Imagine a world without AIDS.
Acknowledgements

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IAVI’s mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Integral to this mission is leaving communities and countries where trials are conducted better off as a result of IAVI’s activities. This goal involves many initiatives, among which is increasing literacy through appropriate and sustainable education and training mechanisms.

All reasonable efforts have been made to ensure the accuracy of information contained in this manual before its publication. However, this information may change from time to time as developments occur in AIDS vaccine research.
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Overview of vaccine literacy (VAXLit)

VAXLit Core Content
The Vaccine Literacy (VAXLit) Core Content contains basic information about AIDS vaccine development explained in simple language in a user-friendly format. The text is divided into eleven chapters covering a range of topics, from basic science and clinical trials to social and ethical issues related to vaccine development, as well as future access and use of vaccines.

VAXLit Toolkit
The VAXLit Core Content is one component of the VAXLit Toolkit, and serves as the technical basis for the other components. The Toolkit contains educational and training materials about AIDS vaccine development that can be readily tailored for use in different countries with a range of audiences. The Toolkit materials aim to provide accurate, globally-consistent information that can be used for audiences who may have little previous knowledge or experience with AIDS vaccine development or clinical trials.

The Toolkit contains the following components:
• Core Content
• Training Manual
• Fact Sheets – set of three
• User Guide CD-ROM containing all components listed above, including PowerPoint® presentations of the Core Content and Training Manual chapters.

Target audience
The Toolkit is primarily meant for use by individuals in the AIDS vaccine field, HIV-prevention research field and other related fields to facilitate AIDS vaccine education and outreach to a broad range of stakeholders.

Various components of the Toolkit can be adapted according to the specific audience(s), geographic location and/or programme objectives. This is explained in more detail in the VAXLit User Guide.
Use of the Core Content

VAXLit Core Content

The Core Content is primarily meant to be used as an informational resource for individuals and groups who are involved or interested in the AIDS vaccine field. It is not meant for general community distribution. Core Content users include, but are not limited to:

• Staff of AIDS vaccine or other HIV prevention clinical research centres.
• Staff of AIDS vaccine trial sponsors (e.g., IAVI, HVTN).
• Members of community advisory boards (CABs).
• Staff of nongovernmental organisations (NGOs).
• Counsellors who provide voluntary counselling and testing (VCT) services.
• Science journalists or other relevant media representatives.

The Core Content serves as a reference manual with basic information about AIDS vaccine development. It can also be used to develop new materials and tools for education and outreach.

For example, the Core Content may be used to develop:

• PowerPoint® presentations.
• Background reading for AIDS vaccine literacy (VAXLit) trainings.
• Informational fact sheets, brochures or other advocacy materials.
• Tools to explain difficult trial concepts to volunteers.
• Educational street plays, videos or radio programmes.
• Public speeches.

These materials and tools might be used for outreach to recruit trial participants, or they might be used to engage communities or national-level stakeholders to build understanding of and support for clinical trials and an eventual AIDS vaccine. The Core Content is organised in eleven chapters, each covering a specific topic, so users can easily select the information most relevant to their purposes.

Developing educational materials

As mentioned above, one of the primary uses of this document is for the development of educational materials. The development of quality
materials requires that certain steps be taken on a formal or informal basis. The final document should be user-friendly, textually concise and visually appealing. The following outlines some basic steps for developing materials.

1 Define the audience and aim
Identify the target audience characteristics and the aim(s) for producing informational material for the audience:

- Determine what the audience already knows about AIDS vaccine development.
- Prioritise the information needed or the primary questions the audience may have about AIDS vaccine development.
- Determine appropriate and applicable methods of message delivery (e.g., print material vs. street play or drama).
- Assess the audience’s ability to read and understand print material and the general literacy level.
- Identify desired information to convey to the audience.

Often, the most efficient and effective way to obtain the information above is through individual interviews, informal group meetings and focus group discussions.

2 Develop key messages
In order to develop key messages based on the Core Content, consider the following:

- Applicable text can be taken directly from the Core Content, where appropriate.
- Based on the characteristics of the audience (identified in step 1) the text can be adapted. Information should be rewritten in the local language, if appropriate.
- Consider using tools to explain concepts that will be effective for the audience, such as illustrations or local metaphors. Focus groups (used in step 1) may be useful in identifying such tools.
- Create draft text for the tool and review it with a technical team or other appropriate reviewers.
- Use the Key Message section at the end of each chapter in the Core Content to focus on the most relevant messages for your audience.
3 Design the tool
Production of print material involves careful graphic design and layout of information and illustrations. The following tips will help produce quality materials:

- Use simple illustrations, limiting each to present only one message.
- Make the material interactive (e.g., by using a question-and-answer format).
- Leave white space – do not overcrowd the material.
- Use familiar, realistic images and appropriate colours.

4 Pre-test and revise
Before materials are finalised, it is advisable to pre-test them with representatives from the target audience. The audience’s reaction and feedback is then used to revise the material before it is finalised and printed. Information gathered should include the audience’s comprehension of the message(s) conveyed, how attractive and acceptable the material is, how much the audience can identify with the information and if the material will cause them to change behaviour(s) or think differently. Pre-tests can be conducted on an individual or group basis. Generally, ‘open-ended’ and ‘probing’ questions are used in pre-tests.

5 Print, disseminate and evaluate
There are several important items to consider when printing materials that have budgetary as well as visual presentation implications: determine the number of copies needed; identify the size and number of pages; decide the number of colours for the design of the material and the type of paper stock. A careful dissemination plan should be in place for the finalised and produced material. Dissemination should also include evaluation by end-users.
Acknowledgement of IAVI and material review

IAVI requests that it be notified of any tools or materials produced using the Core Content by sending an email to pubs@iavi.org.

If IAVI has not been involved in the production of the tool, apart from provision of information through the Core Content, no review of the material is required by IAVI. IAVI requests that appropriate acknowledgment of the AIDS Vaccine Literacy Toolkit be given, but the IAVI logo should not be used.

Navigating the Core Content

For ease of use, each Core Content chapter follows a standardised structure. The purpose of each chapter section is described below.

In This Chapter
A short introduction to the chapter outlining the topics that will be covered in the ‘Key Concepts’ section in bullet points.

Summary Points
An ‘executive summary’ of the chapter listing the major facts, which are further explained in the body of the chapter.

Additional resources for material development


Key Concepts
The primary content of each chapter, arranged in subsections according to content; contains text boxes and diagrams which help to further explain certain concepts.

**Bolded and italicized** words appear in various areas, indicating that the word is contained in the glossary (Appendix 2) with its technical definition.

Certain issues or concepts are covered in more than one chapter. These ‘cross-cutting issues’, such as informed consent, are cross-referenced to other chapters in **bold** text (e.g., ‘For further information on informed consent, see Chapter 7’).

Key Messages Pertaining to AIDS Vaccines
Simple statements about the concepts that are most important to communicate to stakeholder audiences, or concepts that are commonly misunderstood. These messages may be especially useful in creating tools or communicating essential ideas to those who do not require in-depth scientific or technical information.

For Further Information
Provides references to other documents for more in-depth information and all references used to write the chapter.

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1 Information is based on Developing Materials on HIV/AIDS/STIs for Low-Literate Audiences by PATH/FHI. For further information, consult the manual at www.path.org/files/HIV_low-lit.pdf
In this chapter

The AIDS pandemic is one of the worst health crises the world has ever faced. This introductory chapter places AIDS vaccine research in the context of the AIDS pandemic and the global response to HIV and AIDS.

It provides an overview of the following:

- The AIDS pandemic.
- The effect of the AIDS pandemic on women and men.
- The global response to HIV and AIDS.
  - Approaches to prevention
  - Treatment, care and support
  - New tools: Vaccines, microbicides and PrEP
- The need for a comprehensive prevention-to-care continuum.
**Summary points**

1. The effects of the AIDS pandemic are devastating. Sub-Saharan Africa is the region most affected; the pandemic is growing rapidly in the Asia and Pacific regions, parts of Eastern Europe and Central Asia; and newer epidemics are emerging in several additional countries.

2. Epidemics have affected many countries, particularly low- and middle-income countries, where the resources to undertake prevention efforts and to provide care to infected people are limited.

3. Women are disproportionately affected by HIV in many places due to biological vulnerability, gender inequalities and lack of social and economic power.

4. Prevention approaches (such as condom usage) have had some success, but progress has been limited, in part because of the social factors that strongly influence behaviour and because too little has been done, too late, with insufficient resources. There is a need to strengthen existing prevention strategies.

5. Antiretroviral (ARV) drug treatment for people who are HIV infected is becoming more widely available. However, access to treatment is still limited because of cost, lack of infrastructure, limited treatment options, lack of access to HIV testing and stigma. There is a need to work for expanded access to ARV treatment.

6. Prevention is key for people who are not infected with HIV. There is a need for additional prevention tools that are simple, affordable and effective; microbicides and vaccines are new tools—currently in various stages of development—that are likely to have an important role.

7. Preventing new cases will preserve resources for the treatment of those already HIV infected.

8. No single intervention is enough. Incorporating vaccines into a comprehensive response that includes other prevention options, as well as treatment, care and support for those already infected, will be key to ending the AIDS pandemic.
A global view of HIV infection, 2007

33 million people [30-36 million] living with HIV, 2007

Global estimates of HIV and AIDS as of end 2007

The AIDS pandemic

Every two years, the Joint United Nations Programme on HIV/AIDS (UNAIDS) publishes a new report on the global AIDS epidemic. The data provided in this publication is from the *Report on the Global AIDS Epidemic 2008*.

UNAIDS estimated that in 2007, 33 million people globally—about 30.8 million adults and 2 million children—were living with HIV and that there were 2.7 million new infections and 2 million deaths from AIDS-related illnesses.

The effects of the AIDS pandemic are devastating. An estimated 95% of the people living with HIV and AIDS are in low- and middle-income countries, where resources to undertake prevention efforts and to provide treatment and care are limited.

As of 2007, sub-Saharan Africa was the region most affected:

- The region had 67% of the people living with HIV and AIDS in the world.
- AIDS was the leading cause of death in the region—approximately 1.5 million people died from complications of AIDS in 2007.
- HIV prevalence (the percentage of the population infected with HIV at a particular point in time) has remained high and steady over the past few years. In 2007, an average of 5% of the population in these countries was infected, with percentages in countries ranging from 1% to 40%.
- Women were disproportionately affected by HIV compared with men. They accounted for half of all HIV infections globally and almost 60% of infections in sub-Saharan Africa.
- Swaziland had the highest HIV prevalence, at 26.1% among adults aged 15–49, and in Lesotho, Namibia, South Africa and Zimbabwe, more than 20% of adults aged 15–49 were HIV-infected.

As of 2007, HIV infections have continued to grow in other regions of the world, including parts of Eastern Europe and Central Asia; and newer epidemics are emerging in China, Indonesia, Papua New Guinea, Vietnam, several Central Asian Republics, the Baltic States and North Africa.
The epidemic has been growing rapidly in the Asia and Pacific regions. Although in Asia national prevalence rates may seem low, they may obscure serious epidemics emerging in some states and provinces within countries. In addition, although the percentage of the population that is HIV-infected may be low, the actual numbers of HIV cases may be very high in certain countries with large populations.

Examples of this include the following:

- Although India had an HIV prevalence rate of 0.9% (among adults aged 15-49), approximately 5.7 million people were living with HIV.
- Serious epidemics are underway in several Indian states, although this may not be apparent from national statistics.
- Three Asian countries are contending with serious nationwide epidemics. The infection rates among adults aged 15-49 were 0.9% in Cambodia, 1.3% in Myanmar and 1.4% in Thailand in 2007.

The AIDS pandemic has already devastated many countries, communities and families, affecting political, social and economic structures, particularly in low- and middle-income countries. The effect of the global epidemic is reversing many of the hard-won development gains made over the last 50 years. For example, life expectancy is decreasing dramatically, and infant and child mortality is increasing significantly in several African countries with high HIV prevalence.

HIV and AIDS data are constantly changing around the world, and the statistics will vary from year to year. For the most up-to-date statistics, visit the UNAIDS website at www.unaids.org.

Women, men and the AIDS pandemic

The ratio of women to men living with HIV and AIDS has been steadily increasing over the past decade. AIDS now ranks as one of the leading causes of death for women between 20 and 40 years of age in parts of Europe, sub-Saharan Africa and North America. In sub-Saharan Africa, HIV infection rates among women have surpassed those among men: women now account for 60% of all infections in the region. Younger women in particular seem to be more vulnerable than men of their same age. Among those 15 to 24 years of age in sub-Saharan Africa, women are three times more likely to be infected than their male counterparts.
Women are probably disproportionately affected by HIV because of their greater biological vulnerability—HIV may pass more easily from a man to a woman than from a woman to a man. In addition, social factors such as gender inequality and lack of social and economic power make it difficult, if not impossible, for women to negotiate safer sex (see Chapter 8). In many parts of the world, young women in particular are often exposed to HIV by engaging in sexual relations with older men because of economic necessity or tradition.

A range of interventions has been used to address the global AIDS epidemic. Most of the prevention approaches that have been used are based on awareness raising, education and interventions designed to produce changes in risk behaviour. Approaches to preventing sexual transmission of HIV have relied thus far on the limited interventions available: male condoms, female condoms and, most recently, the scaling-up of male circumcision in some countries. Research to develop new prevention tools (e.g., vaccines, microbicides, pre-exposure prophylaxis) is underway, and while progress has been made, it may be some time before these new tools are developed, proven safe and effective and are made available for general use.

AIDS-related treatment, including treatment for opportunistic infections and ARVs for HIV infection itself, have had a dramatic role in decreasing AIDS death rates in places where medications have been economically accessible. Developing countries are making headway in improving access to ARVs, with the number of people receiving treatment increasing tenfold to almost three million people in 2007. But, despite the marked increase, millions more are still without access. Other approaches for addressing HIV and AIDS include: care and support; stigma reduction; community education and mobilisation; interventions to address underlying social and economic structures that create the conditions for HIV transmission; and most importantly, voluntary counselling and testing (VCT), which provides an important entry point for both prevention and treatment.

It has become clear that no single approach works in the absence of others. All of these interventions must work in synergy as components of a comprehensive response to the pandemic.
If we’re five to ten years away from microbicides or vaccines, there’s a desperate human toll to be faced between now and then. At least let the world rally to the prospect of bringing this cataclysm to an end sooner than later. And that means working on every front, on emergency footing simultaneously: care, prevention, treatment, microbicides, vaccines.

—Stephen Lewis, former UN Secretary-General’s Special Envoy for HIV/AIDS in Africa, co-director of AIDS-Free World
February 8, 2004

Approaches to prevention

Despite the devastating effect of the global epidemic, it is important to remember that the vast majority of people throughout the world have not been infected; even in sub-Saharan Africa, the region most affected, more than 95% of all people are uninfected. Prevention remains an urgent priority to help people stay uninfected and to protect future generations.

Efforts to prevent sexual transmission, by far the most common form of transmission, include the following:

- Behaviour-change interventions focusing on the following:
  - Promotion and distribution of male and female condoms
  - Reduction in numbers of sexual partners
  - Mutual monogamy with an uninfected partner
  - Abstinence or delay of onset of sexual activity (sexual debut)
  - Modification or cessation of some harmful cultural practices
- Management of sexually transmitted infections (STIs).
- Promotion of medical male circumcision, where available and appropriate.

Prevention programmes often use mass media, peer education, interpersonal communication and a variety of creative means to increase knowledge and shift people’s attitudes and behaviours in support of HIV prevention. There is also a need to focus on longer-term changes in gender relations and other social norms to address the root causes of HIV vulnerability and to create sustained behaviour change on a larger scale.
Efforts to prevent *nonsexual transmission* of HIV include the following:

- Blood safety, such as screening of donated blood.
- Safe injection practices in formal and informal health care settings.
- Harm reduction programmes, including needle/syringe exchange for drug users.
- Prevention of mother-to-child transmission (infant feeding options, ARVs, supportive interventions).

A variety of supportive interventions complements these efforts. VCT, for example, is both an important strategy in preventing transmission and a critical entry point to other health services, including care and support for those who are HIV infected. Other supportive activities seek to reduce stigma in communities and to link prevention programmes with HIV care and support efforts.

All of these prevention approaches have had some degree of success. In particular, blood safety and the use of ARVs for the prevention of mother-to-child transmission clearly reduce the risk of transmission. Despite these successes in prevention efforts, more than 20 years into the global epidemic it is apparent that progress has been limited, particularly in the prevention of sexual transmission. Behaviour is difficult to change, and social and cultural factors exert a strong influence on behaviour, limiting the effect of behaviour-change interventions. Too little has been done, too late, with insufficient resources.

Behavioural approaches to prevention are also particularly difficult for women. The social factors that increase women’s vulnerability to infection limit their power to implement safer sex practices. For many women it is not their own behaviour, but that of their partners that renders them vulnerable to infection. Socially defined gender norms limit women’s ability to protect themselves and also limit men’s willingness and/or ability to change their behaviour.

It will be important to strengthen these existing prevention approaches while developing new approaches and tools, such as vaccines and microbicides, alongside them.

**Treatment, care and support**

Treatments available for people living with HIV include treatment for opportunistic infections caused by HIV infection and treatment for the HIV infection itself. ARVs can prolong life and reduce the effects of
HIV infection. These drugs were not initially accessible to many people infected with HIV in the developing world, but greater support from governments, global health agencies and nongovernmental organisations, as well as the fact that prices have come down significantly over the past several years, have helped reach more people in need of treatment. Millions more however, are still without access to essential ARVs.

ARVs are available in many low- and middle-income countries because of community mobilisation and activism, gains in political will, financial support from donor agencies and production of generic versions of the drugs by several manufacturers, which has lowered the price dramatically. Access to these drugs will certainly help reduce the effect of the global epidemic, but serious challenges remain:

- **Cost** – The cost of treatment has decreased significantly since the original licensure of drugs. However, the cost is still high relative to the resources available in developing countries, and while access to free or low-cost drugs has increased, they are still not available to a majority of HIV-infected people, especially in low- and middle-income countries.

- **Infrastructure** – The infrastructure and public health systems needed to ensure access to treatment and delivery of care are not yet in place in many resource-limited settings.

- **Treatment** – The treatment itself has limitations, including the complexity of some treatment regimens, adverse side effects (which can be severe), the need to adhere to the treatment regimens for life and the evolution of a virus that is resistant to certain drugs in some patients.

- **HIV testing** – Many individuals who might benefit from treatment have not been tested for HIV. Many do not seek testing because they do not perceive their risk of infection or because they are afraid of the implications of the results. For those who do want to be tested, access to VCT services is still limited in many places. Even where VCT services are available, stigma and fear of discrimination prevent access to and use of VCT services. There is a need for rapid scale-up of VCT services, which will serve as an entry point for treatment. Demand for these services is likely to increase significantly once treatment is more widely available.

A focus on people with HIV and AIDS at the community level has become an important component of care and support efforts,
particularly where treatment is unavailable or limited and health systems are overwhelmed. A host of interventions has been developed to support people with HIV and AIDS medically, economically and socially, and to care for children orphaned or made vulnerable by HIV.

**New tools: Vaccines, microbicides and PrEP**

Even with expanded prevention and treatment efforts, there is an urgent need for additional prevention tools that are simple, effective and affordable to expand the options available to people around the world. It is unknown when an effective vaccine, microbicide, and/or pre-exposure prophylaxis (PrEP) regimen will be available, but all are likely to be important in HIV and AIDS prevention in the future. These various prevention methods, described below, are under various stages of development and testing. These tools will hopefully one day work together with other prevention, treatment and care approaches and alongside strategies to shift social norms, to build health infrastructure and capacity and to address constraints on access to services, all forming part of the global effort to confront the global AIDS epidemic.

Vaccines, microbicides and PrEP, if proven effective, might be important means of reducing women’s vulnerability because they would offer the possibility of using them without a partner’s knowledge or cooperation in cases where informing a partner would place the woman at risk of infection, violence or other consequences. Vaccines and PrEP would offer women more control than current prevention methods, since their use is not associated with the sexual act. Microbicide use can potentially be initiated by women and may offer women more control over their risk of infection than the tools now available.

**Vaccines**

The development of an AIDS vaccine is critical for stopping the AIDS pandemic. An effective AIDS vaccine is a substance that would be introduced into the body (usually by injection) to stimulate the immune system, thus preventing or controlling HIV infection. Many vaccine candidates are being developed and tested, but none has yet been proven efficacious.

The need for an AIDS vaccine is clear. Historically, vaccines have been the most effective public health tool for controlling or eradicating (stopping the circulation of) a disease. Smallpox, for example, has been eradicated worldwide through widespread use of a vaccine. Poliomyelitis has almost been eradicated, also through immunisation.
When combined with existing prevention and treatment options, a vaccine is one of the best hopes for halting the AIDS pandemic. The remaining chapters of this publication discuss in detail the process of developing, testing and delivering an AIDS vaccine.

**Microbicides**

Researchers are now working on developing a new technology for HIV prevention called microbicides. Microbicides are substances such as gels or creams that could be inserted in the vagina or rectum to reduce the risk of HIV transmission. The need for a microbicide has been highlighted by the recognition that women often lack the power to negotiate safer sex and condom use. There is an urgent need for a product whose use women could at least initiate, if not control, and that could possibly be used without a partner’s cooperation.

As of 2009, many microbicide candidates were in various stages of development and testing, but none had been proven safe and effective.

**PrEP**

PrEP is another method of HIV prevention that is currently unproven and undergoing clinical trials. PrEP is an intervention where HIV-uninfected individuals could take one or more ARV drugs on a regular basis to prevent HIV infection. Most candidate PrEP regimens consist of pills taken orally, often on a daily basis.

Similar to vaccines and microbicides, no one currently knows how well this strategy will work against HIV infection, and the exact regimen that will work best. Even if PrEP is proven safe and effective, and licensed as a prevention method, it will be important to promote it as an additional option that should be considered in combination with other proven prevention strategies.

As of 2009, numerous clinical trials for PrEP candidates are ongoing and planned in Africa, Asia, North America and Latin America. Results of these trials are expected as early as 2010. The AIDS Vaccine Advocacy Coalition (AVAC) has written a number of detailed reports on PrEP trials, which can be found on their website; for the most recent report, visit www.avac.org/prep08.pdf.

A comprehensive timeline of current and upcoming major HIV prevention trials can be found on the AVAC website at www.avac.org/
The availability of a vaccine or a microbicide will not eliminate the need for treatment and additional prevention strategies. Treatment will be needed for those who are infected with HIV and a range of prevention strategies, such as vaccines and microbicides, is needed for those who are not infected. It is likely that the first vaccines, microbicides and PrEP regimens to become available will be only partially effective (see Chapter 4 for a full explanation of partial efficacy), so it will be important to continue with other behaviour-change and risk-reduction efforts to ensure their success. People have different needs and preferences. Having a range of prevention tools and options that can be used together can maximise benefits. Prevention of new cases also preserves resources for treatment of those already infected.

Combining technical and supportive interventions will probably have a greater effect on the pandemic than a focus on any particular approach. This is often referred to as a comprehensive prevention-to-care continuum.
AIDS represents one of the worst epidemics the world has ever seen. An AIDS vaccine, once developed, will play a major role in halting it.

Behavioural prevention strategies have slowed the epidemic in some areas of the world, but have not stopped it; a preventive AIDS vaccine is urgently needed.

An AIDS vaccine will never be the only answer. The response to HIV and AIDS must be comprehensive and should include existing behavioural prevention strategies, new technologies, once they are available and treatment and care for those already infected.

Key messages pertaining to AIDS vaccine development

For further information


In this chapter

AIDS vaccine research is an important component of the response to the global AIDS epidemic.

However, vaccine research does not just involve a scientific pursuit. It is also important to engage communities at all levels to build support for conducting trials and to ensure future access to and use of a vaccine. An increasing number of national and international efforts focus on building strong in-country support for trials before the trials even begin. It is particularly important to ensure that in-country stakeholders are fully engaged in the entire trial process.

This chapter discusses:
• Conducting AIDS vaccine research in low- and middle-income countries.
• Country advocate and stakeholder groups.
• Role of in-country stakeholder groups.
• Influence of stakeholder support on trial recruitment.
The conduct of AIDS vaccine trials in developing countries often raises valid concerns.

AIDS vaccine trials cannot be conducted without making country stakeholders integral partners in the efforts.

In-country stakeholders include policymakers, nongovernmental organisations (NGOs), community-based organisations (CBOs), medical professionals, the media and others; these groups are involved in various stages of preparation for trials, trial conduct and follow-up after trial conclusion.

Building support at the country level means raising levels of awareness and education so people are familiar with the idea of future AIDS vaccines and the clinical trials that are conducted; in-country advocates and stakeholders can also be strong allies in increasing the willingness of community members to learn more and consider volunteering for trials.

Advocates should be well-versed in the work carried out in their own countries (and elsewhere) in order to manage expectations, fears and/or misconceptions about the research.

AIDS vaccine research and development is a global effort. This work must be conducted in both the North and in the South, particularly in countries with high HIV prevalence. The best way to know if a vaccine will be relevant, safe and efficacious in a particular population is to include that population in all stages of human testing.

Although the primary goal is to develop a vaccine that can be used worldwide against all HIV subtypes (see box on next page and Chapter 5 for more information about subtypes), it is still unknown whether this goal is achievable. To find out, candidate vaccines should be tested in areas where different subtypes are common.
Is subtype important in deciding where an AIDS vaccine should be tested?

It is important to note that (at time of printing) there is no current scientific proof that subtype plays a part in how effective a vaccine will be in a particular person, or in a particular population. For example, a vaccine developed for HIV subtype A may be protective in a population where HIV subtype A is common, but it may also be protective in a population where HIV subtype C is common.

This is why it is important that a given AIDS vaccine candidate be tested in various countries to see how it works in places where specific subtypes are common.

Partnerships between trial sponsors, researchers and stakeholders in countries in which research takes place are vital to ensure an enabling environment for conducting research. Conducting AIDS vaccine research in developing countries may raise concerns among some individuals or groups about the underlying motivations behind the research, and whether the trials would be beneficial or harmful to individuals and communities who participate. These partnerships with in-country researchers, NGOs and other stakeholders help to ensure that studies are relevant to the region and conducted appropriately taking local circumstances into account.

To counter any false impressions, it is important to emphasise that AIDS vaccine trials are held to the highest international ethical standards. Trials are closely reviewed and monitored throughout their progress; it is important to ensure that communities and stakeholders are aware of these ethical safeguards.

