to be significant. This necessity must be seen in light of the considerable pressure to develop an effective HIV vaccine rapidly.

The interpersonal nature of HIV transmission may create an additional ethical problem pertaining to the beneficent treatment of research subjects. The unit of analysis in AIDS vaccine trials, some have suggested, should *not* be the individual.¹⁶ Given that simply participating in AIDS research may offer some benefits, especially if participation serves to lower risky behavior, researchers may be obliged to recruit, insofar as possible, the sexual—and where applicable, needle-sharing—partners of research subjects.

Indeed, there is presently a study under way in Africa that involves deliberate tracking of HIV-discordant couples to determine the natural history and transmissibility of the disease where condom use is the sole preventive measure.¹⁷ The ethics of such a study are questionable, *unless* the seronegative member of the couple is properly informed of the risk continued sex with his or her partner poses despite condom use. The argument that researchers studying progression of HIV infection in groups of individuals are merely observing events that would take place regardless of the researchers' presence—a so-called study in nature—is untenable. The mere presence of the researchers disturbs the “natural

setting” (certainly it does so in this case since condoms and recommendations regarding their use are distributed). Moreover, physician researchers have incumbent upon them the duty to protect the health of their subjects, even if in so doing they compromise their research.¹⁸

Ethical Standards in Cross-Cultural Perspective

Consideration of Africa as a test site should transcend the standard scientific and ethical concerns outlined above and should incorporate broader concern arising from the conduct of research in disparate sociocultural settings. The conduct of a vaccine trial in Africa will highlight not only practical and scientific differences, but also ethical and cultural differences between Africa and the West.

Soliciting informed consent to participate in research is one of the major areas where variation in ethical standards will be encountered. The Western principle of informed consent is predicated upon the notions of respect for persons as individuals and as autonomous agents.¹⁹ This is at variance with more relational definitions of the person found in other societies, especially in Africa, which stress the embeddedness of the individual within society and define a person by his or her relations to others.²⁰

From this variation in the definition of a person arise important practical implications. Where the notion of persons as individuals is not dominant, the consent process may shift from the individual to the family or to the community.²¹ It may be necessary to secure the consent of a subject's family or social group instead of or in addition to the consent of the subject himself.

Culturally-defined views of personhood may also find expression in determinations of who is deemed able to give informed consent for others. This is acknowledged in the CIOMS guidelines:

Where individual members of a community do not have the necessary awareness of the implications of participation in an experiment to give adequately informed consent directly to the investigators, it is desirable that the decision whether or not to participate should be elicited through the intermediary of a trusted community leader.²²

There will be considerable variation by culture as to who is acknowledged to be a “community leader” and whether such an individual will meet the investigator's expectation regarding who can appropriately give proxy consent.

The principle of community leader consent may

be the only alternative—however unsatisfactory by Western standards—to individual consent in many cases where beneficial research is essential. This alternative may not necessarily be ethically incorrect for the society of which the research subject is a member. Indeed, the desire of research subjects to cooperate with respected local authorities can be instrumental in the success of research in many settings.²³ His or her obedience to a local authority should not be abused, however, by a Western researcher to the detriment of a Third World subject of research. A researcher must respect an individual's manifest refusal to participate, even if consent has been elicited from some other person or group.

Western investigators should also appreciate that what appears to them to be coercion may, from the perspective of local inhabitants, represent cooperation and identification with the group to which the individual belongs. This does not relieve Western investigators of the responsibility to avoid coercion arising from their *own* actions. They must be aware that it is difficult to avoid coercing subjects in most settings where clinical investigation in the developing world is conducted. African subjects with relatively little understanding of medical aspects of research participation, indisposed toward resisting the suggestions of Western doctors, perhaps operating under the mistaken notion that they are being treated, and possibly receiving some ancillary benefits from participation in the research, are very susceptible to coercion. Their vulnerability warrants greater care in procuring consent and necessitates greater sensitivity to protect this class of research subjects.

It is clear that the type of consent practiced in the West, with the signing of an informed consent document containing medical terms, is inappropriate for illiterate or semi-literate peoples. Indeed, signing or even thumbprinting a consent form may be deemed highly suspect in certain societies, as may a physician's "excessive" explanation of the purpose of the research (which may be taken as indicative of some hidden, detrimental purpose). In some cultural settings it may be extremely difficult to convey an accurate understanding of the idea of randomization or other essential scientific concepts.²⁴ Moreover, there may be cultural variations in the understanding of disease, at odds with Western scientific notions, that make truly *informed* consent impossible.²⁵ In the context of an AIDS vaccine trial in Africa, the foregoing concerns will allow for significant variability in the information conveyed in obtaining the subject's consent. Nevertheless, investigators must seek to explain the purpose of the research in culturally relevant terms.

