

Ethical considerations in HIV preventive vaccine research

UNAIDS guidance document



Joint United Nations Programme on HIV/AIDS

UNAIDS

UNICEF • WFP • UNDP • UNFPA • UNODC
ILO • UNESCO • WHO • WORLD BANK

UNAIDS/04.07E (English original, May 2000)
ISBN 92-9173-166-8

Third reprint April 2004

© Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) 2003.

All rights reserved. Publications jointly produced by UNAIDS and WHO can be obtained from the UNAIDS Information Centre. Requests for permission to reproduce or translate UNAIDS publications—whether for sale or for noncommercial distribution—should also be addressed to the Information Centre at the address below, or by fax, at +41 22 791 4187, or e-mail: publicationpermissions@unaids.org.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of UNAIDS or WHO

concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by UNAIDS or WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

UNAIDS and WHO do not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

UNAIDS, 20 avenue Appia, 1211 Geneva 27, Switzerland
Tel. (+41) 22 791 36 66 – Fax (+41) 22 791 41 87
E-mail: unaids@unaids.org – Internet: <http://www.unaids.org>

Ethical considerations in HIV preventive vaccine research

UNAIDS guidance document

May 2000



Joint United Nations Programme on HIV/AIDS

UNAIDS

UNICEF • WFP • UNDP • UNFPA • UNODC
ILO • UNESCO • WHO • WORLD BANK

Introduction	3
Context	6
Suggested guidance	11
Guidance Point 1: HIV vaccines development	11
Guidance Point 2: Vaccine availability	13
Guidance Point 3: Capacity building	15
Guidance Point 4: Research protocols and study populations	17
Guidance Point 5: Community participation	19
Guidance Point 6: Scientific and ethical review	21
Guidance Point 7: Vulnerable populations	22
Guidance Point 8: Clinical trial phases	24
Guidance Point 9: Potential harms	27
Guidance Point 10: Benefits	30
Guidance Point 11: Control group	31
Guidance Point 12: Informed consent	32
Guidance Point 13: Informed consent - special measures	36
Guidance Point 14: Risk-reduction interventions	38
Guidance Point 15: Monitoring informed consent and interventions	39
Guidance Point 16: Care and treatment	41
Guidance Point 17: Women	45
Guidance Point 18: Children	46

Introduction

As we enter the third decade of the AIDS pandemic, there still remains no effective HIV preventive vaccine. As the numbers of those infected by HIV and dying from AIDS increase dramatically, the need for such a vaccine becomes ever more urgent. Several HIV candidate vaccines are at various stages of development. However, the successful development of effective HIV preventive vaccines is likely to require that many different candidate vaccines be studied simultaneously in different populations around the world. This in turn will require a large international cooperative effort drawing on partners from various health sectors, intergovernmental organizations, government, research institutions, industry, and affected populations. It will also require that these partners be able and willing to address the difficult ethical concerns that arise during the development of HIV vaccines.

In an effort to elucidate these ethical concerns, and to create forums where they could be discussed in full by those presently involved in, or considering, HIV vaccine development activities, the UNAIDS Secretariat convened meetings in Geneva (twice), Brazil, Thailand, Uganda and Washington during 1997-1999. These meetings included lawyers, activists, social scientists, ethicists, vaccine scientists, epidemiologists, representatives of NGOs, people living with HIV/AIDS, and people working in health policy. In the regional meetings, efforts were made to include people from a number of countries from that particular region. The entire process involved people from a total of

33 countries.¹ The goals were to : (1) identify and discuss ethical elements specific to development of HIV preventive vaccines; (2) reach consensus when possible, and elucidate different positions, when not; (3) progress in ability to address these matters during pending or proposed HIV vaccine research.

In the present document, UNAIDS seeks to offer guidance emanating from this process. This document does not purport to capture the extensive discussion, debate, consensus, and disagreement which occurred at these meetings. Rather it highlights, from UNAIDS' perspective, some of the critical elements that must be considered in HIV vaccine development activities. Where these are adequately addressed, in UNAIDS' view, by other existing texts, there is no attempt to duplicate or replace these texts, which should be consulted extensively throughout HIV vaccine development activities. Such texts include : the Nuremberg Code (1947); the Declaration of Helsinki, first adopted by the World Medical Association in 1964 and subsequently amended in 1975, 1983, 1989 and 1996; the Belmont Report - Ethical Principles and Guidelines for the Protection of Human Subjects of Research, issued in 1979 by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; the International Ethical Guidelines for Biomedical Research Involving Human Subjects, issued by the Council for International Organizations of Medical

¹ For a full description of the process and participants, see "Final Report, UNAIDS-Sponsored Regional Workshops to discuss Ethical Issues in Preventive HIV Vaccine Trials", available from UNAIDS. See also Guenter, Esparza, and Macklin: Ethical considerations in international HIV vaccine trials: summary of a consultative process conducted by the Joint United Nations Programme on HIV/AIDS (UNAIDS. Journal of Medical Ethics (February 2000), vol. 26, No. 1: 37-43.

Sciences (CIOMS) in 1993 (and developed in close cooperation with WHO); the World Health Organization's Good Clinical Practice (WHO GCP) Guideline (1995); and the International Conference on Harmonisation's Good Clinical Practice (ICH GCP) Guideline (1996).

It is hoped that this document will be of use to potential research participants, investigators, community members, government representatives, pharmaceutical companies, and ethical and scientific review committees involved in HIV preventive vaccine development. It suggests standards, as well as processes for arriving at standards, and can be used as a frame of reference from which to conduct further discussion at the international, national, and local levels.

