
GLOBAL
PROGRAMME
ON AIDS

STATEMENT FROM THE CONSULTATION ON
CRITERIA FOR INTERNATIONAL TESTING
OF CANDIDATE HIV VACCINES

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Consultation on criteria for international testing of candidate HIV vaccines

A consultation on criteria for international testing of candidate HIV vaccines was convened by the World Health Organization's Global Programme on AIDS (GPA) from 27 February to 2 March 1989 in Geneva. A total of 39 participants from 17 countries attended the Consultation, including experts in virology, immunology, vaccine development, epidemiology, bioethics, and law and social science aspects of AIDS.

Introduction

The global strategy for the prevention and control of AIDS has three objectives: (1) to prevent transmission of the human immunodeficiency virus (HIV); (2) to reduce the personal and social impact associated with HIV infection; and (3) to unify national and international efforts against AIDS. The World Health Assembly and the United Nations General Assembly have called upon all countries to establish national AIDS prevention and control programmes in conformity with the Global AIDS Strategy.

The Global AIDS Strategy recognizes that immunization represents one of the most effective approaches for the control of infectious diseases, and that a vaccine capable of protecting against HIV infection would be the ideal prevention technology. However, the development and evaluation of candidate vaccines will raise a number of scientific, ethical, legal and social challenges, especially in an international context. Therefore, it is important to develop consensus on criteria for international testing of candidate HIV vaccines based on critical analysis of our present knowledge of HIV biology and our experience with previous vaccine development.

The consultation had the following objectives:

- (1) To review current state of HIV vaccine development, including basic laboratory aspects and ongoing human trials;
- (2) To review ethical, legal and social issues that would be involved in international field testing of HIV vaccines;
- (3) To reach consensus on the broad scientific and ethical criteria that would justify submitting candidate vaccines to the different levels of testing in man, when these are conducted in an international context;
- (4) To make recommendations to WHO/GPA on facilitating international collaboration in field testing of candidate vaccines.

The consultation developed the following consensus statement

A safe and effective vaccine is urgently needed to prevent HIV infections and AIDS, and its development should be considered a priority. Although it is recognized that such a vaccine may still be several years ahead, it is important to ensure that sufficient support is given now to planning for field evaluation to accelerate vaccine development.

Most of the current efforts put into vaccine development for AIDS are oriented towards the prevention of HIV infection. An alternative strategy would be the development of vaccines that prevent progression from asymptomatic HIV infection to disease. Although the benefits that could be derived from this latter approach are undeniable, a vaccine that prevents infection should be preferred from the public health point of view, because it would have a multiplying effect by interrupting the chain of transmission.

The term "candidate vaccine" will therefore be used throughout this document to refer to both vaccines designed to prevent HIV infection and those designed to protect against the consequences of HIV infection.

1. Research Needs

Current knowledge on immunity to viral infections implicates numerous effector mechanisms contributing to prevention of infection and subsequent recovery. In particular, antibodies which are highly effective at neutralizing infection and cytotoxic T-cells which kill virus-infected cells are considered important. Successful vaccines against viral diseases in man are known to stimulate one or both mechanisms. Those responses induced by live attenuated or non-infectious vaccines are polyclonal, and involve multiple antigenic sites.

In the case of HIV infection of man, current knowledge indicates that the viral envelope protein induces neutralizing antibodies, initially strain specific but becoming more broadly reactive with time. Cytotoxic T-cell (CTL) responses have been reported, which are class I HLA restricted and reactive with *env*, *gag* and *pol* proteins. Other aspects of cellular immunity to HIV such as lymphocyte proliferation, antibody-dependent cellular cytotoxicity and the role of complement are under investigation. While neutralizing antibodies and CTL responses occur after HIV infection in the majority of subjects, there is currently no definite evidence that these responses prevent progression of disease.

Based on current knowledge, most approaches to develop vaccines are based on antigens that elicit these immune responses. However, the Consultation recognized that knowledge on immunity to HIV is incomplete and experimental studies of antigenic and immunogenic responses with all HIV proteins should be given high priority in research programmes.

Potential obstacles to the development of a successful candidate vaccine are the high degree of viral antigenic variability, particularly in the envelope protein and the absence of a readily available animal model. In addition, there have been several reports of immune enhancement of HIV infectivity as detected *in vitro*, and possibly also of auto-immune type of responses. However, the significance of these findings with respect to infection, progression to disease and vaccine development is unclear. The Consultation recommended that further research to clarify the nature and *in vivo* relevance of these obstacles to vaccine development is a matter of priority.