Community members and other country-level stakeholders must be well informed about the reasons for conducting trials in their community or country, the potential benefits that could result from the process and the ethical safeguards included within. Engaging policymakers and other government leaders early on in AIDS vaccine work is particularly important in ensuring meaningful country participation in, understanding of and support for rapid AIDS vaccine research and development.
Trial communities and countries hosting research often experience benefits which may include the following:

- Increased knowledge around HIV, AIDS vaccine development and issues associated with AIDS vaccine trials.
- Increased clinical trials and laboratory capacity, through development of research infrastructure, training and other skills development, and collaboration between sponsors and local researchers in designing and conducting clinical research.
- Improvements in health care infrastructure through efforts to provide services to volunteers and strengthen existing health care services for volunteers and surrounding communities.
- Strengthened regulatory review systems through efforts of international organisations.
- Access to a future vaccine once it is proven safe and efficacious. Efforts are often made to make a vaccine accessible to the volunteers who participated in that vaccine’s clinical trial(s), as well as to the communities and countries that supported the trials, however because access to vaccines is often controlled by national regulations, such access cannot be guaranteed.

It is also important to remember that communities hardest hit by the epidemic have many needs, most of which are more immediate than vaccine research. Vaccine research should be placed in the context of a comprehensive response to the epidemic that includes immediate primary prevention, treatment for those already infected and clinical trials to develop new prevention tools.

NGOs, CBOs and FBOs

Leaders of NGOs, CBOs and faith-based organisations (FBOs) often function as gatekeepers to the community and can be effective allies in facilitating links to the community at large.

Organisations working at the local level can aid in the recruitment of volunteers. NGOs, CBOs and FBOs can facilitate communication between government officials, researchers and communities. Research trial centre teams should reach out to these groups to gain their support and seek their advice. Research centres can inform them about clinical vaccine trial design and procedures and work with them to integrate HIV vaccine research into existing community outreach efforts.
Through their networks, NGOs, CBOs and FBOs can act as advocates, playing a pivotal role in communicating in local languages, building and sustaining community interest, dispelling myths about vaccine research and managing expectations. They can facilitate community participation, ensure a two-way flow of communication and exert influence on local politicians and international stakeholders. Such organisations might also provide researchers with an understanding of community perspectives and participate in technical activities, such as HIV-prevention education, media work and translation.

Parliamentarians, policymakers and ministries of health
Policymakers play an important role at the local, national and global levels of AIDS vaccine work, often involving high-level decisions. Ministries of health in particular are important players in AIDS vaccine research. Members of government should be consulted and established as partners at a very early stage in planning for trials and up through the eventual process of providing access to a licensed AIDS vaccine.

Examples of partnerships between governmental leaders and AIDS vaccine researchers and scientists include the following:

- The government of Thailand has demonstrated a long-standing commitment to and strong support for AIDS vaccine development. The Ministry of Public Health plays a primary role in mobilising participation from public, private and NGO partners and in supporting collaboration among national and international researchers.

- The South African government strongly supports AIDS vaccine research, most evidently through launching the South African AIDS Vaccine Initiative (SAAVI), an organisation established to coordinate the research, development and testing of AIDS vaccines in the country.

- The Kenyan government initiated work on a National AIDS Vaccine Plan in late 2003.

- In Uganda, parliamentarians serve as active partners in AIDS vaccine research through a Standing Parliamentarian Committee on HIV/AIDS Vaccines.

- The prime minister, president, minister of health and other prominent leaders of political parties in India have given vocal and consistent public support for AIDS vaccine research.

- In Rwanda, the president and other prominent political leaders have given strong and direct public support for AIDS vaccine research.
• In Brazil, AIDS vaccine research has been a common advocacy agenda item since the 1990s. Vaccines are perceived and approached as an integral part of the national response to AIDS, with no direct trade-off with other priorities, such as access to treatment and condoms.

Media and journalists
The media serve as an important information source for the community at large and can be influential in shaping public opinion at all levels. It is essential for members of the media to have accurate and current information on AIDS vaccines and trials and the work of local institutions. Research organisations have engaged members of the media and have held AIDS vaccines workshops with them to ensure these individuals are well informed about AIDS vaccines. Because of the complex nature of the information, it is very important to work with members of the media to help them understand the science so that they provide accurate and understandable information to the general public.

The media and journalists can disseminate accurate information and may be able to help with specific recruitment activities, provided that they are well briefed. If they are not, the media could inadvertently spread misconceptions, causing mistrust.

Medical professionals
Community members often look to medical professionals in their community for advice or answers about HIV and AIDS, AIDS vaccine research and clinical trial participation. In communities where trials are being conducted, it is particularly important for all health care providers, including primary health care doctors, nurses and other clinic staff who may not be directly involved in AIDS vaccine research, to be knowledgeable about the science of AIDS vaccines and the process of trial participation. It is also important to include traditional healers (where they exist) in this stakeholder group, since they often serve an important role in giving care and advice to community members.

Academic and religious leaders
Community members often look to academic and religious leaders for advice on important decisions, including joining a vaccine trial. These individuals are often well respected and can shape public opinion. It is important that they be accurately informed, knowledgeable and supportive of AIDS vaccine trials.
Community advisory boards (CABs)

In the 1980s, AIDS activists in the United States (U.S.) and Europe demanded that researchers and regulatory authorities move more quickly to develop medications for HIV. Activists educated themselves about scientific research and HIV and demanded that they have an opportunity to comment on trial proposals. Through an active campaign that included protests, letter writing and lobbying the U.S. government, activists succeeded in changing the U.S. drug approval process. This activity also led to the formation of CABs comprised of non-scientists who review protocols, monitor trials and help educate and inform the rest of the community.

CABs were well established in the U.S. by the early 1990s and were involved in some of the initial AIDS vaccine work. Some of the first CABs, especially in the U.S., were made up mostly of people living with HIV, and in some communities this is still the case. Now, CABs are also made up of leaders and other individuals representing various parts of the community, such as religious groups, schools and universities, media, NGOs and CBOs. Some of the efforts to establish African AIDS vaccine trial CABs began in Uganda in the late 1990s. A CAB orientation meeting took place there in July 1998, after which the first African HIV vaccine trial CAB was formed, in preparation for the trial the next year.

CABs have become a significant part of AIDS vaccine trials throughout the world. They are generally made up of no more than 20 people who serve as the primary liaisons between the community and the trial researchers. Often a senior scientist or physician and/or another member of the trial staff attends CAB meetings with some regularity, which is a sign of the CAB’s significance in the trial process.

CAB members may take a very active role in planning for and undertaking AIDS vaccine trials. Some examples of their activities include the following:

- General community outreach and education.
- Disseminating information about the trial, in order to lay the groundwork for recruitment.
- Providing feedback on trial protocols, including criteria for participation, informed consent forms and processes, and volunteer recruitment and retention.
- Advising investigators regarding potential participants’ perspectives about the trial.
• Providing a safeguard (in addition to institutional ethics review committees) for participants’ rights.
• Representing the community at important national, regional and international meetings and conferences.

Most researchers acknowledge that for a trial to be successful, it is important to obtain general support from the communities that will be involved in the research. The research team often holds consultations with the CAB about an upcoming trial. Then and throughout the trial, CABs may have the opportunity to provide feedback on the actual trial protocol, the informed consent document and any educational materials to be used in the community. These consultations are not part of the formal approval process (see Chapter 10), but researchers may make changes to the trial protocol and other documents so that they reflect community input. The process helps to ensure that communities receive appropriate information, that their concerns are addressed and that the trial will run smoothly.

Country and community stakeholders play a primary role in education and advocacy efforts at the national and local levels. Community education is needed in advance of trials to prepare people for the research process and to lay the foundation for the eventual distribution and use of an effective vaccine. However, it is important to consider the approach and timing, because doing too much vaccine-specific education long before a trial starts may cause confusion and/or raise unrealistic expectations. There is no clear answer about how much education is appropriate or how soon education should be started. Educational efforts should be carefully monitored to assess community response.

It is particularly important to ensure that communities understand general HIV issues as a basis for AIDS vaccine education. Some trial communities may have little knowledge about basic issues, such as HIV transmission and prevention. If this is the case, educational efforts should start with general HIV knowledge, including providing information on and access to voluntary counselling and testing (VCT), before addressing more complex issues of clinical research and the specifics of AIDS vaccine development.
Stakeholder groups can play a role in AIDS vaccine education beyond the community by doing the following:

- **Integrating knowledge about vaccine development into HIV prevention messages.** Vaccine development should be viewed as one part of a broader HIV prevention effort. Where appropriate, existing community outreach networks should be used to discuss AIDS vaccine development.

- **Assessing and shaping current attitudes and awareness about AIDS vaccines.** They can discuss AIDS vaccines with people, helping them understand the role vaccines might have in controlling HIV and addressing any fears, myths and misperceptions. Local meetings and networks can be used as an opportunity to discuss vaccine development.

- **Shaping in-country policy and building advocacy.** Successful implementation of AIDS vaccine clinical trials, particularly large-scale trials, requires that scientists, policymakers, community groups and the media create an ‘enabling environment’ by promoting policies and building capacity to support rapid regulatory review, sufficient community health infrastructure and meaningful community participation.

- **Linking with local, national and global information sources.** Internet-based resources are an excellent source of information on AIDS vaccine development (see the list of websites at the end of this document). At the local level, links can be developed between medical centres, ministries of health, universities, NGOs and others involved in AIDS vaccine development. Nationally, regionally and globally, networks can be created between various audience groups involved in AIDS vaccine development.

- **Sharing information.** The international effort to develop an AIDS vaccine can benefit from the experiences of individual countries and communities. Participating in local, national and international conferences, joining local HIV prevention and care networks and trial sites, and publishing information in newsletters and on websites are good ways to share information. It is important to make sure that local media are well informed about vaccine development.
Country and community stakeholders can play an important role in building trust and credibility for AIDS vaccine trials in the community and country, and in increasing interest in trial participation. Country stakeholders have a key role to play in the following:

- Planning trials.
- Making recommendations on how trials will be carried out.
- Making sure trials are ethical from a community perspective.
- Making sure trials are relevant to the community.
- Disseminating information and raising community awareness about AIDS vaccine research.
- Helping to lay the foundation for access to and delivery of a vaccine once available.

Community leaders can help educate potential participants about the trial. They can also educate the research centre teams about best ways to reach the community by providing information, such as the following:

- Characteristics and cultural practices of the community.
- Risk behaviours in the community.
- Potential ways to recruit study volunteers and reach larger groups of potential volunteers.
- Community perspectives on education and communication strategies related to the informed consent process.

All of these factors will benefit the conduct of the trial, as long as stakeholder groups are well informed and committed, and investigators and/or trial sponsors maintain a positive relationship with these groups.

Country stakeholders play an important role in recruitment of volunteers, and the role of these groups becomes critical when new large-scale efficacy trials are being prepared. Recruiting volunteers takes a major effort. Efficacy trials may require several thousand volunteers who are not infected with HIV, and to recruit that many people, many more must be reached. Large numbers of people must have a basic understanding of AIDS and vaccine research, and they must be motivated to seek VCT to learn their HIV status (see box).
NGOs, CBOs, the media and government programmes working in the area of HIV can be strong allies in helping to mobilise volunteers. These partners can help assess and shape attitudes and awareness about AIDS vaccines, help people understand the role vaccines might have in controlling the epidemic and address fears. The AIDS Support Organisation (TASO) in Uganda and the Kenyan AIDS NGO Consortium (KANCO) are examples of NGOs that have incorporated an AIDS vaccine agenda into their existing outreach programmes. These groups will also be important allies in facilitating future access to a vaccine, once one is available (see Chapter 11).

The following two diagrams further illustrate different communities or factors that influence the mobilisation of volunteers into AIDS vaccine trials.
The funnel diagram below illustrates how stakeholder groups with varying scopes of influence, from broad global policy to more specific trial conduct, all contribute to the eventual access to and use of a vaccine.

<table>
<thead>
<tr>
<th>Stakeholder group</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policymakers, press, donors, researchers, international NGOs</td>
<td>Global Policy &amp; Advocacy</td>
</tr>
<tr>
<td>NGOs, CBOs, policymakers, women's groups, health professionals, religious</td>
<td>National/Regional Outreach</td>
</tr>
<tr>
<td>and civil society leaders</td>
<td></td>
</tr>
<tr>
<td>Study staff, local influential groups and individuals, (e.g., community leaders,</td>
<td>Trial Recruitment</td>
</tr>
<tr>
<td>service providers), potential volunteers</td>
<td></td>
</tr>
<tr>
<td>Volunteers, trial staff, trial review and oversight groups</td>
<td>Trial Conduct</td>
</tr>
</tbody>
</table>

Eventually access to and use of a safe, efficacious, affordable AIDS vaccine
2.2 Participant influences

The following diagram illustrates the different communities that surround an AIDS vaccine trial participant. Starting from the closest layer (a participant’s family and close friends) to the broadest layer (the international level), the diagram shows that there is a vast range of external influences on one individual trial participant. Note that these are external influences, and the diagram is not meant to imply that each of these ‘communities’ is aware of the individual’s trial participation.
Generally, when people learn of an AIDS vaccine trial being conducted in their community, expectations are raised about the outcome of the trial. People may assume, for example, that an efficacious vaccine will become available quickly after the trial is over. However, if the vaccine candidate is only in Phase I or II testing (see Chapter 6), it will need to go through further phases of testing, which takes many years. Even if the vaccine candidate has gone through all necessary phases of testing, data analysis may reveal that the vaccine was not efficacious and/or safe enough to be used in the general population (see Chapter 4 for more information on safety and efficacy). Finally, if the vaccine candidate was shown to be safe and efficacious through the process of all phases of testing, regulatory approval to license a vaccine will take additional time.

It is important that communities be well informed about the vaccine candidate(s) being tested in their particular country, as well as the global picture of AIDS vaccine research. This information will help people understand the ‘big picture’ of AIDS vaccine research in addition to the important lessons that will be learned from individual trials.
AIDS vaccine research is a very slow process. Research has been ongoing since the mid-1980s and will likely continue for many years to come.

Many different types of vaccines are being tested around the world; researchers do not yet know which type of vaccine will work best or for which population or geographical region. The only way to find out is to conduct trials for different types of vaccines in different areas of the world.

Many vaccine trials may need to be conducted before AIDS vaccines are eventually licensed and available; many vaccine candidates are likely to go through testing but will not become licensed.

Many AIDS vaccine candidates have been through trials, and as of 2009, three have gone to the stage of large-scale efficacy trials (Phase IIb or III trials) (see Chapter 6). Even when the results of a trial indicate that a vaccine candidate does not protect against HIV infection, this does NOT mean that the trial was a failure. No matter what the outcome, important lessons are learned from any trial; even learning that the particular vaccine does not work helps scientists decide where to direct research efforts.

If the history of vaccines for other diseases and for HIV is any guide, we can expect that most vaccine candidates tested in trials are likely to produce disappointing results. This is the reason multiple vaccine candidates must be tested at the same time as quickly as possible to improve the chances of identifying the right vaccine to be used worldwide.

If vaccine success will be shared by multiple stakeholder groups, then sharing disappointment is something that politicians, communities, the media and other groups must understand and accept.

Key messages that will help in managing expectations include the following:
Involving community representatives and key stakeholder groups in meaningful dialogue early on can contribute to the success of AIDS vaccine research. These individuals often have important insights that can improve clinical trials.

Trust must be built with communities and in-country stakeholders. They have the right to know about the research and to be involved. Failing to involve them could result in misunderstandings, negative perceptions of trials and delays in progress.

The communities where trials are conducted should experience benefits beyond their contribution to the trial and should be left better off after the trial is completed. Such benefits might include improved services for HIV prevention and care.

There are very important reasons to conduct AIDS vaccine research in low- and middle-income countries, even though some may question the motivations for doing so. We must know that the vaccines work where they are needed most, and conducting trials in those countries will help make them available more quickly.


In this chapter

This chapter describes the immune system in relation to the development of AIDS vaccines. It is not meant to be a comprehensive overview of immunology.

This chapter covers the following:

- Types of immune responses.
- Key components of the immune system, defined.
- The immune system as it relates to HIV.
Summary points

1. The immune system is the set of organs, tissues and cells that help defend the body against infection.

2. The immune system is very sophisticated and will recognise any pathogen (a ‘germ’ or small organism that causes disease) that enters the body that might be harmful, such as viruses, bacteria or parasites.

3. The immune system develops defence responses to invading organisms and it will ‘remember’ this response for any future encounters.

4. HIV is especially harmful to the body because it attacks certain key components of the immune system, making it difficult for the body both to defend itself against the virus and to fight off other infections.

5. HIV is capable of ‘escaping’ certain parts of the immune response. This is one reason why it is so difficult to make an AIDS vaccine.

Key concepts

Types of immune response

Our immune system is divided into two broad categories: ‘innate immunity’ and ‘acquired immunity’.

Innate immune defences are the first to respond to any foreign invader (pathogen) that enters the body. These defences are not specific to one certain pathogen; instead, they are like a security force that patrols the body looking for unusual activity, but not for a particular intruder. This arm of the immune system cannot be ‘taught’ to respond better by a vaccine.

Acquired immune defences are activated only after our immune system has seen and ‘recognised’ a particular pathogen. These specific defences are like police tracking down one certain criminal: all of their activities are directed towards a single, specific intruder. A vaccine ‘teaches’ the acquired immune system to make a quicker and stronger response to the pathogen it represents—vaccines help protect against specific diseases. There are two branches or ‘arms’ of the acquired immune system: cellular (or cell-mediated) immunity and humoral (or antibody-mediated) immunity.
• **Cell-mediated or cellular immune response** – the immune system response coordinated by the *T cell* responses (helper T-cells and killer T-cells); the response targets cells that have already been infected with the pathogen.

• **Humoral or antibody immune response** – includes the antibody/B cell responses (see *B cells*, table below). This is sometimes called the *humoral* immune response, named after the old Greek idea of body fluids called ‘humours’.

The acquired immune responses are those involved in the function of a vaccine. All details covered in this chapter describe acquired immunity.

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**Table: Key immune concepts and how they relate to HIV**

<table>
<thead>
<tr>
<th>Concepts</th>
<th>Explanation/Definition</th>
<th>Relation to HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune system</strong></td>
<td>The immune system is a complex system that enables the body to recognise anything that is different from itself (or ‘foreign’) and that could be harmful to the body; the immune system creates defences against these invaders, which are called <em>pathogens</em>.</td>
<td>HIV damages the immune system, the very system that should defend the body against HIV. At first, the immune system mounts a defence against HIV that can help HIV-infected people remain healthy for some years after becoming infected. Eventually HIV overcomes these defences, causing illness, disease and death. The immune system makes antibodies against HIV. One way of detecting HIV infection is to test for these antibodies. Because the antibodies are in the liquid part of the blood, called ‘serum’, people who are HIV infected are sometimes called ‘seropositive’.</td>
</tr>
<tr>
<td><strong>Pathogen</strong></td>
<td>Foreign, harmful organisms that cause disease in the human body; the most common pathogens are viruses (like HIV), bacteria and parasites such as worms.</td>
<td>HIV is a pathogen; it is a virus that invades the body. HIV infects and weakens the immune system, making it difficult to fight against the virus (and other pathogens).</td>
</tr>
<tr>
<td><strong>Opportunistic infections (OIs)</strong></td>
<td>This term describes illnesses, which occur less frequently or less severely in people with healthy immune systems compared to people with weakened immune systems.</td>
<td>HIV infects key parts of the immune system so the body cannot defend itself against other pathogens. When someone has had HIV for some time, he or she may become ill from pathogens that would not normally cause disease in a person not infected with HIV. The weakened immune system provides an opportunity for infections it would normally be able to fight off.</td>
</tr>
</tbody>
</table>
### Immune response

When a pathogen enters the body, the immune system’s first responders (macrophages and dendritic cells) pick up the invader, package some of its components or pieces (called **antigens**) and present these parts on their outer surfaces, so that other immune cells (lymphocytes) can ‘see’ the pathogen and respond against it.

HIV has many ways of avoiding the immune response. Starting from the first moments of transmission, HIV interacts with various cells in the immune system. HIV uses these cells to make more copies of itself.

It is also capable of ‘escaping’ from immune cells that are designed to attack it by changing certain aspects of its form.

HIV can kill immune cells called CD4+ cells that help make antibodies and direct CD8+ T cells, both of which are major defenders against HIV. Thus, HIV kills the immune cells that are supposed to protect the body against it.

These are some reasons why it is so difficult to develop an effective AIDS vaccine.

### Antigen

A piece or fragment of a pathogen (usually a protein) that is taken up and changed, or ‘processed’, by certain immune cells and is presented to the rest of the immune system so that it can make an immune response.

The term immunogen may also be used to describe antigens that cause immune responses.

One way an AIDS vaccine might work is by producing antibodies that would attach to HIV antigens. This would either make the virus inactive or mark it so that it could be attacked and destroyed by other immune cells. HIV presents a particular challenge, because certain crucial antigens seem to remain hidden from antibodies, which then cannot mark or inactivate the virus.

AIDS vaccine researchers are working to identify the HIV antigens that will stimulate strong immune defences against the virus. Some of the HIV antigens used in AIDS vaccines are gp120, p24, gag, pol and nef.

### Macrophages/ Dendritic cells/ Phagocytes

These are the cells that look out for pathogens. When they encounter a pathogen, they alert other immune cells. Macrophages can also act as **antigen-presenting cells** (APCs).

Dendritic cells and macrophages are thought to have a key role in the early stages of HIV infection.

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**Key immune concepts and how they relate to HIV (continued)**

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<td><strong>Immune response</strong></td>
<td>When a pathogen enters the body, the immune system’s first responders (macrophages and dendritic cells) pick up the invader, package some of its components or pieces (called antigens) and present these parts on their outer surfaces, so that other immune cells (lymphocytes) can ‘see’ the pathogen and respond against it.</td>
<td>HIV has many ways of avoiding the immune response. Starting from the first moments of transmission, HIV interacts with various cells in the immune system. HIV uses these cells to make more copies of itself. It is also capable of ‘escaping’ from immune cells that are designed to attack it by changing certain aspects of its form. HIV can kill immune cells called CD4+ cells that help make antibodies and direct CD8+ T cells, both of which are major defenders against HIV. Thus, HIV kills the immune cells that are supposed to protect the body against it. These are some reasons why it is so difficult to develop an effective AIDS vaccine.</td>
</tr>
<tr>
<td><strong>Antigen</strong></td>
<td>A piece or fragment of a pathogen (usually a protein) that is taken up and changed, or ‘processed’, by certain immune cells and is presented to the rest of the immune system so that it can make an immune response. The term immunogen may also be used to describe antigens that cause immune responses.</td>
<td>One way an AIDS vaccine might work is by producing antibodies that would attach to HIV antigens. This would either make the virus inactive or mark it so that it could be attacked and destroyed by other immune cells. HIV presents a particular challenge, because certain crucial antigens seem to remain hidden from antibodies, which then cannot mark or inactivate the virus. AIDS vaccine researchers are working to identify the HIV antigens that will stimulate strong immune defences against the virus. Some of the HIV antigens used in AIDS vaccines are gp120, p24, gag, pol and nef.</td>
</tr>
<tr>
<td><strong>Macrophages/ Dendritic cells/ Phagocytes</strong></td>
<td>These are the cells that look out for pathogens. When they encounter a pathogen, they alert other immune cells. Macrophages can also act as antigen-presenting cells (APCs).</td>
<td>Dendritic cells and macrophages are thought to have a key role in the early stages of HIV infection.</td>
</tr>
</tbody>
</table>
### Key immune concepts and how they relate to HIV (continued)

<table>
<thead>
<tr>
<th>Concepts</th>
<th>Explanation/Definition</th>
<th>Relation to HIV</th>
</tr>
</thead>
</table>
| **Antigen-presenting cells (APCs)** | APCs engulf the antigens and process them, and present the antigens on their own outer surface in a way that can be ‘seen’ by other immune cells called **lymphocytes**. This process stimulates the lymphocytes to function. Immune cells that act as APCs:  
• B cells (see below).  
• Macrophages.  
• Dendritic cells. | APCs carry pathogens to areas of the immune system that have many CD4+ cells. As CD4+ T cells are primary targets for HIV, this provides an opportunity for HIV to rapidly establish infection in T cells. |
| **Lymphocytes**               | When the dendritic cells present antigens, the lymphocytes are alerted to respond against the pathogen associated with the antigen. The two most important types of lymphocytes are T cells and B cells. | When T cells are activated by HIV, they begin to multiply rapidly to defend the body against HIV. These defences can protect the body against HIV for a while. This is one reason why people do not become sick for a while after HIV infection. |
| **T cells**                   | T cells are the immune cells that can recognise a pathogen or a virus-infected cell. They release substances that cause inflammation and they can kill abnormal or virus-infected cells. There are two types of T cells: CD4+ lymphocytes and CD8+ lymphocytes. | HIV needs to be inside (or infect) human cells to make more copies of itself. T cells can recognise and attack these infected cells. CD4+ T cells are also vulnerable to HIV infection, as they are primary targets of HIV. |
| **CD4+ cells**                | The main function of these T cells is to recognise the antigen when it is presented by the APCs and to help coordinate the rest of the specific immune response for that antigen. Therefore, they are also called ‘helper T-cells’. | HIV specifically targets CD4+ cells. This is why HIV patients must pay attention to their ‘CD4+ counts’. A very low CD4+ count means that HIV has already killed a large number of CD4+ cells. The lower the number of CD4+ cells, the more difficult it is for the body to fight against pathogens. |
| **CD8+ cells**                | These T cells kill cells or slow down activity of cells that have been infected with the pathogen; therefore, they are called **cytotoxic T lymphocytes** (CTLs) or ‘killer T-cells’. They do this through ‘cytotoxic’ activity, a process that kills the infected cell. | For someone infected with HIV, CD8+ cells kill HIV-infected cells. However, because the immune system is weakened, it cannot keep up with the virus’s activity. Most current AIDS vaccine candidates are aimed at inducing strong CTL responses. |
# Key immune concepts and how they relate to HIV (continued)

<table>
<thead>
<tr>
<th>Concepts</th>
<th>Explanation/Definition</th>
<th>Relation to HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>B cell</td>
<td>The B cell response fights the pathogens that have not yet infected a human cell. B cells direct the production of <strong>antibodies</strong>, which are substances that attach to and block the activity of (inactivate) pathogens. There are two main types of B cells: plasma B-cells and memory B-cells.</td>
<td>B cells begin to produce antibodies against HIV shortly after infection takes place, however many of these antibodies fail to stick to HIV or to effectively inactivate it because of HIV's ability to escape from immune defences.</td>
</tr>
<tr>
<td>Plasma B-cell</td>
<td>These cells will produce the <strong>antibody</strong> that is specifically shaped to fit with the antigen.</td>
<td></td>
</tr>
<tr>
<td>Antibodies</td>
<td>Antibodies are proteins dissolved in serum or lymph fluid; they are also found in other bodily fluids (tears, saliva, cervical fluid). An antibody is specifically designed to attach to an antigen. When antibodies lock or bind to the antigens on the surface of the pathogen, they coat the pathogen, making it inactive and marking it so other immune cells can easily kill it. Antibodies can also prevent viruses from getting into cells, which is where they must be to reproduce.</td>
<td>HIV protects itself with a coating and mutates (changes its genes) to avoid recognition by the immune system. Some antibodies are able to attach and inactivate HIV (neutralise it) but many antibodies are not protective.</td>
</tr>
<tr>
<td>Memory B-cells and memory T-cells</td>
<td>Helper T cells, killer T cells and plasma B cells form responses to many infections, such as chickenpox, tuberculosis or malaria. Once the individual has recovered from the infection, a small population of <strong>memory T-cells and memory B-cells</strong> remains in the body. Memory cells ‘remember’ the pathogen and are prepared to start an immune response more quickly and vigorously if the body encounters the same pathogen in the future.</td>
<td>It is not known how important memory cells are in the course of HIV infection. AIDS vaccines would aim to create many memory T and B cells in people not infected with HIV so that these defences can rapidly respond and help protect a vaccine recipient who is later exposed to HIV or infected with HIV.</td>
</tr>
</tbody>
</table>
How antibodies work

Many antibodies fighting HIV are directed against antigens that are inside the virus. But even if the antibodies are directed against parts of the envelope, they do not always block infection. ‘Neutralizing antibodies’ block infection—effective neutralizing antibodies against HIV have been hard to identify. Particular neutralizing antibodies can only neutralize small parts of the HIV virus.