Context

The HIV/AIDS pandemic is characterized by unique biological, social and geographical factors that, among other things, affect the balance of risks and benefits for individuals and communities who participate in HIV vaccine development activities. These factors may require that additional efforts are made to address the needs of participating individuals and communities, including their urgent need for a HIV vaccine, their need to have their rights protected and their welfare promoted in the context of HIV vaccine development activities, and their need to be able to be full and equal participants . These factors include the following :

- The global burden of disease and death related to HIV is increasing at a rate unmatched by any other pathogen. For many countries, it is already the leading cause of death. Currently available treatments are inadequate because they do not lead to cure, but at best slow the progression of disease. The most effective treatment for slowing HIV-related disease progression, antiretroviral medication, is complicated to administer, requires close medical monitoring, is extremely costly, and can cause significant adverse effects. Because of this, antiretroviral medication is not readily available to the vast majority of people affected by HIV/AIDS. These are people living in developing countries and in marginalized communities in

developed countries. There is therefore an ethical imperative to seek, as urgently as possible, a globally effective and accessible vaccine, to complement other prevention strategies. Furthermore, this ethical imperative demands that HIV preventive vaccines be developed to address the situation of those people and populations most vulnerable to infection.

■ Genetically distinct subtypes of HIV have been described, and different HIV subtypes are predominant in different regions and countries. Yet the relevance of these subtypes to potential vaccine-induced protection is not clearly understood. Thus, it is not known whether a vaccine targeted at one subtype will protect against infection from another subtype; and it is likely that a vaccine directed at a particular subtype will need to be tested in a population in which that subtype is prevalent. Therefore, developing a vaccine that is effective in the populations with the greatest incidence of HIV is likely to require experimental vaccines be tested in those populations, even though these populations may for a variety of reasons be relatively vulnerable to exploitation and harm in the context of HIV vaccine development. Additional efforts may need to be made to overcome this vulnerability.

■ Some candidate vaccines may be conceived and manufactured in laboratories of one country (sponsor country or countries), usually in the developed world, and tested in human populations in another country (host country or countries), often in the developing world.

[The term 'sponsor' has usually referred to the individual or institution who either owns the candidate vaccine or provides the material resources necessary to carry out the vaccine development programme. Traditionally, the sponsor has been thought of as a single corporate entity, such as a pharmaceutical company. In modern vaccine development programmes there are commonly multiple sponsors including one or more corporations, one or more national governments and one or more international agencies.] The potential imbalance of such a situation demands particular attention to factors that will address the differing perspectives, interests and capacities of sponsors and hosts with the goal of encouraging the urgent development of effective vaccines, in ethically acceptable manners, and their early distribution to populations most in need. In this regard, potential host countries and communities should be encouraged and given the capacity to make decisions for themselves regarding their participation in HIV vaccine development, based on their own health and human development priorities, in a context of equal collaboration with sponsors.

■ HIV/AIDS is a condition that is both highly feared and stigmatized. This is in large part because it is associated with blood, death, sex, and activities which are often not legally sanctioned, such as commercial sex, men having sex with men, and substance abuse. These are issues which are difficult to address openly - at a societal and individual level. As a result, people affected by HIV/AIDS can experience stigma, discrimination,

and even violence; and governments and communities continue to deny the existence and prevalence of HIV/AIDS. Furthermore, vulnerability to HIV infection and to the impact of AIDS is greater where people are marginalized due to their social, economic and legal status. These factors increase the risk of social and psychological harm for people participating in HIV vaccine research. Additional efforts must be made to address these increased risks, and to ensure that the risks participants take are justified by the benefits they receive by virtue of their participation in the research. A key means by which to protect participants and the communities from which they come is to ensure that the community in which the research is carried out is meaningfully involved in the design, implementation, and distribution of results of vaccine research, including the involvement of representatives from marginalized communities from which participants are drawn, where possible and appropriate.

Suggested guidance

Given the global nature of the epidemic, the devastation being wreaked in some countries by it, the fact that vaccine(s) may be the best long-term solution by which to control the epidemic, especially in developing countries, and the potentially universal benefits of effective HIV vaccines, there is an ethical imperative for global support to the effort to develop these vaccines. This effort will require intense international collaboration and coordination over time, including among countries with scientific expertise and resources, and among countries where candidate vaccines could be tested but whose infrastructure, resource base, and scientific and ethical capacities could be insufficient at present. Though HIV vaccines should benefit all those in need, it is imperative that they benefit the populations at greatest risk of

Guidance Point 1: HIV vaccines development

Given the severity of the HIV/AIDS pandemic in human, public health, social, and economic terms, sufficient capacity and incentives should be developed to foster the early and ethical development of effective vaccines, both from the point of view of countries where HIV vaccine trials may be held, and from the point of view of sponsors of HIV vaccine trials. Donor countries and relevant international organizations should join with these stakeholders to promote such vaccine development.

infection. Thus, HIV vaccine development should ensure that the vaccines are appropriate for use among such populations, among which it will be necessary to conduct trials; and, when developed, they should be made available and affordable to such populations.

Because HIV vaccine development activities take time, are complex, and require infrastructure, resources and international collaboration,

- potential sponsor countries and host countries should immediately include HIV vaccine development in their regional and national AIDS prevention and control plans.
- potential host countries should assess how they can and should participate in HIV vaccine development activities either nationally or on a regional basis, including identifying resources, establishing partnerships, conducting national information campaigns, strengthening their scientific and ethical sectors, and including a vaccine research component to complement other prevention interventions.
- potential donors and international agencies should make early and sustained commitments to allocate sufficient funds to make a vaccine a reality, including funds to strengthen ethical and scientific capacity in countries where multiple trials will have to be conducted and to purchase and distribute future vaccines.
- potential sponsors should establish partnerships

with potential host countries, and begin discussions regarding community consultations, strengthening necessary scientific and ethical components, and eventual plans for equitable distribution of the benefits of research.

Although making a safe and effective vaccine reasonably available to the population where it was tested is a basic ethical requirement, some have argued that it could be a disincentive for industry to conduct studies in countries with large populations, or that it could constitute an undue inducement for a resource-poor country or community to “cooperate”. Given the severity of the epidemic, it is imperative that sufficient incentives exist, both through financial rewards in the marketplace and through public subsidies, to foster development of effective vaccines while also ensuring that vaccines are produced and distributed in a fashion that actually makes them available to the populations at greatest risk.

**Guidance Point 2 :
Vaccine availability**

Any HIV preventive 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 in which it was tested, as well as to other populations at high risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability.

