

Ethical issues in HIV vaccine trials in South Africa

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IN THIS REVIEW WE DESCRIBE THE ETHICAL issues central to local and international debates about HIV vaccine trials. These issues include the physiological and psycho-social risks of trial participation, the preventative interventions to be provided to participants, access to treatment for participants who seroconvert, access to an effective vaccine after the trial, the role of placebo-controlled trials, and obtaining informed consent.

Background

About 30 HIV vaccine initiatives at various stages of development are in progress internationally, and a local vaccine may be ready for testing in clinical trials within the next two years. The trials will probably run over three or four years before conclusive results become available. Local work on vaccines against HIV is described in articles in this issue¹⁻³ (see refs 4-15 for studies conducted elsewhere). The main approaches to vaccine development are summarized in Table 1.

Initiated by international regulatory and advocacy groups, preparatory work began several years ago to identify, debate and start investigation of the ethical issues arising from vaccine development, and organizations like UNAIDS have focused on ethical considerations specific to HIV vaccine trials.

Behavioural issues in South African HIV vaccine trials

Behavioural issues are central to preparing vaccine sites and trial procedures. Thorough assessment is needed of the willingness and readiness of the role players and sectors to be involved directly or indirectly in such trials. The main sectors include communities from which participants are likely to be drawn, national and provincial health ministries, researchers, advocacy groups, funders, brokers and the media. Sexual and other risk behaviours of participants during the trials have to be reliably measured, so as to

control for the possible impact of such factors on trial outcomes.

Vaccine trials may be alien or unwelcome concepts in communities from which participants for trials are drawn. A counter-view posits that, since other forms of immunization and vaccination are already so widespread, HIV vaccine trials may be perceived as extensions of familiar health protective practices. Community attitudes to other forms of vaccination could be surveyed and monitored as part of the preparation for HIV vaccine trials.

Science and ethics

It is widely acknowledged that science and ethics are closely connected, and that poor science is, in principle, unethical. Ethics and review boards routinely consider the scientific integrity of research proposals as part of the process of giving approval. Requests for people to participate in studies with little likelihood of producing meaningful results because

the theoretical basis, design or analysis is fundamentally flawed, are likely to be considered unethical. Such studies waste resources and may foster false expectations that have no possibility of being met, so, from this perspective, good science is a necessary component of sound ethics.¹⁶

Comparatively little is written about the reciprocal way in which sound ethics are a necessary component of good science. The ethical principles of autonomy, beneficence and justice are inscribed in research practices such as informed consent and the protection of confidentiality. These inscriptions tend to be approached as 'add-ons' to scientific procedures rather than intrinsic to them; as additional requirements necessitated by increased sensitivity to human rights in scientific and other spheres of life.

Evidence exists, however, that procedures in scientific investigations associated with ethical practices — including attitudes and the behaviour of investigators — can significantly affect scientific validity, and that in several areas sound ethical practices improve the practice of science. For instance, volunteering and participation are shown to increase through processes that clearly outline and explain the purposes and procedures of the study.¹⁷ Second, more honest disclosures are promoted through assurances and procedures for protecting the confidentiality of participants' responses.¹⁸ Clinical studies depend entirely on vol-

Table 1. HIV vaccine concepts.

Recombinant subunit vaccine

Vaccine produced by genetic engineering, simulating a part of the outer surface envelope or other part of the virus
First-generation subunit vaccines; gp160 and gp120 vaccines
Second-generation subunit vaccines; multiple subunits

Peptide vaccine

Synthetic protein, simulating HIV proteins and used to produce immune response to HIV; V3 loop peptide vaccines

Particles/pseudovirion vaccine

A non-infectious particle resembling HIV and containing one or more HIV proteins; liposomes and other virus-like particles

Live vector vaccine

Live bacteria or viruses, harmless to humans, are used to transport a gene that makes a specific HIV protein. Current vectors include vaccinia virus, canarypox, adenovirus, Venezuelan equine encephalitis virus, poliovirus, *Salmonella*, Bacille Calmette-Gurin (BCG)

Naked DNA or nucleic acid vaccines

Direct inoculation of genetic material that produces HIV proteins, envelope or core DNA

Whole-killed or inactivated vaccine

Live HIV that has been inactivated by chemicals, irradiation, temperature or other means to render it non-infectious

Live-attenuated vaccine

Live HIV that has had its disease-producing potential reduced or removed through the deletion of viral genes responsible for viral replication or disease; *nef/vpr/vpu*-deleted HIV