This diagram shows a virus and the host target cell it will try to infect. The structures on the outer shell of the virus are envelope proteins and act as antigens. The antigens will fit into the virus receptor site on the outside of the host target cell. This allows the virus to infect the host target cell.

This picture shows antibodies, represented by the Y shaped structures. The antibodies have locked onto the antigens, coating the outer surface of the virus. Therefore, the antigens can no longer attach to the virus receptor site, and the virus is unable to infect the host cell and reproduce.

How this relates to HIV

3.2 Structure of HIV

**Definition of terms**

**Proteins (p17, p24)** – compounds that make up the structure and defining characteristics of HIV.

**Glycoproteins (gp41, gp120)** – compounds composed of the carbohydrate(s) and protein(s) that make up the structure and defining characteristics of HIV.

Both proteins and glycoproteins act as antigens in the human body.

**Viral RNA** – the genetic material contained in HIV; HIV is a retrovirus, meaning it contains RNA, rather than DNA (as in most viruses).

**Reverse transcriptase** – an enzyme (a protein that can cause chemical reactions) that allows single-stranded viral RNA to be converted into double-stranded DNA, which is the genetic material needed for cells to reproduce.
The immune system is a powerful tool for fighting infections and keeping us well; it even helps control HIV in the early stages of infection.

HIV is particularly harmful because it directly attacks the parts of the immune system that would normally fight off other infections and it makes the immune system incapable of fighting HIV itself.

An effective AIDS vaccine will teach the immune system to fight HIV. This may prevent initial infection and/or lessen the occurrence of disease after infection.

1 Since an HIV vaccine is developed to protect someone against HIV infection, the vaccine should cause the immune system to produce protective antibodies. In this instance, the individual has antibodies circulating in his/her blood, but is not infected with the virus. See Chapter 7 for further details on falsely testing HIV positive.
This chapter provides a general explanation of vaccines and how they function. It describes the different types of vaccines that are in use today as well as those that are in development, providing examples of each. The information is meant to serve as background for understanding the development and testing of AIDS vaccines.

This chapter includes the following:

- Definition of a vaccine.
- How preventive vaccines work.
- Concepts of prevention versus treatment with vaccines.
- Common vaccine types.
- Definition of additional vaccine concepts, including adjuvant, efficacy, effectiveness and ‘herd immunity’.
Summary points

1. A vaccine ‘teaches’ the immune system how to defend itself against a disease-causing agent, known as a pathogen.

2. A vaccine is designed to prevent infection or disease from a specific pathogen; therefore, a vaccine ‘matches’ with a certain disease.

3. A preventive vaccine is meant for people who have not been infected with the pathogen that the vaccine is designed to protect against.

4. A preventive vaccine is not a treatment or cure for someone who is already infected with the specific pathogen.

5. A vaccine’s efficacy refers to how well it protects against disease or infection when it is tested in a large trial in humans; a vaccine’s effectiveness refers to how well it reduces the amount of disease once it is used in the overall population.

Key concepts

Definition of a vaccine

A vaccine is a substance that is introduced into the body to prevent infection or to control disease due to a certain pathogen (any disease-causing organism, such as a virus, bacteria or parasite). The vaccine ‘teaches’ the body how to defend itself against a pathogen by creating an immune response. Vaccines can be introduced in different ways, such as injection into the muscle (intramuscular) or into or under the skin (intradermal or subcutaneous); by application onto the skin (transdermal); by application to the inside of the nose (nasal); or by being swallowed (oral). In general, vaccines are given to healthy individuals to prevent them from infection and/or disease in the future.

Vaccines that are currently available save millions of lives each year. A few examples are polio, tetanus and measles vaccines, but there are many others. Each vaccine protects against one particular disease, and it will not protect against other diseases. For example, the measles vaccine prevents measles, not polio, while the polio vaccine prevents polio but not measles.
Many vaccines are designed for infants, but adults can also be vaccinated. Some newer vaccines, such as the meningococcal and human papillomavirus (HPV) vaccines, are targeted at older age groups, such as pre-adolescents and young adults.

Every available vaccine has gone through animal and human testing to prove that it is safe and efficacious for use in humans.

Right now, there is no vaccine to protect against HIV and AIDS.

The following steps outline how a preventive vaccine protects an individual from infection or disease:

1. The vaccine introduces safe forms or fragments of a pathogen, called antigens or immunogens, into the body. Immunogens resemble the actual pathogen and cause the body to develop an immune response against it.

2. The presence of the immunogens causes the immune system to initiate B cell and T cell responses against the pathogen.

   **B cell response:**
   - B cells produce antibodies that are specifically shaped to bind to the immunogen.
   - Later, if the actual pathogen ever enters the body, large amounts of these antibodies will be rapidly produced and will bind to the pathogen since it is similar to the immunogen. When antibodies bind to the pathogen or to cells infected with the pathogen, they are either inactivated or marked to be killed by other immune cells.

   **T cell response:**
   - T cells known as helper T-cells and killer-T cells are also activated by the presence of the immunogen in the blood.
   - Later, if the pathogen ever enters the body, helper T-cells will prompt the killer T-cells to recognise and kill the pathogen or any cells that become infected with the pathogen.

3. An ‘army’ of memory B-cells and memory T-cells is formed through this process. If the actual pathogen ever enters the body, these memory cells will quickly recognise it and will initiate strong immune responses to avoid or lessen infection.
Preventive vaccines are the traditional type of vaccine, defined previously, which will protect a person from infection or disease in the future. Preventive vaccines are not a cure for someone who has already become infected or developed disease. They prepare the immune system to respond in case of future exposure to the pathogen. Common examples include polio, measles, hepatitis B and tetanus vaccines. All vaccines currently marketed throughout the world are preventive vaccines. Most of the AIDS vaccine candidates now being tested are preventive vaccines. The remainder of this chapter and the entire Vaccine Literacy Core Content will focus on preventive vaccines.

Another way that a vaccine might work is by starting an immune response after a person has been infected to try to diminish the effects of infection and/or prevent the development of disease. This would be called a therapeutic or ‘treatment’ vaccine. Right now, there is no AIDS vaccine candidate that works this way, although some scientists are trying to develop one. Scientists are also trying to develop therapeutic vaccines for cancer.

There are many ways to design vaccines, each of which uses a different approach to produce a response from the immune system. The following table on pages 51 and 52 lists some (but not all) common types of vaccines, a general description of how each works and, finally, how each concept relates to AIDS vaccines that are in development. The table helps to show that although certain types of vaccines are safe and effective for other diseases, they may not be safe and/or effective when applied to AIDS vaccines.
Whole-killed/Whole-inactivated vaccines

- Uses the entire pathogen to stimulate an immune response.
- Pathogen is killed or is made inactive so that it is not alive and cannot cause infection.
- Vaccine causes the body to make an immune response that will protect against a live pathogen.

Examples: injectable polio vaccine (Salk), cholera vaccine, injectable influenza vaccine.

Live attenuated vaccines

- Uses a weakened form of the pathogen.
- Pathogen is changed in a particular way so it will not be harmful.
- Introduction of this form of the pathogen into a human will mimic true infection and will enable the body to produce an immune response.

Examples: measles vaccine, oral polio vaccine (Sabin), intranasal live influenza vaccine.

Subunit vaccines

- Most subunit vaccines contain a small protein or piece of the pathogen; the protein acts as the foreign antigen (see Chapter 3), which will start the immune response.
- B cells of the immune system will produce antibodies against the antigen.
- Antibodies lock on to the antigen/protein of the pathogen.
- When the entire pathogen enters the body, the antibodies will recognise the foreign antigen and attach to it, coating the pathogen and making it harmless, or ‘neutralizing’ it.
- Certain subunit vaccines are made from smaller pieces of proteins called peptides.

Examples: hepatitis B vaccine, tetanus toxoid.
**DNA vaccines**
- Use copies of single or multiple genes from the pathogen; a gene is a small piece of DNA (genetic material) that contains instructions or a “code” to make protein(s).
- Genes enter into human cells and use the cell’s ‘equipment’ to produce some protein(s) of the pathogen encoded by the gene(s).
- When the protein is produced, the immune system sees it as a foreign or harmful antigen and produces an immune response.
- The immune system remembers this response, which will prepare a response against the whole pathogen.
- This is a common strategy being used for AIDS vaccine development, (see Chapter 5).
- DNA vaccines cannot cause HIV infection because they do not contain HIV. The copies of genes are meant to produce an immune response against HIV, but there is no possibility they will cause HIV infection.

**Vector vaccines**
- Use the same strategy as DNA vaccines, but the genes are carried by a harmless or very weakened bacterium or virus, called a vector.
- Genes are attached to the DNA of the vector, carrying the genes into the human cell.
- Once in the human cell, genes produce protein(s) to which the body produces an immune response, as described above for DNA vaccines.
- This is a common strategy being used for AIDS vaccine development.
- Recombinant vector vaccines will not cause HIV infection for the same reasons described for DNA vaccines above.
- Many scientists believe that the addition of a vector will allow the vaccine to be more effective in creating an immune response than using DNA alone.

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**Additional vaccine concepts**

**Adjuvant**
An adjuvant is a substance that is added to some vaccines to increase the body’s immune response to the antigen.

**Efficacy**
A vaccine’s efficacy refers to the rate of protection from infection and/or disease under optimal large-scale clinical trial conditions.

Efficacy is shown by comparing the rate of infection or disease in the vaccine group to that in a placebo group² (see Chapter 6). This is done by monitoring the rate of infection or disease in the two trial groups for a long period of time. In the case of HIV vaccine trials, the
monitoring will take about two to four years. If the vaccine group has less infection or disease, the vaccine is said to have efficacy or to be efficacious.

After a vaccine has been proven to work, it is still important to find out how well it works when given to people of different ages, people whose immune systems are not strong, people with chronic diseases, in cases of malnutrition, etc. It also is important to find out how long the protection lasts (see Chapter 6).

**Partial efficacy**

The concept of a partially effective vaccine has different meanings. It can refer to either: (a) a vaccine that protects some people in a population who receive the vaccine but not others, or (b) a vaccine that does not completely prevent infection but does help reduce the severity of disease caused by the pathogen.

There is no such thing as a vaccine that provides protection to 100 percent of people, 100 percent of the time. In this sense, all vaccines are partially effective, and the same will be true for future AIDS vaccines. There is also a chance that if an AIDS vaccine does not prevent a person from becoming infected with HIV, it may instead prevent progression to AIDS in people who become infected with HIV through blood or sexual exposure after receiving the vaccine. This is because the vaccine might keep the amount of virus circulating in the blood at a low level, also referred to as lowering the viral load.

AIDS vaccines that are partially effective but prevent progression to disease could have a significant impact on the pandemic by reducing HIV transmission, and delaying the need for antiretroviral (ARV) treatment and illness or death for infected individuals.

**Effectiveness**

*Effectiveness* describes how well a vaccine reduces disease in the overall population when it is being used. This depends on the efficacy, as defined in clinical trials and characteristics of the general population, including how many people actually get vaccinated, as well as whether they take their full series of vaccinations.

**Herd immunity**

It is important for people to receive vaccines that are licensed and available in their communities. When many people in a community are vaccinated against
a disease, even those who are not vaccinated in that community may also get some protection because of a phenomenon called herd immunity. If enough people in the community are vaccinated, there is less chance of the infection spreading from person to person, and unvaccinated individuals may be less likely to get infected because there is a lower risk of exposure. For example, measles and rubella vaccines protect vaccinated people and also cut down on the spread of the disease to people who are not infected. However, if too many people choose not to be vaccinated, herd immunity will not have any effect in the community.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe</td>
<td>does not cause any serious side effects.</td>
</tr>
<tr>
<td>Efficacious</td>
<td>must show that people who are vaccinated have significantly fewer infections or disease compared to un-vaccinated individuals.</td>
</tr>
<tr>
<td>Available</td>
<td>should be able to be produced in large quantities and be deliverable to everyone who needs it.</td>
</tr>
<tr>
<td>Effective</td>
<td>must decrease the disease in the general population.</td>
</tr>
<tr>
<td>Stable</td>
<td>can last for a long time in various conditions or environments.</td>
</tr>
<tr>
<td>Accessible</td>
<td>should effectively reach the populations in need quickly and easily.</td>
</tr>
<tr>
<td>Affordable</td>
<td>should be affordable by governments or individuals who need it most.</td>
</tr>
</tbody>
</table>
Traditionally, vaccines are made to prevent healthy people from getting infection or disease. This is also the goal of developing a preventive AIDS vaccine.

No existing vaccine works on all people 100 percent of the time. It is likely that an AIDS vaccine, once available, will be less effective than some vaccines used for other diseases and will decrease but not eliminate the risk of HIV infection. Even after people receive the vaccine, they will still need to continue other prevention practices (such as using condoms).

The traditional approaches for developing vaccines have either not worked well or would be unsafe when applied to AIDS vaccine development, so scientists are using newer techniques to develop AIDS vaccine candidates. Using these techniques, there is no chance that an AIDS vaccine candidate will cause HIV infection.
In this chapter

A vaccine is the best way to stop an epidemic. With the exception of making clean drinking water accessible, no other public health effort has reduced infectious diseases as much as vaccinations have. Overall, vaccination is the most cost-effective way to improve public health.

Given the extent and severity of the HIV pandemic, the world urgently needs an AIDS vaccine. AIDS vaccine research started in the 1980s and is now underway worldwide. As of 2009, most experts agree that the development, licensure and distribution of an effective AIDS vaccine will likely require many more years of work.

This chapter discusses:

- Basic facts about AIDS vaccine science.
- Preventive AIDS vaccines.
- Science of AIDS vaccines in development.
- History of AIDS vaccine research.
- Links to information about the current status of AIDS vaccine research.
- Challenges of AIDS vaccine development.
- Organisations involved in international AIDS vaccine research.
Summary points

1. Currently, no vaccine to prevent HIV or AIDS exists, meaning an AIDS vaccine has not yet been proven safe and efficacious, licensed and made available to the public.

2. Many experimental vaccines for preventing HIV and/or AIDS are being developed and tested; they involve new vaccine concepts such as recombinant DNA, recombinant vectors and subunits (copies of parts of the HIV virus).

3. As of 2009, AIDS vaccine research has been underway for more than 20 years; it is likely to take many more years until an AIDS vaccine is available.

4. Developing an AIDS vaccine involves unique scientific challenges.

5. Many organisations throughout the world are involved in AIDS vaccine work, from basic scientific research and clinical trials to advocacy, education and policy development.

Key concepts

Basic facts about AIDS vaccine research and development

- To date, there is no AIDS vaccine available anywhere in the world. Many AIDS vaccine candidates are in various stages of research, development and testing (see Chapter 6).
- AIDS vaccine research began soon after the discovery of HIV in the 1980s. It takes many years to develop and test any vaccine, and it is likely to take many more years until one or more AIDS vaccines are proven highly effective and subsequently licensed, manufactured and made available around the world.
- Most AIDS vaccines being developed are preventive vaccines, although some work is being done on the development of therapeutic vaccines (see Chapter 4 for further information).
- A preventive AIDS vaccine is a substance given to someone who has not been infected with HIV to ‘teach’ the person’s immune system to fight HIV infection in the case of future sexual or blood exposure to the virus.
- A preventive AIDS vaccine could work in one of two ways:
  - Blocking infection, so the vaccinated person does not become HIV infected through blood or sexual exposure in the future.
- Modifying the course of infection and disease so that even if it were not successful in preventing HIV infection, it would keep the amount of virus circulating in the blood (known as viral load) at a low level, potentially preventing progression to AIDS.

- AIDS vaccines being developed for testing in humans contain copies of small segments of genetic material from HIV. No part of HIV is used directly in a vaccine; instead, these copies of HIV's genetic material are made artificially (see box below). The genes are chosen because they produce proteins that should trigger the immune system to develop a response to HIV if it ever enters the body. There is no risk that they will cause HIV infection.

- AIDS vaccine clinical trials started in 1987; as of 2009, more than 150 clinical trials were completed or ongoing throughout the world.

- In the early years of vaccine research, most vaccines were developed for subtype B of HIV, the subtype now most common in North America and Europe.

- Since the mid-1990s, more emphasis has been placed on developing vaccines for countries where HIV disease burden is highest, focusing on subtypes common in Central and South America, Africa and Asia.

- Many different types of vaccines will need to be tested in different regions of the world before a safe and effective AIDS vaccine will be approved and licensed.

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**What does the term ‘copies of genes’ mean?**

This term is used when describing AIDS vaccines under development because the genes that are included in vaccines do not come directly from HIV. Instead, scientists make artificial copies of these genes in the lab and use the copies in the vaccine. This process is comparable to making a photocopy of a famous painting: the copy would look the same but would not have the same value as the original because it is not authentic. Similarly, the gene copies look like ‘real’ HIV genes but are not ‘authentic’ genes taken directly from the virus.
**DNA vaccines**

DNA vaccines contain copies of individual genes of HIV. Genes are small pieces of DNA (genetic material) that contain instructions or a ‘code’ to make the virus’s proteins, which are its building blocks. When the DNA vaccine is injected the genes are picked up by the body’s own cells, which are then able to produce the proteins coded for by the genes. The proteins are meant to generate a cellular and/or antibody immune response (see Chapter 3) against HIV. The selected genes are harmless and cannot make a whole virus; therefore, there is no way they can cause HIV infection.

Because of mutation, HIV’s DNA changes relatively often. The segments of DNA that change the least are often chosen for use in a given candidate AIDS vaccine. These particular genes are also chosen because they have been shown to generate immune responses in animals.

**Vector vaccines**

Vector vaccines use the same basic concept used in DNA vaccines with the addition of a vector, or delivery vehicle that carries the gene copies contained in the vaccine into the human cell. A vector is a different virus, which is unrelated to HIV and will not cause disease in humans. When the HIV gene copies and the vector are mixed together, the genes insert themselves into the vector and combine with its genetic material. By ‘piggy-backing’ on the vector, the HIV gene copies can enter into human cells more efficiently than if they were used alone in the vaccine.

Examples of vectors include pox viruses, alpha viruses, adenoviruses and adeno-associated viruses.

**Subunit vaccines**

A subunit refers to any part or small piece of a virus, such as a protein. AIDS vaccine candidates that were developed using this concept generally used a copy of a protein from the outside envelope of HIV. In theory, this protein will cause the human body to create a protective antibody response against HIV. Subunit vaccines may also be referred to as component or peptide vaccines. Another type of subunit vaccine is a virus-like particle vaccine (VLP), which contains copies of several or more (but not all) proteins from the virus.
5.1 Timeline

Major points in the history of AIDS vaccine research

2009
Largest-ever AIDS vaccine trial completed in Thailand. Prime-boost combination vaccine of a canarypox vector-based component and a gp120-based subunit showed about 30% efficacy in preventing HIV infection in this Phase III trial.

Two powerful new broadly neutralizing antibodies to HIV discovered, revealing a new target on HIV. Antibodies are first to be extracted from individuals in the developing world. (Discovery made by IAVI, The Scripps Research Institute, Theracloone Sciences and Monogram Biosciences.)

2007
STEP and Phambili Phase IIb test-of-concept trials of Merck adenovirus type-5 AIDS vaccine candidate prematurely halted due to failure of the product to show efficacy in preventing new infections.

2003
First two Phase III trials of gp120-based vaccines (conducted by VaxGen, Inc.) completed and results of no vaccine efficacy released.

2001
The same subtype A vaccine trial begun in Kenya, with the Kenya AIDS Vaccine Initiative.

2000
First AIDS vaccine trial for clade/subtype A (the clade most common in East Africa) begins at the University of Oxford in the United Kingdom in collaboration with IAVI.

1999
First volunteer recruited into the HIVNET 007 trial in Uganda, the first AIDS vaccine trial in Africa, which tested a recombinant vectored vaccine (ALVAC).

HIV Vaccine Trials Network (HVTN) formed from two existing AIDS vaccine organisations and funded by the U.S. National Institutes of Health (NIH).

Second Phase III trial begins for gp120-based vaccine in Thailand (conducted by VaxGen, Inc.).

1998
First Phase III trial begins for a gp120-based vaccine in North America and Europe (conducted by VaxGen, Inc.).

1997
U.S. President Clinton announces a 10-year goal for development of an AIDS vaccine.

1996
International AIDS Vaccine Initiative (IAVI) forms with support from the Rockefeller Foundation to accelerate the development of an AIDS vaccine, especially for the developing world.

1992
First Phase II trial begins on gp120 subunit–based vaccine.

1987
First clinical trial (Phase I) of an AIDS vaccine candidate begun by the U.S. government.

1984
United States (U.S.) Secretary for Health and Human Services announces that an AIDS vaccine may be developed within two years.

1983
HIV identified as the cause of AIDS.
Additional concepts related to AIDS vaccine candidates

Prime-boost
This is a series of immunisations meant to ‘prime’ or prepare the immune system with the first vaccination and ‘boost’ the immune system with the next vaccination(s). The same or different types of vaccine may be used for the prime and boost.

Recombination
This is a general term for a process in which pieces of genetic material are taken from two different sources and joined together. Genes from the different sources will combine together, or ‘recombine’, to make a new strand of genetic material. Therefore, ‘recombinant’ is a scientific term which applies to technology used in AIDS vaccine research.

Vector vaccines are sometimes referred to as recombinant vector vaccines, since, as described above, the HIV gene copies combine with the genetic material of the vector virus.

Status of AIDS vaccine trials

AIDS vaccine trials database
IAVI’s bimonthly publication, IAVI Report, maintains a database of all completed and ongoing AIDS vaccine trials, available at www.iavireport.org/trials-db/. This database allows users to search for any vaccine that is being tested or that has been tested in any part of the world.

Efficacy trials of candidate AIDS vaccines
As of 2009, three vaccine candidates have completed Phase III trials (see Chapter 6), and an additional vaccine candidate started Phase IIb testing, although the trial was not completed. Subunit gp120–based vaccines (AIDSVAX B/B and AIDSVAX B/E, developed by VaxGen Inc.) were found not to be efficacious in two Phase III trials completed in 2003, the first in the U.S., Canada and the Netherlands, and the second in Thailand. Results showed that the vaccines were not efficacious in preventing HIV infection or in modifying the progression of HIV infection, nor did they have effect on the amount of virus in individuals who became HIV-infected after vaccination.

A Phase IIb test-of-concept trial (see Chapter 6 for definition) of the Merck adenovirus type-5 vector vaccine, known as the STEP study, was initiated in the Americas and Australia in December 2004. A sister Phase IIb test-of-concept trial of the same candidate was initiated in South Africa in February 2007; this trial was known as Phambili. These trials were prematurely halted when data from the STEP study were
un-blinded for an interim analysis in September 2007. The data showed that the vaccine was not efficacious in preventing infection, indicating that the trials should not move forward. Early analysis of data also indicated (but did not prove) that in a subset of volunteers, those who received the vaccine may have been more susceptible to HIV infection than those who received the placebo. As of late 2009, data from these trials were still being analysed to understand more fully why the candidate vaccine was not successful.

A Phase III trial of a prime-boost combination vaccine (canarypox viral vector-based prime, boosted by AIDSVAX B/E) was initiated in October 2003 in Thailand by the U.S. Military HIV Research Program and the Thai Ministry of Public Health. Results were released in late 2009, indicating that the vaccine combination reduced the risk of HIV infection by about 30% but did not have any effect on the amount of virus in individuals who became HIV-infected after vaccination. These were the first results to show that an AIDS vaccine provided benefits in humans. The results will help guide ongoing and future AIDS vaccine design and development efforts.

Important lessons are obtained from all clinical trials, even those that have not shown efficacy, because in those cases researchers learned what does not work. It is only through trial and error that research moves forward.

The lessons learned from previous efficacy trials are being used to develop new, more promising AIDS vaccine candidates. For more information on the discovery and design of candidate AIDS vaccines, please see IAVI’s 2008 Scientific Blueprint at www.iavi.org/blueprint.

**Evidence that an AIDS vaccine is possible**

As explained in the previous section, data released in 2009 from the Phase III trial in Thailand showed for the first time that an AIDS vaccine can reduce the risk of HIV infection in humans. Previously, the field only had evidence of potential efficacy of an AIDS vaccine in animal models. There is additional scientific evidence indicating that the human immune system can be effective against HIV.