The chimpanzee is a relevant animal model for HIV infection, but its significance as a disease model remains to be established. These animals are in limited supply and a costly resource. In addition, they are acknowledged to be an endangered species in their natural habitat. Studies with Simian Immunodeficiency Virus (SIV) in monkeys suggest that this is a relevant and useful model for infection and disease, and is fully discussed in the WHO report on animal models for AIDS¹. HIV-2 has also been shown to infect some monkey species, presenting a further opportunity for vaccine research and development.

1. *Animal models for HIV infection and AIDS: Memorandum from a WHO meeting* Bulletin of the WHO, 66 (5): 561-574 (1988).

The Consultation encourages the use of the SIV/monkey model and all other relevant animal models for evaluating vaccine strategies as a prerequisite to extensive clinical studies in man. The SIV/monkey model gives flexibility in the evaluation of imaginative strategies in vaccine design and the use of novel antigen presentations and adjuvants. In addition, vaccine development will be helped by the systematic collection and characterization of HIV-1 and HIV-2 viruses from diverse geographical locations at different points in time. The Consultation encourages the collection of such comparative data on virus variability.

2. Ethical, social and legal issues

The general guiding principles to be considered in the international testing of candidate vaccines against AIDS and HIV infection should conform to the Declaration of Helsinki as revised by the Assembly of the World Medical Association² and the Proposed International Guidelines for Biomedical Research Involving Human Subjects³. However, the development of candidate vaccines poses special ethical, social and legal considerations which require additional clarification and elaboration.

Whereas some of the issues are elaborated in this document, it is considered necessary to prepare more detailed international guiding principles for trials of candidate vaccines by specially constituted working groups with special reference to the needs and capacities of both developed and developing countries. In efforts to develop such guidelines the WHO should continue to play a leading role.

2.1 Ethics

The development of vaccines is pursued in stages that require decisions and judgements to be made based on scientific, practical and political factors, as well as ethical issues. It is not therefore possible to lay down a single formula for such decisions - they can only be made on the basis of circumstances prevailing at a particular time. For example, the issue of when to proceed to preliminary clinical studies of candidate vaccines in humans is now (March 1989) timely to debate, particularly since such trials have already begun in some countries.

There is continuing discussion on how work should now proceed. **However, AIDS vaccine trials should adhere to the three basic ethical principles of biomedical research in humans: beneficence, justice and autonomy.** Authoritative guidance on the application of these principles is in the aforementioned international guidelines. Following are the consultation's judgements on some specific issues not addressed explicitly in these guidelines.

Beneficence refers to the obligation to do no harm, with maximization of benefits and minimization of risks. Thus, the degree of confidence on efficacy should increase as one progresses from phase I to phase III. Moreover, one should establish in advance guidelines that will determine when there is sufficient confidence in efficacy to discontinue clinical trials and to recommend general use of the vaccine.

Justice requires equitable sharing, among the population, of the risks involved, and of the benefits that will derive from the research. The population in which the vaccine is tested is entitled to first priority in receiving the vaccine after its safety and efficacy have been established.

2 Declaration of Helsinki, adopted by the 18th Assembly of the World Medical Association (WMA), Helsinki, Finland, June 1964, amended by the 29th WMA, Tokyo, Japan, October 1975, and the 35th WMA, Venice, Italy, October 1983

3 A joint project of the WHO and the Council for International Organizations of Medical Sciences (CIOMS), Geneva, 1982.

Autonomy requires that subjects be treated with respect as free and independent individuals and that they be afforded opportunity to choose freely whether or not they will participate in research. Informed consent requires as a minimum a full disclosure of purposes, risks, benefits and alternatives. There must be clear statements of any limitations on the ability to protect confidentiality. While consent procedures must be adapted to accommodate cultural mores, there must always be a requirement for consent from the individual prospective subject. In groups such as military and prisoners, there is an especially strong need to assure subjects of their freedom to refuse to consent or to withdraw without prejudice. In certain circumstances, payment to an individual for participation in a clinical trial is compatible with autonomy.

2.2 Social issues

Vaccine trials for HIV infection and AIDS differ markedly from most other clinical trials in carrying significant associated risk of social discrimination or harm. Trial investigators should therefore consider the social risks associated with participation in vaccine trials before detailed planning begins. At all stages during the planning they should give equal consideration to the adverse social consequences and to the possible adverse medical effects of the candidate vaccine.

Social discrimination and/or harm can arise at a number of stages in a trial including volunteering to participate, receiving counselling prior to having an HIV antibody test, and subsequently becoming HIV antibody positive as a result of immunization.

