Developing Vaccines for HIV and AIDS

Preparedness

An Introduction for Community Groups

An International Council of AIDS Service Organizations Publication

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ICASO works to strengthen the community-based response to HIV/AIDS in all the regions of the world. Our mission is to:

- mobilize communities and their organizations to participate in the response to HIV/AIDS;
- articulate and advocate the needs and concerns of communities and their organizations;
- ensure that community-based organizations, particularly those with fewer resources and within affected communities, are strengthened in their work to prevent HIV infection, and to provide treatment, care and support for people living with and affected by HIV/AIDS;
- promote the greater involvement of people living with, and affected by HIV/AIDS in all aspects of prevention, treatment, care and support, and research;
- promote human rights in the development and implementation of policies and programs responding to all aspects of HIV/AIDS.

HIV/AIDS Vaccine Primer for Community Groups

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Introduction

The human toll of AIDS is staggering. An estimated 20 million men, women and children have died from AIDS. More than 40 million people are living with HIV. Each day, another 14,000 people are infected.

AIDS is overwhelming health care systems and national economies in a number of developing countries. More than 95% of all new infections are in developing countries, making HIV/AIDS a serious threat not only to global health, but also to global development. According to the United Nations, medical and human costs of AIDS have actually reversed economic and social development in several countries.

Preventing people from becoming infected is the best way of controlling the epidemic. Current prevention efforts - including condom education, clean needle distribution, peer counselling, providing HIV treatments to reduce mother to child transmission, and making blood supplies safer - have slowed the spread of HIV, but have not stopped it. Clearly these activities need to be expanded and made more widely available throughout the world.

In parallel to current efforts to expand access to prevention methods scientists are working to develop new prevention technologies. Two exciting new technologies are preventive vaccines and microbicides, products that women can apply vaginally or rectally before sex to protect themselves from being infected by HIV and other sexually transmitted

infections[1]. Both technologies are currently undergoing clinical trials in a number of countries but there is still considerable work that needs to be done and it will still be 7 or more years before they will become widely available.

Community groups and NGOs can play an active role in accelerating the development of these products and ensuring future access by advocating today for:

- An increase in the funding for product development;
- An increase in emphasis during product development on the particular needs of developing countries (i.e product development efforts need to focus on products that will be readily useable in developing countries);
- The ethical conduct of clinical trials; and
- Commitments from international donors to ensure that funding will be available so that once these products are developed they can be made readily and widely available at an affordable price to those who need them most.

In addition, community groups and NGOs in countries where clinical trials are planned or on going can play an important role in facilitating the trials.

The expansion of access to prevention technologies and the development of new technologies, however, needs to be done hand in hand with efforts directed at improving the access of people who are infected with HIV to care and treatment – and in encouraging those who may be infected to be tested and

[1] There are several microbicides under development in laboratories and clinics around the world but none are available yet. For more information on microbicides contact the Global Campaign for Microbicides and Prevention Options for Women, c/o PATH, 1800 K Street, Suite 800, Washington DC 20006, USA. (Website: www. Global-campaign.org)

counseled to ensure appropriate medical management.

This document provides a basic introduction to HIV/AIDS vaccine development and is the first in a series of primers that ICASO is planning covering issues around the development of new HIV/AIDS prevention technologies. We hope that this document will increase people's awareness of HIV/AIDS vaccine development and will encourage individuals and organizations to become actively involved in the development of new HIV/AIDS prevention technologies.

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How Can this Document Be Used to Promote HIV/AIDS Vaccine Development?

This document contains a basic introduction to HIV/AIDS vaccine development. Organizations and individuals can use this document in one or more of the following ways:

- As a way to start learning about what vaccines are and how they are developed.

  This document provides basic information and lists sources for additional information.

- As a way of sharing information with others.

  This document can be used to inform other organizations and the general public about HIV/AIDS vaccine issues.

- As a way of determining how to participate in the international HIV/AIDS vaccine development effort.

  This document describes some of the ways that individuals and organizations can become more involved in the process.

- As a way to begin defining questions, concerns, and policy issues.

  This document can be used by organizations and individuals to begin defining advocacy positions around HIV/AIDS vaccine development.

Readers who would like more detailed information on HIV/AIDS vaccine development should consult the list of resources at the end of the document. Readers who would like more detailed information regarding vaccine science should refer to ICASO's science primer.

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An Introduction to Vaccines

Vaccines save millions of lives each year and protect many more people from getting sick from a number of diseases including measles, chicken pox, influenza, hepatitis A and B, mumps, pertussis and rubella. They are one of the most powerful and cost-effective health interventions available today. For example, extensive use of the smallpox vaccine eradicated that disease from the world. As well, widespread vaccination against polio has reduced the number of cases of the disease dramatically (see chart); today, the Western Hemisphere, Europe, and many parts of Asia are free from polio. Unfortunately, however, there are a number of important diseases for which we have yet to develop an effective vaccine, including HIV/AIDS, malaria and tuberculosis.