Almost everyone who becomes infected with HIV manages to control the virus without drugs, generally for many years, before developing AIDS. The Joint United Nations Programme on AIDS (UNAIDS) estimated in 2008 that the average person can control HIV infection for 11 years
without drugs. Scientists have shown that a rare group of HIV-infected people control their infection indefinitely by means of their immune systems without needing antiretroviral (ARV) treatment. These individuals are sometimes called long-term non-progressors or elite controllers.

Another group of rare individuals, known as highly-exposed seronegatives, also provide evidence that the immune system can fight HIV infection. These are individuals who, despite repeated exposure to HIV (generally through higher-risk behaviour such as sex work), never become HIV-infected.

Various research efforts carried out in a species of monkeys known as rhesus macaques are also promising. This research shows that certain vaccines are highly effective in preventing infection in monkeys against the monkey form of HIV, known as simian immunodeficiency virus (SIV). Results of these studies help researchers understand the protective immune responses generated by a vaccine in monkeys, which helps them better understand the human immune responses needed to design an effective AIDS vaccine for humans.

Scientists are constantly using this information to learn how to generate a vaccine that will ultimately make the human immune system stronger than HIV, and that will effectively prevent infection and/or disease.

In spite of the evidence indicating that an AIDS vaccine is possible, the process involves challenges that have not been faced to the same degree in the development of other vaccines. The primary challenges are outlined here.

### Designing the vaccine

Researchers must make sure that an AIDS vaccine will not cause HIV infection. This means that they cannot use some of the scientific strategies used to develop vaccines for other diseases.

Vaccine development strategies that worked well for other diseases (such as measles) use weakened, harmless forms of the virus in the vaccines. This strategy is NOT used in AIDS vaccine development given the concern that the harmless form could revert into the disease-causing form of HIV.

Instead, only a few artificial copies of genetic material that resemble HIV genes are used in AIDS vaccines. Science shows that the selected
genes are harmless and cannot make a whole virus; therefore, there is no way they can cause HIV infection.

Researchers are working to identify which bits of genetic material will cause the body to successfully generate a strong immune response against HIV.

**Animal models**

Before being tested in humans, all vaccines go through testing in animals. Normally, an ‘animal model’ is used, such as a mouse, rabbit or monkey. Animal models usually give scientists a good idea of what effects (safety and immune response) the vaccine may have in humans.

Testing AIDS vaccines in animals has not yet accurately predicted how they will work in humans. This makes vaccine research and human trials more difficult to design, and reinforces that clinical (human) trials are the only way to answer questions relevant in humans.

However, researchers are constantly learning about the human immune response to HIV through animal testing. This should help develop more promising vaccine candidates.

**Correlates of protection**

When a person naturally recovers from a disease, or when a vaccine successfully protects a person against a disease, scientists can measure immune responses that were effective against the pathogen. This enables researchers to determine the immune responses that link, or correlate, with protection, called the ‘immune correlates of protection’.

Because there is currently no effective AIDS vaccine, and because no human has ever naturally recovered from HIV infection, these correlates are currently unknown. However, scientists are learning from unique individuals who do not become infected despite repeated natural exposure to HIV, as well as individuals who are infected with HIV, yet naturally do not progress to AIDS. Learning the correlates of protection gives scientists important clues about what is required for an effective AIDS vaccine.

**HIV mutation**

The different forms of HIV that have evolved over time can be thought of as members of a large family: They are different but related to each other. The different branches of the family tree are called subtypes, also referred to as ‘clades’. Each subtype is about 30 percent different
5.2 Global distribution of HIV-1

HIV-1 subtypes and recombinants

Source: Adapted from: Francine E. McCutchan, Henry M. Jackson Foundations (Rockville, Maryland). McCutchan and colleagues are indebted to the many international collaborators who helped develop the data used to generate this map.
in its genetic makeup from any of the others. Scientists have given the subtypes letters as names. Sometimes viruses are a combination of two subtypes; these are called ‘recombinant’ forms.

Subtype C is common in Southern Africa, Ethiopia, China and India, for example, while subtype B is most common in the U.S., Europe, the Caribbean and South America. In the early days of vaccine research and development, most candidates were based on subtype B. Now, however, many vaccines are being developed and tested for subtypes that exist in countries where the burden of disease is greatest.

Summary: What challenges does HIV mutation place on vaccine development?

Different forms of HIV within an individual
HIV can mutate inside a person. Mutation means the genes undergo a change. So, as HIV mutates, an infected person can have slightly different forms of the virus circulating in his or her body. It is hard for the immune system to develop an effective response against all of these different forms of HIV. The response may work against most of the forms of the virus, but a few of the viruses still manage to ‘escape’ the immune response. In a similar way, the HIV in a person may mutate to become resistant to some ARV drugs. Researchers do not know whether an AIDS vaccine would be protective against different forms of HIV in an individual.

Different forms of HIV throughout the world
Because of mutation, different subtypes exist in different parts of the world. Researchers do not know yet if a vaccine designed for a subtype in one part of the world will work for subtypes in other parts of the world.

The subtype distribution may vary throughout the world as the virus evolves. An ideal AIDS vaccine would protect people against infection with all HIV subtypes, but it is not yet known if this is possible. Therefore, many different vaccines need to be tested against different subtypes.

Additionally, HIV is extremely effective at evading the immune system because it can mutate within an individual. Different forms of HIV within
It is important to remember that the purpose of scientific research is to overcome challenges. Previous challenges in HIV research, which initially were thought to be very difficult, have been overcome. When HIV was first discovered, scientists did not think it would be possible to develop drugs for treatment, because only a few drugs had been developed against viruses at that point. This thinking was proven wrong, of course, and more drugs have been developed to treat HIV than any other viral infection. What’s more, the Phase III trial results released in 2009 showed for the first time that an AIDS vaccine can reduce the risk of HIV infection in humans—the most promising evidence that an AIDS vaccine is possible.

Many universities, organisations and companies are involved in various aspects of AIDS vaccine research, education, policy development or advocacy. The following is a select list of organisations that are involved in clinical trials and international advocacy as of 2009.

<table>
<thead>
<tr>
<th>Name</th>
<th>Brief description</th>
<th>For further information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>African AIDS Vaccine Programme (AAVP)</strong></td>
<td>Established in 2000 by the World Health Organisation (WHO)-UNAIDS HIV Vaccine Initiative (HVI). The mission is to ‘advocate and support a coordinated effort to contribute to the global HIV vaccine development goals, ensuring that appropriate and affordable vaccines are developed for Africa in the shortest possible time’.</td>
<td><a href="http://www.who.int/vaccine_research/diseases/hiv/aavp/en">www.who.int/vaccine_research/diseases/hiv/aavp/en</a></td>
</tr>
<tr>
<td>Name</td>
<td>Brief description</td>
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<tr>
<td>AIDS Vaccine Advocacy Coalition (AVAC)</td>
<td>Nonprofit organisation founded in 1995 to speed the ethical development and global delivery of AIDS vaccines. It does not conduct AIDS vaccine research itself but instead engages in advocacy, educational outreach and building awareness both in the U.S. and internationally.</td>
<td><a href="http://www.avac.org">www.avac.org</a></td>
</tr>
<tr>
<td>Canadian HIV Vaccine Initiative (CHVI)</td>
<td>Canada’s contribution to the Global HIV Vaccine Enterprise and global efforts to ‘develop a safe, effective, affordable and globally accessible HIV vaccine’. It is the result of a five-year collaboration between the Government of Canada and the Bill and Melinda Gates Foundation and it represents a key element in the Canadian government’s commitment to a domestic and international response to HIV and AIDS.</td>
<td><a href="http://www.chvi-icvv.gc.ca/index-eng.html">www.chvi-icvv.gc.ca/index-eng.html</a></td>
</tr>
<tr>
<td>HIV Vaccine Trials Network (HVTN)/National Institutes of Health (NIH)</td>
<td>Formed in 1999 from two existing groups, the AIDS Vaccine Evaluation Group (AVEG) and HIVNET, by the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID), a component of the U.S. National Institutes of Health (NIH). The mission is to ‘develop and test preventive HIV vaccines’. Research is done through multicentre clinical trials conducted simultaneously in the U.S. and international research centres.</td>
<td><a href="http://www.hvtn.org">www.hvtn.org</a></td>
</tr>
<tr>
<td>Institute for Human Virology (IHV)</td>
<td>Focuses on chronic viral diseases, including HIV, and virally linked cancers. Part of their work is to ‘find an effective and affordable vaccine against HIV’.</td>
<td><a href="http://www.ihv.org">www.ihv.org</a></td>
</tr>
<tr>
<td>International AIDS Vaccine Initiative (IAVI)</td>
<td>Nonprofit organisation formed in 1996. Mission is to ‘ensure the development of a safe, effective, preventive HIV vaccine for use throughout the world’. The work focuses on four areas: mobilising support through advocacy and education; moving scientific research forward; encouraging industrial participation in AIDS vaccine development and ensuring global access. Regional offices are in New Delhi, India; Nairobi, Kenya; Johannesburg, South Africa; and Amsterdam, the Netherlands.</td>
<td><a href="http://www.iavi.org">www.iavi.org</a></td>
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</tbody>
</table>
## Select organisations involved in international AIDS vaccine research

<table>
<thead>
<tr>
<th>Name</th>
<th>Brief description</th>
<th>For further information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kenya AIDS Vaccine Initiative (KAVI)</strong></td>
<td>Mission is to ‘contribute to a world without AIDS by developing a safe, effective and affordable preventive HIV vaccine’. Formed by a partnership between the University of Nairobi, Oxford University and IAVI.</td>
<td><a href="http://www.kaviuon.org">www.kaviuon.org</a></td>
</tr>
<tr>
<td><strong>South African AIDS Vaccine Initiative (SAAVI)</strong></td>
<td>Formed in 1999 as a programme of the Medical Research Council (MRC) of South Africa. Established to coordinate the research, development and testing of candidate AIDS vaccines in South Africa. Based at the MRC, it works with key national and international partners to produce an affordable, effective and locally relevant preventive AIDS vaccine in as short a time as possible.</td>
<td><a href="http://www.saavi.org.za">www.saavi.org.za</a></td>
</tr>
<tr>
<td><strong>U.S. Military HIV Vaccine Research Program (USMHRP)</strong></td>
<td>A division of the U.S. Army, it conducts international HIV vaccine research on vaccine candidates that are designed specifically for HIV subtypes found in regions where the U.S. military is present. Works in East and West Africa and partners with governments and academic institutions in Uganda, Kenya, Tanzania, Cameroon and Thailand. Affiliated with the Walter Reed Army Institute of Research.</td>
<td><a href="http://www.hivresearch.org">www.hivresearch.org</a></td>
</tr>
<tr>
<td><strong>Vaccine Research Center (VRC)</strong></td>
<td>Established by the U.S. NIH to facilitate vaccine research, as part of an initiative by former U.S. President Bill Clinton to develop an AIDS vaccine. The VRC conducts research for vaccines against a variety of human diseases.</td>
<td><a href="http://www.niaid.nih.gov/vrc">www.niaid.nih.gov/vrc</a></td>
</tr>
<tr>
<td><strong>WHO-UNAIDS HIV Vaccine Initiative (HVI)</strong></td>
<td>Programme of WHO with mission to ‘promote the development, facilitate evaluation, and address future availability of preventive HIV vaccines, with a focus on the needs of developing countries’.</td>
<td><a href="http://www.who.int/vaccine_research/diseases/hiv/en">www.who.int/vaccine_research/diseases/hiv/en</a></td>
</tr>
</tbody>
</table>
No licensed effective AIDS vaccine currently exists, but there are a number of candidate vaccines being developed and tested.

There is no chance that any candidate AIDS vaccine could cause HIV infection.

Developing an AIDS vaccine is very difficult for many scientific reasons. The effort involves challenges that have not been faced to the same degree in developing other vaccines.

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1 At the time of printing, further analysis to understand how the vaccine combination provided protection, albeit modest protection, was ongoing.
There are many steps involved in the development of any vaccine before it can be licensed and used in humans. After a vaccine is designed or developed in the laboratory and is tested in animals for safety, immune response and toxicity, it must go through a series of clinical trials in humans. Many candidate AIDS vaccines clinical trials have been conducted. Because clinical trials are complex, this chapter focuses on the general process and issues that are particularly relevant to AIDS vaccine trials.

This chapter discusses
• Definition of ‘clinical trial’.
• Phases of clinical vaccine trials.
• Regulation of clinical vaccine trials.
• Key vaccine trial concepts: Placebo, randomisation, blinding, efficacy and effectiveness.
Clinical trials are studies conducted in human volunteers and must be undertaken for any new vaccine to show that it is safe and protects against disease.

A new vaccine must pass through a series of trial phases to determine if the vaccine is safe and works well in humans; each phase progressively has a larger number of people.

Phases I and II trials study safety, the dose (how much), the regimen (how many times and how far apart), the route (by mouth, skin, injection and so on) of a vaccine, as well as the strength and type of immune response it produces in the body.

Phase III trials, which test the vaccine in thousands of people, determine how safe and efficacious the vaccine is in preventing infection and/or disease.

All clinical trials involve both risks and benefits for trial volunteers.

All clinical trials are carefully reviewed and regulated by various committees to ensure that they are conducted ethically and safely and that they have scientific value.

**Key concepts**

**Definition of ‘Clinical trial’**

A clinical trial is a study done in humans to help determine whether a new vaccine or drug is safe, and, in later-stage trials, effective. All vaccines and drugs must go through clinical trials to determine if they can be made available to the general public. While undergoing testing, experimental vaccines or drugs are referred to as ‘candidate’ vaccines or drugs. A series of trials determine whether the candidate vaccine or drug is both safe and efficacious.

Before clinical trials begin, all candidate vaccines and drugs are tested in animals; animal studies may be referred to as pre-clinical studies. Animal studies are required before clinical trials of any candidate vaccine or drug in order to get an idea of how it will work in humans.
Clinical vaccine trials examine the following main issues:

- Safety – establishing that the vaccine does not cause adverse events (AEs) (see definitions below), which would prevent its use. AEs can be mild, moderate or severe, and may or may not be caused by the vaccine. An example of a severe AE that is probably not caused by a candidate drug or vaccine is a car accident.

Common reactions or side effects that are expected for vaccines include fever, headache, tiredness or body aches. They usually last only a few days. Rare (occurring in 1 in 1 million people) or uncommon (occurring in 1 in 1,000) side effects can only be seen after many people have received the vaccine. Thus, safety information is actively collected in all clinical trial studies. Even after a vaccine has been approved for use, safety is monitored by the reporting of side effects through central data collection systems.

- Adverse event/reaction (AE) – any unfavourable event or physical condition that an individual experiences during participation in a clinical trial; the event may be sudden or may develop over time. The unfavourable event may or may not be causally related to the candidate drug or vaccine.

- Serious adverse event (SAE) – an event that causes death, is life-threatening, requires hospitalisation, produces significant disability or produces congenital abnormality (birth defect) in a child of a vaccinated person. As with AEs, SAEs may or may not be causally related to the candidate drug or vaccine.

Vaccines are expected to be safe when used in humans. Many marketed vaccines may cause sore arms and some can cause mild fever or tiredness, but serious illness is very rare. Any local side effects or illnesses that might be related to the vaccine are carefully studied in clinical trials to determine whether the vaccine is safe enough to be moved on to further trials and eventually to market.

One of the most important tasks of researchers is to assess whether an adverse event is related to the vaccine being tested or not. For example, if a volunteer experiences fever due to malaria while in an AIDS vaccine trial, then it is not related to the vaccine. However, if no other cause (such as malaria) can be found, the fever may be related to the experimental vaccine.
• *Dose, regimen and route* – defining how much to give (dose), how often to give it and how far apart the doses should be (regimen), and the mode by which to give the vaccine (route), such as by mouth, through the skin, by injection in the muscle and so on.

• *Immunogenicity* – the ability, strength and type of immune responses in humans. Immune responses are measured through laboratory tests on samples of volunteers’ blood or other body fluids.

• *Efficacy* – the ability of a candidate vaccine to protect against infection or disease. For example, in an AIDS vaccine trial, the vaccine should prevent HIV infection or progression to AIDS in volunteers who received the vaccine in contrast to those who received the inactive placebo. See more information on efficacy below.

• *Effectiveness* – how well the vaccine reduces disease when it is used in the overall population. This is determined through additional studies conducted after a vaccine has been through clinical trials and is licensed and used in the general population (see section on Phase IV studies). See Chapter 4 for further information on effectiveness.

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**What does ‘safety’ mean in the context of AIDS vaccine trials?**

The term ‘safety’, as used in clinical trials, means that researchers are testing to make sure the vaccine does not cause side effects (e.g., fever, sore arm) in a significant number of people or to a significant or severe degree in any person.

People may think safety means safe from HIV infection, but that is not the meaning of the term safety as used in clinical trials. There is no chance of getting HIV infection from candidate AIDS vaccines because they do not contain HIV. AIDS vaccines are designed using newer scientific approaches that ensure they cannot cause HIV (see Chapter 5).

While candidate AIDS vaccines cannot directly cause HIV infection, it is unknown if they may increase a person’s risk of acquiring HIV through traditional means, i.e., sexual or blood exposure. A person’s risk of infection might be less, the same or more than if the individual had not received the candidate vaccine.
Phases of clinical trials

No matter how promising a candidate vaccine looks in laboratory and animal testing, any new vaccine must go through a careful process of clinical trials before it is proven to be safe and effective. A series of carefully conducted phases of trials, described below, is the fastest way to see if a new vaccine protects people from infection or disease. Please note that definitions are generic and describe the standard process of clinical trial testing. Specific details such as the number of volunteers and type of population may vary depending on the objectives of a given trial.

Phase I
These trials are the first tests in humans of an experimental vaccine. They measure safety and immunogenicity in a small group (generally 20 to 80, but possibly as low as 10 or up to 100) of healthy volunteers. Several Phase I trials may be conducted to obtain this information, possibly involving different routes of injection or doses. If a vaccine is immunogenic, this means that immune responses have been observed in volunteers’ blood after they receive the vaccine. It is not known whether this immune response will protect a person against infection or disease. Phase I trials often last 12 to 18 months.

Phase II
These trials measure safety and immunogenicity in a larger group of healthy volunteers (generally 100 to 500, but may be as low as 50). Here the goal is also to find the best dose, route of injection and regimen. Phase II trials may last up to two years or longer.

In some cases, a Phase II trial may be conducted in volunteers who represent a population at higher risk for infection, aiming to measure safety and immunogenicity in this group of people. This population is generally included in larger scale trials (Phase IIb and III, see below), but conducting a smaller trial will give researchers an initial indication as to whether the candidate vaccine might protect some people in this population, and whether to move to larger trials. They may be referred to as screening-test-of-concept trials because they screen for evidence of possible efficacy.

Phase IIb
A Phase IIb trial is a smaller Phase III trial (see below). It is designed to give researchers an indication of whether a candidate vaccine will show efficacy (prevention of infection in the trial) and is worth testing
in larger Phase III trials. As in a Phase III trial, the volunteers represent the population at higher risk for infection, but the number of volunteers involved in a Phase IIb trial is smaller than in a Phase III trial. Phase IIb trials are easier to manage, faster to complete and less costly than Phase III trials. They can help researchers determine which vaccine candidates to move forward in a Phase III trial without expending more time and money. Phase IIb trials may also be referred to as test-of-concept trials since they test the concept of whether the particular vaccine candidate can protect against infection or disease, but do not definitely prove it. Because Phase IIb trials are conducted in smaller populations, the data do not predict how the vaccine will work in the general population as accurately as data from a full Phase III trial. Therefore, a Phase IIb trial cannot be used to licence a vaccine for general use.

**Phase III**

Phase III trials evaluate the safety and measure efficacy of the vaccine in a much larger number of people (for HIV vaccines, estimates vary depending on the number of infections per year in the population and other variables such as circumcised males) who may be at significant risk of infection (generally anywhere from 1,000 to 20,000 volunteers). The number of volunteers is usually calculated based on the frequency of infection or disease that is estimated to occur in the study population within a given period of time, also known as incidence.

Immunogenicity may be measured in some or all volunteers to ensure that the vaccine is inducing the same immune response it did in earlier trials. This is particularly important if the same vaccine is from a different manufacturing batch or has been made in larger quantities. Phase III trials can last for several (3 to 5) years.

The whole process, including all phases of testing, can take 10 years or more. A vaccine must be proven safe and efficacious before it can be reviewed and approved for licensure by regulatory agencies, licensed and distributed to the community.
Further studies

Additional populations

Groups of people who were not originally included in early trials, such as babies, adolescents, the elderly and people who are not completely healthy (also called immune-compromised), may be included in further studies to ensure that the performance of the vaccine is adequate in these groups.

Phase IV

One type of Phase IV study, called an expanded access study, is usually conducted during the interval between the end of the efficacy trial and approval of the product. This allows for the collection of safety data in a larger population of people, as well as access to the candidate vaccine before it is fully approved and licensed.

Phase IV studies may also look at the safety and effectiveness of the vaccine after it is licensed and in use by large populations. These studies examine how the vaccine performs under real-life conditions, as opposed to the controlled conditions of a clinical trial. These studies are sometimes called post-marketing surveillance studies or field studies.

In all cases, collection of safety data and data on rare AEs are primary goals of Phase IV studies.
6.1
Summary of clinical vaccine trial phases

<table>
<thead>
<tr>
<th>Phase</th>
<th>Volunteers</th>
<th>Length</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>20 - 80</td>
<td>12 - 18 months</td>
<td>Safety, Immunogenicity, dose, regimen, route</td>
</tr>
<tr>
<td>II</td>
<td>50 - 500</td>
<td>2 years</td>
<td>Safety and immunogenicity with selected dose, regimen, route</td>
</tr>
<tr>
<td>IIb</td>
<td>1,000 - 5,000</td>
<td>2 - 5 years</td>
<td>Safety and indication of efficacy</td>
</tr>
<tr>
<td>III</td>
<td>1,000 - 20,000</td>
<td>3 - 5 years</td>
<td>Safety, efficacy</td>
</tr>
<tr>
<td>IV</td>
<td>5,000 - 50,000</td>
<td>Varies</td>
<td>Safety</td>
</tr>
<tr>
<td></td>
<td>Surveillance studies/field studies</td>
<td>50,000 - millions</td>
<td>Safety, effectiveness</td>
</tr>
</tbody>
</table>

Note: Details listed are general characteristics and may not apply to all trials.

Source: IAVI
What are the benefits and risks of participating in an AIDS vaccine trial? (Adapted from National Institutes of Health Clinical Trials website)

Benefits
Clinical vaccine trials that are well designed and well executed may offer certain benefits to participants, including the following:

• Contributing to important medical research that may be beneficial to others.
• Medical evaluation during the trial with referral for care and treatment if needed.
• Compensation for the effort of participation. This generally comes in the form of food at the clinic visit or payment for cost of travel to clinic visits.

Risks
Any experimental vaccine may pose certain risks, including the following:

• Medical risks such as unpleasant reactions or side effects from receiving the vaccine, such as headache, fever and soreness; in clinical research there is always a possibility that the experimental substance may cause serious reactions.
• Not being able to donate blood, bone marrow or organs.
• Social risks, such as stigma or discrimination, that may be associated with participating in a vaccine trial if the participant chooses to disclose his or her participation.
• Testing ‘antibody positive’—a volunteer may falsely test HIV positive because of antibodies stimulated by the vaccine, even though he or she is not infected with HIV (see Chapter 7). This may or may not occur, and if it does occur, it is not certain how long this effect will last.

Researchers do not know what effect the candidate vaccine will have on a person’s risk of HIV infection through sexual or blood exposure; the level of risk may be less, the same or more than if the person did not receive the candidate vaccine.

Researchers and other authorities on the trial must balance the potential risk and potential benefit for volunteers.
The same legal and ethical standards that are used for regular medical practice also apply to clinical trials. Additional consideration is given for the protection of trial participants. All clinical trials are conducted according to a carefully controlled protocol, which is a detailed description or a set of guidelines for how the trial will be carried out.

All protocols have to be carried out according to strict international standards, such as guidelines set by the International Conference on Harmonisation for Registration of Pharmaceuticals for Human Use (ICH) on good clinical practice (GCP) and good clinical laboratory practice (GCLP).

Before any protocol can begin, it must be reviewed and approved by an ethics committee and relevant regulatory committees.

For complete details on these standards, see Chapter 10.

**Placebo**

Many vaccine trials involve the use of a placebo, which is a harmless, inactive substance that looks like the vaccine. Sometimes the placebo is called a ‘dummy’ or a ‘blank’. The placebo may be given to one group of volunteers, while the candidate vaccine is given to another group. When the placebo is used in a group of volunteers, the group is usually called the control group. It is only through comparison of the vaccine and control groups that researchers can evaluate the safety, immunogenicity and efficacy of the candidate vaccine.

A placebo is not always used. Sometimes a new vaccine might be compared with an old vaccine that is known to be effective. Because there are no vaccines against HIV that are effective, placebos are needed for the comparison.

**Randomisation**

Participants in a trial are assigned to the vaccine and control (placebo) groups by chance or by random selection, sometimes using a computer. Neither the researchers nor the participants can decide which study group each participant will go into. This process is known as randomisation.

Randomisation is the best way to make sure that the different testing groups have the same characteristics. If researchers or participants
could choose which group to go into, the groups could become unfairly divided and not alike. If the groups are not comparable, the effects of the vaccine cannot be measured fairly.

**Blinding**

*Blinding* refers to the fact that the participants do not know whether they have received the experimental vaccine or the placebo; therefore they are ‘blind’ to what has been administered when they received an injection in the trial. This is also sometimes called ‘masking’. The purpose of blinding is to make sure that side effects are not interpreted differently according to whether someone has received the vaccine or placebo and to make sure that participants do not change their behaviour or what they report (for example, side effects) based on whether they received the vaccine or a placebo.

In many trials, neither the researchers nor the participants know who is getting the vaccine. This is called double-blinding. Double-blinding ensures that researchers are not biased, or unfairly influenced, by knowing what the participant has received. If researchers know whether the participant received the vaccine or the placebo, they may over- or under-report side effects. The individuals responsible for randomisation (generally statisticians, but never anyone on the clinical trial staff) keep the information in a safe location until the end of the study. Most clinical trials are double-blinded.

After the trial is complete and all data have been collected, researchers unblind the study to see which participants received the vaccine and which received the placebo. Once the trial is unblinded, the volunteers are also told what they received. In some special cases researchers may need to see whether the volunteer was in the vaccine or placebo group before the trial is complete. This is very rare, especially in vaccine trials, for several reasons, but mainly because serious reactions to vaccines are very rare.