Discrimination may spring from ignorance or prejudice, e.g., hostility from neighbours, difficulty in keeping or obtaining employment. In other circumstances, discrimination may come from organizations (e.g., insurance companies refusing life insurance) or authorities (immigration authorities of some countries refusing entry).

Strategies must be devised to minimize the social harm to HIV vaccine trial participants which may result from discrimination. These strategies are likely to include:

- a) Making it an essential condition of the trial that reliable laboratory tests are available to distinguish between immune responses due to vaccine alone and immune responses due to natural infection with HIV (or immunization followed by natural infection).
- b) Seeking assurances from bodies such as those representing the insurance industry, that they will accept evidence of the kind referred to in (a).
- c) Ensuring that, subject to appropriate safeguards, trial investigators are ready to provide information, in confidence, about any individual trial participant, to an outside body, at the request of the participant himself.
- d) Maintaining a confidential register of individuals who are participating in HIV vaccine trials, and documentation explaining their status with regard to HIV. Confidential ID cards should be offered to trial participants.
- e) Keeping all trial records for the lifetime of the participants, in an appropriately secure form.
- f) Considering the possibility of anti-discrimination legislation.

Counselling must play a role at all stages as part of the conduct of trials.

a) Before enrollment:

- Providing information about AIDS and HIV;
- Providing advice on avoidance of risk behaviour;
- Providing information about the trial and its aims and what will be required of participants;
- Ensuring participants understand the risk of social discrimination;
- Assessing eligibility to participate against predetermined criteria;
- Answering questions, helping individuals to address concerns.

b) During the trial:

- Being available for consultation by trial participants and their families and associates to discuss any new concerns;
- Acting as advocate in the event of social discrimination.

c) After the trial:

- Continued availability for consultation.

The counsellor, in conjunction with the principal investigator, will need to make a judgement about whether a potential participant has understood all the issues sufficiently to give fully informed consent to participate in the trial.

HIV-positive people not qualifying for trials should be offered the same kind of counselling as that offered to individuals testing positive in other circumstances.

Whenever possible, the effectiveness of counselling should be assessed during trials. Advice on methodology should be sought from appropriate experts at an early stage. Preparation for such evaluation could begin now.

Support for the avoidance of risk behaviour should continue during phase III trials. While this will reduce the incidence of HIV infection in the trial population, it would be unrealistic to expect it to be wholly effective so that some measurable rate of new infections will likely continue to occur in the study population.

2.3 Legal issues

There currently exists in some countries several bodies of law governing or effecting the testing, licensing, and regulation of candidate vaccines, and the rights and responsibilities of all those involved in vaccine development, investigation, and distribution, as well as those who are human subjects of research and recipients of a vaccine. In the case of candidate vaccines, existing law may provide somewhat less protection to vaccine recipients than may be considered appropriate according to ethical principles. At a minimum it will be necessary to ensure compliance with existing administrative, regulatory, contract, constitutional, insurance, criminal, and other law. In some situations, it may be desirable to consider enacting new laws or modifications where existing laws cannot be readily applied to protect vaccine recipients.

Among the legal principles of special importance to vaccine development and distribution are those governing the conduct of clinical trials and the requirements for vaccine licensure. It may be useful to review the duties and functions of research review committees in both sponsoring and potential host countries to ensure that they are aware of the implications of their decisions.

In any clinical trial of a candidate vaccine, manufacturers, sponsors and investigators should maintain confidentiality. The law and regulations of participating states (both the sponsoring and the host state) should be reviewed to assure that it will be maintained.

An important reason for confidentiality is to ensure protection from discrimination against persons who are participating or are planning to participate in vaccine clinical trials. Additional safeguards may be found in laws designed to protect persons against discrimination with respect to housing, employment, insurance and access to social services. In the absence of such adequate anti-discrimination protection, participation in vaccine trials may be discouraged.

A second key legal determinant of progress in clinical vaccine trials is making provision for compensation for injuries suffered during participation in the trials. The Consultation considered that two principles should apply:

- a) Guidelines should be adopted which provide compensation for clinical trial participants when the causal link is established between the injury and the trial. Negligence should not be a factor. As called for by proposed guidelines of the Council for International Organizations of Medical Sciences (CIOMS), the participant should be fully compensated for temporary or permanent disability which would include medical and associated expenses, and reimbursement for lost wages during disability. Punitive damages where wrongful misconduct has been demonstrated could be sought through the courts.
- b) A fund should be considered on a national or international level which will assure that compensation be made available for participants where a legal/administrative system would otherwise not provide it. It is believed that this approach to compensation will reduce concern over liability on the part of manufacturers, individuals and any organizations producing AIDS vaccines.

