RESPONSE

Addressing ethical concerns in the Indian HIV vaccine trials

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Ethical practice requires that researchers should ensure the safety and welfare of participants, and protection of their rights.

Vaccines are considered the most cost-effective prevention tools for infectious diseases such as acquired immunodeficiency syndrome (AIDS) where behavioural change may not always be successful. There are some advocates of a therapeutic vaccine (1), but in view of the relative success of antiretroviral therapy (ART) in suppressing viral load and opportunistic infections, and in improving the quality of life, it is difficult to imagine how therapeutic vaccines would work better—though they might act as an adjunct to ART. Further, recognising the limitations of secondary prevention, an ideal public health prevention strategy should focus on primary prevention directed at a much larger vulnerable population.

Even with increased financing for HIV/AIDS prevention and treatment, the AIDS vaccine effort remains grossly inadequate (2). Nevertheless, there is a global endeavour for the development of AIDS vaccines.

AIDS is a chronic, currently incurable and inevitably fatal disease that carries social stigma. Ethical concerns in AIDS vaccine trials are related not only to the nature of the virus, but also to the social stigma (3). They focus on the physiological and psychosocial risks to trial participants, issues related to informed consent, and complex trial design, access to treatment within a trial and access to an effective vaccine afterwards (4). The research must have high social value and scientific validity, and should be conducted fairly and with appropriate independent review. People from the target population should be included in decisions on the design and implementation of the trials (5). Further, when research is conducted in developing countries, it must be based on true partnerships and respect for local investigators, participants and the community (6).

Undertaking HIV vaccine trials in developing countries

The AIDS epidemic in some developing countries in Africa and Asia has led to an eagerness to initiate AIDS vaccine trials. Trials may be initiated even with economic constraints, sub-optimal infrastructure and technical capacities, low levels of awareness among politicians and the community, inadequate experience on protection of human rights and limited access to health care (7). Policy-makers, programme managers, researchers and the community should decide to initiate a vaccine trial only after carefully reviewing the level of programmatic, scientific and community preparedness in the host country.

Ethical review of research

There are international guidelines for ethical conduct of research and clinical trials. Although international trials are sometimes reviewed by international ethics committees (ECs), ethical review has to be done in the country hosting the trial (8). The Indian Council of Medical Research (ICMR) has published a set of guidelines for biomedical research on human subjects that are on par with other international guidelines (9) and will be applicable to Indian HIV vaccine trials.

Ethics committees reviewing research must examine the safety and protection of vulnerable human participants, value of the research, appropriateness of the methods, balance of the risks and benefits, and arrangements for taking voluntary, informed consent from participants. They must ensure that research is not restricted to specific populations, is inclusive of future beneficiaries and that local regulations are followed.

The guidelines of the International Council of Harmonization on good clinical practice in research recommend that the ECs should provide public assurance that research participants are protected (8). Other international guidelines note that local ECs must focus on questions such as whether the researcher is suitably qualified, the research environment is appropriate, facilities are available, and information is provided in the local language (10).

The process of informed consent

The ethical guidelines of the Council for International Organizations of Medical Sciences (CIOMS) require that ethical standards governing human subject research be

no less stringent in developing nations than in developed nations (11). This can be difficult if the levels of literacy are lower, understanding about the nature and causation of diseases is sub-optimal, and personal identity and individuality are not considered important (12–13).

The following information must be made clear to potential participants of a clinical trial:

1. They are being asked to participate in a research study to test a vaccine against HIV.
2. They have the right to refuse to participate or withdraw at any time without losing the benefit at the trial site.
3. They will need to commit to a specified number of visits involving certain procedures and collection of specimens.
4. The vaccine being tested is of an experimental nature with no proven safety and efficacy in humans.
5. In a placebo-controlled trial, they may receive a placebo. In a blinded trial, they will not be aware of what they receive
6. They may experience some expected and/or unexpected side-effects of the experimental vaccine.