As health and research communities build HIV preventive vaccine research programmes, attention needs to be given immediately to how a successful vaccine, and other benefits resulting from the research, will be made readily and affordably available to the communities and countries where such a vaccine is tested, as well as to other communities and countries at high risk for HIV infection. This process of discussion and negotiation should start as soon as possible and should be carried on through the course of the research.

At a minimum, the parties directly concerned should begin this discussion before the trials commence. This discussion should include representatives from relevant stakeholders in the host country, such as representatives from the executive branch, health ministry, local health authorities, and relevant scientific and ethical groups. It should also include representatives from the communities from which participants are drawn, people living with HIV/AIDS, and NGOs representing affected communities. The discussions should include decisions regarding payments, royalties, subsidies, technology and intellectual property, as well as distribution costs, channels and modalities, including vaccination strategies, target populations, and number of doses.

Furthermore, the discussion concerning availability and distribution of an effective HIV vaccine should engage international organizations, donor governments and bilateral agencies, representatives from wider affected communities, international and regional NGOs and the private sector. These should not only consider financial assistance regarding making vaccines available, but should also help to build the capacity of host governments and communities to negotiate for and implement distribution plans.

Potential host countries and communities have the right, and the responsibility, to take decisions regarding the nature of their participation in HIV vaccine research. Yet disparities in economic wealth, scientific experience, and technical capacity among countries and communities can lead to undue influence over and possible exploitation of host countries and communities. The development of an HIV vaccine will require international cooperative research, which should transcend, in an ethical manner, such disparities. Real or perceived disparities should be resolved in a way that ensures equality in decision-making and action. The desired relationship is one of collaboration among equals. Factors that may increase vulnerability to exploitation of host countries and communities may include, but are not limited to, the following:

- level of the proposed community's economic capacity, such as is reflected in the Human Development Index of the UNDP
- community/cultural experience with, and/or understanding of, scientific research

**Guidance Point 3 :
Capacity building**

Strategies should be implemented to build capacity in host countries and communities so that they can practise meaningful self-determination in vaccine development, can ensure the scientific and ethical conduct of vaccine development, and can function as equal partners with sponsors and others in a collaborative process.

- local political awareness of the importance and process of vaccine research
- local infrastructure, personnel, and technical capacity for providing HIV health care and treatment options
- ability of individuals in the community to provide informed consent, including the effect of class, gender, and other social factors on the potential for freely given consent
- level of experience and capacity for conducting ethical and scientific review, and
- local infrastructure, personnel, and technical capacity for conducting the proposed research.

Strategies to overcome these disparities could involve:

- scientific exchange, and knowledge and skills transfer between sponsor countries and institutions, and host countries and communities
- capacity-building programmes in the science and ethics of vaccine development by relevant scientific institutions and international organizations
- support to development of national and local ethical review capacity (see **Guidance Point 6**)
- support to affected communities and communities from which participants are drawn regarding information, education, and capacity and consensus-building on vaccine development, and
- early involvement of affected communities in the design and implementation of vaccine development plans and protocols (see **Guidance Point 5**).

In order to be ethical, clinical trials of vaccines should be based on scientifically valid research protocols, and the scientific questions posed should be rigorously formulated in a research protocol that is capable of providing reliable responses. Valid scientific questions relevant to HIV vaccine development are those that seek:

**Guidance Point 4 :
Research protocols
and study populations**

In order to conduct HIV vaccine research in an ethically acceptable manner, the research protocol should be scientifically appropriate, and the desired outcome of the proposed research should potentially benefit the population from which research participants are drawn.

- to gain scientific information on the safety, immunogenicity (ability to induce immune responses against HIV) and efficacy (degree of protection) of candidate vaccines
- to determine immunological correlates or surrogates in order to identify the protective mechanisms and how they can be elicited
- to compare different candidate vaccines; and
- to test whether vaccines effective in one population are effective in other populations.

Furthermore, the selection of the research population should be based on the fact that its characteristics are relevant to the scientific issues raised; and the results of

the research will potentially benefit the selected population. In this sense, the research protocol should:

- justify the selection of the research population from a scientific point of view
- outline how the risks undertaken by the participants of that population are balanced by the potential benefits to that population
- address particular needs of the proposed research population
- demonstrate how the candidate vaccine being tested is expected to be beneficial to the population in which testing occurs, and
- establish safeguards for the protection of research participants from potential harm arising from the research.

These general principles will be further elaborated below.

Involvement of community representatives should not be seen as a single encounter, nor as one-directional. The orientation of community involvement should be one of partnership - towards mutual education and consensus-building regarding all aspects of the vaccine development programme. There

should be established a continuing forum for communication and problem-solving on all aspects of the vaccine development programme from phase I through phase III and beyond, to the distribution of a safe, effective, licensed vaccine. All participating parties should define the nature of this ongoing relationship. It should include appropriate representation of the community on committees charged with the review, approval, and monitoring of the HIV vaccine research. Like investigators and sponsors, communities should assume appropriate responsibility for assuring the successful completion of the trial and of the programme.

Appropriate community representatives should be determined through a process of broad consultation. Members of the community who may contribute to a vaccine

Guidance Point 5 : Community participation

To ensure the ethical and scientific quality of proposed research, its relevance to the affected community, and its acceptance by the affected community, community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of HIV vaccine research.

development process include representatives of the research population eligible to serve as research participants, other members of the community who would be among the intended beneficiaries of the developed vaccine, relevant nongovernmental organizations, persons living with HIV/AIDS, community leaders, public health officials, and those who provide health care and other services to people living with and affected by HIV.

Participation of the community in the planning and implementation of a vaccine development strategy can provide the following benefits:

- information regarding the health beliefs and understanding of the study population
- input into the design of the protocol
- input into an appropriate informed consent process
- insight into the design of risk reduction interventions
- effective methods for disseminating information about the trial and its outcomes
- information to the community-at-large on the proposed research
- trust between the community and researchers
- equity in choice of participants
- equity in decisions regarding level of standard of care and treatment and its duration, and
- equity in plans for applying results and vaccine distribution.