3. Scientific criteria for progress of candidate vaccine trials

The World Health Organization serves important advisory and information functions relevant to the introduction of vaccines into the different phases of clinical testing. These functions include review of protocols for which WHO sponsorship is requested, review of protocols as requested by member states and the facilitation of information exchange in order to assist local control authorities in decision making. It is anticipated that WHO should serve an essential function in facilitating international efficacy trials of candidate vaccines. In addition, the principle that studies of a candidate vaccine should generally commence in the country of origin before beginning in another country is reaffirmed. It is not recommended that WHO set requirements for introduction of vaccines into clinical trials (i.e., Phase I studies), within individual member states. This report includes recommended principles to be considered by WHO or by national authorities when reviewing proposed studies of candidate vaccines. These recommendations are made in the absence of any specific recommendations regarding Phase II/III studies, which will be prepared in the future as data are developed. The ongoing evaluation of preparations for introduction into clinical trials should be viewed as an evolving scientific process which is responsive to emerging findings.

The introduction of candidate vaccines into different phases of clinical evaluation should be based on sound scientific principles. As with all vaccines, studies in animal models are an essential part of characterization of such preparations. Ideally, such animal models can be used to assess safety and immunogenicity including the quantity and quality of humoral and cell-mediated immunity, the potential for immunopathology, immune enhancement, and protection against live virus challenge. To date, animal models have

shown limited usefulness for assessment of protective immunity against HIV infection and AIDS. Even though the mechanism of immunity may be different in humans, one approach to evaluate the protective potential and safety of candidate vaccines in human beings, is through chimpanzee immunization and challenge studies. Therefore, the requirement for such tests should be at the discretion of the National Control Authority. Other approaches for assessing the protective potential and safety of candidate vaccine preparation may also be acceptable. Thus, studies of HIV-2 and SIV in other non-human primates should be encouraged since the application of such models may be critical for decision-making regarding expansion of clinical trials. It is reasonable for National Control Authorities to require substantially greater evidence of potential safety and efficacy of HIV vaccines before embarking on Phase II and III studies as compared to Phase I studies.

3.1 Candidate vaccine

Studies in a variety of animal species can provide useful information regarding experimental vaccines. Rodents (e.g., mice and guinea pigs), rabbits, sheep and/or goats can be used in preliminary studies. Studies in non-human primates as stated above are of special importance. Reasonable preclinical evaluation of experimental vaccines would usually involve limited studies in chimpanzees and more extensive evaluation in monkeys, employing the SIV model.

It is now possible to study many immunological responses to experimental vaccines. Testing that may be relevant to evaluation of such vaccines in animals includes:

- binding antibodies;
- neutralizing antibodies;
- antibody-dependent, cell-mediated cytotoxicity;
- enhancing antibodies;
- blocking antibodies;
- lymphocyte proliferation responses; and
- cytotoxic T-cell responses.

The specificity of the immune response should be determined. In addition, animals immunized can be examined for adverse effects.

Principles applicable to vaccine development, characterization and testing are generally applicable to experimental vaccines against HIV infection and AIDS. Examples of such principles are virus seed lot and cell bank requirements, and other recommendations pertinent to live and killed virus vaccines, products derived by recombinant DNA techniques, monoclonal antibodies, and other requirements set by national control authorities.

3.2 Clinical trials

The merits of proposed study protocols depend in part on their capacity to yield data that will facilitate subsequent decision making. Two issues that are particularly relevant in this regard are the potential safety for subsequent study populations and the potential for person-to-person spread of live recombinant vaccines, such as recombinant vaccine viruses. Phase I studies should be designed so as to yield data that will facilitate product development.

a) Phase I

Phase I trials refer to the first introduction of the candidate vaccine preparation in the human population with the purpose of initial determination of its safety and biological effects including immunogenicity. This phase may include studies of dose and route of administration and usually involves less than 100 volunteers.

Persons included in this group should be healthy, HIV-seronegative individuals who have no recognized risk behaviour for HIV infection. It is recommended that pregnant women be excluded from this group. All participants should be fully informed volunteers. In general, initial Phase I trials should be conducted in the country of origin of the vaccine. Phase I results including those that indicate toxicity which prevents further trials of the vaccine, should be made public.

b) Phase II

Phase II trials refer to the initial trials examining potential effectiveness in a limited number of volunteers (usually between 200 and 500 individuals). In the case of candidate vaccines, the principal focus of this phase is immunogenicity.