Potential participants should also be told about the kind of care that would be provided to them during and after the trial, and steps that would be taken to maintain confidentiality, with details of who would have access to trial-related data.

Informed consent of competent potential participants must be taken without fraud, inducement or coercion. Investigators should document informed consent, which may be subject to both external and internal monitoring, and audit.

Researchers must also confirm that trial participants have understood the information given to them. In the case of AIDS vaccine trials, they must understand that the vaccine is experimental and not yet proven to be protective, and hence they must always practice safe behaviour. Comprehension tests can range from multiple choice tests to essays and oral questionnaires. Community advisory boards can advise on the appropriate method in a particular population.

Use of placebo controls

There are generally no concerns about the use of placebos when testing interventions for conditions that have no proven treatment or prevention effect. There is an overall agreement that trial participants who received a placebo in the clinical trial of a vaccine should be offered the vaccine once it is licensed.

Inducement

It is universally accepted that subjects may be paid for the inconvenience caused to them, the loss of wages and the time spent, and they should be reimbursed for expenses incurred in connection with their participation in research. They may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgement and wishes.

Standard of care for trial participants and treatment of those who get infected with HIV

Though trial participants will be counselled to engage in safer sexual practices, initial test vaccines are not likely to be 100% effective. There will be a predictable and unavoidable incidence of HIV infection among vaccine recipients. There will be infections among those in the control arm who practise risk behaviour despite counselling. There are different views on researchers' responsibility to provide treatment in such situations. These range from providing the 'best proven treatment' to 'the prevailing standard of care available in the host country'. Antiretroviral drugs are expensive, their availability is limited, and need to be taken lifelong. Among the ethical questions to be considered is: When the intervention being tested is a vaccine and not therapy, are sponsors or investigators ethically obliged to provide treatment? (7) Requiring provision of the best treatment available globally can undermine biomedical research aimed at improving global health (14, 15). On the other hand, in many developing countries, the prevailing standard of care can be equivalent to no care at all.

If ethics demand that treatment be given to individuals infected with HIV in vaccine trials, should vaccine trials be conducted in developing countries if the cost of therapy is prohibitive? Will a decision to provide the best available therapy constitute unreasonable inducement? If ART is initiated, should the commitment be for the duration of the trial, for a specified time after the termination of the trial, or for life? There are no definitive answers. The CIOMS guidelines state that provision of services beyond those necessary for research, including treatment of an infectious disease contracted during the trial of a vaccine against that disease is not required but is 'morally praiseworthy' (11).

Provision of insurance and ART for a stipulated period has been advocated by many (16–18). Developing countries hosting a vaccine trial should have a clear policy on these issues. They should negotiate the required arrangements with the trial sponsors and share some responsibility as well. If researchers and sponsors cannot

make adequate commitment for treatment and care, this should be clearly explained during the informed consent process.

Compensating for injury

International ethical guidelines require that participants be compensated for research-related injuries since they put themselves at risk in these trials. Although there is often a provision for compensation for physical injuries, non-physical injuries or 'social adverse events' such as loss of a job, housing, income, insurance, medical care or reputation, often cannot be materially compensated. Further, provisions for survivors in case of uncommon events such as a participant's death (likely to be a rare event in a vaccine trial) need to be delineated in the trial protocol. The CIOMS guidelines suggest that financial or other assistance should compensate participants and the survivors equitably for any temporary or permanent impairment or disability related to the trial (11).

Potential participants should be aware of the provision for compensation in case of physical injury, and the circumstances in which they or their dependants would (or would not) receive it.

Post-trial access to a vaccine

There is a general agreement that any vaccine, which is proved effective, must be made available to the populations in the countries where the trials are conducted at an affordable cost. However, two questions arise: How can accessibility be ensured and how broadly can the product be made available? Should access be limited to those at risk for acquiring the infection or be extended to the general population? Even before initiating the trial, the host countries should review their economic and political mechanisms, and their infrastructural abilities to determine if they can ensure such access. Some strategies to ensure availability of vaccines to populations that need them the most are financial rewards to enable manufacture, technology transfer and negotiation of intellectual property (7).

