

Ethical considerations in AIDS vaccine trials

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The Joint United Nations Programme on HIV/ AIDS (UNAIDS) estimated (1) at the end of 1998 that around 33.4 million people were living with Human Immunodeficiency Virus (HIV) infection all over the world, over 90% of them in developing countries. However, in developing countries, promising newer therapeutic options for HIV/ AIDS are unaffordable, and prevention through behavioural change has not been successful due to illiteracy and low level of awareness. On the other hand, prophylactic vaccination has shown remarkable success in the control of many communicable diseases. Therefore global efforts are ongoing to develop vaccines (3) to prevent infection among persons exposed to HIV (prophylactic) or prevent HIV-infected persons from progressing to AIDS (therapeutic vaccine).

Present status of AIDS vaccine trials

Developing a safe and effective AIDS vaccine has been a challenge due to lack of understanding of the correlates of protective immunity to HIV, the absence of an appropriate animal model, strain variation and difficulties in phase III evaluation of candidate vaccines (4,5).

Any new vaccine has to be evaluated at many levels: Phase 1: safety, Phase 2: safety and immunogenicity, Phase 3: large-scale trials for efficacy and Phase 4: post-marketing surveillance. Over 34 different HIV candidate vaccines have been tested in phase 1 trials and three in phase 2 trials (6). Difficulties in initiating large-scale efficacy trials of preventive AIDS vaccines include unanswered ethical issues regarding how such trials would be conducted, fear that trial failure would make successive trials impossible to conduct, and controversy among the scientific community regarding the usefulness of the available vaccines to protect against

HIV infection (7).

However, with the continued spread of HIV despite educational efforts, and evidence of the safety and efficacy of many products to elicit immune responses among vaccinees (8, 9), it is increasingly felt that Phase 3 trials of such vaccines are necessary. Therefore, despite an incomplete understanding of HIV pathogenesis and correlates of protection, large Phase 3 efficacy trials have been initiated in the US, Thailand and Uganda (10). Cohorts are also being established, and sites prepared for efficacy trials when appropriate vaccine candidates become available (8).

Deciding when and how to proceed to Phase 3 trials is often complex (6,11). Some scientists in developing countries are concerned about the deteriorating HIV/ AIDS scenario in their countries and the long time required to complete clinical trials in developed countries. They argue that as the beneficent intent in conducting vaccine trials is clear, trials could be initiated simultaneously in developing countries (12, 13).

There are several reasons to consider conducting trials of AIDS vaccines in developing countries (14, 15). A majority of HIV infections occur in developing countries where an effective vaccine will be most beneficial. The high incidence of HIV infection makes it easier and cost-effective to assess trial end-points. It is easier to assess vaccine efficacy of therapeutic vaccines among HIV-infected people who have not received anti-retroviral therapy. Different routes or co-factors in HIV transmission and the presence of various HIV subtypes may have a differential influence on vaccine protection in developed and developing countries.

To conduct an AIDS vaccine trial, the developing country must have a cohort with defined epidemiologic characteristics, and the technical and scientific capacity to perform clinical procedures and laboratory assays. But such a trial can also raise ethical controversies, as critics, investigators, volunteers, sponsors and regulatory agencies may have conflicting opinions, mandates and expectations. Open communication between the

organisations involved and the participating community can minimise this possibility (16).

Trial-related concerns

Participants may fear developing adverse reactions or HIV infection; a post-vaccination positive HIV test result and consequent discrimination; and problems in freedom of travel, insurance, employment and immigration. They may also worry that spouses or partners informed about their trial participation will stigmatise them. The participating community will ask if investigators can ensure adequately informed consent; if trial participants will face discrimination; and if they will receive post-trial benefits. Countries participating in vaccine trials will expect to discuss and approve trial protocols, that researchers will adhere to the highest scientific and ethical standards, that regulatory bodies will do periodic monitoring, and that the population will get substantial post trial benefits. Researchers can refer to various international ethical guidelines while planning AIDS vaccine trials (17, 18, 19, 20).

Ethical issues in the pre-trial phase

Before selecting a candidate vaccine, and deciding whether or not to initiate a vaccine trial, policy makers, experts and community representatives must have a national discussion on the trials' scientific justification, the clinical and laboratory expertise available and the community feasibility of a vaccine trial. Most current vaccines are based on subtype B of HIV-1. Testing subtype B based vaccines in countries where other subtypes are predominant raises ethical questions, though evidence of cross-clade immunity may justify such a trial. Separately, industries in developed countries may not be interested in developing non-B type of AIDS vaccines for countries who cannot buy them. Capacity-building efforts must therefore be made to develop vaccines in developing countries with the help of competent industries in developed countries.

Developing countries may ask if the

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vaccine has been tested in the country of manufacture. Why should the research be carried out in developing countries? The rationale for conducting the trial must be explained to the community. A network of community-based organisations, people living with AIDS, local medical practitioners, leaders and the media can ensure that the trial is in the community's best interest. It can help disseminate information on the proposed vaccine trials, clear doubts and ensure public support and participation in the proposed trial. Specific cultural, clinical and economic settings influence local ethical expectations and must be addressed while designing field trials (21). Qualitative research should be used to identify the community's fears, so that correct information can be provided in an ongoing manner.