Proposed HIV vaccine research protocols should be reviewed by scientific and ethical review committees that are located in, and include membership from, the country and community where the research is proposed to take place.

This process ensures that the proposed research is analysed from the scientific and ethical viewpoints by individuals who are familiar with the conditions prevailing in the potential research population.

**Guidance Point 6 :
Scientific and ethical review**

HIV preventive vaccine trials should only be carried out in countries and communities that have the capacity to conduct appropriate independent and competent scientific and ethical review.

Some countries do not currently have the capacity to conduct independent, competent and meaningful scientific and ethical review. If the country's capacity for scientific and ethical review is inadequate, the sponsor should be responsible for ensuring that adequate structures are developed in the host country for scientific and ethical review prior to the start of the research. Care should be taken to minimize the potential for conflicts of interest, while providing assistance in capacity-building for scientific and ethical review. Capacity-building for scientific and ethical review may also be developed in collaboration with international agencies, organizations within the host country, and other relevant parties.

Some countries or communities, often described as “developing”, have been perceived as inappropriate participants for some phases of clinical research, due to a real or perceived increased level of vulnerability to exploitation or harm. The usefulness of the “developing/developed” terminology for assessing risk of harm and exploitation, however, is limited. It refers

primarily to economic considerations, which are not the only relevant factors in HIV vaccine research. It also establishes two fixed categories, whereas in reality, countries and communities are distributed along a spectrum, characterized by a variety of different factors that affect risk. It is more useful to identify the *particular* aspects of a social context that create conditions for exploitation or increased vulnerability for the pool of participants that has been selected. These aspects should be described in the protocol, as should the measures that will be taken to overcome them. In some potential research populations (countries or communities), conditions affecting potential vulnerability or exploitation may be so severe that ensuring adequate safeguards is not possible. In such populations, HIV preventive vaccine research should not be conducted.

**Guidance Point 7 :
Vulnerable populations**

Where relevant, the research protocol should describe the social contexts of a proposed research population (country or community) that create conditions for possible exploitation or increased vulnerability among potential research participants, as well as the steps that will be taken to overcome these and protect the dignity, safety, and welfare of the participants.

Some factors to be considered are those listed in **Guidance Point 3** which influence the disparity in real or perceived power as between sponsors and host countries, as well as the factors listed below that can also increase the nature and level of risk of harm to participants:

- governmental, institutional or social stigmatization or discrimination on the basis of HIV status
- inadequate ability to protect HIV-related human rights, and to prevent HIV-related discrimination and stigma, including those arising from participation in an HIV vaccine trial
- social and legal marginalization of groups from which participants might be drawn, e.g. women, injecting drug users, men having sex with men, sex workers
- limited availability, accessibility and sustainability of health care and treatment options
- limited ability of individuals or groups in the community to understand the research process
- limited ability of individuals to understand the informed consent process
- limited ability of individuals to be able to give freely their informed consent in the light of prevailing class, gender, and other social and legal factors, and
- lack of meaningful national/local scientific and ethical review.

Initial stages in a vaccine development programme entail research in laboratories and among animals. The transition from this pre-clinical phase to a phase I clinical trial, in which testing involves the administration of the candidate vaccine to human subjects to assess safety and immunogenicity, is a time when risks may not be yet well defined. Furthermore, specific infrastructures are often required in order to ensure the safety and care of the research participants at these stages. For these reasons, the first administration of a candidate HIV vaccine in humans should generally be conducted in less vulnerable research populations, usually in the country of the sponsor.

There may be situations, however, where developing countries choose to conduct phases I/II and/or III (large-scale trials to assess efficacy) among their populations that are relatively vulnerable to risk and exploitation. For instance, this

Guidance Point 8 : Clinical trial phases

As phases I, II, and III in the clinical development of a preventive vaccine all have their own particular scientific requirements and specific ethical challenges, the choice of study populations for each trial phase should be justified in advance in scientific and ethical terms in all cases, regardless of where the study population is found. Generally, early clinical phases of HIV vaccine research should be conducted in communities that are less vulnerable to harm or exploitation, usually within the sponsor country. However, countries may choose, for valid scientific and public health reasons, to conduct any phase within their populations, if they are able to ensure sufficient scientific infrastructure and sufficient ethical safeguards.

could occur where an experimental HIV vaccine is directed primarily towards a viral strain that does not exist in the sponsor country but does exist in the potential host country. Conducting phase I/II trials in the country where the strain exists may be the only way to determine whether safety and immunogenicity are acceptable in that particular population, prior to conducting a phase III trial. A country may also decide that, due to the high level of HIV risk to its population and the gravity of HIV/AIDS already in country, it is willing to test a vaccine concept that is not being tested in another country. Such a decision may result in obvious benefits to the country in question if an effective vaccine is found. It may also provide an important capacity-building experience, if phase I or phase II trials are conducted in a host country prior to a phase III trial being initiated there.

Establishing a vaccine development programme that entails the conduct of some, most, or all of its clinical trial components in a country or community that is relatively vulnerable to harm or exploitation is ethically justified if :

- the vaccine is anticipated to be effective against a strain of HIV that is an important public health problem in the country
- the country and the community either have, or with assistance can develop or be provided with, adequate scientific and ethical capability and administrative and health infrastructure for the successful conduct of the proposed research
- community members, policy makers, ethicists and investigators in the country have determined that

their residents will be adequately protected from harm or exploitation, and that the vaccine development programme is necessary for and responsive to the health needs and priorities in their country; and

- all other conditions for ethical justification as set forth in this document are satisfied.

In cases in which it is decided to carry out phase I or phase II trials first in a country other than the sponsor country, due consideration should be given to conducting them simultaneously in the country of the sponsor, where this is practical and ethical. Also, when the host country or community is not familiar with conducting biomedical research in human subjects, phase I/II trials that have been performed in the country of the sponsor should ordinarily be repeated in the community in which the phase III trials are to be conducted.