Common vaccine preventable diseases:

- Chicken pox
- Hepatitis A
- Hepatitis B
- Hib disease
- Influenza
- Measles
- Mumps
- Pertussis
- Pneumococcal pneumonia
- Polio

What is a Vaccine?

The term vaccine is usually used to describe products that are designed to prevent individuals from getting a disease. All of today's licensed vaccines are preventive vaccines. In other words they are not cures and are not designed to help people who are sick or who already have a disease to recover.

Scientists, however, are also trying to develop what are called "therapeutic vaccines." Therapeutic vaccines are

designed to treat disease, not to prevent it, and could be used by people who are already infected. Scientists are currently trying to develop therapeutic vaccines that will help the immune systems of people with HIV, cancer, hepatitis C and a number of other conditions. Therapeutic vaccines for HIV, however, are still very much in the early stages of development and no product has been licensed for use. In this document the term vaccine is used to refer to preventive vaccines, not therapeutic vaccines.

How do Vaccines Work?

Preventive vaccines work by provoking a response from a person's immune system, their body's mechanism for fighting disease. When an individual is given a vaccine against disease X the vaccine stimulates the body's immune system and teaches it to recognize that disease. This response is then stored in the immune system's memory so that if he or she is exposed to disease X at a later stage the immune system is ready to respond rapidly and to fight off the potential infection before

An ideal HIV/ AIDS vaccine would:

- Be effective regardless of the nutritional and health status or ethnicity of the population;
- Protect individuals against all subtypes of HIV;
- Protect against any route of HIV infection;
- Be inexpensive to manufacture;
- Be easy to transport and administer;
- Be stable under field conditions; and
- Provide long lasting protection - i.e., require few (if any) follow-up inoculations.

Given the rate of spread of HIV worldwide, even a less-than-ideal vaccine would provide substantial public health benefit and help contain the epidemic.

Adapted from Scientific Blueprint for AIDS Vaccine Development International AIDS Vaccine Initiative.

it can cause disease.

How Safe are Vaccines?

When properly manufactured and used, vaccines are among the safest of health products. Vaccine safety is ensured by undertaking extensive research in laboratories, animals and human volunteers before the vaccine is approved for use. In undertaking these studies researchers are looking for any potential side effects that may be associated with the vaccine. In order for a vaccine to be approved by national authorities it must produce protective immunity with only minimal side effects (such as redness and soreness at the vaccination site) for the overwhelming majority of those who receive it. More discomfort in side effects may, however, be acceptable if the disease the vaccine is designed to prevent is very serious. For example, most people would consider vaccine side effects that had symptoms similar to a bad cold acceptable if the vaccine protected them from HIV infection. In addition, once a vaccine is approved for public use, national and international health agencies and regulatory bodies continuously monitor its safety and will remove the product approval if serious side effects are discovered.

How Likely is It That an HIV/AIDS Vaccine Will Be Developed?

The scientific consensus is that an HIV/AIDS vaccine is an achievable goal. This consensus is based on more than a decade of careful scientific research. Monkeys have been protected by experimental vaccines, and a number of candidate vaccines have been shown to be safe in Phase I trials and to trigger immune responses. However, it is also important to remember that vaccine development is a long and complicated process and while

there are exciting advances and more vaccine candidates moving into human trials there is no guarantee that one of the vaccines currently being tested will prove to be effective.

Will an HIV/AIDS Vaccine Protect Me from Getting HIV?

None of the child or adult vaccines that are currently in use are totally effective. Rather they substantially reduce the risk of infection. This will almost certainly be the case with an HIV/AIDS vaccine and hence it will be important that people continue to make use of other prevention methods as well. This will be particularly important if the vaccine provides low levels of protection. This possibility is an important concept for communities to understand so that expectations are realistic. (Please refer to the Science primer for further information on partially effective vaccines)

Is There Any Risk of Becoming Infected From an HIV/AIDS Vaccine?

There is no risk of becoming infected with any of the HIV/AIDS vaccines currently in human clinical trials. These vaccines make use of small, synthetic pieces of the HIV specifically designed to stimulate the immune system. In other words, they are made in a laboratory and contain only a fraction of the virus.

The approaches scientists are using to develop HIV/AIDS vaccines are different from the approaches that account for many of the other vaccines in use today. Many of the vaccines used widely today are based on killed or weakened forms of the bacteria or virus that causes the disease the vaccine prevents. When prepared correctly, vaccines made of killed or weakened

agents carry no risk of infection either. At present, however, no company or organization is currently pursuing either of these strategies for an HIV/AIDS vaccine because of the concerns that improper preparation might result in a vaccine that is infectious.

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How are Vaccines Developed?