Prime-boost vaccine

Live recombinant vaccine (poxvirus or alphavirus vectors) plus a boost with a recombinant gp120/gp140 vaccine in various combinations

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untary participation. Participants who do not feel respected, or who are not confident that their interests are being protected, are less likely to volunteer to participate, less likely to adhere to intervention requests, less likely to return for follow-up and less likely to answer questions truthfully. Participant cooperation, therefore, and the way volunteers are treated, are essential for the scientific success of trials.^{19,20}

Because research is primarily motivated by scientific objectives such as developing or testing new knowledge, temptations may remain to subordinate the welfare of volunteers to these objectives, and treat human subjects as a means to an end.²¹ Research may also be motivated by financial gains where expediency obscures ethics. Ethical rules, therefore, typically emphasize the protection and promotion of participants' welfare in interactions between researchers and participants.

Biomedical ethical principles relevant to HIV vaccine research

Codes of biomedical research ethics are generally founded on three principles: autonomy, beneficence, and justice. Autonomy refers to an individual's personal liberty of thought and action, and is justified by respect for persons with the right to determine their own destiny. Autonomy gives research participants the freedom to deliberate and perform chosen acts, and allows for special measures to protect the interests of those whose autonomy is diminished.²² Beneficence refers to the moral obligation to minimize possible harms and actively to maximize possible benefits. It involves explicit consideration of benefit in relation to risk²³ and includes stringent obligations not to injure intentionally (sometimes expressed as the separate principle of non-maleficence). Justice refers to fairness in distribution and translates into an ethical obligation to ensure that the burdens and benefits of research are fairly and equitably distributed. Research participants are not to be exposed to a disproportionate share of the research risks without an equal share of the benefits.²⁴

These ethical principles guide decision making in research, and justify choice of action. Researchers keep information confidential, for example, because disclosing it might cause participants distress. Volunteers also have the right to determine autonomously the content and recipients of their information. Such principles often need balancing in complex ways.²⁵ Reward for participation, for

instance, may be a legitimate benefit, but should not be great enough to constitute undue influence that impairs autonomy. Furthermore, it is often difficult to recognize when the obligation captured in an ethical principle has been discharged, and to determine precisely to whom, and to which relationships, the ethical principles apply.²⁶

HIV vaccine trials must be started as collaborations involving many role players. Ethical principles apply to relationships at different levels. Within a particular community, acceptable informed consent procedures must be established, for example, where researchers are properly informed about participants' expectations, and volunteers are properly advised about the details of research participation.²⁷ Ethical principles should also apply to relationships between sponsors and participants, as in recommendations that sponsors assist with scientific and ethical capacity building in host communities.^{28,29} Ethical principles should govern relationships among communities, researchers and the media, through recommendations for authorization from communities for media releases about research taking place there. Most research to date has focused on micro-social ethical considerations of HIV vaccine trials and has largely neglected ethical issues at the macro-social level. Following demonstrations by public-health research of the importance of recognizing distinctive stages in health interventions, ethical principles should apply at all stages of vaccine trials. Informed consent for participation must occur at the pre-recruitment stage as well as for subsequent testing and participation, for instance, and not be a 'once-off' at the start of a trial.

There is considerable debate as to whether ethical principles are universal or relative. Because morals are social constructions, ethical standards can vary from culture to culture. Ethical principles were propounded, however, to restrain biomedical research wherever it occurs. They are therefore specific to the activity, not the setting, and should apply worldwide,²⁷ though researchers are called to implement such principles with sensitivity to local cultural and ethical expectations.³⁰ HIV vaccine trials, therefore, must include mechanisms for ongoing dialogue of ethos and ethics — where 'ethos' refers to established customs and practices that are informed by culture, and 'ethics' refers to ethical principles that apply universally. Plans for HIV vaccine trials must include procedures that acknowledge local cultural norms and

ethical expectations. To illustrate, first-person consent must be sought from research participants drawn from African communities, augmented, where possible, by support and endorsement from marital partners and community leaders.²⁷

International ethical guidelines relevant to HIV vaccine research

Since the first code of ethics for research involving human subjects was drafted in 1947,³⁰ the Declaration of Helsinki in 1964, and subsequent revisions by the World Medical Association, have attempted to expand and explicate the rights of human research subjects.³¹ The WHO and CIOMS²⁸ drafted guidelines to deal with transcultural research and inequalities. While ethical guidelines must respond to changing realities,³² elements of these guidelines have provoked criticisms³³ that have extended to the development of guidelines for HIV vaccines.^{34,35}

The recent UNAIDS code of ethics²⁹ specifically deals with international vaccine trials for HIV. Its 18 guidance points address the anticipated ethical issues, and sketch broad recommendations. They require further operational elaboration, and then implementation, by combined teams representing sponsors, investigators, host government and community representatives. This document attempts to make more explicit and consistent the ethical reasoning underlying the guidance points, thereby increasing its educational value.