The target group should be made up of fully informed HIV-seronegative volunteers. It should include representation of all population groups that might be included in a phase III trial. Moreover, since in phase III trials HIV-positive individuals may receive vaccine, it may be appropriate to include a small group of such individuals in phase II trials. Participants must be prepared to avoid behaviours which place them at risk of acquiring HIV infection. Phase II studies in persons below the age of consent should not be embarked upon until those in adults have been evaluated.

c) Phase III

Phase III trials are intended to provide for a more complete assessment of safety and effectiveness in the prevention of disease, involving larger numbers of volunteers in a multi-centered, adequately controlled study.

These trials must satisfy the highest standards of scientific investigation. The study design should be appropriate to the vaccine and the study population. The ideal would be a controlled double blind, fully randomized trial. They should be performed in groups of individuals which represent all of the major routes of HIV infection (sexual, parenteral and mother to infant). These trials should preferably be conducted simultaneously. The populations included in these trials should have a sufficient incidence of seroconversion to satisfy sample size requirements. The geographical site for these trials should have:

- Adequate resources for education about the prevention of HIV infection;
- National, qualified, experienced personnel;
- The necessary infrastructure in terms of laboratories and field capability, including epidemiological, managerial and clinical personnel with experience in vaccine trials.

4. Role of WHO

The World Health Organization, by virtue of its international character, its Constitution and its prestige in the world, is uniquely situated to facilitate and coordinate international testing of candidate HIV vaccines ensuring the highest scientific and ethical standards. With regard to clinical trials of candidate vaccines, WHO can play an extremely important role in the exchange of scientific, ethical, social and legal information and advise member states and other organizations on these issues. This may require the establishment of specialist working groups. Likewise, WHO's traditional role in standardizing reagents and supplying them to investigators throughout the world will be most valuable in the evaluation of responses to candidate vaccines and of new animal models for AIDS and in monitoring HIV genetic/antigenic variability.

AIDS is one of the most serious challenges that medical science has ever faced. The Consultation considers that there is no better body than WHO to establish general guidelines for entry and progression of candidate vaccines into the various phases of clinical trials and to provide the forum for the review of results of various vaccine trials to arrive at a consensus.

Insofar as developing countries are concerned, the meeting recommends that every trial carried out in a developing country be seen as an opportunity to strengthen the institutional capabilities of that country and to support research related to vaccine evaluation. At the request of Member States, WHO can render advice on steps to be taken in anticipation of clinical trials of emerging candidate vaccines, e.g., provision of opportunities for training of developing country scientists.

The Consultation considers that WHO has a special role to play in securing the cooperation of industry, not only in developing safe and effective vaccines but also in ensuring their availability at affordable prices to developing countries, and in assisting the transfer of technology of vaccine manufacture to selected developing countries where it is likely to be used. In this regard, WHO, in collaboration with other United Nations organizations such as the United Nations Childrens Fund (UNICEF) and the United Nations Development Programme (UNDP), has been able to provide vaccines and to facilitate their local production in developing countries.

5. Recommendations to WHO

WHO should play an important role in the facilitation and coordination of international trials of HIV candidate vaccines by:

- a) Serving as a forum for the exchange and validation of scientific information, through the organization of scientific meetings and consultations in different aspects of HIV vaccine development;
- b) Providing advice to member states on the scientific, ethical, legal and social aspects related to vaccine trials conducted in an international context;
- c) Promoting and supporting research relevant to operational aspects of vaccine trials in developing countries, including the development and validation of appropriate epidemiological, laboratory and other support methods and training of personnel necessary for the field evaluation of vaccines;
- d) Working together with member states in the identification, assessment and preparation of field sites and institutional basis for future trials, including the training of personnel and the strengthening of activities related to AIDS prevention and control;
- e) Facilitating international collaboration among scientists in vaccine related areas, such as standardization of reagents and techniques for the evaluation of immune response to candidate vaccines, identification and evaluation of new animal models, and monitoring genetic variability of HIV strains from different geographical areas;
- f) Promoting and facilitating international consensus for the analysis and evaluation of results from vaccine trials in humans, including future collaborative studies to evaluate different candidate vaccines. The planning of design and location of large vaccine efficacy trials will be an extended, complex process which should be considered a major objective;

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- g) Promoting strategies that would be necessary to ensure vaccine availability and delivery worldwide, once one or more acceptable vaccines are developed. It is considered essential that a vaccine or vaccines developed or evaluated through international scientific collaboration be made available to developing countries under the most advantageous possible conditions and the Consultation calls upon WHO to seek mechanisms to achieve this goal through collaboration with scientists, institutions, nongovernmental organizations, member states, and other United Nations organizations.

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