Vaccine development is a lengthy process of testing ideas and products. Vaccines are developed through a series of experiments designed to answer scientific questions and evaluate possible vaccine concepts. This research effort involves a number of different stakeholders from the private and public sectors - scientists and clinicians working in private companies and research agencies, government officials and community groups. Vaccine concepts are usually tested and improved many times before they are ready for use. This process of developing ideas into usable vaccines can be divided into five stages. They are described below (using HIV/AIDS as an example):

Idea Generation (Basic Science)

The first stage of vaccine development occurs in universities, research institutes and private companies. Scientists working with existing scientific knowledge and laboratory tools develop ideas for how an HIV/AIDS vaccine could function. They examine cells from the human immune system and parts of the HIV virus for clues about what might work and how a vaccine might be designed. Hundreds of scientists all over the world are now contributing to this stage of vaccine development. Many new designs are generated each year; only a very small number are successful enough in the laboratory to move forward to the next stage.

Pre-Clinical Development

In the second stage, scientists test vaccine preparations in cell-culture. If the results are promising, the vaccines are then tested in animals. Animals are used at this stage to see if the vaccine is safe and if it works in the way scientists believed. In HIV/AIDS vaccine development, monkeys or baboons are used because these animals can also become infected with a monkey version of HIV called SIV. Scientists also use the information from animal studies to improve the design of the experimental vaccines. Only a small percentage of the vaccines that make it to the pre-clinical development stage are deemed to be safe enough and promising enough to be evaluated in people.

Clinical Trials

If a vaccine is found to be safe and promising in laboratory and animal testing, it moves to the third stage: clinical trials in humans. A clinical trial is a research study used to assess the benefits and risks of a new vaccine. Clinical trials are conducted in

The Three Phases of Clinical Trials

Phase I: looks at safety, side effects and measures immune responses (immunogenicity) in a small group of low risk HIV negative volunteers.

Phase II: looks at safety and immunogenicity in a larger group and helps determine the number of doses needed. If volunteers in Phase II are at higher risk, some information might be gained about whether the vaccine 'works', or has efficacy, but it is not enough for licensure or widespread use.

Phase III: looks at efficacy (how well the vaccine works) in large groups of high-risk HIV negative individuals.

three sequential steps or phases and the whole process can take a number of years.

Licensing

If the clinical trials are successful and the company or vaccine sponsor decides to market the vaccine it has to obtain a license from the relevant government authorities. This involves making an application to the government department responsible for regulating pharmaceutical products in each of the countries it wants to market the product in. In the past, this process has taken several years. Today, policy makers and global health advocates are working to develop more rapid licensing and approval processes to avoid this delay when an HIV/AIDS vaccine becomes available.

Delivery

Developing and licensing a vaccine, however, will not help people from becoming infected unless they have access to it. This in turn, will require significant investments in ensuring that appropriate procurement and delivery systems are in place and the necessary funding to purchase the vaccines and support vaccine delivery. Historically, delivery of vaccines to people around the world has proved to be a difficult task. In fact, even today many safe and effective vaccines are unavailable to most people in the world. It is now nearly 20 years since the Hepatitis B vaccine was licensed and yet only 30% of the newborn infants in the world are receiving it. Ensuring the timely delivery of safe, effective vaccines is a key component of the HIV/AIDS vaccine development effort.

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How Close Are We to Having an HIV/AIDS Vaccine?

Since HIV was identified as the virus that causes AIDS in 1984, over 30 preventive vaccine candidates have been tested in Phase I trials. Only one vaccine candidate, however, has progressed to Phase III efficacy trials and only two other concepts have reached the stage of Phase II trials.

The vaccine currently in Phase III trials has been developed by VaxGen and is a recombinant subunit vaccine. There are currently two Phase III trials of this product underway. One trial is being conducted in the United States, Canada and the Netherlands primarily in men who have sex with men, using a vaccine based on HIV subtype B. The other trial is being conducted among intravenous drug users in Bangkok, Thailand, using a vaccine based on HIV subtypes B and E. Results from these trials should be available in late 2002 or early 2003.

To date, the vast majority of the clinical trials have been conducted in developed countries, and most of these vaccines have been based on HIV subtype B, the subtype of HIV that predominates in North America, Europe, Latin American, Australia and New Zealand. Subtype B, however, accounts for only a small percentage of new infections. So far, only two HIV vaccines have been tested that are based on the two most prevalent subtypes of HIV - A and C -, which together account for about two-thirds of all HIV infections worldwide. Both of these vaccines are based on subtype A and are currently in Phase I trials in Kenya. A number of products based on subtype C, however, are in pre-clinical development and hopefully will be ready to start clinical trials shortly.

At this time, it is not clear how important HIV subtypes are.

However, in order to increase the chance of finding out if a vaccine works or not most of the groups working on HIV/AIDS vaccines plan to match their candidate vaccine to the subtype that is found where they are planning to test the vaccine. Once we know if a matched candidate vaccine works then it will be important to find out if also provides protection against other subtypes as this would simplify and speed up availability of an HIV/AIDS vaccine.

The following table records the trials that have been conducted or are being conducted in 2000/02. The table also lists the type of vaccine approach that has been tested.

For more information on these different vaccine approaches see: ICASO science primer, IAVI Scientific Blueprint, US National Institutes of Health.

