

# core content



## Aids Vaccine Literacy Toolkit



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## Acknowledgements

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### First printing.

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The text of the *AIDS Vaccine Literacy Core Content* may be found online at <http://www.iavi.org/vaxlit>.

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IAVI's mission is to ensure the development of a safe, effective, accessible, preventive AIDS vaccine 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 HIV/AIDS vaccine research.

	<b>Introduction</b>	<b>8</b>
<b>1</b>	<b>Vaccines and the Global Response to HIV/AIDS</b>	<b>14</b>
	• The HIV/AIDS pandemic	17
	• Women, men and the HIV/AIDS pandemic	19
	• The global response to HIV/AIDS	19
	– Prevention approaches	
	– Treatment, care and support	
	– New technologies: vaccines and microbicides	
	• The need for a comprehensive prevention-to-care continuum	24
		<b>26</b>
<b>2</b>	<b>Building a Supportive Environment for AIDS Vaccines</b>	<b>27</b>
	• Conducting AIDS vaccine research in developing countries	
	– Box: Is subtype important in deciding where an AIDS vaccine should be tested?	29
	• Country advocate and stakeholder groups	
	– NGOs, CBOs and FBOs	
	– Parliamentarians, policymakers and ministries of health	
	– Media and journalists	
	– Medical professionals	
	– Academic and religious leaders	
	– Community advisory boards	33
	• AIDS vaccine education in advance of trials	35
	• The role of advocates and stakeholders in the trial site community	35
	• Mobilising volunteers	
	– Box: VCT services: Key entry point and support for AIDS vaccine trials	
	– Diagram: Stakeholder funnel	
	– Diagram: Participant influencers	39
	• Managing expectations	
		<b>42</b>
<b>3</b>	<b>Immune System and HIV/AIDS</b>	<b>43</b>
	• Types of immune response	44
	• Key immune concepts and how they relate to HIV	
	– Immune system	
	– Pathogen	
	– Opportunistic infections	
	– Immune response	
	– Antigen	
	– Macrophages/Dendritic cells/Phagocytes	
	– Antigen-presenting cells	
	– Lymphocytes	
	– T cells	
	– CD4 <sup>+</sup> cells	
	– CD8 <sup>+</sup> cells	
	– B cells	
	– Plasma B cells	
	– Antibody	
	– Memory B cells and memory T cells	48
	• Diagram: How antibodies protect	49
	• Diagram: Structure of HIV	
		<b>52</b>
<b>4</b>	<b>Vaccines</b>	<b>53</b>
	• Definition of 'vaccine'	54
	• How preventive vaccines work	54
	• Preventive versus therapeutic vaccines	55
	• Common vaccine types	
	– Whole-killed/Whole-inactivated vaccines	
	– Live attenuated vaccines	

- Subunit vaccines
- DNA vaccines
- Recombinant vector vaccines
- Additional vaccine concepts 57
  - Adjuvant
  - Efficacy
  - Effectiveness
  - Herd immunity
  - Characteristics of an ideal preventive vaccine

## 5

**AIDS Vaccine Development 60**

- Basic facts about AIDS vaccine science 61
  - Box: What does the term 'copies of genes' mean? 62
- Types of AIDS vaccine candidates 62
  - DNA vaccines
  - Vector vaccines
  - Subunit vaccines
- Additional concepts related to AIDS vaccine candidates 63
  - 'Prime-boost'
  - Recombination
- Major points in the history of AIDS vaccine research 64
- Status of AIDS vaccine research as of January 2004 65
  - AIDS vaccine trials database
  - Results of the first AIDS vaccine Phase III efficacy trial
- Challenges of AIDS vaccine development 66
  - How to make the vaccine
  - Lack of a known predictive animal model
  - Insufficient knowledge about immune correlates of protection
  - Complexities related to mutation and sub-type
  - Summary box: What challenges does HIV mutation place on vaccine development?
- Organisations involved in AIDS vaccine research 70
  - African AIDS Vaccine Programme (AAVP)
  - AIDS Vaccine Advocacy Coalition (AVAC)
  - AIDS Vaccine Integrated Project (AVIP)
  - Canadian Network for Vaccines and Immunotherapeutics (CANVAC)
  - European Vaccine Effort Against HIV/AIDS (EUROVAC)
  - HIV Vaccine Trials Network (HVTN)/National Institutes of Health (NIH)
  - Institute for Human Virology (IHV)
  - International AIDS Vaccine Initiative (IAVI)
  - Kenya AIDS Vaccine Initiative (KAVI)
  - South Africa AIDS Vaccine Initiative (SAAVI)
  - IAVI at Uganda Vaccine Research Institute (UVRI)
  - US Military HIV Vaccine Research Program (USMHRP)
  - Vaccine Research Center (VRC)