**Level of efficacy**

A vaccine’s *efficacy* refers to the rate of protection from infection and/or disease under optimal Phase III clinical trial conditions.

The efficacy level in preventing infection is measured by comparing the rate of infection in the vaccine group to the rate of infection in the placebo group. This is done by monitoring the two trial groups for a long period of time, usually 2 to 4 years, to see how many people
There is a great deal of discussion about how high the efficacy needs to be to have an effect on the disease in the community. Complex mathematical models are used to determine the potential effect of a vaccine on a population at different levels of efficacy. Many different factors need to be taken into account in these models to determine appropriate levels of efficacy for approval. Some of these factors include the following:

- Rate of infection in the community.
- Rate of transmission in the community.
- Number of people infected in a community.
- Number of people who received the vaccine and completed all vaccinations.
- How quickly the vaccine works and how long protection lasts.

The formula used for calculating efficacy is as follows:

\[
\text{Efficacy} = \frac{\text{Infection rate in those who received placebo}}{\text{Infection rate in those who received vaccine}} \times 100
\]

If a significantly lower number of people in the vaccine group have acquired infection than in the control group, this is an indication that the vaccine protects against infection, and it is said to have efficacy or to be efficacious. Efficacy is generally expressed as a percentage indicating the percent of the population it is expected to protect.

The degree of efficacy may be important as well. No vaccine is 100 percent efficacious (see Chapter 4 for further information on partial efficacy). Regulators and researchers agree on the minimum efficacy that will be acceptable for approval and distribution in the general population. The level of efficacy that researchers want to find affects how the trial is designed.
Experimental versus licensed vaccines

An experimental or candidate vaccine is one that has not completed required phases of trials (generally Phases I–III) and has not been approved by a regulatory authority for use in the general population. This means that researchers, scientists, doctors and regulatory authorities do not yet know if the vaccine works or the degree of safety. Trials must be completed and the data must be analysed and reviewed by researchers and regulatory authorities before the vaccine becomes available. Experimental or candidate vaccines are not available to the general public. Additionally, there may be a Phase IV or post-marketing studies that continue to look at the safety of approved and licensed vaccines before they are widely available in the general population. Examples of experimental vaccines include AIDS and malaria vaccines.

Licensed vaccines are those that have been through the required phases of clinical trials, are approved and are being used in the general public. There are many licensed vaccines available today; a few examples are the polio, the measles and the hepatitis B vaccines.

Clinical research versus standard health care

Many different types of clinical trials take place all over the world. Often, clinical trials are seen as a way for community members to gain access to health interventions that they would not normally be able to obtain, especially in developing countries. However, it is very important to distinguish between interventions given in clinical trials and those given as part of standard health care.

Clinical trials involve candidate vaccines whose safety and efficacy have not yet been proven. When volunteers participate in a clinical trial, they cannot rely on an experimental vaccine to protect against infection or disease. Furthermore, there is always the chance that volunteers will receive a placebo (an inactive substance) during the trial, and they will not know if they received the candidate vaccine or placebo until the trial is over.

Vaccines provided as part of standard health care are always approved and licensed by regulatory agencies based on safety and efficacy levels that have previously been proven in clinical trials.

Researchers who run clinical trials have the responsibility to make sure that potential volunteers understand the difference between drugs or vaccines that they receive in clinical trials and those they receive as part of standard health care.
Before a clinical trial is completed and the data are analysed, no one knows whether any experimental AIDS vaccine is protective, so volunteers in any AIDS vaccine trial cannot assume that they are protected against HIV.

Like all clinical trials, AIDS vaccine trials have benefits and risks for volunteers; however, there is no risk that the candidate vaccine itself will cause HIV infection and no volunteer is ever intentionally exposed to HIV.

All clinical trials are held to the same high ethical and scientific standards, no matter where in the world they are conducted.

Clinical Research Resources. Website with a comprehensive list of resources such as the Code of Federal Regulations and the International Committee on Harmonization Guidelines. Available at: www.clinicalresearchresources.com.


Participating in an AIDS vaccine trial can be a lengthy and involved process, as well as a rewarding experience. Volunteers have to make a major commitment when they join a clinical trial, especially an AIDS vaccine trial.

This chapter outlines some things volunteers need to know:

- General criteria for participation.
- Flow chart of steps involved in trial participation.
- Key aspects of the participation process.
- Volunteer protection and confidentiality.
- Treatment and care for trial volunteers.
1 Participation in any clinical trial is voluntary, and enrolment only occurs after a lengthy and thorough process of obtaining informed consent.

2 Before the volunteer can be enrolled, he or she must meet trial eligibility criteria.

3 Participation in a typical AIDS vaccine trial involves many visits to the trial centre to receive medical evaluation, counselling, HIV testing, laboratory tests and injections of an experimental vaccine or placebo, as well as other activities, all detailed in the trial protocol.

4 Volunteers’ health, welfare and human rights are strictly protected by international and national guidelines and through consultation by the research centre with community advisory boards (CABs).

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**Key concepts**

Every trial has different requirements. In general, to join a preventive AIDS vaccine trial, someone must meet the following criteria:

- Fully understand the trial and be willing to give informed consent.
- Be healthy, as determined by medical history and physical examination.
- Not be infected with HIV.
- Match the rules in the protocol for age, health and so on.
- Be willing to stay in the study for the amount of time required by the trial, generally up to 18 months for Phase I/II trials and up to 4 years for efficacy trials.
- Women must not be or become pregnant and must use an effective contraceptive method for the period defined in the protocol.
- Agree to receive HIV testing until a certain time has passed after the last injection and to participate in risk-reduction counselling to prevent HIV.
**Steps involved in trial participation**

1. **Trial participation**
   - A potential volunteer learns about the trial from general information sessions, video, meetings or discussions with trial staff
   - Has private discussion of details with a trial counsellor, doctor or nurse
   - Understands details of screening and trial participation; completes pre-screening questionnaire
   - Decides not to participate

2. **Screening process**
   - HIV test with pre- and post-test counselling
   - Screening questionnaire
   - Medical history & exam
   - Positive HIV test
   - Post-test counselling and referral for care
   - Does not meet requirements of study
   - Decides not to participate (can occur at any point)

3. **Trial participation**
   - Fully eligible, knowledgeable and willing volunteer enters into trial
   - Random assignment to vaccine or placebo group
   - Injection of vaccine or placebo
   - Medical exam and lab tests, including HIV test with pre- and post-test counselling
   - Volunteer returns to report on health or problems, and for further vaccinations according to protocol
   - Volunteer withdrawal (can occur at any point)
   - Follow-up after all vaccinations, data collection and trial enrollment completion

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**Source:** IAVI
The flowchart depicts a generic course of trial participation. The exact details will vary according to country, community and trial centre. Further details of trial participation are described below; these details are also general and may not apply exactly to all AIDS vaccine trials.

Before joining the trial
Following community outreach, education and/or other recruitment activities, the study team provides the potential volunteer with information about the trial and answers any questions. Potential volunteers then answer questions to see if they are eligible for the study. If they are eligible and want to join the trial, an appointment will be made for a screening visit at the research centre.

Informed consent
Each trial participant must give informed consent—a written agreement indicated by a signature, fingerprint, etc.—before he or she enters into the screening process and trial. For this to happen, researchers must ensure that the individual has a full understanding of all aspects of trial participation, which involves extensive education for the individual. Another important aspect is outreach to the broader community, particularly to community leaders, in order to build a general understanding and preparedness within the community at large. Providing general education about AIDS vaccine trials in a community enhances individual knowledge and decreases the stigma attached to participation in a trial, both of which ensure that individuals in the community are able to give true informed consent, should they decide to participate. See Chapters 2 and 9 for further information about informed consent and community support for the trial.

The screening visit
As part of the process described above for obtaining informed consent, potential participants receive information about the screening process, including HIV testing. Researchers may test individuals to make sure they fully understand key information about participation. After giving informed consent for the study, the volunteer enters into the screening process, which may involve a complete medical history and a physical exam. Also, blood and urine samples may be taken for routine tests, including a test for HIV infection and a pregnancy test for women. The volunteer returns when the test results are ready. If eligible, then he or she can join the study. If the volunteer changes his or her mind, he or she can drop out of the trial at any time.
HIV counselling and testing during the trial
Counselling provides the opportunity for a confidential discussion between members of the study team and volunteers. A counsellor is available to provide risk-reduction counselling at each scheduled visit and at other times if the volunteer asks for counselling.

Counselling is conducted every time blood is taken for an HIV test. The counselling that takes place before the HIV test is called pre-test counselling. The counsellor explains the test, conducts a risk assessment, discusses risk-reduction strategies and safer sexual practices, explains the meaning of positive and negative results and what the test results mean to the volunteer, and obtains informed consent for the test. When the test results are ready, the counsellor meets with the volunteer again for a post-test counselling session. During this session, the counsellor gives the volunteer the test results, discusses the meaning of those results, talks about feelings, reviews risk-reduction plans and makes referrals for any services needed. If the test is positive, the counsellor addresses the volunteer’s emotional response to the news, explains treatment and support options and discusses self-care, options for informing the volunteer’s partner(s) and prevention of HIV transmission to others. It is important to note that test results and all information revealed during these counselling sessions are kept confidential, although confidential reporting of test results may be required depending on local legal requirements.

Determination of HIV infection at screening
If a potential volunteer is found to be HIV-infected at screening for a preventive HIV vaccine trial, he or she will not be eligible to enrol in the study. Instead, he or she will receive counselling and will be referred to services for further counselling and HIV treatment, care and support. (See further information under treatment and care for trial volunteers.)

The AIDS vaccine trial candidate and candidate administration
Most AIDS vaccine candidates are injected into the muscle of the upper arm (intramuscular), under the skin (subcutaneous) or in the skin (intradermal). In the future, AIDS vaccines may also be given via mouth (oral) or nose (intranasal).

Volunteers are randomised to receive either the experimental vaccine OR the placebo; this is a decision determined randomly, like tossing a coin. In most studies, volunteers will not know what they received until the study is completed; in this case, the study is said to be ‘masked’,
Do trial participants get VCT services?
HIV voluntary counselling and testing (VCT) is critically important to vaccine trials. Vaccine trials cannot be carried out if people are not willing to be tested and to know their results. As more people are willing to be tested, stigma and discrimination may be reduced in the community. The Joint United Nations Programme on HIV/AIDS (UNAIDS) has standardised best practices for VCT and encourages countries to establish national policies along these uniform lines. See Chapter 2 for further information on how strong VCT services can build a supportive environment for trials.

The HIV counselling and testing that takes place within the trial itself, however, is not called VCT because it is not exactly the same as the standardised process described above. The process is in fact voluntary, and the individual will also receive quality counselling before and after being tested and receive test results. However, the process does not necessarily fit the standard model as it exists in VCT centres that may be available in the community, where people only go to determine their HIV status. First, in a vaccine trial, counselling includes trial-specific issues, and the visit includes trial-related follow-up. Also, risk-reduction counselling and HIV testing are done several times during the course of the trial. Because of the ongoing nature of the process, a relationship can be built between the participant and trial team, which is not normally the case between a VCT counsellor and client during standard VCT services.

or blinded. Double-blinded means that the research staff also does not know which volunteers received the vaccine or placebo, to be sure that the study is fair. In this case, the vials of vaccine and the inactive placebo look the same except for a particular code that is not revealed until the end of the study. (See Chapter 6 for further information on these concepts). After injections, volunteers may need to stay in the clinic for observation, usually for thirty minutes or an hour.

Blood samples taken during the trial
Researchers take samples of blood from volunteers at various times during the trial. Researchers examine the blood in the laboratory to find out whether the vaccine causes any changes in the way a
volunteer’s organs (such as kidneys or liver) work and the effects the vaccine has on the immune system. Laboratory tests will tell whether the vaccine can stimulate the immune system to react to HIV. Even if there is a reaction, it does not necessarily mean that the volunteer will be protected if he or she is exposed to HIV through blood or sexual contact.

What volunteers receive as part of the trial
It is usually not considered ethical to pay volunteers to participate in vaccine trials. However, they may be paid for the costs they incurred to participate in the trial; for example, their travel costs to get to the clinic. Food and/or child care may also be provided at the clinic visit. This is to compensate for the time and effort volunteers must go through to come to clinic visits. The ethics committee at each research centre decides what sort of compensation is fair.

A benefit of participating in the trial is medical examinations and care related to the trial. The volunteer can benefit from knowing about his/her health status, although this cannot replace standard health care and specialised medical services that the volunteer may need or want to use on his/her own. Another benefit for volunteers is receiving counselling and gaining additional knowledge about HIV and how to prevent it. Some volunteers join trials because they want to ‘make a difference’ in the fight against AIDS, and this altruistic feeling is often considered a personal benefit.

If a volunteer experiences a vaccine-related injury, the informed consent document explains how this occurrence will be handled. In many trials, he/she will receive appropriate treatment free of charge.

Falsely testing HIV positive
When a person receives an experimental AIDS vaccine, his or her body may produce antibodies against HIV (see Chapter 3). This response indicates that the immune system has developed antibodies that hopefully would protect the person from HIV infection. These may be the same types of antibodies that standard HIV tests look for. There are several important points for volunteers to remember about this:

- Candidate vaccines used in humans cannot cause HIV infection.
- If volunteers in an AIDS vaccine trial test HIV positive on an antibody test, it does not necessarily mean that they are HIV infected. If needed, more tests will be performed to distinguish between vaccine-induced antibodies and antibodies due to true HIV infection.
• While in the trial, volunteers should *not* have an HIV test outside the trial clinic. The researchers can tell the difference between vaccine-induced antibodies and true HIV infection, but a testing centre probably cannot.

• If an HIV test outside the trial clinic shows a ‘positive’ result, this may be a false-positive result, meaning that the volunteer is not infected. Sometimes researchers refer to this as being ‘antibody positive’, because the person is producing antibodies against HIV and is not actually HIV-infected. In this case, it is important for the person to go to the trial clinic for an additional HIV test.

• If volunteers need an HIV test as a requirement for health or life insurance, travel or employment, they should get tested at the study centre.

• Volunteers are asked not to donate blood, bone marrow or organs during the trial.

**Becoming HIV infected while in the trial**

AIDS vaccine candidates cannot cause HIV infection. Volunteers receive HIV risk-reduction counselling throughout the trial; however, it is possible that some people will become infected through blood or sexual exposure, such as unprotected sex or injection drug use. A volunteer’s risk of HIV infection if exposed through such means might be less, the same or more than if the volunteer had not received the experimental vaccine.

Volunteers will be tested for HIV a few times during the trial. If a volunteer is found to be infected with HIV, in most cases he or she will no longer receive injections as part of the study. In all cases, however, he or she will be referred to appropriate medical services for counselling, care and treatment and will be monitored for the remainder of the study.

**Regular daily activities**

Volunteers can and should continue with their regular daily lives. As most vaccine studies enrol healthy volunteers, the normal habits of the volunteers should not change. Volunteers do not need any additional food supplements or special diets. The amount of blood drawn in a study is small compared with that of a blood donation, and the body will easily create more blood to replace it.
Sexual activity
Volunteers may continue sexual activity, and are counselled to practice safer sex behaviours. They are informed that they cannot count on protection against HIV infection from the vaccine, and that they may have received the placebo. In most trials, volunteers receive condoms as part of risk-reduction counselling. Counselling reinforces the need to avoid both sexually transmitted infections, including HIV, and pregnancy.

Pregnancy
Researchers do not know if there are any effects of candidate vaccines on a foetus if given to a pregnant woman. This is the reason that female volunteers are required to use a reliable form of contraception for at least four months after receiving the last vaccination. Female volunteers have pregnancy tests at the time of screening, before each vaccination and several additional times. Male volunteers should also use condoms for at least four months after receiving the last vaccination to avoid pregnancy in a spouse or partner.

If a female participant becomes pregnant during the trial, she will not receive any further injections as part of the study. She will be monitored until the end of the trial and through the end of the pregnancy, and her baby will be examined during the first month of life, to check the health of the baby.

Counselling for sexual partners
During most trials, a volunteer’s sexual partner can receive counselling. However, this can ONLY be done with consent from the participant. Prevention of sexually transmitted infections and pregnancy are generally discussed.

Study conclusion
Phase I and II AIDS vaccine trials last anywhere from one to three years; Phase III trials may last up to five years. After the actual study, during which the volunteer receives the experimental injection(s), there is a ‘follow-up’ period, during which the trial staff monitors the volunteer’s health. At the end of the trial, volunteers will be informed about the results of the study.
Participating in a trial involves certain risks that a person may not encounter in normal daily life. In this respect, volunteers partner with researchers and participate in the advancement of medical science. Researchers have a responsibility to help ensure volunteers’ confidentiality and safety. Part of this process involves meeting the following standards:

- Maintaining strict respect for the confidentiality of volunteers’ participation and of their medical files.
- Avoiding stigma and discrimination due to their participation in the vaccine trial.
- Providing treatment for vaccine-related injuries.
- Helping volunteers avoid discrimination; for example, by providing special ID cards or letters for insurance purposes in the case of false-positive HIV tests after vaccination (see Falsely testing HIV positive section above). (Not all trials will do this the same way.)
- Consistent risk-reduction counselling for participants and partners (if consented).

For further information, see Chapter 9.

Volunteers have access to some health care and HIV prevention services from the trial centre for the duration of the trial. Comprehensive care, support and appropriate compensation are provided to trial participants who suffer any injuries directly due to the trial vaccine.

Trial volunteers are healthy and are not infected with HIV at the start of a preventive AIDS vaccine trial. They receive condoms and risk-reduction counselling to help them remain uninfected with HIV. However, despite these interventions, some volunteers may become infected with HIV through risk factors, such as sexual activity or blood exposure. During most trials, volunteers who do become infected with HIV have access to comprehensive HIV treatment and care, prevention and counselling services. Trial sponsors are at various stages of developing policies that specifically address their commitment related to providing antiretroviral (ARV) treatment to volunteers. In addition, national ARV programmes are being implemented in many countries, which may affect trial-related policies.
Most experimental AIDS vaccines have been designed to prevent HIV infection. This is why most trials only enrol volunteers who are not infected with HIV.

The decision about whether or not to participate in a trial should be made by the individual volunteer; it is unethical for anyone (family members, trial staff and so on) to convince or coerce someone else to participate.

All volunteers should continue to use condoms and practice other forms of risk-reduction, as they cannot count on the experimental AIDS vaccine to protect them against HIV infection and because they may receive a placebo.

During the trial, a volunteer who becomes HIV infected through sexual or blood exposure is provided with or linked to available health care; he or she continues to be followed to find out if the candidate vaccine affects HIV.

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For further information


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1 The trial team will know the names of participants, as well as numbers that are assigned to each participant. Maintaining this confidentiality is a primary responsibility held by the trial team, and each staff member signs a confidentiality agreement indicating that the information will not be shared with anyone outside of the trial centre.
Vaccines and the Global Response to HIV/AIDS
This chapter provides an overview of gender issues as they relate to HIV and AIDS, vaccine development and AIDS vaccine trials.

It explains the following:

- The concept of gender versus sex.
- The role of sex and gender in social and biological vulnerability to HIV infection.
- The role of vaccines in reducing women’s vulnerability to HIV.
- Rationale for including women in AIDS vaccine trials.
- How gender could affect clinical AIDS vaccine trials.
- Approaches to making clinical trials gender equitable and ensuring women’s participation.
- The effect of gender on future access and use of an AIDS vaccine.
**Summary points**

1. Women are both biologically and socially vulnerable to HIV, based on gender-related social norms and cultural, economic and legal factors.

2. An AIDS vaccine offers promise in addressing women’s vulnerability; it is a method that women could control and that would require little or no partner negotiation.

3. It is important for both men and women to be involved in AIDS vaccine trials in order to detect trends in effect, and to determine if the vaccine affects men and women differently.

4. Gender can affect trials in many ways: it may be more difficult to recruit women or men into trials, depending on the setting; ensuring informed consent can be difficult because women are often vulnerable to coercion; women may be more vulnerable to stigma, discrimination and violence if confidentiality is breached; and effective voluntary counselling and testing (VCT) must take gender factors into account.

5. A range of actions can be taken to ensure that women and men participate in sufficient numbers, and that trials are gender equitable.

6. Gender can affect the future access and use of a vaccine and should be addressed in vaccine preparedness activities.

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**Key concepts**

The terms ‘gender’ and ‘sex’ sometimes cause confusion and debate. The terms are often used interchangeably, but they also have very distinct meanings. In this chapter, we have used distinct meanings for the words, recognising how they are interrelated.

**Sex** generally refers to biological characteristics (anatomical, physiological and genetic) that define a person as male or female.

**Gender**, on the other hand, is a term often used to reflect the socially constructed nature of male and female identities. Gender refers to the characteristics that society defines as ‘masculine’ or ‘feminine’.
It includes men’s and women’s positions in society and the level of power that women and men have in relation to each other. **Gender roles** are the socially and culturally determined attitudes, behaviours, responsibilities and expectations for males and females. For example, women may be expected to be passive and sensitive, while men are expected to be strong and unemotional. These roles vary within and between cultures. One is not born with gender, but people become socialised within gender roles.

This document often collapses the two terms and simply uses ‘gender’. This is done acknowledging that society and biology both have a role in men’s and women’s vulnerability to HIV and their potential to benefit from an AIDS vaccine.

**Effect of gender on women’s vulnerability to HIV infection**

Nearly half of all infections worldwide now occur among women, and in certain countries with generalised epidemics, HIV prevalence among women has surpassed that of men. Biological factors related to sex and social factors related to gender both have important roles in increasing women’s vulnerability to HIV. Factors related to **biological vulnerability** include the following:

- A greater exposed surface area in the female genital tract than in the male genital tract and a higher concentration of HIV in semen than in vaginal fluids allows the virus to enter more easily in women.
- Coercive or forced sex can lead to microlesions (very small tears) in the vagina that facilitate entry of the virus.
- Young women in particular may be more vulnerable to microlesions, as they have less-mature tissues, and may also be more vulnerable to forced sex.
- Women often have sexually transmitted infections (STIs) that are left untreated, which increases vulnerability to HIV.

Economic, social, cultural and legal factors together create an unequal balance of power between men and women, which compounds the risks women and men face. Gender-related social norms and economic pressures, in particular, increase women’s **social vulnerability**. The following are examples:

- Cultural norms often limit women’s access to knowledge and information related to sex and sexual health and to related health care.
- Women often lack the power to negotiate safer sex or demand fidelity in a relationship because of cultural norms and economic
dependency; it is men who often make the decisions about when, where and how to have sex.

• Women may fear physical violence, abandonment or loss of economic support if they try to negotiate condom use, discuss fidelity with their partners or leave relationships they perceive to be risky.

• Women are often expected to remain monogamous, yet are often at risk because of the sexual behaviour of their male partners.

• Social pressure to bear children may affect women’s choices about protecting themselves against HIV infection; they may fear the social consequences of not becoming pregnant if they use condoms to protect themselves against HIV.

• Poverty may force women to engage in unsafe sex or may force them to exchange sex for money or material favours as a means of survival or to support their children.

• Women are at greater risk of being raped, sexually coerced or forced into sex work.

Men are also affected by gender norms that encourage risky behaviour, increasing women’s vulnerability as well as their own. For example, in many societies the following are true:

• Men are not expected to remain monogamous and may even be encouraged to have multiple partners.

• Men are expected to be knowledgeable about sexuality and to be experienced, which might prevent them from seeking information regarding sexual health and protection.

• Men are socialised to be self-reliant and to not seek help.

• Men may also face social and economic pressures to reproduce.

Current prevention options, which require changes in sexual behaviour, are not feasible for many people, particularly for women. For many women, it is not their own behaviour but that of their partners that makes them vulnerable to infection. Prevention tools that women can initiate or control are greatly needed. Vaccines, as well as microbicides, offer promise as future female-initiated and controlled methods. Vaccines may offer women more control than current prevention methods, as their use is not associated with the sexual act. They can potentially be used without a partner’s knowledge in cases when a woman may fear that informing her partner would place her at risk of infection, violence or other consequences.
Rationale for including women in vaccine trials

It is important to ensure adequate numbers of women and men in vaccine trials in order to determine whether the vaccine affects men and women differently. There are also ethical reasons for the inclusion of both women and men in trials, as well as a need to collect data that will ensure that the vaccine is approved and licensed for women as well as men.

Detecting differences in effect

To know that a vaccine is efficacious both for women and men, it is important to enrol enough participants of both sexes in clinical trials. Any single particular trial may not be able to determine whether the vaccine works differently for men than for women, but it can detect trends in the effect of vaccines. Some past clinical trials have not included enough women participants and sometimes have been unable to distinguish such trends. It is still unknown whether an AIDS vaccine will have a different effect in women and men.

It is possible that the vaccine will work differently for men than for women because of several factors:

- Differences in male and female anatomy and biology can lead to differences in risk of infection or could lead to differences in the effect of a vaccine.
- Viral loads (the amount of virus in the blood) after infection may differ between men and women, which may lead to differences in the effect of a vaccine developed to delay disease progression (see Chapter 5).

Licensure

Regulatory authorities require that a product be tested in the populations in which it will be used. Enrolment of sufficient numbers of women and men is therefore critical to ensure that there is enough information to approve the vaccine for both women and men.

Ethical issues

The principles of health equity require that women be involved in all appropriate clinical research. AIDS vaccine research programmes are likely to benefit all participants—those receiving the test vaccine and those receiving a placebo—because the education, counselling and care components of these trials can reduce every participant’s risk of contracting HIV. Excluding women from trials deprives them of these benefits.
Recruitment and retention

The participation of women in AIDS vaccine trials might be inhibited by social factors that limit their decision-making power, as well as logistical factors and responsibilities that make participation difficult. It may therefore be necessary to put extra effort into the recruitment and retention of women.

Couples’ counselling, in which a woman and a man go for HIV counselling and testing as a couple, is an example of an approach that may assist the recruitment of women into AIDS vaccine trials. Women who have limited decision-making power may be more able to access VCT and to participate in a trial if their decisions are made with the support of their partners. This approach may be effective for some but not all women, as it is dependent on the nature of the relationship with their partners. Choices about VCT, trial participation and disclosure should be left completely up to the woman, and her confidentiality must be respected.