World Wide HIV Vaccine Trials: 2000-2002

COUNTRY	VACCINE APPROACH	TYPE OF TRIAL	SPONSORING INSTITUTION	YEAR TRIAL STARTED OR IS PLANNED
Brazil, ,Haiti, Trinidad and Tobago	Multiple vaccines • ALVAC vCP 1452: env, gag, pol genes and additional CTL epitopes from HIV-1subtypes B, plus vaccinia virus enhancer sequences, in canary pox vector (Aventis Pasteur) • AIDSVAX B/B: envelope protein subunits from two HIV –subtype B strains	Phase 11	NIAD	June 2000
U.S.A	Multiple vaccines • ALVAC Vcp 1452: env, gag, pol genes and additional CTL epitopes from HIV-1subtypes B, plus vaccinia virus enhancer sequences, in canary pox vector (Aventis Pasteur) • AIDSVAX B/B: envelope protein subunits from two HIV –subtype B strains	Phase 11	NIAD, HVTN	Dec 2000
UK	Multiple Vaccines; • HIVA: gag gene and approximately 25 CTL epitopes from HIV-I subtype A in a DNA plasmid (Cobra Pharmaceuticals) • MVA.HIVA : gag gene and approximately 25CL epitopes from virus Ankara (MVA) vector (Impofstoffwerk Dessau-Tornau GmbH (IDT)	Phase1/11	MRC/Oxford, IAVI	April 2002
Thailand	Multiple Vaccines • ALVAC Vcp125 1521: env (from HIV-1 subtype E) and gag/pro genes (from HIV subtype B), expressed in canary pox vector (Aventis Pasteur) • Gp 160 THO 23 /LAI-DID (Aventis Pasteur) • CM235 (ThaiE)gp 120 plus SF2(B) gp 120: gp 120 envelope protein subunit from HIV-1 subtype E(Chiron)	Phase 1/11	WRAIR RV 132	March 2000
Thailand	Multiple Vaccines: • ALVAC Vcp125 1521: env (from HIV-1 subtype E) and gag/pro genes (from HIV subtype B), expressed in canary pox vector (Aventis Pasteur) • Envelope protein subunit from HIV-1 envelope derived peptide from HIV –1 subtype B (UBI)	Phase 1/11	WRAIR RV I35	April 2000

COUNTRY	VACCINE APPROACH	TYPE OF TRIAL	SPONSORING INSTITUTION	YEAR TRIAL STARTED OR IS PLANNED
France	Lipopeptides containing CTL epitopes from HIV-1 subtype B and a tetanus toxoid helper epitope (Biovector)	Phase 1	ANRS – VAC 12	May 2001
USA	VRC 4302 : gag/pol fusion protein in a DNA plasmid (Vical)	Phase 1	VRC; NIAD 01-1-0079	January 2001
USA	Recombinant, adjuvanted candidate HIV vaccine – Nef, Tat, and gp 120 formulated wit the proprietary adjuvant Aso2 (GlaxoSmithKline)	Phase 1	GlaxoSmithKline HVTN	February 2002
Kenya	• MVA.HIVA : gag gene and approximately 25CL epitopes from virus Ankara (MVA) vector (Impofstoffwerk Dessau-Tornau GmbH (IDT)	Phase 1	KAVI - MID;IAVI	February 2002
UK	HIVA: gag gene and approximately 25 CTL epitopes from HIV-I subtype A in a DNA plasmid (Cobra Pharmaceuticals)	Phase 1	University of Oxford	August 2000
USA	ALVAC v CP205:env,gag and pol genes from 2 HIV-1subtype B strains in canary pox vector (Aventis Pasteur)	Phase 1	NIAD – AVEG 038	March 2000
UK	MVA.HIVA : gag gene and approximately 25CL epitopes from virus Ankara (MVA) vector (Impofstoffwerk Dessau-Tornau GmbH (IDT)	Phase 1	MRC/Oxford; IAVI HAMOX-1-MID	March 2001
Kenya	HIVA: gag gene and approximately 25 CTL epitopes from HIV-I subtype A in a DNA plasmid (Cobra Pharmaceuticals)	Phase 1	KAVI;IAVI KAVI-1-DIM	February 2001
UK	HIVA: gag gene and approximately 25 CTL epitopes from HIV-I subtype A in a DNA plasmid (Cobra Pharmaceuticals) MVA.HIVA : gag gene and approximately 25CL epitopes from virus Ankara (MVA) vector (Impofstoffwerk Dessau-Tornau GmbH (IDT)	Phase 1	MRC/ Oxford; IAVI	October 2001

Source: Adapted from Scientific Blueprint for *Aids Vaccine Development, International AIDS Vaccine Initiative* (IAVI)

HIV Vaccine Trials Planned for 2002/03

MANUFACTURER	VACCINE	ANTICIPATED START DATE	COUNTRIES
H.Robinson	DNA-pGA2/JS2	June/July 2002	USA
Alphavax	VEE-gag C	May/June	USA/RSA
ANRS	Lipopeptide 5	June/July	USA
Eppimune	Poly CTL Epitope	Aug/Sept	USA/Botswana
Globeimmune	Yeast Vectpr gag	Sept/Oct	USA
VRC	Multiclade DNA	Sept/Oct	USA
Therion	MVA/FPV	Sept/Oct	USA
Merck	DNA +adenovirus	Sept	USA + 5 international sites
Wyeth	CTL peptides		USA
Wyeth	DNA-gag/gag + IL-12	2003	USA
Chiron	Gp140 clade B	2003	USA +
B.Moss	MVA-pGA/Js2	2003	

Compiled by ICASO

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How Do We Know Whether the Trial is Ethical?