Participation in HIV preventive vaccine research may involve physiological, psychological and social risks. With regard to the physiological risks, the purpose of an HIV preventive vaccine is to induce an immunological response in the human body to counteract the HIV virus if it enters the body, or to prevent it from entering at all. Vaccines currently being considered for human trials are not capable of causing infection, i.e. they do not include replicating HIV.² Several candidate HIV vaccines have been tested in laboratories, and some have been tested in human subjects. Not all of these candidate vaccines are the same, and not all candidate vaccines carry the same risks for harm. Thus far, however, significant adverse biological effects have not been observed. Nevertheless, some of the more likely physiological risks of participating in vaccine research include the following:

**Guidance Point 9 :
Potential harms**

The nature, magnitude, and probability of all potential harms resulting from participation in an HIV preventive vaccine trial should be specified in the research protocol as fully as can be reasonably done, as well as the modalities by which to address these, including provision for the highest level of care to participants who experience adverse reactions to the vaccine, compensation for injury related to the research, and referral to psychosocial and legal support, as necessary.

² Some of the most effective viral vaccines are based on live-attenuated viruses and some investigators have proposed a similar approach for HIV vaccines. Any decision regarding testing a live-attenuated HIV vaccine in humans would have to be carefully assessed in view of the significant safety concerns associated with such a vaccine approach.

- A person who has received a candidate vaccine and is then exposed to HIV may have a greater risk of developing established infection, or of progressing more rapidly once infected, than if the vaccine had not been administered. This potential harm has not been observed in trials thus far.
- An HIV vaccine may require that several injections be given over months or years, resulting in pain, occasional skin reactions, and possibly other biological adverse events, such as fever and malaise.
- Injuries may be sustained due to research-related activities during the course of the trial.

The potential for adverse reactions to the candidate vaccine, as well as possible injuries related to HIV vaccine research, should be described, as far as possible, in the research protocol and fully explained in the informed consent process. Both the protocol and the consent process should also describe the nature of medical treatment to be provided for injuries, as well as compensation for harm incurred due to research-related activities, including the process by which it is decided whether an injury will be compensated. HIV infection acquired during participation in an HIV preventive vaccine trial should not be considered an injury subject to compensation unless it is directly attributable to the vaccine itself, or to direct contamination through research-related activities. In addition to compensation for biological/medical injuries, appropriate consideration should be given to compensation for social or economic harms, e.g. job loss as a result of testing positive following vaccine administration.

With regard to psychosocial risks, participation in a complicated, lengthy trial involving intensely intimate matters, involving repeated HIV testing, and involving exposure to culturally different scientific and medical concepts may cause anxiety, stress, depression, as well as stress between partners in a relationship. Participation, if it becomes publicly known, may also cause stigma and discrimination against the participant if s/he is perceived to be HIV-infected. Finally, some people may develop a positive HIV test after receiving a candidate HIV vaccine, even though they are not truly infected with HIV, i.e. a 'false positive' HIV test. This may result in the same negative social consequences that exist for those actually HIV-infected. The protocol should describe these, as well as ensure that the research occurs in communities where confidentiality can be maintained and where participants will have access to, and can be referred to, ongoing psychosocial services, including counselling, social support groups, and legal support. Consideration should also be given to setting up an ombudsperson who can intervene with outside parties, if necessary and requested, on behalf of participants, as well as to providing documentation to participants that they can use to show that their "false positive" is due to their participation in research.³

³ When a vaccine is tested, laboratory techniques should be available to differentiate HIV-positivity due to vaccination from that due to actual HIV infection.

Some of the activities related to the conduct of HIV vaccine trials should benefit those who participate. At a minimum, participants should :

- have regular and supportive contact with health care workers and counsellors throughout the course of the trial
- receive comprehensive information regarding HIV transmission and how it can be prevented
- receive access to HIV prevention methods, including male and female condoms, and clean injecting equipment, where legal
- have access to a pre-agreed care and treatment package for HIV/AIDS if they become HIV-infected while enrolled in the trial (see **Guidance Point 16**)
- receive compensation for time, travel and inconvenience for participation in the trials, and
- if the vaccine is effective, develop protective immunity to HIV.

**Guidance Point 10 :
Benefits**

The research protocol should outline the benefits that persons participating in HIV preventive vaccine trials should experience as a result of their participation. Care should be taken so that these are not presented in a way that unduly influences freedom of choice in participation.

A vaccine with proven efficacy in preventing infection or disease from HIV does not currently exist. Therefore, the use of a placebo control arm is ethically acceptable in appropriately designed protocols.

Participants in the control arm of a future phase III HIV preventive vaccine trial should receive an HIV vaccine known to be safe and effective when such is available, unless there are compelling scientific reasons which justify the use of a placebo. Compelling scientific reasons to use a placebo rather than a known effective HIV vaccine in the research population include the following :

- The effective HIV vaccine is not believed to be effective against the virus that is prevalent in the research population.
- There are convincing reasons to believe that the biological conditions that prevailed during the initial trial demonstrating efficacy were so different from the conditions in the proposed research population that the results of the initial trial cannot be directly applied to the research population under consideration.

**Guidance Point 11 :
Control group**

As long as there is no known effective HIV preventive vaccine, a placebo control arm should be considered ethically acceptable in a phase III HIV preventive vaccine trial. However, where it is ethically and scientifically acceptable, consideration should be given to the use in the control arm of a vaccine to prevent a relevant condition apart from HIV.

In an effort to address the concern of lack of benefit to those randomly placed in a placebo control arm, apart from the benefits described in **Guidance Point 10**, it is recommended that the provision to these persons of another vaccine, such as for hepatitis B or tetanus, be considered. The appropriateness of such a step should be analysed in terms of the scientific requirements of the trial, the health needs of the population of participants, and the balance of benefits and risks to the active versus control arms of the trial.