Conducting HIV vaccine trials in India

Sustained advocacy at the socio-political level is needed to prioritise resources for development and testing of HIV vaccine in India. The community must be informed and involved for success of the trials. Acquiring truly informed consent will require engagement of the communities in which the trial has to be done (18). The trial will be influenced by stigma, illiteracy and gender norms. For example, members of our Community Advisory Board stressed that involvement and concurrence of men would be needed for married women to participate.

While India is on the verge of initiation of Phase I HIV vaccine trials, there will always be questions about the ability of Indians to make informed decisions to participate in vaccine trials, the use of vulnerable populations, quality of the regulatory infrastructure, safety monitoring mechanisms and transparency (1). It is important that the government, researchers, sponsors and the community have a clear understanding of how various ethical issues related to the HIV vaccine trial will be addressed in the upcoming trials.

In India, trials involving investigational products come under the purview of the Office of the Drugs Controller General of India. The ICMR approves biomedical research and also convenes a national EC for ethical review of all protocols of national importance, and local institutional ethics committees also provide their approval. These bodies should ensure that information sheets and consent forms are appropriately designed with in-built mechanisms for the research team to verify comprehension by the research subjects. The study materials should be simple, adequately explanatory and informative. It is important to involve the community from the beginning in the whole process. To ensure transparency, the mass media should be closely involved. Community members and potential volunteers need to be fully informed about the vaccine trial process, the use of placebos, randomisation and blinding. This could be done through peer educators (19).

Lengthy documents, such as consent forms, requiring signatures might be viewed with suspicion in India. Every consent form ends with a disclosure statement which states that the purpose of the research, risks and benefits, information related to procedures and rights of the participating individual have been explained to the participant, that questions or doubts have been cleared and he or she is willing to participate in the research study of his or her own free will. This is followed by signatures of the participant and a witness. While this signifies protection of individual autonomy, it also makes assumptions about people's legal status, literacy and capacity to comprehend medical information. In India, people often equate signatures with legal documents. Therefore, it might be necessary to develop pictorial or audio–visual consents to facilitate the informed consent process.

In a traditional society with overall low levels of awareness, trial participants may be considered at 'high risk' of AIDS and thus face discrimination (20). Researchers should ensure that participants of a vaccine trial are protected from such harm by disseminating information and keeping in touch with the community.

Participants of a vaccine trial will need sustained risk-reduction counselling, which is a scientific and ethical requirement. Sensitive monitoring of trial participants' behaviour would ensure adequacy of counselling procedures (21).

A major challenge, if the vaccine proves effective, is to set up mechanisms to ensure a sustained supply of the vaccine to the population. Fortunately, India has the expertise, and the biotechnological and pharmaceutical infrastructure to make this happen with the support of trial sponsors. Some Indian industries, with a proven track record of vaccine manufacture, have been recently involved in discussions to explore the possibility of their manufacturing the HIV vaccine, if it proves to work.

The government will have to take decisions on post-trial care and providing ART to trial participants thoughtfully and with caution because decisions once made need to be adhered to in future larger trials as well. Merely talking about global access does not help. In spite of the major research achievement of ART, these drugs are not easily accessible in resource-poor countries. In view of the proposed Indian AIDS vaccine trials, this issue was discussed in a national consultation involving public and private agencies. There was a consensus that a corpus fund should be raised for the purpose and the sponsors, government and society should make contributions. There was also a consensus on sponsors supporting trial-related injuries and on exploring the possibility of providing insurance to cover injuries occuring during the trial. The mechanism to decide the causality of lasting injuries and to address disagreements through an arbitration board has been defined in the context of the upcoming HIV vaccine trial in India.

It is necessary to establish a national HIV vaccine policy outlining a vaccine development plan, an operational plan and an action plan to steer the country from Phase I to Phase III of the clinical trials and beyond.

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