Any new vaccine, no matter how promising it appears in laboratory and animal testing goes through a careful process of clinical trials in humans before its usefulness can be determined. The detailed plan for a trial is called a protocol. The protocol explains procedures for how the vaccine will be given, who is eligible to take part, what the timetable is for tests and clinical visits by participants, how long the study will last, how the results will be assessed, and so forth. (Please refer to the Science Primer for more detailed information)

All protocols undergo strict scientific and ethical review by the relevant national scientific and ethical review committees in the country where the trial is taking place. In addition, trials that are financed or involve researchers from other countries often have to be approved by review bodies in their countries. These bodies, which should be independent of the people running or financing the trial, are responsible for protecting the rights and interests of the people in the trial and in ensuring that the trial is scientifically and ethically sound. Any concerns they have must be addressed before the trial can begin. In countries where the capacity does not currently exist to conduct an independent and meaningful scientific and ethical review trials should not start until this capacity has been developed.

In addition, prior to a vaccine trial being started an independent Data and Safety Monitoring Board should be established. This group is responsible for monitoring the safety of the trial and making sure that trial volunteers are not put at risk. In order to do their job properly they require full access to the safety data as it emerges from the study and have the power to stop the trial if they are concerned about the incidence of side effects. In addition, they may review the clinical data part way through the trial and can stop the trial

if the experimental product is proving to be extremely successful or harmful.

In most clinical trials researchers randomly allocate the volunteers into two groups or study arms. One group receives the product being tested and the other group, known as the control group, receives a placebo, an inactive harmless substance that is delivered in the same way as the experimental product. The reason researchers randomly allocate the participants is to try to make sure that the participants in the two groups of the trial are broadly similar so that the effects of the vaccine can be reliably measured. In addition, in most trials, neither the researchers nor the participants know who is getting the experimental product. This is called double blinding. (If only the researchers know who is getting the vaccine, this is single blinding). The purpose of blinding is to make sure that the results of the trial are not biased or influenced by people's expectations. For example, if volunteers in a trial know they have been given the active substance and take more risks because they think they might be protected this will affect the study results.

To determine how effective an HIV/AIDS vaccine is the scientists and clinicians involved in a Phase III trial will need to monitor the health of the two groups for a period of time, probably in the order of three or more years, and will keep track of how many volunteers get HIV despite the trial's prevention efforts. The researchers then "unblind" the study and compare the results in the two groups. If fewer people get HIV in the vaccine group than in the control group, then the vaccine can be declared at least a partial success.

Some Ethical Issues Surrounding HIV/AIDS Vaccine Trials

Organizations and individuals involved in HIV/AIDS vaccine clinical trials need to be able to and willing to address the difficult ethical concerns that arise during the development and testing of HIV/AIDS vaccines. One of the best sources of information is the UNAIDS Guidance Document, "Ethical considerations in HIV preventive vaccine research". This document was issued in 2000 and is based on a series of forums held in different parts of the world. This document lists 18 different guidance points ranging from community involvement to access to treatment. This section touches on a few of the issues raised.

What is informed consent?

Before a person can participate in a vaccine trial he or she must give informed consent. Informed consent is an ongoing process and should be obtained from each individual when he or she is screened to see if they are eligible to participate in the trial and again before he or she is enrolled in the trial. Efforts should also be made to ensure that participants continue to understand and to participate freely as the trial progresses.

In order for a person to give informed consent they must understand:

- What participating in the trial will involve – e.g. Number of clinic visits, what will happen during those visits
- The risks and benefits associated with participation in the trial
- That they have the right not to participate
- That they have the right to withdraw at any time

Is it ethical to give some people a placebo?

The UNAIDS ethical guidance document (point 11) suggests that as long as there is no known effective HIV preventive vaccine, a placebo control group should be considered ethically acceptable in a Phase II HIV preventive vaccine trial. However, where it is ethically and scientifically acceptable, they recommend that consideration should be given to the use in the control group of a vaccine to prevent a relevant condition apart from HIV (e.g. hepatitis B). Details of what is being given to the control group are included in the trial protocol.

What sort of prevention methods should be offered to trial participants?

In the case of an HIV/AIDS vaccine trial the UNAIDS ethical guidance document (point 14) recommends that appropriate risk-reduction counseling and access to prevention methods (e.g. condoms, sterile injection equipment (where legal), and treatment of sexually transmitted infections) should be provided to all vaccine trial participants, with new methods added as they are discovered and validated.