A process of consultation between community representatives, researchers, sponsor(s) and regulatory bodies should be used to design an effective informed consent strategy and process. Issues such as illiteracy, language and cultural barriers, and diminished personal autonomy should be addressed in this consultative process. In some communities, special efforts may be required to achieve adequate understanding of 'cause and effect',

Guidance Point 12 : Informed consent

Independent and informed consent based on complete, accurate, and appropriately conveyed and understood information should be obtained from each individual while being screened for eligibility for participation in an HIV preventive vaccine trial, and before s/he is actually enrolled in the trial. Efforts should be taken to ensure throughout the trial that participants continue to understand and to participate freely as the trial progresses. Informed consent, with pre- and post-test counselling, should also be obtained for any testing for HIV status conducted before, during, and after the research.

'contagion', 'placebo', 'double blind', and other concepts involved in the scientific design of the research.

HIV preventive vaccine trials require informed consent at a number of stages. The first stage consists of screening candidates for eligibility for participation in the trial, which will involve, among other things, an assessment of the individual's risk-taking behaviour and a test for HIV status. Informed consent should be obtained during this screening process after the candidate has received all material information regarding the screening procedures, as well as an outline of the vaccine trial in which he will be invited to enrol, if found eligible. Fully informed consent should also be given for the test for HIV status, which should also be accompanied by pre-and post-test counselling, and referral to clinical and social support services, if found positive.

The second stage at which informed consent is required occurs once a person is judged eligible for enrolment. That individual should then be given full information concerning the nature and length of participation in the trial, including the risks and benefits posed by participation, so that s/he is able to give informed consent to participate.

Once enrolled, efforts should then be made throughout the trial to obtain assurance that the participation continues to be on a basis of free consent and understanding of what is happening. Informed consent, with pre- and

post-test counselling, should also be given for any repeated tests for HIV status. Throughout all stages of the trial and consent process, there should be assurance by the investigator that the information is understood before consent is given.

In some communities, it is customary to require the authorization of a third party, such as a community elder, in order for investigators to enter the community to invite individual members to participate in research. Other situations which make individual informed consent difficult include those in which an individual requires approval of another person or group in order to make decisions, where there is coercion, and where there is a cultural tradition of sharing risks and responsibilities, e.g. in some cultures where men hold the prerogative in marital relationships, where there is parental control of women, and/or where there are strong influences by community and/or religion or hierarchy (see **Guidance Point 13**). Such authorization or influence must not be used as a substitute for individual informed consent. Nor should trials be conducted where truly individual and free consent cannot be obtained. Authorization by a third party in place of individual informed consent is permissible only in the case of some minors who have not attained the legal age of consent to participate in a trial. In cases where it is proposed that minors will be enrolled as research participants, specific and full justification for their enrolment must be given, and their own consent must be obtained in light of their evolving capacities (see **Guidance Point 18**).

In addition to the standard content of informed consent, prior to participation in an HIV vaccine trial, each

prospective participant must be informed, using appropriate language and technique, of the following specific details:

- Prospective participants of phase II and III trials of HIV preventive vaccines should be informed that they have been chosen as prospective participants because they are at relatively high risk of HIV infection.
- Prospective participants for phase I, II and III trials should be informed that they will receive counseling and access to the means of risk reduction (in particular, male and female condoms, and clean injecting equipment, where legal) concerning how to reduce their risk of infection; and that in spite of these risk reduction efforts, some of the participants may become infected, particularly in the case of phase III trials where large numbers of participants at high risk are participating.
- They should be informed that it is not known whether the experimental vaccine will prevent HIV infection or disease, and further, that some of the participants will receive a placebo instead of the candidate HIV vaccine, when such is the case.
- They should be informed of the specific risks for physical harm, as well as for psychological and social harm, and of the types of treatment and compensation that are available for harm, and of services to which they may be referred should harm occur.
- All prospective participants of phase I, II or III trials should be informed of the nature and duration of care and treatment that is available,

and how it can be accessed, if they become infected with HIV during the course of the trial (see **Guidance Point 16**).

There are several categories of persons who are legally competent to consent to participate in a trial, and who have sufficient cognitive capacity to consent, but who may have limitations in their freedom to make independent choices. Those who plan, review, and conduct vaccine trials should be alert to the problems presented by the involvement of such persons, and either exclude such persons, if their vulnerability cannot be addressed, or take appropriate steps to ensure meaningful and independent ongoing informed consent, respect their rights, foster their well-being, and protect them from harm. The following are individuals or groups who should be given extra consideration with regard to their ability to provide informed consent in HIV preventive vaccine trials:

- Persons who are junior or subordinate members of hierarchical structures may be vulnerable to undue influence or coercion in that they may fear retaliation if they refuse cooperation with authorities. Such persons include members of the armed forces, students, government employees, prisoners, and refugees.

Guidance Point 13 :
Informed consent - special measures

Special measures should be taken to protect persons who are, or may be, limited in their ability to provide informed consent due to their social or legal status.

- Persons who engage in illegal or socially stigmatized activities are vulnerable to undue influence and threats presented by possible breaches of confidentiality and action by legal forces. Such persons include sex workers, intravenous drug users, and men who have sex with men.
- Persons who are impoverished or dependent on welfare programmes are vulnerable to being unduly influenced by offers of what others may consider modest material or health inducements.
- Women living in cultures where their autonomy as individuals is not sufficiently recognized are vulnerable to influence and coercion from male partners, family, or community members.

Steps that might be taken to ensure that ongoing free and informed consent is given by participants from these groups include :

- appointment of an independent ombudsperson and/or group to monitor these issues
- expansion of the responsibilities of the clinical trial monitor to include adherence to the informed consent and counselling process, or appointment of an independent counselling monitor
- training of the counsellors on these issues, and
- group counselling and/or interaction with local NGOs representing the groups from which such participants are drawn.

Reducing the risk of HIV infection throughout the trial among participants is an essential ethical component of HIV preventive vaccine trials. All trial participants should receive comprehensive counselling concerning methods of decreasing the risk of transmission of HIV. This should include the basic principles of safe sexual practice and safe use of injection equipment, as well as education concerning general health and treatment of sexually transmitted infections (STIs). Investigators should provide trial participants appropriate access to condoms, sterile injecting equipment (where legal) and treatment for other STIs. All trial participants should also be counselled prior to enrolling in a clinical trial regarding the potential benefits and risks of post-exposure prophylaxis with antiretroviral medication, and how it can be accessed in the community.