Trial staff must be aware of the gender-related factors that might prevent women from participating:

- Many women do not have the freedom to make their own decisions about HIV testing or joining a trial; husbands, fathers, partners or other family members may greatly influence or make decisions.
- Women often carry additional responsibilities of childcare, care of the elderly and housework and may not be able to take the time to attend education sessions or frequent clinic visits.
- Women may not have the means to physically travel to a trial research centre by themselves.
- In cultures in which a woman’s perceived worth is often tied to her fertility, trial requirements that she avoid pregnancy during the trial may affect her choice to participate.
- Women may fear that if they participate, they will be stigmatised as high-risk and will face discrimination.

Informed consent

Ensuring informed consent from all trial volunteers is an essential requirement. Volunteers must make an independent, voluntary decision to join the trial and must fully understand the implications of participating. Communicating the complete information and ensuring understanding can be complex and difficult, particularly for vulnerable groups, including women.
Women may be vulnerable to unfair influence and coercion from husbands, family, community members and healthcare providers. Information must be presented in language that all participants understand, in a way that prepares people to fully understand their rights, risks and benefits and in an environment that supports independent decision-making. All volunteers should fully understand the information provided before they sign an informed consent form. Ethics review committees should include individuals with gender expertise to ensure that gender issues are taken into account in review of the informed consent process and that decision-making is truly informed and voluntary.

Many women may want to discuss potential participation with important people in their lives, including husbands, partners and fathers. It is important for these women to have the opportunity to consult with whomever they wish, but they should know that this is not required for informed consent. To participate in a trial, only the woman’s personal, individual informed consent is required. As explained below, her confidentiality is always protected if she wants to participate but does not want to inform others, including a partner.

As part of the process of ensuring informed consent, the community at large is provided with information about the trial. Although this helps to create an environment that will help enable women to participate in trials, giving informed consent and participating is the woman’s individual decision.

**Confidentiality**

Confidentiality is critical for all trial participants. Women may be particularly vulnerable if confidentiality is broken, as disclosure of participation in trials itself may lead to stigma, discrimination and violence. If a woman is known to be participating in a trial, people may assume she is engaging in risky behaviour or that she is protecting herself from the risky behaviour of her partner. All trial staff must be trained in handling confidentiality in a gender-sensitive manner.

**VCT and counselling**

The counselling process in VCT must also take gender issues into account. Counselling should assist volunteers in perceiving and determining their risks of infection based on knowledge of their partners’ behaviours, rather than examining only their own behaviour. Prevention counselling must take into account the social and economic
factors that influence women’s risks and the limits on women’s power to negotiate safer sex. Despite prevention counselling, female volunteers may have less control than male volunteers over their risk of becoming infected during the trials.

Disclosure of test results can also be particularly complicated for women. Voluntary or involuntary disclosure to families, communities or providers can lead to stigma and discrimination, blame, violence or abandonment. Women who choose to disclose should be assisted to determine the best and safest approaches to disclosure.

A range of actions can be taken to ensure that gender issues are adequately taken into account in AIDS vaccine clinical trials. These actions are intended to make sure that both women and men participate in and benefit equally from trials and are intended to take into account the more vulnerable position of women and their needs.

Preventing the trial centre
A woman-friendly physical environment includes, for example, a non-stigmatising, convenient location; a welcoming environment; privacy; and accommodation for families and children who might accompany a trial participant. Gender balance, in terms of staff with participant contact and staff trained to address women’s and men’s concerns, may also be important elements of a woman-friendly environment.

Involving community groups and women’s organisations
Community groups and women’s organisations can be strong allies for AIDS vaccine trials. They can provide a valuable link to those communities and can help to address some of the gender-specific issues. They can make communities aware of the need for women to be enrolled as trial participants to benefit from the research.

Community advisory boards (CABs) and gender advisory groups in several trial countries have played a significant role in educating the community on vaccine development and the trials and in mobilising volunteers. Ideally, CABs should have gender balance and gender expertise in their membership.

Developing gender-sensitive guidelines and protocols
In developing protocols, guidelines, brochures and questionnaires, a gender-analysis framework can be applied to the various components of the trial, including informed consent; inclusion and exclusion criteria;
care and counselling; reimbursement; confidentiality; and related issues of stigma and discrimination. This framework can be applied to identify issues and concerns across all phases and steps of a trial.

**Gender training for trial team**
All individuals and organisations involved in conducting trials should be trained in understanding and ‘mainstreaming’ gender concerns in all aspects of the trial. These include protocol managers, researchers, trial administrators, counsellors, doctors, social scientists, the ethics review committee and the CABs. For some, the focus should be on building skills (for example, counsellors) and for others, on building gender sensitivity and a gender perspective.

**Establishing accountability mechanisms**
Some trials might include a system to ensure gender sensitivity is included in all aspects of trial conduct. The system would vary from trial to trial, but it may include a ‘gender audit’ mechanism that is overseen by an external gender advisory board or it could include incorporation of gender expertise into other, existing advisory boards.

**Understanding and addressing barriers to trial participation**
The barriers that women face for participating in trials may vary from culture to culture and from community to community. Trial sponsors can speak with community members to better understand potential problems and solutions, work though CABs to develop solutions, and conduct social research to determine barriers and facilitating factors.

In the same way that traditional gender norms can inhibit women’s participation in vaccine trials, these gender norms could ultimately prevent women from accessing vaccines once they are available. Gender should be taken into account in efforts to prepare for access and future use.

**Acceptability**
To ensure that a vaccine is acceptable, both men and women must be prepared with knowledge and understanding of the characteristics, advantages, risks and limitations of AIDS vaccines. Acceptability may differ between men and women, and the factors that may influence this must be well understood and anticipated in introduction strategies.
Social and political environment
Gender must be taken into account in assessing and preparing the social and political environment. Women’s health advocates could potentially be an important constituency in advocating for vaccine research and in supporting the introduction and future use of both vaccines and microbicides.

Strategies for vaccine promotion and delivery
Strategies for delivering vaccines, as well as information, education and marketing strategies to support vaccines generally, may have different requirements for different audiences. These strategies should be developed based on good social science research and an understanding of needs, desires and perceptions of different audiences.

Key messages pertaining to AIDS vaccine development
Although the AIDS pandemic is affecting women at greater rates than men in many places, current HIV prevention options are not feasible for many women. There is an urgent need for new prevention options that women can more easily initiate and control.

Once available, an AIDS vaccine will be an important tool for reducing women’s vulnerability to infection; it is a method that women will be able to use with or without men’s cooperation, since it is not tied to the sexual act.

It is important that women participate in vaccine trials to determine whether a vaccine will work for them. However, they often find it difficult to participate for social, cultural and logistical reasons. Efforts should be made to support women’s involvement in trials and to ensure that they make voluntary, independent and well-informed decisions to participate.


In this chapter

Ethical issues are of primary concern in the conduct of clinical studies. These concerns apply to all clinical research and are given special attention by AIDS vaccine researchers and the many authorities that review clinical trials.

This chapter discusses the following:

- Primary principles of ethical research.
- The informed consent process.
- The informed consent document.
- Risks versus benefits of participation.
- Volunteer rights and protection.
- Ethical review of trials.
Summary points

1. AIDS vaccine trials must meet international ethical standards.

2. All medical research is governed by principles of ethics; informed consent is one of the most important ethical requirements.

3. Obtaining true informed consent involves a process of delivering information about the trial, making sure people understand the information and ensuring that volunteers participate based on their own decisions. Community and individual education are important in supporting this process.

4. All trials involve certain risks and benefits for volunteers; to be ethically sound, the trial must maintain the right balance between risks and benefits.

5. It is the duty of researchers to make sure that local standards of health and human rights of volunteers are upheld.

6. AIDS vaccine research involves certain unique ethical issues; UNAIDS has helped to address them by issuing an official ethics guidance document.

Key concepts

Primary principles of ethical research

Researchers and ethical authorities work to ensure that research is conducted according to high ethical standards. Seven primary principles form a basis for ethical conduct of clinical trials. These are principles for all types of clinical research and are applied to AIDS vaccine trials.

1. Value – should answer a question that will enhance health or provide useful knowledge in the health field.

2. Validity – should have an appropriate, careful and practical design and methodology.

3. Fair participant selection – volunteers should be selected in a fair manner, based on scientifically and ethically sound factors.

4. Favourable risk/benefit ratio – participating in any trial involves both benefits and risks; neither should be significant, and they should balance each other out.
5 Independent review – independent ethical and regulatory committees must review and give approval for the study.

6 Informed consent – every volunteer must understand the process, risks and benefits of trial participation so she or he can make an educated and independent decision to participate.

7 Respect for participants – the rights and welfare of participants must be protected throughout the entire trial, its conclusion and follow-up.

These principals and the information that follows in this chapter apply to both AIDS vaccine clinical trials and other types of AIDS vaccine-related clinical studies. While the information contained in the consent process for trials may be more complex, the process is often the same for other clinical studies.

**Informed consent** is one of the foundations of ethical research. It is an agreement between the researcher and the volunteer, showing that the volunteer fully understands and agrees to all aspects of participating in the trial. The agreement is shown when the volunteer signs the informed consent document (described below), but researchers cannot rely on this document alone to ensure that the individual truly understands the trial. The agreement is made through a process of education and dialogue between researchers, communities and potential volunteers.

Researchers recognise the importance of obtaining true informed consent, which can be a challenge, especially in communities that may not be familiar with medical research or with AIDS vaccines, and in populations or individuals that may be vulnerable to pressures from others. This means that potential volunteers fully understand key aspects of trial participation, including the potential risks and benefits, before they sign the informed consent form. In many research centres, this involves two levels of outreach, one to the broader community and one to the individual.

Outreach to the broader community extends beyond the scope of trial recruitment. It involves informing the leaders in a community well in advance of the study as an important channel for building understanding and support among the community at large. Having leaders who are informed and supportive of the trial will also minimise stigma that may be attached to community members who participate.
or who even ask for information about the trial.

Most AIDS vaccine research centres have active community advisory boards (CABs), which are an important form of outreach to the broader community. These groups act as liaisons between the trial researchers and the community, and they help to tailor and deliver the proper information to potential participants. See more detailed information on the community’s role in trials in Chapter 2.

For outreach to the individual, a research centre may offer general information sessions about AIDS vaccine development and the vaccine trial. There may also be one-on-one counselling sessions, at which potential volunteers learn about the study in more detail. Finally, some studies require that before signing the informed consent, potential volunteers complete an assessment of understanding, which is usually in the form of a questionnaire containing true/false, multiple choice, narrative questions or combination of these, to test their comprehension of the AIDS vaccine trial.

Although informed consent is not the only factor in ensuring the ethical conduct of a trial, it is a key factor. The researchers must explain to participants many important facts about the study. In the case of a clinical trial, this would include, for example, its purpose, the vaccine that will be tested, the number of clinical visits required and possible benefits and harms. Volunteers also need to know that they have the right not to participate or that they can withdraw at any time. Importantly, researchers must be sure that the participant’s decision is free from inducement or coercion of any kind.

The informed consent document is the paper signed by each volunteer for a trial or other clinical study that indicates his or her understanding of and agreement to the following:

1. Why the research is being done.
2. What researchers want to accomplish and who is responsible for the study.
3. What will be done during the trial and for how long.
4. What risks are involved.
5. What is expected of trial participants.
6. What, if any, benefits can be expected from participation.
7. The system in place for care and support of participants.
8. What other interventions are available.
9. The participant’s right to leave the trial at any time.
Participating in any clinical trial involves both risks and benefits. When someone is deciding whether or not to participate in a trial, that person must fully understand the risks and benefits involved in order to make an informed decision as to whether the benefits outweigh the risks of participation for him or herself personally.

When researchers plan a study, they must make sure that the risks and benefits of participation are balanced. If the relative balance of risks and benefits is not reasonable, the trial will not be considered fair. If there are many risks, it is unfair to ask people to participate. If there are too many benefits, people will participate for the wrong reasons, and the study may be considered coercive.

<table>
<thead>
<tr>
<th>Potential risks and benefits of AIDS vaccine trial participation</th>
<th>An ethical review board determines the balance of risks and benefits. Every study plan, or protocol, must be reviewed by such a board (see Chapter 10). Examples of potential risks include:</th>
</tr>
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<tbody>
<tr>
<td>Physical side effects of the experimental vaccine, such as a sore arm, headache or fever and possible serious adverse events (SAEs).</td>
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</tr>
<tr>
<td>Social risks such as stigma or discrimination that may be associated with participating in a vaccine study or trial.</td>
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<tr>
<td>A false sense of protection from the vaccine, which may cause participants to be less careful about exposure to HIV or to engage in risk behaviour.</td>
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</tr>
<tr>
<td>False-positive HIV antibody tests in a person who received a candidate vaccine but is not infected with HIV (see Chapter 7). The risk of this happening and the time it might last are unknown.</td>
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<tr>
<td>Volunteers may not be able to donate blood during or after the trial if they have antibodies that cause their blood to falsely test positive.</td>
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It is important to note that candidate AIDS vaccines in clinical trials cannot cause HIV infection. Hence, infection from the vaccine is NOT considered a risk of participation (see Chapter 5). Researchers do not know for sure how a candidate vaccine might affect a volunteer’s risk of HIV infection if he or she is exposed through sexual transmission or blood exposure—the level of risk might be less, the same or more than if the volunteer had not received the experimental vaccine.
Examples of potential benefits:

- A rewarding feeling from being involved in the clinical trial team—some participants report feeling that the staff becomes a ‘family’ and the study clinic, a place of comfort.
- A rewarding feeling from contributing to important medical research.
- Better understanding of HIV and how to avoid becoming infected.
- Receiving medical attention. Although this must NOT be confused with standard healthcare, individuals may receive services that they would not receive otherwise—for example, HIV counselling and testing and routine blood analysis and monitoring.
- Receiving food at clinic visits or monetary compensation for travel to clinics.

Volunteer participation involves certain risks that a person may not encounter in normal daily life, as discussed above. Thus, volunteers do a service for researchers and for medical science in general, and researchers uphold their duty to make sure volunteers are properly treated. Protection of research volunteers is a human rights issue and has become a defining factor in the conduct of AIDS vaccine trials.

Examples of protecting volunteers participating in trials:

- Strict respect of their confidentiality before, during and after the study.
- Adequate time and information to ensure understanding of the study before informed consent is obtained.
- Medical attention associated with trial participation.
- Medical treatment (or compensation for medical treatment) needed because of the vaccine or trial participation. (Trial staff would routinely treat minor symptoms such as headache or fever.)
- Assistance with any social discrimination received because of trial participation.
- Where possible, a special identification process for insurance or other purposes in the case of false-positive HIV tests (see Chapter 7).
- Regular risk-reduction counselling for participants and partners (if participant consents).
- Involvement of community representatives in the planning and review of trials.
- Special consideration to socially vulnerable groups (including women), if they are included in the trial population, to ensure that these individuals are well represented in the trial and that they give informed consent without inducement. The protocol also adequately describes any vulnerable population and how it will be protected.
Confidentiality of volunteer information
The study team must keep all information about volunteers highly confidential. Information in the trial should not be disclosed to anyone except study staff without the consent of the participant. However, participants may disclose their participation to whomever they wish to at any time they choose.

If a volunteer sees a doctor who is not involved in the trial for a medical problem, it is helpful to let the doctor know that he or she is participating in the trial, so the doctor can do a better job of treating the individual. However, the volunteer must provide that information himself or herself; the study team will not give the doctor information unless requested by the participant (the volunteer might need lab tests and so on from the study team).

Right to withdraw at any time
Every informed consent document has a section explaining that a volunteer has the right to withdraw from the study at any time.

Trials are very carefully designed and monitored, and researchers count on the volunteers to participate until the end of the trial. Even though this is very important, vaccine trials last many months or even years, and during that time there may be many reasons that a volunteer would need to withdraw from the trial.

Volunteers should never feel trapped or forced to stay in the trial. Volunteers should know that if they need to leave the trial for any reason, they have the right to do so.

Review of trials by an ethics committee
To ensure that trials are conducted according to ethical standards, a locally based ethics committee must review the proposed trial protocol, informed consent document and other study-related materials. The ethics committee may be called an ethical review committee (ERC) or an institutional review board (IRB). The main concerns of the ERC or IRB are the safety and respect of human rights of trial participants and the ethical conduct of the trial.

Ethical review is one form of review given to a proposed trial (for complete information on the overall review process, see Chapter 10). These committees are made up of scientists, ethicists, community members and other experts who are independent of the trial sponsors.
and investigators and are trained in evaluating research proposals. This combination of people provides an unbiased, fair and well-rounded evaluation of the study proposal. In addition to the ethics review, the ERC, IRB or a related committee usually also conducts a scientific review.

Internationally recognised guidelines exist for the conduct of clinical trials. These guidelines create uniform ethical and scientific standards for all trials with human participants and are therefore an integral factor in ethical aspects of AIDS vaccine trials.

Several sets of guidelines outline regulations for conducting clinical trials, such as the guidelines developed by the International Conference on Harmonisation for Registration of Pharmaceuticals for Human Use (ICH) on good clinical practice (GCP). These are fully discussed in Chapter 10.


The document outlines a series of guidance points around topics including community participation, capacity building around trials, care and treatment in trials, the use of control groups, and involving key populations at higher risk for HIV. Additionally, UNAIDS reviews some protocols for ethical and scientific considerations.
All AIDS vaccine trials follow the same set of international ethical guidelines to ensure that each volunteer’s health, dignity and well-being are protected.

National and international authorities that are independent of trial researchers and sponsors, such as regulatory authorities and ethics committees, conduct ongoing monitoring of research projects to ensure that they meet ethical standards.

Obtaining each volunteer’s informed consent to participate in a trial is essential to ethical research; the purpose is to ensure that participants fully understand essential information about the trial and that they can freely decide whether or not to participate.


Ethical Issues in AIDS Vaccine Trials
In this chapter

Every clinical research project or clinical study involving humans must go through a standard review process. The process includes review of both the product to be tested and the protocol (the plan for how the study will be done). The purpose of the review is to ensure first and foremost that the product is safe for testing in humans and that the reason for performing a specific study is sound. This review process is not unique to AIDS vaccine trials but applies to any drug, vaccine or medical device proposed for use in humans.

This chapter will outline the process of approving an AIDS vaccine trial including the following:

- Review groups.
- Review by a regulatory authority.
- Review by an independent ethics committee(s).
- Example of an in-country review process.
- Standard guidelines on trial regulation.
1. Before a trial can be conducted anywhere in the world, it must go through scientific and ethical reviews.

2. There are three primary types of review: regulatory, scientific and ethical.

3. Some bodies have been created specifically to review or give advice regarding the review of AIDS vaccine trials.

4. Official, standardised guidelines, laws and regulations exist for the regulation of trial conduct throughout the world.

Review of experimental products and protocols is conducted by various committees in the country in which the research is to be conducted, and often by boards or committees associated with the institutions sponsoring or conducting the research. These groups include ethical review committees and regulatory authorities and sometimes other committees at a local level, such as biosafety committees or national genetically modified organism review boards.

Although certain community representatives, such as community advisory boards (CABs), often provide feedback on research protocols, this is not considered official approval. Such groups often provide valuable insight that helps improve the trial process and are therefore important for a successful trial. The role of these groups is discussed in Chapter 2.

A national regulatory authority (NRA) generally reviews the information about the product (for example, the candidate drug or vaccine) as a whole, as well as the protocol that explains how the particular study of the product will be done. The NRA is responsible for approval of the product and the specific study. This approval is for studies in the country itself, and if a study is done in more than one country, a regulatory authority from each country must give...
approval. Every six months or year, a report on the progress and results of the trial is sent to the NRA.

Scientific review ensures that the trial is asking valid scientific questions and that the study is well-designed to answer these questions. The NRA also reviews how the product is made. The procedures are different in different countries. In Europe, there is an overall agency for the region, the European Medicines Agency (EMEA), and it establishes some overall regulations for the NRAs and reviews products when the sponsor asks for a product to be licensed.

Before an AIDS vaccine is tested in people, independent ethics committees (IECs), also called ethics review committees (ERC) or institutional review boards (IRBs), from the institutions where the clinical trial will be conducted must review specific documents and approve the trial. This review process is designed to ensure the safety, human rights and well-being of the volunteers involved in the trial (see Chapter 9 for further information). The names of these review committees can differ from country to country, but they are all set up in a similar way and abide by the same set of principles.

Who is a part of an independent ethics committee?
These committees are made up of several members including scientists, ethicists, community members and other experts who are independent of the trial sponsors. They evaluate the science, medical aspects and ethics of the proposed trial. In the United States (U.S.) (or if the trial is funded by the U.S. government), the committee should include at least one member whose interest is non-scientific and one member who is independent of the institution where the trial is being conducted. This combination of people provides a thorough evaluation of the proposed study.

Interaction with trial sponsor and investigator
The ethics committee is responsible for reviewing the qualifications of the trial investigator according to relevant documentation.

The investigator may provide information about the trial to the ethics committee, but cannot be involved in their deliberations or voting procedures. The sponsor of the trial may also provide information about the trial upon request, but must not influence the ethics committee.
Materials reviewed by the IEC
Committees review trial-related materials to make certain that all information, including informational materials provided to volunteers, can be easily understood and that none is coercive.

The following documents must be submitted to an ethics committee for review and approval:

1. The trial protocol contains in-depth information on every aspect of the trial conduct, including the following:
   - The specific vaccine (also called ‘vaccine candidate’ or ‘investigational product’) that will be tested.
   - The objectives and design of the study.
   - The criteria for including or excluding volunteers.
   - The number of visits that volunteers will be asked to make to the trial centre.
   - Procedures to be completed during each participant visit, including the amount of blood that will be drawn, the samples that will be obtained and what tests will be done on the blood.
   - The type of information that will be collected and how it will be analysed.
   - The plan for care if injuries are caused by the study procedures or product(s).

2. Advertisements (flyers, newspaper ads, radio ads, television ads) that may be used to recruit volunteers.

3. The informed consent document (see Chapter 9 for further information on informed consent).

4. Any documents provided to or seen by potential volunteers and volunteers. This may include everything from general community outreach strategies (ways of getting the word out about the trial) to the process of recruiting for potential volunteers; it can also include documents such as brochures, videos and short quizzes that may be used in the informed consent process.

5. Plans for compensation, if any, such as travel costs to and from the trial centre, to ensure that they do not unfairly influence volunteers’ decision to participate, and that the risks do not outweigh the benefits of participation.

6. The investigator’s brochure (in most, but not all cases), a document that contains all relevant information (particularly about safety) on the product from previous preclinical and clinical testing. The brochure provides a ‘rationale’ for understanding key aspects of the product, including dosage, frequency and route of
administration, and is a summary of the large package of information about the product that must be reviewed by the NRA.

How ethics committees approve and monitor trials

After the IEC reviews the protocol and all trial-related documents, they may make suggestions and recommend or require changes. The committee will document its recommendations to the research centre’s principal investigator or designee by formal letter that states the protocol title and protocol version number. The principal investigator will then communicate the recommendations or requirements to the sponsor. Trial sponsors and principal investigators may respond to concerns in writing. If required changes are made to the protocol or other documents, they need to be resubmitted for approval. A trial can begin only after all of the committees have given their final written and dated approval. More than one ethics committee may need to approve a protocol if different groups are involved.

After an AIDS vaccine trial begins, committees receive regular reports, including safety data summaries, notification of serious adverse events (SAE) according to their requirements (see Chapter 6), and new information on the vaccine that allows them to monitor the safe and ethical conduct of the trial. In particular, committees make sure the investigator and sponsor are fulfilling their obligations to participants. These committees also have the power to stop the trial if there are any concerns for safety or if the trial is not being conducted ethically.

All countries have systems for ethical and scientific and regulatory review of clinical trials. A few countries have formed committees specifically to advise government bodies about AIDS vaccine research. In many cases, committees have been formed in response to trials that are proposed in the country.

International advisory committees have also been formed, such as the Vaccine Advisory Committee of the HIV Vaccine Initiative (HVI) of the World Health Organisation (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS). This is an independent body made up of a rotating group of 10 to 20 leaders in the AIDS vaccine field. One of the responsibilities of this group is ‘impartial and authoritative review and assessment of research proposals and other vaccine-related projects, to ensure their scientific quality and ‘relevance’. This body acts as an additional review for vaccine trial
It makes recommendations to governments of countries where trials are proposed.

In general, there are three types of review processes for any given trial: regulatory, scientific and ethical\(^2\). Certain review committees may be involved in one or more of these areas depending on the structure and function of the committees in countries and institutions involved in a given trial protocol.

<table>
<thead>
<tr>
<th>Summary of types of review</th>
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<tr>
<td><strong>Ethics and scientific advisory committees</strong></td>
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<table>
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<tr>
<th>Focus of information reviewed</th>
<th>Regulatory</th>
<th>Scientific</th>
<th>Ethics</th>
</tr>
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<tr>
<td>The package for review includes all relevant information about the product, including all previous tests (preclinical and clinical) conducted on the product and how it will be tested in humans, including protocol for testing the product, and the investigator’s brochure.</td>
<td>Scientific committee review ensures that the trial is asking legitimate scientific questions and that the study is well-designed to answer these questions.</td>
<td>The package for review includes all relevant information about the protocol, focusing on one study of the product to be conducted at a specific institution. Some also include review of the product, usually based on investigator’s brochure.</td>
<td></td>
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| Level of committee | National, appointed by government; sometimes regional. | Institution/university or country/national. | Institution/university in most cases; national in some cases. |

| Materials reviewed | Product specific materials—the entire package of information on preclinical and clinical testing of the product, its safety and biological effects and rationale for specific details of testing; trial-specific materials (such as the protocol) are also reviewed. | Product- and trial-specific materials. | Trial-specific materials: study protocol, including the informed consent document and advertisements for study recruitment. |

| Examples | U.S. Food and Drug Administration (FDA), the National Council of Science and Technology of the Government of Kenya. | Institutional Review Board (IRB) at an academic institution involved in the trial. | Kenyatta National Hospital Ethical and Research Committee—a joint committee between the University of Nairobi and Kenyatta National Hospital. |
Examples of country-specific AIDS vaccine trial approval processes

Kenya
In the case of the vaccine trials run by the Kenya AIDS Vaccine Initiative (KAVI), based at Kenyatta National Hospital, which is part of the University of Nairobi, the following institutions must review and approve the trial protocol:

- The Kenyatta National Hospital Ethical and Research Committee—this is a joint committee between the University of Nairobi and Kenya National Hospital.
- The Ministry of Education, Science and Technology, through the National Council of Science and Technology.
- A relevant international advisory committee (e.g., WHO/UNAIDS) may be requested by the Government of Kenya to review the protocol.
- Authorities responsible for other locations if it is a multicentre trial; for example, if the study is also conducted at St. Thomas’ Hospital in London, the study is reviewed by the ethics committee at the hospital and by the United Kingdom Medicines and Healthcare products Regulatory Agency (UK MHRA).