In order to ensure that a research participant receives the necessary information to make an informed decision, it is important to provide each participant with:

- Description of the research and participant's participation, including identification of experimental procedures
- Description of reasonably foreseeable risks
- Description of expected benefits
- Potentially advantageous alternatives to participation
- Explanation of confidentiality
- Explanation of compensation for injuries
- Whom to contact about the research and participants' rights
- Explanation that participation is voluntary

What sort of care should be made available to people who participate in a trial and become infected?

Care and treatment for HIV and its associated conditions should be provided to participants in HIV/AIDS vaccine trials (UNAIDS Guidance Point 16). This package of treatment and care should be agreed upon by the sponsor, host country, and community where the trial is taking place prior to the trial starting. At present, there is no universal consensus regarding the level of care and treatment that should be provided. Ideally, the best-proven therapies should be provided.

What protection will be offered to people who participate in a trial who are not infected but test HIV positive as a result of the vaccine?

HIV/AIDS vaccines are designed to stimulate the body to create immune defenses against HIV infection. Some of the vaccine candidates currently being tested generate responses that are similar to those that are used in the standard tests used to see if someone is HIV positive. As a result, it is possible that a volunteer participating in an HIV/AIDS vaccine trial could test HIV positive on one of these tests. This, however, does not mean that he or she is necessarily infected. The clinicians involved in the study will do other tests that can discriminate between a vaccine response and a genuine infection.

In order to protect participants in vaccine trials, it will be important that the tests that can discriminate between a vaccine response and HIV infection continue to be available after the trial ends and that participants can access these tests if required.

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What can communities and NGOs do to get involved in HIV/AIDS vaccine development?

Lessons from clinical trials for drugs and other prevention technologies have highlighted the importance of the involvement of NGOs, health advocates and communities in medical research. The inclusion of communities in research activities not only leads to better science but can also play an important role in ensuring that research findings are translated rapidly into accepted and effective programs. History also demonstrates that when medical and public health research is planned and conducted without considering the human context of such work, or without regard for human rights, the individuals who participate in research activities, along with the communities they belong to, may well be harmed.

Global Advocacy

At the global level, community groups and NGOs can help ensure that HIV/AIDS vaccine research and development activities are firmly established on national, regional and international agendas and that the necessary steps are being taken so that when a vaccine is developed it will be made available rapidly in those countries where it is most needed.

In particular, community groups and NGOs can play an active role in advocating today for:

- Increased funding for product development;
- Increased emphasis during product development on the particular needs of developing countries (i.e. product development efforts need to focus on products that will be

readily useable in developing countries);

- The ethical conduct of clinical trials; and

- Commitments from international donors to ensure that funding will be available to finance the purchase and distribution of vaccines.

Informing Communities

Another way for community representatives to become involved is by working with and informing communities about HIV/AIDS vaccines. Community education needs to start now to prepare people for the research process, and to lay the foundation for vaccination programs in countries around the world. Community groups and NGOs can accomplish this by:

- Assessing and shaping current attitudes and awareness about HIV/AIDS vaccines:
  Discuss HIV/AIDS vaccines with people. Help them understand the role vaccines might play in controlling HIV/AIDS. Use local meetings and networks as an opportunity to discuss vaccine development. Address people's fears.

- Linking with local, national and global information sources:
  Internet-based resources are an excellent way to find information on HIV/AIDS vaccine development (see the list of websites at the end of this document). At the local level, develop links and partnerships with relevant other stakeholders who are involved with HIV/AIDS vaccine development.

- Sharing information:
  The international effort to develop an HIV/AIDS vaccine can benefit from the experiences of your community. Participating in local, national and international conferences, joining local HIV/AIDS prevention and care networks, and publishing in newsletters and on websites are good ways to share information. It is also important to work with community media and make sure they are well informed about vaccine development.

- Integrating knowledge about vaccine development into HIV/AIDS prevention messages:
  Vaccine development should be viewed as one part of a broader HIV/AIDS prevention effort. Use existing community outreach networks to discuss and educate about HIV/AIDS vaccine development.

Country Planning

In countries where trials are on-going or planned community representatives can work with others within their country and internationally to assess how the country can and should participate in HIV/AIDS vaccine development activities. This could involve:

- Establishing partnerships with other stakeholders (Such as Government and civil society groups) that have an interest in vaccine development

- Developing appropriate information and education campaigns and interventions;

- Identifying resources needed for trials and meaningful community participation

- Bringing community perspective and issues to the attention of those who are planning the trial and the relevant

scientific and ethical committee; and

- Assisting in the development of strategies for ensuring that the media is well informed.

Even in countries where vaccine trials are not currently being planned community groups can do many of these activities. Delivering an effective vaccine will require many of the same steps as vaccine trials: building public awareness and political will, and identifying resources and gaps to ensure that once a vaccine is developed it will be widely available.