Ethical considerations in an ongoing trial

All the fundamental ethical principles (22) — beneficence, non-maleficence, autonomy and justice — apply to AIDS vaccine trials. For the researchers, this includes ensuring that the study is in the participants' best interests; ensuring that all participants (24) give their informed consent without coercion or inappropriate inducement (19); using comprehensible and informative consent forms and procedures meeting international guidelines and also approved by the Ethical Review Board (ERB); and getting modifications of the protocol and the consent form re-approved by the ERB(23).

Participants should include all groups who may benefit from the vaccine, in particular those with a high incidence of HIV infection. Though children are not included in Phase 1 or 2 vaccine trials, it may be ethically justified to do Phase 2 trials on children (with their guardians' consent) if a therapeutic vaccine shows evidence of working. Most AIDS vaccine trials will enroll HIV sero-negative persons, which would necessitate a two-step consent procedure with initial consent and counseling for HIV testing and later for trial participation. Respect for local standards such as by taking permission of community leaders does not eliminate the need for individual

consent.

Investigators must clearly inform trial participants that the vaccine may not work, and provide risk reduction counseling for AIDS prevention. If there is a placebo arm, potential participants must be told about the placebo, and that they could receive either the vaccine or the placebo.

It is absolutely essential to safeguard the confidentiality of trial participants. Researchers' responsibility to maintain confidentiality (with coded forms and samples delinked from the participants' names) is particularly important in trials relating to HIV/AIDS. Maintaining confidential records may be complicated by the fact that since participants could develop complications in the long term, trial records may have to be preserved for an extended period.

Earlier, randomisation was equated with clinical equipoise — no arm in a trial is known to have an added benefit — making it impossible to test products with some favourable data in randomised clinical trials. This was later revised to suggest that randomisation could be ethical if there were overall uncertainty about the product's utility. Also, in the context of AIDS, behavioural factors and STDs are known to affect HIV transmission and only randomised controlled clinical trials can provide substantive evidence about vaccine efficacy.

Regulatory mechanisms

The Ethical Review Board, which includes experts in pharmacology, pathology, clinical medicine, social science and law (25), should not only review the research proposal but also guarantee that the trial proceeds according to plan and fulfils ethical requirements. The Scientific Advisory Committee's review should cover issues such as the need for the trial, capability and infrastructure at the site, choice of candidate vaccine, methods and appropriateness of selection of subjects, plan for recruitment and retention, mechanism for reporting and management of adverse events and quality control procedures. The Data Safety and Monitoring Board, which may include some trial participants, should periodically review performance reports, protect participant

safety, define criteria for vaccine or trial failure, for which it has the authority to stop the trial. The Community Advisory Board, composed of local workers and community representatives, should liaise between researchers and the community; advise on study procedure and consent and data forms in order to protect the community; play a significant role in community information and education, and help in recruitment and retention of study participants.

The post-trial phase

Once a vaccine is proved to be safe and effective, the vaccine trial sponsors and the host country are morally and ethically obliged to make a commitment for a continued supply of the vaccine in the post-trial phase. The community where the trial was done must either continue to receive the vaccine or be helped to develop the capacity to produce a sustainable supply of the vaccine. This point can be negotiated with the manufacturers before initiating the trial. International agencies can play a major role in this regard (26). Post-marketing studies and surveillance should be undertaken to consider the vaccine's inclusion in ongoing prevention and control programmes.

HIV-uninfected persons considering participation in a prophylactic vaccine trial will be anxious on finding out that as a result of the vaccination, they will always test positive for HIV. This can create problems of discrimination in insurance, travel, jobs and housing. To tackle this problem, those conducting HIV tests for insurance, employment, health care or other reasons should be made aware that HIV vaccines can cause false-positive HIV test results, and trial participants should receive documents confirming their participation in vaccine trials. Social risks and harms to trial participants should be monitored as seriously as physical harms(27).

Some researchers feel that if countries cannot afford to give three-drug therapy to vaccine recipients who develop breakthrough HIV infection, they should not take up HIV vaccine trials. Other researchers from developing countries feel that this is not financially sustainable; giving the three-drug regimen to vaccine trial participants in



a country where it is not otherwise available is unethical because it can be an undue incentive itself. One suggested option is to treat breakthrough infections with two drugs without a protease inhibitor. However, most researchers agree that therapy for breakthrough infections should be given for life and should be on par with the best standards of locally available care. The sponsors and ERB should ensure that such provisions are made and actually followed. However, it might be important to clearly explain to the participants that if they acquire HIV infection and if the vaccine fails, compensation can't be given.

Feedback: Adequate feedback must be given to the community in which the trial was conducted. This could be done through the Community Advisory Board. Effective communication is essential to ensure sustained public support for research.

Conclusion

According to India's Parliamentary Standing Committee on Dreaded Diseases, an estimated eight million people are infected with HIV(28). The Prime Minister has stated that developing an AIDS vaccine is a top national priority. A formal AIDS vaccine development programme in India will probably be implemented through the coordinated effort of the government of India (28). International agencies have stated that they will help strengthen vaccine development capabilities in developing countries (29). These efforts must be supported by advocacy for a clear governmental policy on AIDS vaccine development, identifying and training researchers for vaccine development and evaluation and testing, and public education for future community support to vaccine trials.

AIDS vaccine trials may soon commence in India. While we must ensure that the various codes of research are observed in such trials, research participants' protection ultimately depends on the ethics and commitment of individual investigators (30). Indian researchers should ensure that all future AIDS vaccine trials conform to the highest ethical standards.

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