Human rights and HIV vaccine trials

The philosophy of inalienable birth or human rights has been translated into international documents such as the 1948 Universal Declaration of Human Rights and, in many instances, into law. South Africa's Constitution contains a Bill of Rights outlining every individual's right to dignity, life, equality, privacy and access to health care services. This Bill has led to changes in the treatment of disease, and increasing acceptance that human rights and public health programmes have common goals.³⁷ Human rights questions have been raised most particularly in the context of HIV/AIDS, where affected people suffer extensive stigma and discrimination. Promoting human rights protects the inherent dignity of persons affected by HIV/AIDS, and is necessary for achieving the public health goals of reducing vulnerability to HIV infection, lessening the adverse impact of HIV/AIDS on those affected, and empowering individuals and communi-

ties to respond to the epidemic.³⁸

Much HIV vaccine development work will take place in under-resourced communities, where people are at high risk of HIV infection, so the human rights implications for participants and other members of the community need careful consideration in issues of resource allocation to HIV vaccine development, the protection of trial volunteers from the risks of participation, and access to a successful vaccine.

Vaccines form a very small part of the international pharmaceutical market and vaccine development for years lacked adequate funding or support, so organizations like the International AIDS Vaccine Initiative (IAVI) took up the development of an HIV vaccine as a human rights issue of pressing ethical concern.

Review of debates in HIV vaccine development

Risks of participation in HIV vaccine trials

Participation in HIV vaccine trials presents significant risks. Physiological risks for individual participants include the chance of developing:

- rapidly progressing or established infection if a vaccinee is subsequently exposed to HIV;²⁹
- serious infection if a participant has undetected HIV infection and is vaccinated;³⁹
- mild or severe adverse reactions to the vaccine itself;⁴⁰
- immune tolerance that may affect the capacity to receive a more effective vaccine developed in the future;⁴¹
- injuries due to research-related activities, as well as repeated injections and associated pain or malaise.²⁹

Psychosocial risks for individual participants include:

- inconvenience and participation fatigue associated with lengthy research;
- anxiety induced by repeated HIV testing;
- stress caused by exposure to culturally unusual medical and research concepts;²⁹
- attendant discrimination accorded to individuals perceived to be at high risk of HIV infection;
- vaccine-induced seropositivity on conventional screening methods and associated negative consequences, such as the potential for discrimination in employment, insurance and health care;⁴¹
- raised expectations of gaining immunity to a deadly infection⁴⁰ or speedy access to an effective vaccine;

- a false sense of security leading to increase in risky behaviour;⁴²
- stress between partners as a result of the participation of one partner in a vaccine trial.²⁹

Risks to the community from which participants are drawn include:

- the stigma that may attach to them from the manner in which they are portrayed in the popular press and scholarly journals;
- vulnerability to exploitation by research groups from the West and within their own countries, due to prevailing conditions including impoverishment, inadequate health care and lack of familiarity with research methods.^{22,29,43}

The beneficent treatment of participants requires measures to minimize potential harm. Accordingly, research protocols must specify the nature and probability of potential harms and specify the means by which they will be offset. Recommended means include providing participants with:

- documentation indicating that their seropositivity on conventional screening methods is related to research participation;²⁹
- access to counselling, support groups, and legal advice;
- differential antibody testing by the sponsor;⁴⁴
- ombudsmen who can intervene on their behalf with outside parties such as insurance companies;
- compensation for social or economic harm.²⁹

The potential for community vulnerability can be offset by measures including:

- scientific and ethical capacity building;
- early and sustained involvement in vaccine development programmes²⁹ through, for example, community advisory boards;
- informing the community about the results of the trials, and community involvement in the publication of such results, particularly with regard to the identity of the sample community;
- establishing how the law will protect individual human rights at the recruitment stage, and proposed measures for protect participants from abuse and discrimination.