Involvement in Clinical Trials

In countries where HIV/AIDS vaccine trials are being planned or are on-going community groups and NGOs have an important role to play in all stages of the design, planning and implementation of the trials and in the dissemination of trial results. Their involvement is key to ensuring the ethical and scientific quality of the research and to ensuring its relevance to the affected community. Specific benefits from the active involvement of community groups and NGOs include:

- Ensuring that the protocol and informed consent process are sensitive to local social and cultural factors;

- Providing insight into the health beliefs of the study population and the appropriate design of risk reduction interventions;

- Facilitating the development of trust and understanding between the community and researchers;

- Assisting in the dissemination of information about the proposed research; and

- Making potential volunteers more comfortable with the trial and hence increasing participation and follow-up rates.

In addition, it is important that:

- Community perspectives are represented in the scientific and ethical committees reviewing proposed HIV/AIDS vaccine research protocols; and

- Community groups and NGOs are involved in any discussions on the levels of care and treatment study participants will receive and how this can best be achieved.

There are a number of ways that community groups and NGOs can become involved - one method that has been used is to establish a community group or board that acts as a link between the trial organizers and the community (see Box).

Once a trial is ongoing there are a number of things that community representatives can do to ensure that the concerns of the participants and their families are addressed and to help facilitate the trials. These include:

Community Platforms

Topics to cover include:

a) Objectives
b) Structure
c) Things that these groups can do:

- Work with researchers, sponsors and regulatory bodies to design a culturally informed consent strategy and process;

- Share information with communities where the trial is being planned on the HIV/AIDS vaccine development process and clinical trials;

- Relay community concerns to scientists and clinicians involved in the trial;

d) Examples: CABS (a US Concept) but put in place in the Uganda trial, Community Working Groups; Community Health Forums

- Monitoring the trial recruitment process to make sure that volunteers fully understand the risks and benefits of participating;

- Ensuring that the community is kept well informed about the trial;

- Relaying community concerns to the scientists and clinicians involved in the trial;

- Creating a supportive environment for those involved in the trial and for the communities they come from;

- Acting as an effective information resource for other community groups, other stakeholders and the media;

- Working to minimize the risk of an increase in transmission rates associated with participation in the trial or knowledge that a vaccine trial is being conducted; and

- Working to reduce the possibility of discrimination against trial volunteers should their participation become known.

Some Useful Questions to Ask the Researchers Planning a Clinical Trial

What is the goal of this research study?
Why are you doing this study? What vaccines are you testing? What questions do you want to answer from this study? What will you do with the answers? Have you or others done this type of research before? Have you done it in this country or in this community? What did you learn then, and how did you share your discoveries with the research volunteers and the community?

Who is responsible for this study?
Who is running this study? Whose idea was this study? Were people like me a part of putting it together? Who are the researchers? Are they doctors or scientists? Who do they work for? Have they done studies like this before? Is my government a part of this study? Who else is a part of this study? Who is paying for this study? Who will make money from the results of this study?

How are communities involved in this study?
How will the study be explained in my community? Aside from the government and researchers, who else will have reviewed the study before it starts? Who else in the community did you talk to? Do you have a Community Advisory Board (CAB) or other open process where people can get information? Who is on your CAB? When does it meet? Where? Whom from the study can I go to with ideas, questions, or complaints? How will people like me find out about how the study is going?

Who is being recruited for this study?
What kinds of people are you looking for? Why? Are you recruiting people less than 18 years of age? Are you recruiting people who cannot say no because of their job or for other reasons? How are you finding people for this study? Will you answer questions before a volunteer signs the consent form? Can a volunteer quit the study at any time?

What are the benefits to research volunteers?
Is payment involved? How will volunteers be paid? Will volunteers get free health care or other services if they participate? And if yes, for how long? Will volunteers get general health care and psychological care if they participate? And if yes, for how long?

How will volunteers be protected from harm?
What are the anticipated risks involved in participating in the trial? What evidence is there that the vaccine is safe? Will all volunteers get treated equally? If volunteers are harmed, who will take care of them? Will they get needed treatment and care? Who pays for their treatment and care? How will my organization or my community learn about any risks or harms faced by volunteers?

How will privacy be protected?
Who is going to see the information? Will names be used with the information? What happens to the information on volunteers who quit the study? Is there a written guarantee of privacy?

What will happen when this research study is completed?
What will you do with the results of the study? How will the public learn about the results? Will you send volunteers a copy of the results? When? What other studies are you planning to do in my country and in my community?

Source: Adapted from Participating in a Clinical Trial, United States National Institutes of Health

Glossary

Control Group
In vaccine clinical trials, the control group is given either another vaccine, if one exists, or a proven vaccine for another disease, or an inactive substance called placebo. The control group is compared with one or more groups of volunteers given experimental vaccines to detect any effects of the vaccine.

Data and Safety Monitoring Boards (DSMB)
A committee of independent clinical research experts who review data while a clinical trial is in progress. The DSMB ensures that participants are not exposed to undue risk and looks for any differences in effectiveness between the experimental and control group. The DSMB may review the data in such a way that they know which group received the vaccine and which did not. This group may recommend that a trial be modified or stopped if there are safety concerns, or if the trial objectives have been achieved.