Brazil
Any vaccine trial conducted in Brazil must receive approval by the following institutions:

- IRB of the university or research institution that will be conducting the trial.
- National Ethics in Research Committee (CONEP) – an independent, multi-sector body linked to the Ministry of Health, which is the highest ethical review body in the country; this body reviews the protocol if the IRB needs a second opinion.
- National Technical Committee on Biosafety (CTNBio) – an independent committee linked to the Ministry of Science and Technology; if a protocol is using a genetically modified organism, it must be approved by this body.
- The National AIDS Program has its own research committee, made up of AIDS researchers and community representatives, which often has access to and provides input for AIDS vaccine research proposals, although its role is more of an advisory one and its review is not mandatory.
All of these committees follow internationally agreed-upon guidelines that provide a detailed definition of the requirements for ethical research. These guidelines create uniform ethical and scientific standards for all trials with human participants, wherever they take place.

Several sets of guidelines exist that outline regulations for conducting clinical trials.

**International Conference on Harmonisation**

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project designed to bring together regulatory authorities from various countries, in order to come to global consensus on regulations for worldwide conduct of clinical research and for eventual licensure of pharmaceutical products. By achieving consensus, the project aims to reduce duplication of effort and therefore avoid delay in global development of new drugs and vaccines while maintaining international standards and safeguards.

**Good Clinical Practice**

Official guidelines for good clinical practice (GCP) were established by the U.S. FDA, in agreement with the ICH. The purpose of the guidelines is to establish standards for designing, conducting, recording and reporting clinical trials. These guidelines establish the requirements needed for effective review and approval of proposed clinical studies.

**Good Clinical Laboratory Practice**

Many well accepted GCP and good laboratory practice (GLP) guidelines govern the conduct of clinical trials internationally. Although GCP guidelines are vague with respect to the analysis of human samples in the laboratory, GLP guidelines refer to the analysis of samples from nonclinical studies (nonhuman). A specific set of minimum standards and requirements for practical implementation in clinical trial laboratories has been developed and is a ‘hybrid’ and ‘interpretation’ of existing GCP and GLP guidelines, called good clinical laboratory practice (GCLP). GCLP standards have recently been recognised and adopted in at least one country (South Africa) and are being proposed to others.

GCLP guidelines address resources, rules for the conduct of studies (protocols and standard operating procedures), documentation and
quality assurance. IAVI has developed a GCLP checklist detailing all the requirements expected to be in place at each of the trial laboratory centres. It is a comprehensive checklist that will be invaluable to laboratory management and staff in their quest for accreditation.

**Good Participatory Practice**

In 2007, UNAIDS and the AIDS Vaccine Advocacy Coalition (AVAC) issued a document titled *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*. The document aims to provide internationally recognised standards for community engagement in HIV prevention trials. While not an official part of any regulatory approval process, the guidelines provide a universal reference for researchers, funders, trial communities, civil society, etc. in striving for relevant community involvement. They are meant to be put into practice similarly to GCP and GCLP standards.

The guidelines were drafted and updated with input from a wide variety of stakeholder groups from all over the world, including research staff, community advocates and civil society groups. They are considered a living document to be updated as the HIV prevention research field and perspectives on community engagement evolve.

**Code of Federal Regulations**

The Code of Federal Regulations (CFR) was developed specifically for clinical studies regulated by the U.S. FDA. It outlines all details of clinical trials, from what should be included in an informed consent form to how an IRB should operate. In the U.S. the CFR is used in conjunction with ICH/GCP guidelines, which are accepted worldwide.

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1 Referred to informally as ‘ethics committees’.

2 In some cases in certain countries, additional types of review may include bio-safety or ‘genetically modified organism’ committees, in which case trials must also be reviewed by existing committees.

3 If a research project is sponsored by international sources its review by both the IRB and the CONEP is mandatory. International projects also need to have been approved by an ethics committee in their country of origin.

4 This is technical analysis of safety of the product and not an ethics review process, but it is still mandatory, and often the CONEP requests for their technical input before approving a project that involves some kind of genetically modified organism.
All clinical trials, including AIDS vaccine trials, are carefully reviewed before they begin to ensure that they are scientifically and ethically sound and safe for volunteers.

Review committees and regulatory authorities are completely independent of the people who sponsor and conduct the trial; these authorities conduct additional reviews as a trial is carried out and have the power to stop a trial at any time.

Clinical trials must be reviewed and approved by appropriate committees in every country and/or institution where the trial is to be conducted.

**Key messages pertaining to AIDS vaccine development**


Making a preventive AIDS vaccine available to the world requires much more than developing the vaccine and proving that it is safe and effective. This chapter describes some of the challenges that need to be addressed in advance to ensure that once a vaccine is tested and approved it will be quickly distributed to and used by the people who need it most throughout the world.

The chapter includes information on:

- Conducting AIDS vaccine trials in low- and middle-income countries.
- Challenges to introduction, access, and use of a vaccine.
Summary points

1. AIDS vaccines should be tested in countries that are hardest hit by HIV and AIDS, and where a vaccine is most needed.

2. Historically, vaccines have taken up to 20 years from approval and licensure to reach developing countries. Addressing potential barriers to access during the vaccine development stage can help lead to faster access once licensure has been achieved.

3. Potential barriers to immediate access include: acceptability, regulatory capacity for licensure, financing mechanisms, manufacturing capacity and effective delivery systems.

4. Although an AIDS vaccine may be many years away, important steps can be taken now to prepare for eventual access to this technology. These include addressing pricing and financing, streamlining approval processes and learning from the current introduction of other new vaccines.

Key concepts

Conducting AIDS vaccine trials in low- and middle-income countries

AIDS vaccine trials are conducted in high- as well as low- and middle-income countries. There are various factors that may affect how a vaccine works that differ from place to place. It is logical to test AIDS vaccine candidates in countries hardest hit by HIV to ensure that they are appropriate for those settings. Testing vaccines in these countries will provide data needed to speed future approval and access where AIDS vaccines are needed the most.

Other vaccines that have been developed and tested in the U.S. and Europe have taken up to 20 years to become available in developing countries, and often at prices that limit their utilisation. For example, while a vaccine against hepatitis B virus has been available since 1981, about 60 percent of the world’s children were not receiving the vaccine more than 20 years later. The urgency of the AIDS pandemic makes it crucial that no such delay occurs with the development of an AIDS vaccine.
Testing vaccines in various countries at the same time will help facilitate future access in several ways:

- **Ensuring that it is safe and effective for the population.** It is important to know that a vaccine can protect against the type or types of HIV most common in the population. Some subtypes of HIV (also called clades) are common in certain regions of the world, while others are more common elsewhere (see Chapter 2 and Chapter 5 for further information). Differences across these subtypes (as well as differences within them) may affect how well a vaccine works in a particular area. The genetic make-up and health status of individuals, as well as the route by which HIV is transmitted, may also affect how a vaccine works. It is therefore important to test vaccines in different areas of the world.

- **Ensuring that delivery systems are in place.** Conducting clinical trials in-country can provide an initial understanding of existing vaccine delivery systems. It may also help identify outstanding needs or ways that systems could be adapted to make them more efficient for delivery once vaccines become available.

- **Facilitating national regulatory approval.** Conducting trials will provide relevant data to support vaccine approval in the countries where the trials are conducted.

- **Raising awareness and empowering communities.** Conducting a clinical trial will help increase knowledge and awareness of AIDS vaccine development among key stakeholders and communities. The impact of clinical trials includes enhanced health education and better healthcare services for communities, empowerment of community structures and civil society, and capacity building at multiple levels.

A comprehensive set of publications on global policy issues related to AIDS vaccine access can be found on IAVI’s website at: www.iavi.org.

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**Future global access to AIDS vaccines is fundamental to the goal of AIDS vaccine development.**
Tiered pricing is one solution to the potential high cost of an AIDS vaccine once it is on the market. This is when a vaccine is offered at different prices in different countries, based on a country’s ability to pay. Low and middle-income countries would receive the vaccine at a lower price, made possible by higher prices paid by wealthier countries. The system allows developing countries to receive favourable prices, but also provides commercial firms with a reasonable profit on vaccine production.

Challenges to future introduction, access and use of a vaccine

There are many challenges when introducing a new vaccine into a country, such as making it accessible to key populations and ensuring that it will be used. It is important to begin addressing these challenges now and to prepare for access well before a vaccine is proven efficacious or licensed. Such advance planning will help accelerate access to and uptake of a new vaccine once it is available.

Challenge 1: Global funding, finance mechanisms and pricing

Financial mechanisms must be set up to ensure that there are sufficient funds in place to purchase and deliver vaccines as soon as a product is licensed. A large sum of money—likely billions of dollars—will be needed to purchase and deliver AIDS vaccines globally. Most of this funding will need to come from governments and other donors including philanthropic organisations and multinational bodies like the World Bank and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

To help guarantee sufficient funding, purchasing mechanisms can be put into place. One example is an *advance market commitment* (AMC), which is an agreement between vaccine manufacturers and donor groups purchasing the vaccine for developing countries. An AMC would create a legally-binding contract that commits donors to buying a certain number of AIDS vaccine doses from vaccine manufacturers at a price that would generate profits matching those from other health products in the global market. In turn, after the established number of doses is purchased at that price, the manufacturer would be obligated to sell the vaccine at a lower price, one which low- and middle-income countries could afford.

Ensuring demand through this strategy may also encourage investment by pharmaceutical and biotech firms, which might otherwise be reluctant to invest in developing a product that would have limited
potential for profit. When combined with other incentives, an AMC could speed the development and widespread uptake of an AIDS vaccine.

**Challenge 2: Acceptability**

The acceptability of a future AIDS vaccine is important on various levels. If it is acceptable to policymakers and other influential people, they may be more willing to approve and license the vaccine, introduce the vaccine in-country and integrate it as part of the national health programme. If it is acceptable to the medical community and nongovernmental organisations (NGOs), they may be more willing to support and promote use of the vaccine. And if it is acceptable to individuals and communities, they may be more willing to be vaccinated. Acceptability therefore affects accessibility and uptake of a vaccine.

A number of factors may affect the level of acceptability of any particular AIDS vaccine:

**Efficacy**

Given that existing vaccines do not currently provide absolute protection to everyone who receives them, an AIDS vaccine is also unlikely to offer full protection for everyone (see Chapter 4 for more information on efficacy and partial efficacy). The first generation of AIDS vaccines to be licensed and made available to the public may be of low-to-moderate efficacy in comparison to some vaccines that are available for the prevention of other diseases. The level of efficacy may influence acceptability on all levels. The vaccine’s efficacy level may be considered by governments in decisions to make vaccines a public health priority, by medical providers in their decisions to promote and/or recommend its use, and by individuals in their decisions to be vaccinated. It is critically important that stakeholders at all levels understand the benefits of a partially effective vaccine when making decisions.

Even an AIDS vaccine with relatively low efficacy would have a significant impact on epidemics in high incidence countries if given to a large segment of the population. IAVI’s work on modelling the future course of AIDS epidemics and the impact that a vaccine could have on a global scale demonstrates that a vaccine that is 50 percent effective, given to just 30 percent of the population could reduce the number of new HIV infections in the developing world by more than half over 15 years.
Potential behaviour change

Even though a partially effective vaccine can have a strong public health impact, the benefits could be diminished or lost if people’s risk behaviour increases (often referred to as “disinhibition”). Some policymakers or medical providers might be concerned that if partially effective AIDS vaccines or microbicides are available, people who receive them will think they no longer need to practice other preventive behaviours. For instance, people may stop using condoms (sometimes referred to as condom migration or condom substitution), they may not practice partner reduction or they may begin using non-sterile injecting equipment. Such behaviour change will potentially increase their risk for both HIV and other sexually transmitted infections (STIs). It is therefore essential that programmes continue to promote existing prevention and risk-reduction strategies and integrate vaccines, microbicides and other new prevention interventions into these programmes.

Product characteristics

The characteristics of any vaccine product are strong determinants of its acceptability to the end user. A vaccine that requires one or two doses will likely be more acceptable than a vaccine that requires more doses, while an oral vaccine might be more acceptable than an injected vaccine for some people. Unfortunately, it is unlikely that scientists will have much control over the vaccine characteristics, given the difficulty of developing a vaccine.

Stigma and risk perception

As with other AIDS interventions, stigma and perceived risk are likely to affect future access to and use of AIDS vaccines. First, stigma can affect risk perception. People often believe that only certain stigmatised groups (e.g., people who engage in ‘dangerous’ sexual activities or drug use) are at risk of infection. They may not believe they are at risk or need to be vaccinated. Second, even if people do understand their risk of HIV infection and the benefits of vaccination, they might fear that they will be stigmatised or judged to be high risk if they seek vaccination. Women in particular might fear that they will be accused of unfaithfulness, and they might experience violence from or abandonment by partners. These issues need to be addressed within vaccine delivery plans.
Fears and misconceptions

Access will depend on disseminating accurate information to individuals, communities and authorities. Undue fears, rumours and misconceptions about the vaccine may have a negative impact on acceptability at all levels. Some common concerns based on myths and rumours include:

- Worry that the vaccine may cause HIV infection.
- Concern that any illness following vaccination is due to the vaccine.
- Fear that the vaccine could cause sterility.

Knowledge of AIDS vaccines and their potential benefit will have an impact on whether or not governments make vaccines a public health priority. It is important that AIDS advocates, community groups and vaccine developers increase awareness and support among government officials to help ensure vaccine access.

In addition, to make sure that vaccines are accepted, supported and used by the public, education campaigns should build knowledge among communities and societies about the characteristics, advantages, risks and limitations of AIDS vaccines.

Why promote risk reduction education along with a vaccine?

Since an AIDS vaccine will most likely be partially effective, it will be very important to avoid creating a false sense of security among people who receive it. If people think they are fully protected against HIV infection they may return to risky behaviour, increasing their vulnerability to HIV—the opposite of the vaccine’s intended effect.

It is therefore critical to promote risk reduction behaviour along with an AIDS vaccine. Information on existing prevention methods, such as the use of condoms, partner reduction and abstinence, and referrals to programmes that provide male circumcision, clean needles and syringes for injection drug use, where available, should be delivered with administration of the vaccine and will need to be incorporated into community AIDS education programmes. Stakeholders at all levels will need to understand the implications of efficacy and the importance of continued risk reduction even after a vaccine is available to the general population.
**Global demand for AIDS vaccines is an important part of future access.**

**Challenge 3: Estimating demand and use**

In order to plan for manufacturing and delivery of a vaccine, it is important to predict both the number of people who will be *willing* to be vaccinated and the number of people who will actually be vaccinated.

Potential factors that need to be taken into account in predicting demand and use include:

- The level of efficacy of the vaccine.
- The length of time a vaccine offers protection.
- The number of doses required for protection.
- Acceptability and the likelihood of use (see above).
- Affordability and the predicted price of the vaccine.
- Country capacity for vaccine or service delivery.

Information about the demand for a future AIDS vaccine can help plan for production, delivery, education programmes and financial needs. It will be crucial for making investment decisions, as well as for determining how a vaccine programme can best be designed and implemented.

**Challenge 4: Regulatory approval/licensure**

In order to make a vaccine available in a country, it must be licensed or approved by NRAs, such as a country’s ministry of health, the Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA). Historically, there have been delays of many years between initial licensure in the North and widespread approval in low- and middle-income countries. Vaccine developers often seek approval first in the places where there is a more profitable market, which is usually in high-income countries.

Approval of a new product requires review of a detailed record that presents the safety and efficacy of the vaccine. Since the approval process and the type of data needed for approval may vary between countries, vaccine developers may be required to prepare and submit multiple applications for approval. It is important to work with
regulatory authorities when designing the clinical trials to ensure that the trial will provide the necessary data to support eventual licensure. Working with the appropriate authorities in advance may prevent unnecessary delays and ensure a smoother approval process. Efforts to better coordinate and standardise regulatory processes across regions and internationally may facilitate approval.

Approval in some developing countries usually relies on prior approval by regulatory agencies from the U.S. and Europe. Stronger regulatory review mechanisms are needed in many low- and middle-income countries, and should be better coordinated internationally. One potential approach is to pool expertise and resources across regions and link them with more experienced regulatory bodies for technical support. The World Health Organisation (WHO) has been instrumental in providing guidance to low- and middle-income countries on the approval on new drugs and vaccines, including advising on the quality and safety of specific vaccines through its pre-qualification process.

**Challenge 5: Manufacturing**

Manufacturing a novel AIDS vaccine will require hundreds of millions of U.S. dollars and entails two costly elements: building a large-scale manufacturing facility, and developing biological processes (bioprocesses) to produce large quantities of the vaccine.

It is likely to take at least five years to build sufficient capacity for manufacturing, so work should begin well in advance of vaccine availability. Policy action is needed to ensure that this capacity exists, whether through creating incentives for large companies to work on scale-up for manufacturing or through direct investments. One effective way to achieve these goals is by creating partnerships between the public and private sectors.

**Challenge 6: Delivery**

Unlike current vaccination programmes, most of which benefit children, AIDS vaccines will first be made available to adults and adolescents, both of which are populations that may be difficult to reach through current vaccine delivery systems. Efforts to reach the highest-risk populations such as sex workers or injecting drug users may be even more difficult. Strategies for delivery should be well planned and placed within a country’s broader national AIDS prevention agenda. They should also be compatible with national vaccine programmes. A delivery strategy should address:

- Transportation and logistics (including a cold chain system).
• Human resources.
• Appropriate venues for delivering vaccines (e.g., clinics, community settings).
• Storage facilities and conditions.
• Education and social marketing appropriate to specific populations.
• Linkages with voluntary counselling and testing (VCT) systems.

As of 2009, the introduction of an AIDS vaccine is still many years away, and it is important to consider the appropriate steps to take now to prepare for speedy access for developing countries in the future. Although both healthcare and policy environments may be different in many years, important lessons can still be learned from the current introduction of both new HIV prevention tools and new vaccines.

Vaccine pricing
Several new vaccines that are important for the developing world have recently come to market (rotavirus, pneumococcal and human papillomavirus (HPV) vaccines). These vaccines are expensive, as an AIDS vaccine is likely to be, and people who need them the most cannot afford to pay for them. Purchasing mechanisms are set up through groups such as The United Nations Children’s Fund (UNICEF), the Pan American Health Organization (PAHO) and the GAVI Alliance (GAVI) to provide vaccines to the general public in developing countries. In some cases, governments themselves will purchase vaccines directly from manufacturers for their national immunisation programmes.

Typically, low- and middle-income countries pay manufacturers a significantly lower price for vaccines than wealthier countries pay. This difference in price has varied historically from vaccine to vaccine, so the discount for resource-limited countries is hard to predict.

Approval processes
Understanding the current approval process for new vaccines in low- and middle-income countries can help clarify ways to streamline the system for future vaccines, and eventually an AIDS vaccine. Along with NRAs in individual countries, the WHO is one of the primary players in the approval of new vaccines for low- and middle-income countries. It will be important to review WHO mechanisms to seek opportunities to enhance the system, and to strengthen regulatory agencies as a means of facilitating access to new products in the future.
Comprehensive lessons from current vaccine introduction

Introduction of the HPV vaccine, which prevents cervical cancer, in low- and middle-income countries provides an unprecedented opportunity for researchers to learn lessons that could be applied to future AIDS vaccine introduction. While there are critical differences between the HPV vaccine and a potential AIDS vaccine, a number of common characteristics exist.

The HPV vaccine is typically targeted at pre-adolescent and adolescent girls, which will be an important group for AIDS vaccines. Also, because HPV is sexually transmitted, working with this population provides an opportunity to better understand issues around sexuality, stigma and fears about infertility, all of which could impede AIDS vaccine introduction.

Delivery strategies and infrastructure issues may also be common between HPV and AIDS vaccines. Because most national immunisation programmes are targeted at infants, HPV vaccine introduction requires new strategies, possibly involving school- or clinic-based delivery, or other new campaigns.

The experience of developing messaging and communications materials about HPV vaccines also provides ample opportunity to learn lessons that could be applied to future communications about AIDS vaccines. Complex information around partial efficacy, the target population and continuing screening and prevention behaviours must go along with HPV vaccine delivery. These will also be extremely important messages with AIDS vaccine introduction.

Estimates of demand for the HPV vaccine, combined with the current levels of financing for new technologies for the developing world underscore key challenges for vaccine manufacturers, governments, and purchasing organisations such as GAVI and UNICEF. The price of the HPV vaccine remains high, but work is ongoing to lower the cost to low- and middle-income countries.

Women are a key audience for HPV vaccines at individual, national and international levels. Reproductive and women’s health and rights groups can help build advocacy and awareness at national and global levels around ensuring access for women who need the vaccine the most. Women also play a primary role in family health care decisions, particularly for pre-adolescents. Maternal and child health programmes may serve as an important mechanism for vaccine delivery. All of these aspects stand to be similar for future AIDS vaccines.
Historically, vaccines have taken up to 20 years after approval and licensure to become available to people in developing countries where they are most needed. This delay must not happen in the case of a future AIDS vaccine.

There are questions about how soon to address access issues for a product that is not yet developed, but it is necessary to focus on the issues at an early stage, given the history of delayed access to important public health interventions.

Working on eventual access to a vaccine can go hand-in-hand with clinical trials for AIDS vaccines. This may be a very efficient way to address some of the barriers to access.
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AE</td>
<td>adverse event or effect</td>
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<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<td>AMC</td>
<td>advance market commitment</td>
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<td>ART</td>
<td>antiretroviral therapy</td>
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<td>ARV</td>
<td>antiretroviral</td>
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<td>AVAC</td>
<td>AIDS Vaccine Advocacy Coalition</td>
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<td>CAB</td>
<td>community advisory board</td>
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<td>CBO</td>
<td>community based organisation</td>
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<td>CTL</td>
<td>cytotoxic T lymphocyte</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<tr>
<td>ECBS</td>
<td>Expert Committee on Biological Standardization</td>
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<tr>
<td>ERC</td>
<td>ethics review committee</td>
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<tr>
<td>FBO</td>
<td>faith-based organisation</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>GACVS</td>
<td>Global Advisory Committee on Vaccine Safety</td>
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<tr>
<td>GAVI</td>
<td>GAVI Alliance (formerly Global Alliance for Vaccines and Immunisation)</td>
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<tr>
<td>GCLP</td>
<td>good clinical and laboratory practice</td>
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<td>GCP</td>
<td>good clinical practice</td>
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<tr>
<td>GPP</td>
<td>good participatory practice</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>HPV</td>
<td>human papillomavirus</td>
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<td>HVTN</td>
<td>HIV Vaccine Trials Network</td>
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<td>IAVI</td>
<td>International AIDS Vaccine Initiative</td>
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<td>ICH</td>
<td>International Committee on Harmonization</td>
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<td>IDU</td>
<td>injecting drug user</td>
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<tr>
<td>IEC</td>
<td>independent ethics committee</td>
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<td>IRB</td>
<td>institutional review board</td>
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<td>LDC</td>
<td>least-developed countries</td>
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<tr>
<td>MOH</td>
<td>ministry of health</td>
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<tr>
<td>MSM</td>
<td>men who have sex with men</td>
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<tr>
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<td>nongovernmental organisation</td>
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<td>NIH</td>
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<td>NRA</td>
<td>National Regulatory Authority</td>
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<td>PAHO</td>
<td>Pan American Health Organization</td>
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<tr>
<td>PI</td>
<td>principal investigator</td>
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<tr>
<td>PMTCT</td>
<td>prevention of mother-to-child transmission</td>
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<tr>
<td>Q&amp;A</td>
<td>question and answer</td>
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<tr>
<td>SAE</td>
<td>serious adverse event</td>
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<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts</td>
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<tr>
<td>STI</td>
<td>sexually transmitted infection</td>
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<tr>
<td>SW</td>
<td>sex worker</td>
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<tr>
<td>TOT</td>
<td>training of trainers</td>
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<tr>
<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<tr>
<td>VCT</td>
<td>voluntary counselling and testing</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Adjuvant: a substance sometimes included in a vaccine formulation to enhance or modify the immune-stimulating properties of a vaccine.

Advance market commitment (AMC): a binding contract, typically offered to a manufacturer by a government, multilateral donor, or other financial entity, used to guarantee a viable market if a vaccine or other medicine is successfully developed. AMCs typically focus on products for neglected diseases for which viable markets would not otherwise exist. The AMC provides a legally-binding promise to manufacturers to pay a price for a future product that would generate profits matching those from other health products in the global market. After donors buy a certain quantity at this price, the manufacturer is obligated to sell the product at a lower price that developing countries can afford.

Adverse event: in a clinical trial, an unwanted effect detected in participants. The term is used whether or not the effect can be attributed to the vaccine under study.

Adverse reaction (side effect): in a clinical trial, an unwanted effect detected in participants and attributed to the study vaccine.

AIDS (acquired immunodeficiency syndrome): the late stage of HIV disease, characterized by a deterioration of the immune system and a susceptibility to a range of opportunistic infections and cancers.

ALVAC-HIV™: a genetically engineered HIV vaccine composed of a live, weakened canarypox virus (ALVAC™) into which parts of genes for non-infectious components of HIV have been inserted. When ALVAC™ infects a human cell, the inserted HIV genes direct the cell to make HIV proteins. These proteins are packaged into HIV-like particles that bud from the cell membrane. These particles are not infectious but fool the immune system into mounting an immune response to HIV. ALVAC™ can infect but not grow in human cells, an important safety feature. (See also canarypox.)

Anergy: the loss or weakening of immune response to an irritating agent or antigen. Anergy can be thought of as the opposite of allergy, which is an overreaction to a substance. The strength of the immune response is often quantitatively evaluated by standardised skin tests. A small amount of solution containing an antigen known to cause a response, such as tetanus or mumps, is injected under the skin and the area checked for a localized skin reaction after 48 to 72 hours. Healthy people will develop a measurable area of redness at the injection site; people who are immune suppressed, such as people with AIDS, will have no measurable response to these skin tests.

Antibody: an infection-fighting protein molecule in blood or secretory fluids that tags, neutralises, and helps destroy pathogenic microorganisms (e.g., bacteria, viruses) or toxins. Antibodies, known generally as immunoglobulins, are made and secreted by B lymphocytes in response to stimulation by antigens. Each specific antibody binds only to the specific antigen that stimulated its production. (See also immunoglobulin; binding antibody; enhancing antibody; functional antibody; neutralizing antibody.)