Preventative interventions to be provided to trial participants

Volunteers are selected for participation in Phase III HIV vaccine trials because they are at risk of HIV infection.⁴⁰ Beneficence obligations simultaneously apply to investigators to reduce harm to these volunteers. Vaccine efficacy trials require

seroconversions in participants, yet effective prevention methods may decrease sero-incidence.¹⁷ This moral predicament for researchers must be explicitly and publicly resolved,²⁴ especially given that the basic premise of a vaccine trial is the inevitability of infection for a proportion of participants despite preventative interventions.⁴¹

There is general agreement that trial participants should have access to barrier methods, treatment for STDs, and risk-reduction counselling.^{29,45} The debate centres on the intensity, quality and quantity with which these should be provided, and which party is most suited to provide them. UNAIDS²⁹ recommends 'appropriate' levels of preventative intervention, and a plan for monitoring the adequacy of such interventions, to be decided by relevant stakeholders. Risk reduction programmes should focus on specific patterns of risk behaviour in the gender and age groups targeted for participation, and be integrated into locally existing services, where possible, to ensure sustainability.¹⁷ Preventative interventions through impartial counsellors independent of the scientific team, while not forcefully recommended by UNAIDS,²⁹ are also crucial.

Level of treatment to be provided to trial participants

The treatment available to trial participants who seroconvert during the course of the trial has attracted the most controversy locally and internationally. Access to antiretroviral medication, not routinely available in many countries outside of private care for the more affluent minority, is central to this debate. Ethical considerations relevant to treatment for trial participants include global equity for participants in HIV vaccine trials and sponsor obligation to provide care and treatment according to their resources.²⁹ Scientific caution is based on the manner in which antiretroviral treatment would compromise measures of vaccine efficacy in preventing disease and reducing viral load.³² Proposed responses include:

- (1) taking at least one viral measurement from participants who became infected prior to providing treatment,⁴⁶
- (2) delaying treatment until viral load can be determined at specific intervals,³⁷ or
- (3) specifically recruiting volunteers from developing countries unable to provide antiretroviral drugs to vaccine trial participants.³⁷

The latter two options are clearly an ethical problem.

It has been argued that providing the highest standard of treatment (including antiretrovirals) fulfils ethical obligations most faithfully. In resource-poor communities, however, where individuals do not have routine access to such treatment, the availability of drugs solely through participation in a trial is likely to constitute undue inducement. Participants have the right to receive direct benefits as a result of their participation, but it is not easy to determine what is an acceptable treatment package that constitutes a benefit for participants without exposing them to undue coercion.²⁴ The level of treatment provided must also be sustainable beyond the end of the trial, so that participants are not compromised.⁴⁴

Debate has focused on whether treatment should be offered at the level available in the sponsor country (including antiretroviral therapy), at the level available in the host country, or at a level decided upon by the host.³⁶ Sanctioning treatment provision at the level available in the host country may effectively consign participants in resource-poor countries to inadequate treatment or even no treatment at all.³⁴ The UNAIDS guidelines²⁹ present all three as possible levels of treatment, but assert that account must be taken of the higher standards and additional resources brought in by the sponsor.²⁹ Participants are not, therefore, to be consigned to poorer standards of treatment than could reasonably be provided for them as part of the research protocol.⁴⁷ Deliberations should involve multiple relevant parties.²⁹ The UNAIDS guidelines provide detailed criteria, and suggest including some or all of the following options: counselling, treatment for STDs, prevention and treatment of opportunistic infections, palliative care, home-based care and antiretroviral therapy.²⁹ The following package has been suggested as appropriate for South Africa: pre-, post- and ongoing counselling, basic screening to detect disease and immune status, effective prevention and prophylaxis, and treatment for common morbidity.⁴⁵ Benefits must be balanced, but not operate as inducements to volunteers.

Use of placebo-controlled trials

Concerns have been voiced at the lack of benefit that accrues to control arm volunteers from being randomized to placebo.⁴⁴ It has been recommended that such volunteers be provided with a vaccine of proven effectiveness against another disease³⁶ as may be appropriate for the population. Guidelines state that it

is ethically acceptable to use placebo controls when there is no proven effective preventative method. It is difficult, however, to establish the level of efficacy to warrant replacing placebo with the 'effective' vaccine in the control arm of a trial. If a vaccine is proved to be only marginally effective against HIV, should it replace placebo in the control arm even if this were to undermine measurement of the efficacy of a more promising candidate vaccine?³² Controversy has arisen about the conditions in which placebo-controlled trials would be acceptable if an effective vaccine were available. If a host country has not adopted a vaccine that had proved effective elsewhere, would it be justifiable for a host country trial to use a placebo control arm?³² Current guidelines attempt to outline conditions that may compel the continued use of placebo despite the availability of an effective vaccine.²⁹ It has been argued that reliance on randomized placebo-controlled trials undermines alternative study designs that could provide efficacy data whilst subjecting the fewest number of subjects to the hazards of placebo conditions.⁴⁴