**Guidance Point 14 :
Risk-reduction interventions**

Appropriate risk-reduction counselling and access to prevention methods should be provided to all vaccine trial participants, with new methods being added as they are discovered and validated.

The technique and frequency of counselling should be agreed upon by the community-host government-investigator-sponsor partnership, and should be based upon reliable information about the prevailing social and behavioural characteristics of the study population. Consideration should be given to providing counselling through an agency or organisation that is independent of the investigators in order to prevent any real or perceived conflict of interest. Local capacity should be developed to employ such means in a culturally suitable and sustainable fashion, guided by the best scientific data.

The provision of counselling to reduce risk should be monitored to ensure quality and to minimize the potential conflict of interest between the risk-reduction goals and the vaccine trial's scientific goals. As new methods of prevention are discovered and validated, these must be added to the preventive methods being offered to trial participants.

The value of informed consent depends primarily on the ongoing quality of the process by which it is conducted, and not solely on the structure and content of the informed consent document. The informed consent process should be designed to empower participants to allow them to make appropriate decisions. Similarly, there are many ways in which risk reduction (counselling and access to means of prevention) can be conducted, with some methods being more effective than others in conveying the relevant information and in reducing risk behaviour.

**Guidance Point 15 :
Monitoring informed consent and interventions**

A plan for monitoring the initial and continuing adequacy of the informed consent process and risk-reduction interventions, including counselling and access to prevention methods, should be agreed upon before the trial commences.

A method for monitoring the adequacy of these processes should be designed and agreed upon by the community-host-government-investigator-sponsor

partnership. Consideration should be given to the expansion of the responsibilities of the clinical trial monitor to include adherence to the informed consent and counselling process, and/or the appointment of an independent counselling monitor, as suggested in **Guidance Point 13**. The appropriateness of such plans should be determined by the scientific and ethical review committees that are responsible for providing prior and continuing review of the trial. This recommendation supplements the usual guidelines for the monitoring of vaccine trials for safety and compliance with scientific and ethical standards and regulatory requirements.

Sponsors need to ensure care and treatment for participants who become HIV-infected during the course of the trial. At present, there is no universal consensus regarding the level of care and treatment that should be provided. This was evidenced at the UNAIDS-sponsored regional workshops to discuss ethical issues in preventive HIV vaccine trials at which the following three different conclusions were reached. Care and treatment for those who become infected should be provided:

- at the level of that offered in the sponsor country, and should include preventive risk behaviour counselling, general HIV

Guidance Point 16 : Care and treatment

Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of the circumstances listed below. A comprehensive care package should be agreed upon through a host/community/sponsor dialogue which reaches consensus prior to initiation of a trial, taking into consideration the following :

- ***level of care and treatment available in the sponsor country***
- ***highest level of care available in the host country***
- ***highest level of treatment available in the host country, including the availability of antiretroviral therapy outside the research context in the host country***
- ***availability of infrastructure to provide care and treatment in the context of research***
- ***potential duration and sustainability of care and treatment for the trial participant.***

care and treatment, post-exposure prophylaxis and antiretroviral therapy, according to the best scientific evidence for effectiveness available at the time of the trial; and should last at least for the duration for the trial, and longer, if so negotiated

- at a level decided upon by the host country, e.g. it might include immunological monitoring, physician visits, prevention and treatment of opportunistic infections, and palliative care, but not necessarily antiretroviral therapy; and should be made reasonably available for the lifetime of the participants
- at a level consistent with that available in the host country; there is no imperative to provide a level of care consistent with that in the sponsoring country, or with the highest available in the world.

Competing considerations that have led to disagreement about the standard of care and treatment include:

- the need to achieve equity in care and treatment for all participants in HIV vaccine trials globally; in particular, to achieve equity between potential participants from sponsor countries and host countries
- an ethical obligation of sponsors to provide care and treatment according to their resources
- concern that a high level of care and treatment will constitute undue incentives and inducements for countries and communities to participate
- concern that governments might abdicate on their responsibility to provide care and treatment

if sponsors fill this role

- governments' desire to be able to attract research into their countries in order to address the critical need of their populations for an HIV preventive vaccine
- the right and responsibility of sovereign nations and communities to determine for themselves the balance of risks and benefits they are willing to accept.

In the light of these competing concerns, it is recommended that:

- A consensus on the standard/level of care and treatment, its duration, and who will bear the costs should be reached prior to a decision to host HIV vaccine development.
- This consensus should emerge from an extensive dialogue involving the above-mentioned competing concerns among sponsors, and representatives from the potential host country and communities from which potential trial participants would be drawn, e.g. government officials, national scientific and ethical communities, affected populations, relevant NGOs, local religious and community leaders.
- Such a consensus should aim for achieving, as closely as possible, the ideal of provision of the best proven therapy for trial participants, in the light of relevant conditions and concerns.
- Sponsors should seek, at a minimum, to ensure access to a level of care and treatment that approaches the best proven care and treatment that are attainable in the potential host country.

- Those participating in the planning of vaccine development programmes should seek to provide a comprehensive care and treatment package based, at a minimum, on standards of care developed by the community, but also taking into account the additional resources and higher standards brought by the sponsor into the research setting.
- Sponsors should contribute to the building up of both the research capacity and the health care delivery capacity of the community where the research is to be carried out, in such a way that they become integrated into the infrastructure of the community.

Such a care and treatment package should include, but not be limited to, some or all of the following items, depending on the type of research, the setting, and the consensus reached by all interested parties before the trials begin:

- counselling
- preventive methods and means
- treatment for other STIs
- tuberculosis prevention and treatment
- prevention/treatment of opportunistic infections
- nutrition
- palliative care, including pain control and spiritual care
- referral to social and community support
- family planning
- home-based care
- antiretroviral therapy

Women, including pregnant women, potentially pregnant women and breast-feeding women, should be eligible for enrolment in HIV preventive vaccine trials, both as a matter of equity and because in many communities throughout the world women are at high risk of HIV infection. Therefore, the safety, immunogenicity, and efficacy of candidate vaccines should be established for women, and for their fetus and breast-fed child, where applicable.