Antibody-mediated immunity: also called humoral immunity. Immunity that results from the activity of antibodies in blood and lymphoid tissue.

Antigen: any substance that stimulates the immune system to produce antibodies. Antigens are often foreign substances such as invading bacteria or viruses. (See also immunogen.)

Antiretroviral therapy (ART): Treatment with drugs that inhibit the ability of retroviruses, such as HIV, to multiply in the body. The antiretroviral therapy recommended for HIV infection is referred to as highly active antiretroviral therapy (HAART), which uses a combination of drugs to attack HIV at different points in its life cycle.

Antigen-presenting cell (APC): B cell, macrophage, dendritic cell or other cell that ingests and processes foreign bodies such as viruses and displays the resulting antigen fragments on its surface to attract and activate the CD4+ T cells that respond specifically to that antigen. (See also dendritic cell; macrophage.)

Apoptosis: cellular suicide, also known as programmed cell death. A possible mechanism used by HIV to suppress the immune system. HIV may cause apoptosis in both HIV-infected and HIV-uninfected immune system cells.

Arm: a group of participants in a clinical trial, all of whom receive the same treatment, intervention or placebo. The other arm(s) receive(s) a different treatment.

Attenuated: weakened. Attenuated viruses are often used as vaccines because they can no longer produce
disease but still stimulate a strong immune response, like that to the natural virus. Examples of attenuated virus vaccines include oral polio, measles, mumps, and rubella vaccines.

**autoimmunity:** in HIV vaccination, a theoretical adverse effect in which the vaccine causes immune responses that are inappropriately directed at a person’s own tissues.

**B lymphocyte (B cell):** one of the two major classes of lymphocytes, B lymphocytes are white blood cells of the immune system that are derived from the bone marrow and spleen. B cells develop into plasma cells, which produce antibodies.

**baseline:** the time point in a study just before initiation of intervention (vaccination) when starting measurements are taken. Measurements taken at later time points may be compared with those taken at baseline to study variations.

**binding antibody:** an antibody that attaches to some part of HIV. Binding antibodies may or may not lead to the killing of the virus.

**blinded study:** a clinical trial in which participants are unaware as to whether or not they are in the experimental or control arm of the study. (See also double-blind study.)

**booster:** a second or later vaccine dose given after the primary dose(s) to increase the immune response to the original vaccine antigen(s). The vaccine given as the booster dose may or may not be the same as the primary vaccine. (See also prime-boost.)

**breakthrough infection:** an infection, which the vaccine is intended to prevent, that occurs in a volunteer during the course of a vaccine trial. Such an infection is caused by exposure to the infectious agent and may occur before or after the vaccine has taken effect or all doses have been given.

**canarypox:** a virus that infects birds and is used as a live vector for HIV vaccines. It can carry a large quantity of foreign genes. Canarypox virus cannot grow in human cells, an important safety feature. (See also ALVAC-HIV™; vector.)

**CD4+ T lymphocyte:** immune cell that carries a marker on its surface known as “cluster of differentiation 4” (CD4). These cells are the primary targets of HIV. Also known as helper T cells, CD4+ T cells help orchestrate the immune response, including antibody responses as well as killer T cell responses. (See also T cell.)

**CD8+ T lymphocyte:** immune cell that carries the “cluster of differentiation 8” (CD8) marker. CD8 T cells may be cytotoxic T lymphocytes or suppressor T cells. (See also cytotoxic T lymphocyte (CTL); T cell.)

**cell-mediated immunity (cellular immunity):** the immune response coordinated by helper T cells and CTLs. This branch of the immune system targets cells infected with microorganisms such as viruses, fungi and certain bacteria.

**challenge:** in vaccine experiments, the deliberate exposure of an immunised animal to the infectious agent. Challenge experiments are never done in human HIV vaccine research.

**clade:** also called a subtype. A group of related HIV isolates classified according to their degree of genetic similarity (such as of their envelope proteins). There are currently two groups of HIV-1 isolates, M and O. M consists of at least nine clades, A through I. Group O may consist of a similar number of clades. (See also isolate.)

**clinical trial:** any precisely controlled test of an experimental drug, vaccine, or other intervention, performed in human volunteers.

**cohort:** groups of individuals who share one or more characteristics in a research study and who are followed over time. For example, a vaccine trial might include two cohorts, a group at low risk for HIV and a group at higher risk for HIV.

**complement:** blood proteins that play an important role in the immune response. Generally, complement proteins amplify the effects of antibodies and inflammation.

**control:** in vaccine clinical trials, the control group is given either the standard treatment for the disease or an inactive substance called a placebo. The control group is compared with one or more groups of volunteers...
given experimental vaccines to detect any effects of the vaccines.

core: the protein capsule surrounding a virus' DNA or RNA. In HIV, p55, the precursor molecule to the core, is broken down into the smaller molecules p24, p17, p7 and p6. HIV's core is primarily composed of p24.

correlates of protection (correlates of immunity): the immune responses that must be present to protect an individual from a certain infection. The precise correlates of immunity in HIV transmission are unknown.

cytokine: a soluble, hormone-like protein produced by white blood cells that acts as a messenger between cells. Cytokines can stimulate or inhibit the growth and activity of various immune cells. Cytokines are essential for a coordinated immune response and can also be used as immunologic adjuvants. HIV replication is regulated by a delicate balance among cytokines.

cytotoxic T lymphocyte (CTL): immune system cell that can destroy cancer cells and cells infected with viruses, fungi or certain bacteria. CTLs, also known as killer T cells, carry the CD8 marker. CTLs kill virus-infected cells, whereas antibodies generally target free-floating viruses in the blood. CTL responses are a proposed but unproven correlate of HIV immunity. (See also CD8+ T lymphocyte.)

deletion: elimination of a gene either in nature or in the laboratory.

dendritic cell: immune cell with threadlike tentacles called dendrites used to enmesh antigen, which they present to T cells. Langerhans cells, found in the skin, and follicular dendritic cells, found in lymphoid tissues, are both types of dendritic cells. (See also antigen-presenting cell.)

DNA (deoxyribonucleic acid): the double-stranded, helical molecular chain found within the nucleus of each cell. DNA carries the genetic information that encodes proteins and enables cells to reproduce and perform their functions.

DNA vaccine (nucleic acid vaccine): direct injection of a gene(s) coding for a specific antigenic protein(s), resulting in direct production of such antigen(s) within the vaccine recipient in order to trigger an appropriate immune response.

domain: a region of a gene or gene product. A neutralizing domain is a specific site on the virus to which a neutralizing antibody is directed.

dose-ranging study: a clinical trial in which two or more doses (starting at a lower dose and proceeding to higher doses) of a vaccine are tested against each other to determine which dose works best and has acceptable side effects.

dose-response relationship: the relationship between the dose of a vaccine and an immune or physiologic response. In vaccine research, a dose-response effect means that as the dose of the vaccine increases, so does the level of the immune response (antibodies and CTL activity).

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 produce objective results, since the researcher's and volunteer's expectations about the experimental vaccine do not affect the outcome.

DSMB (Data and Safety Monitoring Board): 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 groups. The DSMB may review the data in such a way that they know which group received the vaccine and which group did not. This group may also recommend that a trial be modified or stopped if there are safety concerns or if the trial objectives have been achieved.

EBV (Epstein-Barr Virus) cell line: a herpes virus; in vaccine research, used to make target cells for CTL assays.

effectiveness: the measurement of how well a vaccine works once it is licensed and made available to the general public; the ‘real world’ efficacy of a vaccine.
**efficacy:** in vaccine research, the ability of a vaccine to produce a desired clinical effect, such as protection against a specific infection, at the optimal dosage and schedule in a given population. A vaccine may be tested for efficacy in Phase III trials if it appears to be safe and shows some promise in smaller Phase I and II trials.

**ELISA (enzyme-linked immunoabsorbent assay):** a blood test that detects antibodies based on a reaction that leads to a detectable color change in the test tube. The HIV ELISA is commonly used as the initial screening test because it is relatively easy and inexpensive to perform. Because the HIV ELISA is designed for optimal sensitivity—that is, it detects all persons with HIV antibodies as well as some who don’t have them (false positives)—a positive HIV ELISA test must be confirmed by a second, more specific test such as an HIV Western Blot.

**elite controllers:** also called long-term non-progressors. People infected with the human immunodeficiency virus (HIV) whose bodies have kept the microbe at undetectable levels in their bloodstreams without treatment.

**empirical controllers:** based on experience or observational information and not necessarily on proven scientific data. In the past, vaccine trials have been performed based exclusively on empirical data and without a full understanding of the disease processes or correlates of immunity.

**endpoint:** the results of an intervention such as vaccination compared among different study groups in a clinical trial. In early vaccine trials, common endpoints are safety and specific types and intensities of immune responses (neutralizing antibodies, CTL responses).

**enhancing antibody:** a type of binding antibody, detected in the test tube and formed in response to HIV infection, that may enhance the ability of HIV to produce disease. Theoretically, enhancing antibodies could attach to HIV virions and enable macrophages to engulf the viruses. However, instead of being destroyed, the engulfed virus may remain alive within the macrophage, which then can carry the virus to other parts of the body. It is currently unknown whether enhancing antibodies have any effect on the course of HIV infection. Enhancing antibodies can be thought of as the opposite of neutralizing antibodies.

**enzyme:** a protein produced by cells to accelerate a specific chemical reaction without itself being altered. Enzymes are generally named by adding the ending “-ase” to the name of the substance on which the enzyme acts (for example, protease is an enzyme that acts on proteins).

**envelope (Env):** outer surface of a virus, also called the coat. Not all viruses have an envelope. (See also virus)

**epidemiology:** the study of the frequency and distribution of disease in human populations.

**epitope:** a specific site on an antigen that stimulates specific immune responses, such as the production of antibodies or activation of immune cells.

**expression system:** in genetic engineering, the cells into which a gene has been inserted to manufacture desired proteins. Chinese hamster ovary (CHO) cells and baculovirus/insect cells are two expression systems that are used to make recombinant HIV vaccines.

**functional antibody:** an antibody that binds to an antigen and has an effect that can be demonstrated in laboratory tests. For example, neutralizing antibodies are functional antibodies that inactivate HIV or prevent it from infecting other cells.

**genetic engineering:** the laboratory technique of recombining genes to produce proteins used for drugs and vaccines.

**genome:** the complete set of genes present in a cell or virus.

**gp:** abbreviation for glycoprotein. A protein molecule that is glycosylated, that is, coated with a carbohydrate, or sugar. The outer coat proteins of HIV are glycoproteins. The number after the gp (e.g., gp160, gp120, gp41) is the molecular weight of the glycoprotein.

**gp41:** glycoprotein 41. A protein imbedded in the outer envelope of HIV that anchors gp120. gp41 plays a key role in HIV’s infection of CD4+ T cells by facilitating the fusion of the viral and cell membranes. Antibodies to
gp41 can be detected on a screening HIV ELISA.

gp120: glycoprotein 120. One of the proteins that forms the envelope of HIV. gp120 projects from the surface of HIV and binds to the CD4 molecule on helper T cells. gp120 has been a logical experimental HIV vaccine because the outer envelope is the first part of the virus that encounters antibody.

half-life: the time required for half the amount of a substance to be eliminated from the body or to be converted to another substance(s).

helper T cell: lymphocyte bearing the CD4 marker. Helper T cells are the chief regulatory cells of the immune response. They are responsible for many immune system functions, including turning antibody production on and off, and are the main target of HIV infection. (See also CD4+ T lymphocyte.)

herd immunity: resistance of a group to an attack of a disease to which a proportion of the members of the group are immune; if a significant percentage of a population are immune, the entire population is likely to be protected, not just those who are immune.

homologous: similar in appearance, structure and usually function. For HIV, the same strain of the virus.

host: a plant or animal harboring another organism.

HLA (human leukocyte antigen): two major classes of molecules on cell surfaces.

human papillomavirus (HPV): a common virus which infects the skin and mucous membranes. Over 40 types of HPV exist which can infect the genital areas of men and women, including the skin of the penis, vulva (are outside the vagina), and anus, and the linings of the vagina, cervix, and rectum. HPV is sexually transmitted and most individuals become infected with at least one type after becoming sexually active. Most HPV infections do not lead to symptoms or health problems. But sometimes, certain types of HPV can cause genital warts in men and women. Other HPV types can cause cervical cancer and other less common cancers, such as cancers of the vulva, vagina, anus, and penis. The types of HPV that can cause genital warts are not the same as the types that can cause cancer. Two types of HPV (HPV-16 and HPV-18) are the primary cause of cervical cancer.

humoral immunity: see antibody-mediated immunity.

hypothesis: a tentative statement or supposition, which may then be tested through research.

immune complex: the result of a reaction between an antigen and a specific antibody. This combination of antigen bound by antibody may or may not cause adverse effects in a person.

immune deficiency: a breakdown or inability of certain parts of the immune system to function, thus making a person susceptible to diseases that they would not ordinarily develop.

immunity: natural or acquired resistance provided by the immune system to a specific disease. Immunity may be partial or complete, specific or nonspecific, long-lasting or temporary.

immunisation: the process of inducing immunity by administering an antigen (vaccine) to allow the immune system to prevent infection or illness when it subsequently encounters the infectious agent.

immunogen: a substance capable of provoking an immune response. Also called an antigen.

immunocompetent: capable of developing an immune response; possessing a normal immune system.

immunogenicity: the ability of an antigen or vaccine to stimulate immune responses.

immunoglobulin: a general term for antibodies, which bind to invading organisms, leading to their destruction. There are five classes of immunoglobulins: IgA, IgG, IgM, IgD and IgE. (See also antibody.)

immunotherapy: a treatment that stimulates or modifies the body’s immune response.

incidence: the rate of occurrence of some event, such as the number of individuals who get a disease divided
by a total given population per unit of time. (Contrast with prevalence.)

inclusion/exclusion criteria: the medical or social reasons why a person may or may not qualify for participation in a clinical trial. For example, some trials may exclude people with chronic liver disease or with certain drug allergies; others may include only people with a low CD4+ T-cell count.

IND (investigational new drug): the status of an experimental drug after the FDA agrees that it can be tested in people.

informed consent: an agreement signed by prospective volunteers for a clinical research trial that indicates their understanding of (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, and (7) the participant’s right to leave the trial at any time.

intervention: a vaccine (or drug or behavioural therapy) used in a clinical trial to improve health or alter the course of disease.

in vitro: an artificial environment created outside a living organism (e.g., in a test tube or culture plate) used in experimental research to study a disease or biologic process.

in vivo: testing within a living organism, e.g., human or animal studies.

IRB (institutional review board): a committee of physicians, statisticians, community advocates and others that reviews clinical trial protocols before they can be initiated. IRBs ensure that the trial is ethical and that the rights of participants are adequately protected.

isolate: a particular strain of HIV-1 taken from a person.

live-vector vaccine: a vaccine that uses a non-disease-causing organism (virus or bacterium) to transport HIV or other foreign genes into the body, thereby stimulating an effective immune response to the foreign products. This type of vaccine is important because it is particularly capable of inducing CTL activity. Examples of organisms used as live vectors in HIV vaccines are canarypox and vaccinia.

lymphocyte: a type of white blood cell produced in the lymphoid organs that is primarily responsible for immune responses. Present in the blood, lymph and lymphoid tissues. (See also B cell and T cell.)

lymphoid tissue: tonsils, adenoids, lymph nodes, spleen and other tissues that act as the body’s filtering system, trapping invading microorganisms and presenting them to squadrons of immune cells that congregate there.

macrophage: a large immune system cell in the tissues that devours invading pathogens and other intruders. Macrophages stimulate other immune cells by presenting them with small pieces of the invaders. Macrophages also can harbor large quantities of HIV without being killed, acting as reservoirs of the virus.

mean: the arithmetic average, or the sum of all the values divided by the number of values.

median: the midpoint value obtained by ranking all values from highest to lowest and choosing the value in the middle. The median divides a population into two equal halves.

memory cell: a subset of T cells and B cells that have been exposed to specific antigens and can then proliferate (recognize the antigen and divide) more readily when the immune system re-encounters the same antigens.

MHC (major histocompatibility complex): the gene cluster that controls certain aspects of the immune response. Among the products of these genes are the histocompatibility antigens, such as HLA class I antigens, which are present on every cell with a nucleus and serve as markers to distinguish self from non-self. (See also HLA.)

microbicide: a new type of product being developed that people could use vaginally or rectally to protect themselves from HIV and possibly other sexually transmitted infections. A microbicide could be produced in many forms, including gels, creams, suppositories, films, or as a sponge or ring that releases the active ingredient over time.
MN: an HIV-1 strain belonging to clade B, the clade to which most HIV-1 found in North America and Europe belong. MN is used in vaccine development. (See also clade.)

monoclonal antibody: custom-made, identical antibody that recognises only one epitope.

monocyte: a large white blood cell in the blood that ingests microbes or other cells and foreign particles. When a monocyte passes out of the bloodstream and enters tissues, it develops into a macrophage.

monovalent vaccine: a vaccine that contains only one antigen.

mucosal immunity: resistance to infection across the mucous membranes. Mucosal immunity depends on immune cells and antibodies present in the linings of reproductive tract, gastrointestinal tract and other moist surfaces of the body exposed to the outside world.

neutralizing antibody: an antibody that keeps a virus from infecting a cell, usually by blocking receptors on the cells or the virus.

neutralizing domain: a section of HIV (most commonly on the envelope protein gp120) that elicits antibodies with neutralizing activity. (See also V3 loop.)

NK cell (natural killer cell): a non-specific lymphocyte. NK cells, like killer T cells, attack and kill cancer cells and cells infected by microorganisms. NK cells are “natural” killers because they do not need to recognise a specific antigen in order to attack and kill.

nucleus: the central controlling body within a living cell, usually a spherical unit enclosed in a membrane and containing genetic codes for maintaining life systems of the organism and for issuing commands for growth and reproduction.

open-label trial: a clinical trial in which doctors and participants know which vaccine is being administered to all participants.

opportunistic infection: an illness caused by an organism that usually does not cause disease in a person with a healthy immune system. People with advanced HIV infection suffer opportunistic infections of the lungs, brain, eyes and other organs.

P24: a protein in HIV's inner core. The p24 antigen test looks for the presence of this protein in a person's blood.

parenteral: administered intravenously or by injection. For example, medications or vaccines may be administered by injection into the fatty layer immediately below the skin (subcutaneous), or into the muscle (intramuscular). Medications, but not vaccines, can also be administered into a vein (intravenously).

pathogen: any disease-causing organism.

pathogenesis: the origin and development of a disease. More specifically, the way a microbe (bacteria, virus, etc.) causes disease in its host.

peptide: a short compound formed by linking two or more amino acids. Proteins are made of multiple peptides.

Phase I vaccine trial: a controlled clinical trial of a vaccine conducted in a small number of healthy volunteers. A Phase I trial is designed to determine the vaccine's safety in humans, its metabolism and pharmacologic actions, and side effects associated with increasing doses.

Phase II vaccine trial: controlled clinical study of a vaccine to identify common short-term side effects and risks associated with the vaccine and to collect information on its immunogenicity. Phase II trials enroll some volunteers who have the same characteristics as persons who would be enrolled in an efficacy (Phase III) trial of a vaccine. Phase II trials enroll up to several hundred participants and have more than one arm.

Phase IIb vaccine trial: a controlled clinical study which is a possible intermediate step between Phase II and Phase III trials, sometimes called a test-of-concept or proof-of-concept trial. It is meant to determine if the vaccine concept or the type of vaccine being tested might be effective. A Phase IIb trial is not designed to establish efficacy of a particular candidate but rather to help researchers decide if a candidate is worth testing
in larger Phase III trials. The number of volunteers required is smaller, around 2,000 to 5,000, compared to over 10,000 volunteers for Phase III trials.

**Phase III vaccine trial:** large controlled clinical study to determine the ability of a vaccine to produce a desired clinical effect on the risk of a given infection, disease, or other clinical condition at an optimally selected dose and schedule. These trials also gather additional information about safety needed to evaluate the overall benefit-risk relationship of the vaccine and to provide adequate basis for labeling. Phase III trials usually include several hundred to several thousand volunteers.

**placebo:** an inactive substance administered to some study participants while others receive the agent under evaluation, to provide a basis for comparison of effects.

**post-exposure prophylaxis (PEP):** an intervention in which people who have been exposed to HIV through a needle, rape, etc., immediately begin taking ARVs in hopes of preventing infection.

**pre-exposure prophylaxis (PrEP):** a currently experimental method of HIV prevention which is undergoing clinical trials. The intervention is one in which HIV-uninfected individuals could take one or more antiretroviral (ARV) drugs regularly before they were exposed to HIV with the hopes that it would lower the risk of infection if exposed to HIV. Most candidate PrEP regimens consist of pills taken orally, often on a daily basis.

**prevalence:** the number of people in a given population affected with a particular disease or condition at a given time. Prevalence can be thought of as a snapshot of all existing cases at a specified time. (Contrast with incidence.)

**preventive HIV vaccine (AIDS vaccine):** a vaccine designed to prevent HIV infection and/or AIDS.

**prime-boost:** in HIV vaccine research, administration of one type of vaccine, such as a live-vector vaccine, followed by or together with a second type of vaccine, such as a recombinant subunit vaccine. The intent of this combination regimen is to induce different types of immune responses and enhance the overall immune response, a result that may not occur if only one type of vaccine were to be given for all doses.

**priming:** giving one vaccine dose(s) first to induce certain immune responses, followed by or together with a second type of vaccine. The intent of priming is to induce certain immune responses that will be enhanced by the booster dose(s).

**priming prophylaxis:** prevention of disease.

**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 trial design.

**randomised trial:** a study in which participants are assigned by chance to one of two or more intervention arms or regimens. Randomization minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms.

**reactogenicity:** the capacity of a vaccine to produce adverse reactions.

**reagent:** any chemical used in a laboratory test or experiment.

**receptor:** a molecule on the surface of a cell that serves as a recognition or binding site for antigens, antibodies or other cellular or immunologic components.

**recombinant DNA technology:** the technique by which genetic material from one organism is inserted into a foreign cell in order to mass produce the protein encoded by the inserted genes.

**regulatory gene:** HIV genes (nef, rev, tat, vpr) that regulate viral replication in infected cells.

**retrovirus:** HIV or other viruses that carries their genetic material in the form of RNA rather than DNA and has the enzyme reverse transcriptase that can transcribe it into DNA. In most animals and plants, DNA is usually made into RNA, hence "retro" is used to indicate the opposite direction.

**reverse transcriptase:** the enzyme produced by HIV and other retroviruses that enables them to direct a cell to synthesize DNA from their viral RNA.
RNA (ribonucleic acid): a single-stranded molecule composed of chemical building blocks, similar to DNA. The RNA segments in cells represent copies of portions of the DNA sequences in the nucleus. RNA is the sole genetic material of retroviruses.

Screening test-of-concept trials (STOC): a trial approach designed to obtain efficacy data from human subjects in a shorter timeframe and with fewer volunteers. STOC trials involve relatively small cohorts (300-600 individuals) from higher-risk populations, and expedite preliminary indications of potential efficacy, helping guide product development for new vaccines that represent a marked improvement over existing candidates.

serious adverse event (SAE) or serious adverse drug reaction (serious ADR): Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

seroconversion: the development of antibodies to a particular antigen. When people develop antibodies to HIV or an experimental HIV vaccine, they “seroconvert” from antibody-negative to antibody-positive. Vaccine-induced seroconversion does not represent an infection. Instead, vaccine-induced seroconversion is an expected response to vaccination that may disappear over time.

serostatus: positive or negative results of a diagnostic test, such as an ELISA, for a specific antibody.

sexually transmitted infection (STI): any infection spread by the transmission of organisms from person to person during sexual contact.

SHIV: genetically engineered hybrid virus having an HIV envelope and an SIV core.

side effect: (See adverse reaction.)

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

statistical significance: the probability that an event or difference occurred as the result of the intervention (vaccine) rather than by chance alone. This probability is determined by using statistical tests to evaluate collected data. Guidelines for defining significance are chosen before data collection begins.

sterilizing immunity: an immune response that completely prevents the establishment of an infection.

strain: one type of HIV. HIV is very heterogeneous and no two isolates are exactly the same. When HIV is isolated from an individual, and worked on in the lab, it is given its own unique identifier, or strain name (i.e., MN, LAI).

stratification: separation of a study cohort into subgroups or strata according to specific characteristics.

subtype: also called a clade with respect to HIV isolates, a classification scheme based on genetic differences.

subunit vaccine: a vaccine that contains only part of the virus or other microorganism. HIV subunit vaccines produced by genetic engineering are referred to as recombinant subunit HIV vaccines.

surrogate marker: an indirect measure of disease progression. In HIV disease, the number of CD4+ T cells per cubic millimeter of blood is often used as a surrogate marker.

T cell: white blood cell critical to the immune response. Among these are CD4+ T cells and CD8+ T cells. The “T” stands for the thymus, where T lymphocytes mature. (See also lymphocyte.)

T lymphocyte proliferation assay: a test used to measure the memory of T cells to antigens or microbes, such as HIV.

therapeutic HIV vaccine: a vaccine designed to boost the immune response to HIV in a person already infected with the virus. Also referred to as an immunotherapeutic vaccine.
V3 loop: a section of the HIV gp120 surface protein that appears to be important in stimulating neutralizing antibodies. (See also neutralizing domain.)

vaccine: a preparation that stimulates an immune response that can prevent an infection or create resistance to an infection.

vaccinia: a cowpox virus, formerly used in human smallpox vaccines. Employed as a vector in HIV vaccines to transport HIV genes into the body.

vector: in vaccine research, a bacterium or virus that does not cause disease in humans and is used in genetically engineered vaccines to transport genes coding for antigens into the body to induce an immune response. (See also vaccinia and canarypox.)

viremia: the presence of virus in the bloodstream.

virion: a mature infectious virus particle existing outside a cell.

virus: a microorganism composed of a piece of genetic material – RNA or DNA – surrounded by a protein coat. To replicate, a virus must infect a cell and direct its cellular machinery to produce new viruses.

Western blot: a blood test to detect antibodies to several specific components of a virus such as HIV. This test is most often used to confirm a positive ELISA.
Appendix 3: Compiled Reference List

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Clinical Research Resources. Website with a comprehensive list of resources such as the Code of Federal Regulations and the International Committee on Harmonization Guidelines. Available at: www.clinicalresearchresources.com.


Chapter


Chapter


Imagine a world without AIDS