Double Blind Study
A clinical trial in which neither the study staff nor the participants know which participants are receiving the experimental vaccine and which are receiving a placebo or another therapy. Double –blind trials are thought to generate objective results, since the researchers' and participants' expectations about the experimental vaccines do not affect the outcome.

Informed Consent
A process that is supported by a signed agreement between prospective participants for a clinical research and the researchers that ensures that the participants understand (1) Why the research is being done (2) What researchers want to accomplish (3) What will be done during the trial and for how long (4) What risks are involved (5) What, if any, benefits can be expected from the trial (6) What other interventions are

available (7) the participants right to leave the trial at any time.

Placebo
An inactive substance administered to some study participants while others receive the agent under evaluation, to provide a basis for comparison of effects.

Protective Immunity
Natural or acquired resistance provided by the immune system to a specific disease. Immunity may be partial or complete, specific or non-specific, long-lasting or temporary.

Protocol
The detailed plan for a clinical trial that states the trial's rationale, purpose, vaccine dosages, routes of administration, length of study, eligibility criteria and other aspects of the trial design.

Recombinant DNA Technology
The technique by which genetic material from one organism is inserted into a foreign cell of another organism in order to mass-produce the protein encoded by inserted genes.

Recombinant Subunit Vaccine
A vaccine that uses one or more components of a disease-causing organism, rather than the whole, to stimulate an immune response. HIV subunit vaccines produced by genetic engineering are referred to as recombinant subunit HIV vaccines – a subunit vaccine made using recombinant DNA technology.

Synthetic
Chemically engineered.

SIV (Simian immunodeficiency virus)
An HIV-like virus that infects and causes an AIDS-like disease in some species of monkeys.

Subtype
Also called clades. With respect to HIV isolates, a classification scheme based on genetic differences.

Resources

The following organizations are a good source of information on HIV vaccine development:

AIDS Vaccine Advocacy Coalition (AVAC)
5 years and counting
http://www.avac.org

Family Health International
Research Ethics Curriculum
http://www.fhi.org

HIV Vaccine Trial Networks
http://www.hvtn.org

International AIDS Vaccine Initiative (IAVI)
http://www.iavi.org

International Council of AIDS Service Organizations (ICASO)
Developing Vaccines to Prevent HIV and Aids:
An Introduction for Community Groups
http://www.icaso.org/vaccines/vaccineprimer.htm

National Institute of Health
(National Institute of Allergy and Infectious Diseases - NIAID)
Understanding Vaccines and HIV Vaccine Glossary
http://www.niaid.nih.gov

World Health Organization (WHO)
United Nations Joint Effort Against HIV/AIDS (UNAIDS)
HIV Vaccine Initiative
http://www.who.int | http://www.unaids.org

Websites with Information on HIV Vaccine Development

AIDS Fonds
http://www.aidsfonds.nl

AIDS Vaccine Advocacy Coalition
http://www.avac.org

African Aids Research Network
http://www.refer.sn/sngal_ct/rec/rars/rars.htm

Africa News
http://www.africanews.org

Canadian HIV/AIDS Legal Network
www.aidslaw.ca/Maincontent/issues/vaccines.htm *or*
www.aidslaw.ca/francais/Contenu/themes/vaccins.htm

Centres for Disease Control
http://www.cdc.gov/nip/publications/pink/

Children's AIDS Fund
http://www.childrensaidsfund.org/resources/vaccine.htm

Family Health International
http://www.fhi.org/en/aids/hivnet/nhivnet.html

Global Alliance for Vaccines and Immunization
http://www.vaccinealliance.org

Grupo Pela Vidda
http://www.pelavidda.org.br

Health Knowledge Network of South Africa
http://www.healthnet.org.za/hivaids/hivaids.htm

Infoweb
http://www.infoweb.org/top/vaccines/vaccines.html

International Association of Physicians for AIDS Care (IAPAC)
http://www.iapac.org

International Council of AIDS Service Organizations
http://www.icaso.org

Joint United Nations Programme on HIV/AIDS (UNAIDS)
http://www.unaids.org

Medical Research Council of South Africa
http://www.mrc.ac.za

Nationals AIDS Trust
http://www.nat.org.uk

National Institute of Allergy and Infectious Diseases, National Institutes of Health
http://www.niaid.nih.gov/daids/vaccine/default.htm

Pasteur Institute
http://www.pasteur.fr

Resolving legal, ethical and human rights challenges in HIV Vaccine Research
http://www.aidslaw.ca/durban2000/e-durban2000.htm

University of California at San Francisco
http://hivinsite.ucsf.edu/topics/vaccines/

V
Vaccines

ICASO

ICASO, the International Council of AIDS Service Organizations, works to strengthen the community-based response to HIV/AIDS, by connecting and representing NGOs throughout the world. Founded in 1991, ICASO operates from regional secretariats based on all five continents, guided by a central secretariat in Canada.

www.icaso.org