In these situations, the clinical trials should be designed with the intent of establishing the effects of the candidate vaccine on the health of the woman and the fetus and/or breast-fed infant, where applicable.

Although the enrolment of pregnant, potentially pregnant, or breast-feeding women complicates the analysis of risks and benefits, because both the woman and the fetus or infant could be benefited or harmed, such women should be viewed as autonomous decision-makers, capable of making an informed choice for

Guidance Point 17 : Women

As women, including those who are potentially pregnant, pregnant, or breast-feeding, should be recipients of future HIV preventive vaccines, women should be included in clinical trials in order to verify safety, immunogenicity, and efficacy from their standpoint. During such research, women should receive adequate information to make informed choices about risks to themselves, as well as to their fetus or breast-fed infant, where applicable.

themselves and for their fetus or child. As with all research participants, steps should be taken to ensure that pregnant or breast-feeding women who are enrolled in vaccine trials are capable of giving informed consent, as indicated in **Guidance Points 12** and **13**. Furthermore, in order for (pregnant) women to be able to make an informed choice for their fetus/breast-fed infant, they should be duly informed about any potential for teratogenesis and other risks to the fetus, and/or the breast-fed infant. If there are risks related to breast-feeding, they should be informed of the availability of nutritional substitutes and other supportive services.

Children⁴, including infants and adolescents, should be eligible for enrolment in HIV preventive vaccine trials, both as a matter of equity and as a function of the fact that in many communities throughout the world children are at high risk of HIV infection. Infants born to HIV-infected mothers are at risk of becoming infected during birth and during the post-partum period through breast-feeding. Many adolescents are also at high risk of infection due to

Guidance Point 18 : Children

As children should be recipients of future HIV preventive vaccines, children should be included in clinical trials in order to verify safety, immunogenicity, and efficacy from their standpoint. Efforts should be taken to design vaccine development programmes that address the particular ethical and legal considerations relevant for children, and safeguard their rights and welfare during participation.

sexual activity, lack of access to HIV prevention education and means, and engagement in injecting drug use.

Therefore, vaccine development programmes should consider the needs of children for an effective HIV vaccine; should explore the legal, ethical and health considerations relevant to their participation in vaccine research; and should enrol children in clinical trials designed to establish safety, immunogenicity, and efficacy for their age groups, once they can be so enrolled in terms of meeting the health needs and ethical considerations relevant to their situation. Those designing vaccine development programmes that might include children should do so in consultation with groups dedicated to the protection and promotion of the rights and welfare of children, both at international and national levels.

Unless exceptions are authorized by national legislation in the host country, consent to participate in an HIV vaccine trial must be secured from the parent or guardian of a child who is a minor before the enrolment of the child as a participant in a vaccine trial. The consent of one parent is generally sufficient, unless national law requires the consent of both. Every effort should be made to obtain consent to participate in the trial also from the child according to the evolving capacities of the child.

⁴ As defined by the Convention on the Rights of the Child, Article 1 :
“... a child means every human being below the age of eighteen years unless, under the law applicable to the child, majority is attained earlier.”

In some jurisdictions, individuals who are below the age of consent are authorized to receive, without the consent or awareness of their parents or guardians, such medical services as abortion, contraception, treatment for drug or alcohol abuse, treatment of sexually transmitted diseases, etc. In some of these jurisdictions, such minors are also authorized to consent to serve as participants in research in the same categories without the agreement or the awareness of their parents or guardians provided the research presents no more than “minimal risk”. However, such authorization does not justify the enrolment of minors as participants in vaccine trials without the consent of their parents or guardians.

In some jurisdictions, some individuals who are below the general age of consent are regarded as “emancipated” or “mature” minors and are authorized to consent without the agreement or even the awareness of their parents or guardians. These may include those who are married, parents, pregnant or living independently. When authorized by national legislation, minors in these categories may consent to participation in vaccine trials without the permission of their parents or guardians.

The Joint United Nations Programme on HIV/AIDS (UNAIDS) brings together eight UN agencies in a common effort to fight the epidemic: the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the United Nations Population Fund (UNFPA), the United Nations International Drug Control Programme (UNDCP), the International Labour Organization (ILO), the United Nations Educational, Scientific and Cultural Organization (UNESCO), the World Health Organization (WHO), and the World Bank.

UNAIDS, as a cosponsored programme, unites the responses to the epidemic of its eight cosponsoring organizations and supplements these efforts with special initiatives. Its purpose is to lead and assist an expansion of the international response to HIV/AIDS on all fronts. UNAIDS works with a broad range of partners—governmental and nongovernmental, business, scientific and lay—to share knowledge, skills and best practices across boundaries.

Produced with environment friendly materials

As the number of people infected by HIV and dying from AIDS increases, the need for an effective HIV preventive vaccine becomes more urgent. Developing such a vaccine will require an extensive international cooperative effort, drawing on partners from various health sectors, governments, intergovernmental organizations, research institutions, industries and affected populations. These partners will also be required to address the difficult ethical concerns involved in the development of HIV vaccines.

This document highlights some of the critical elements that must be considered in HIV vaccine development activities. It suggests standards, as well as processes for arriving at standards, and can be used as a frame of reference from which to conduct international, national and local-level discussions. It is hoped that this document will be of use to potential research participants, investigators, community members, government representatives, pharmaceutical companies, and ethical and scientific review committees involved in the development of a preventive HIV vaccine.

Joint United Nations Programme on HIV/AIDS (UNAIDS)
UNAIDS - 20 avenue Appia - 1211 Geneva 27 - Switzerland
Telephone: (+41) 22 791 36 66 - Fax: (+41) 22 791 41 87
E-mail: unaids@unaids.org - Internet: <http://www.unaids.org>



Joint United Nations Programme on HIV/AIDS

UNAIDS

UNICEF • WFP • UNDP • UNFPA • UNODC
ILO • UNESCO • WHO • WORLD BANK