Access to the vaccine post-trial

Access to a demonstrably safe and effective HIV vaccine finds ethical justification in both justice and beneficence obligations. Access is also a critical human rights issue involving complex questions of equity and global availability of appropriate health care. Regional forums have had debates about which groups should have access — trial participants (especially placebo recipients), the community from which they are drawn, high-risk groups residing in the host country, other inhabitants of the host country — and about mechanisms for ensuring such access. UNAIDS guidelines²⁹ recommend that:

- any HIV vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials, as well as to other populations at high risk of HIV infection;
- epidemiological investigations to identify groups most at risk;
- plans be made at the initial stages of HIV vaccine development to ensure availability of benefits.

Despite constraints to detailed early assurances (such as inadequate knowledge of vaccine effectiveness and costs of production) early declarations of commitment are not precluded.⁴⁴ Commitments should be captured in writing.³⁴

Informed consent

Informed consent has been an ethical foundation of medical research for the past half century, and has also been recognized as central to HIV vaccine trials. The subject is reviewed in the article by Lindegger and Richter in this issue.⁴⁸

Concluding remarks

The specific risks for the South African context remain to be articulated, and consensus on potential benefits (such as access to treatment, preventative methods, or to the vaccine) that are appropriate for our circumstances is still to be achieved. These efforts must predate attempts to specify the informational components of consent. It will be necessary to establish strategies and procedures that allow each individual and community to choose the balance of risks and benefits that they are willing to accept for themselves.²⁹

The South African AIDS Vaccine Initiative (SAAVI), launched in 1999 with funds voted by Parliament and the private sector, most notably Eskom, supports the development of a South African vaccine by 2005. Local investment in the vaccine stems both from the distinctive clade and type of HIV found in southern Africa, as well as from the complexities of drug patents and subsequent affordability in developing countries. SAAVI has awarded R7 million to local vaccine initiatives in three categories: the development of specific candidate vaccines; vaccine advocacy and education; and ethical issues in conducting vaccine trials.

The last award was made to a multi-disciplinary team under the auspices of the School of Psychology at the University of Natal (Pietermaritzburg), comprising four psychologists, an ethicist, a virologist, and lawyers expert in human rights and medical jurisprudence. The HIV AIDS Vaccines Ethics Group will research the ethical aspects of HIV vaccine trials (including the ethical expectations of participants and their communities, motivations for trial participation, and expectations of benefits from participation), and aims to facilitate debate about local ethical issues, set up training processes for the various groups involved in HIV vaccine trials, and develop guidelines to assist in the practice of ethically sound HIV vaccine trials.

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HIV prophylaxis: are South African health-care students being neglected?

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SOUTH AFRICAN HEALTH-CARE WORKERS are at high risk of occupational HIV exposure, illustrated in part by the high general HIV prevalence. This, in turn, highlights the plight of health-care students already burdened by the very nature of their training. HIV should be recognized as a medical education issue of critical importance and medical educators must advocate strongly for a national policy on HIV prophylaxis, applicable to all training institutions.

HIV prophylaxis

The concept of prophylaxis is not a new phenomenon recently devised to cope with the infectious diseases of the last few decades of the 20th century, nor should it be seen as exclusively chemical or biological. Prophylaxis has been successfully applied throughout human medical history and anti-microbial therapy is well known amongst the infectious diseases armamentarium.^{1,2} Human immunodeficiency virus (HIV) post-exposure prophylaxis is a reality and the first international guidelines recommending antiretroviral drugs for this purpose appeared in 1990.³ The use of antiretroviral agents in HIV post-exposure management evoked controversy from the initial recommendation; however, recent data have come out strongly in its support.⁴ Thus it can now be readily accepted and reasonable to expect most health-care professionals in South Africa to know what to do, what to take, or what to prescribe, in the event of occupational exposure to HIV.

South Africa is a violent society in which the reported incidences of sexual offences and rape cases are on the increase.^{5,6} This societal problem has been covered extensively in the media. An editorial comment in the *South African Medical Journal*, in August 1999, highlighted additional problems, namely:

- that HIV post-exposure prophylaxis is considered neither harmless, nor cheap,
- that there are significant side-effects and toxicity problems associated with

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