The principle of respect for persons is also

ordinarily taken to imply a respect for individual privacy and confidentiality. In some societies, as we have seen, it may be necessary that this individual claim yield to a somewhat larger group, as with, for example, informing a husband of his wife's participation in a research endeavor. Yet, insofar as feasible, confidentiality should be respected. One example of unnecessary violation of this principle that has led to irritation on the part of some African officials is the practice of publishing photographs of African AIDS patients in the Western press.²⁶

A relational concept of personhood may also result in ethical decisions that, by Western standards, unduly favor the interests of society at large over those of the individual. Western ethical standards generally accord considerable import to the welfare of the individual in the conduct of research. The Declaration of Helsinki, for example, states that "concern for the interests of the subject must always prevail over the interests of science and society."²⁷ The Belmont Report, an ethical standard developed within the U.S., more explicitly acknowledges the difficulties in balancing the rights of the individual versus those of society and states that ethical codes "have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society...." It notes, however, that "in balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight."²⁸

The calculus of such balancing will be different in different sociocultural settings. In some situations, cultural expectations may be that the anticipated benefit to society will justifiably outweigh the anticipated risk to the individual. Societal values may be such that the interests of the subject do not take precedence over the interests of society. Thus, furthering the interest of society at large may not necessarily compromise the rights and interests of the individual research participant within the particular value system the individual espouses. Even more fundamentally, an African may perceive that it is "difficult to see how the interests of the subject conflict with the interests of the society except, of course, if the society is not his own."²⁹ That is, the interest of the subject and of society are necessarily congruent. Problems arise only if the values and expectations of a society of which the individual is not a member are imposed upon him. In this light, imposing Western ethical values upon African research subjects is inappropriate.

Considerations of beneficent treatment of research subjects are also modified by cultural and social concerns. In developing countries, resources are often so scarce as to force particularly difficult

decisions regarding allocation.³⁰ Moreover, assessment of the acceptability of a particular medical intervention will differ in developed as compared with developing countries as a result of different patterns of illness and different medical and practical constraints acting upon the population. Risk/benefit assessments may yield different outcomes, and hence different acceptabilities, depending on the society.³¹ AIDS may be so widespread and deadly a disease in Africa that a higher degree of research risk must perforce be tolerated to deal with the problem, and this may well be socially sanctioned.

But while greater risk may be tolerated in Africa, this does not mean that Westerners should indiscriminately benefit from research conducted in Africa if Africans are systematically subjected to excess research risks with the prospect of deriving but little benefit. This would violate the principle of justice. This principle involves a sense of "fairness in distribution" or "what is deserved," and as applied to human subjects research is usually taken to address the question of who should receive the benefits of the research and who should bear the burdens.

Under the principle of justice, research subjects should be chosen "for reasons directly related to the problem being studied," and not "because of their easy availability, their compromised position, or their manipulability."³² Thus, the practical concerns that make an AIDS vaccine trial easier to conduct in Africa do not alone constitute sufficient justification to use Africans as subjects. Only the scientific concerns related directly to the problem of establishing the ability of a vaccine to prevent HIV infection are relevant.

The principle of justice also requires that those who stand to benefit from the research should, in fact, be those to bear the burden. Much of the world stands to gain from the development of an effective AIDS vaccine and the burden of research risks should therefore be fairly distributed, as should the benefits. In Central and Western Africa much of the population at large stands to gain by introduction of an effective vaccine. Yet economic constraints may well prevent even moderately extensive distribution of a beneficial vaccine in Africa, should one become available. The benefits to Africans are thus only hypothetical unless there is a financial commitment by the developed world to provide the vaccine. In this light, it would be frankly unethical to subject Africans to a disproportionate share of the research risks. A contingency of any trial of an AIDS vaccine in Africa by Western scientists should thus be to provide access to the technology once it is developed—possibly in the form of free or subsidized vaccine.

Research Ethics in the Face of a Pandemic

Conduct of research throughout the world on a pandemic disease—which perforce occurs in disparate sociocultural settings—forces reevaluation of a uniform, international view of research ethics. The straightforward application of ethical standards across cultural barriers is problematic.³³ Confronting AIDS will require a rethinking of a narrow, parochial formulation of ethics.

This is not to assert that standards for research ethics should be culturally relative, but rather that they should be culturally *relevant*. Some ethical standards can and should be met worldwide. An important challenge to Western scientists conducting AIDS vaccine trials is to conform to certain minimum ethical standards regardless of the setting: 1) The trial should be of suitable design and scientific merit; 2) it should involve the free, and, where possible, informed consent of the participants; 3) all participants should benefit from proper counseling regarding avoidance of risky behaviors; 4) due consideration should be given to the risks of research participation, using the highest standard of risk/benefit analysis possible; and 5) the countries participating in the study should be allowed fair access to any vaccine arising from the research.

An equally important—and possibly more difficult—challenge to investigators conducting AIDS vaccine trials throughout the world is to be culturally sensitive. Proper conduct of an AIDS vaccine trial must be informed not only by the epidemiology and biology of HIV infection in different settings, but also by the ethical norms and cultural constraints prevailing in such settings. Beyond certain minimum standards, there should be tolerance of variability. Variability, as we have seen, is especially apt to arise in the informational content of consent, in the acceptability of proxy consent, and in the tolerance of an increased risk/benefit ratio.

What is essential is not that the research meet the same ethical standard worldwide. What is essential is that the research manifest a culturally sensitive and ethically sophisticated concern for the wellbeing of subjects throughout the world.

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