## 6

**Clinical Vaccine Trials 74**

- Definition of 'clinical trial' 75
  - Box: What does 'safety' mean in the context of AIDS vaccine trials?
- Phases of clinical trials 77
  - Phase I
  - Phase II
  - Phase III
- Further studies 78
  - Additional populations
  - Phase IV
- Diagram: Summary of vaccine studies 80

- Box: What are the benefits and risks of participating in an AIDS vaccine trial? 81
- Regulation of clinical vaccine trials 81
- Key vaccine trial concepts 82
  - Placebo
  - Randomisation
  - Blinding
  - Level of efficacy
- Box: Mathematical modelling for efficacy 85
  - Experimental versus licensed vaccines
  - Clinical research versus standard health care

## 7

**Participation in AIDS Vaccine Trials 88**

- General criteria for participation 89
- Flow chart: Steps involved in trial participation 90
- Trial participation process 91
  - Before joining the trial
  - Informed consent
  - The screening visit
  - HIV counselling and testing during the trial
  - Box: Do trial participants get VCT services?
  - Determination of HIV infection at screening
  - The trial vaccine and vaccine administration
  - Blood samples taken during the trial
  - What volunteers receive as part of the trial
  - Falsely testing HIV positive
  - Becoming HIV infected while in the trial
  - Regular daily activities
  - Sexual activity
  - Pregnancy
  - Counselling for sexual partners
  - Study conclusion
- Volunteer protection and confidentiality 96
- Treatment and care for trial volunteers 97

## 8

**Gender Issues in AIDS Vaccine Trials 100**

- The concept of gender 101
- Effect of gender on women's vulnerability to HIV infection 102
- Role of vaccines in reducing women's vulnerability to HIV 103
- Rationale for including women in vaccine trials 104
  - Detecting differences in effect
  - Licensure
  - Ethical issues
- The potential effect of gender on AIDS vaccine trials 105
  - Recruitment and retention
  - Informed consent
  - Confidentiality
  - VCT and counselling
- Strategies for making clinical trials gender equitable and ensuring women's participation 107
  - Preparing the site
  - Involving community groups and women's organisations
  - Developing gender-sensitive guidelines and protocols
  - Gender training for trial team
  - Establishing accountability mechanisms
  - Understanding and addressing barriers to trial participation
- Effect of gender on future access and use of an AIDS vaccine 108
  - Acceptability
  - Social and political environment
  - Strategies for vaccine promotion and delivery

## 9

<b>Ethical Issues in AIDS Vaccine Trials</b>	<b>112</b>
• Primary principles of ethical research	113
• The informed consent process	114
• The informed consent document	115
• Risks versus benefits of participation	115
• Volunteer rights and protection	117
– Confidentiality of volunteer information	
– Right to withdraw at any time	
• Review of trials by an ethics committee	118
• Trial guidelines	118
• UNAIDS guidance document: Ethics of AIDS vaccine research	119

## 10

<b>Review and Approval for AIDS Vaccine Trials</b>	<b>122</b>
• Review groups	123
• Review by a regulatory authority	123
• Review by an independent ethics committee	124
– Who is part of an IEC?	
– Interaction with trial sponsor and investigator	
– Materials reviewed by the IEC	
– How the IEC approves and monitors a trial	
• Ethics and scientific advisory committees	126
• Summary of types of review	127
• Examples of country-specific AIDS vaccine trial approval processes	128
– Kenya	
– Brazil	
• Guidelines for trial regulation and conduct	128
– International Conference on Harmonisation	
– Good Clinical Practice	
– Good Clinical Laboratory Practice	
– Code of Federal Regulations	

## 11

<b>Preparing for Access and Use of an AIDS Vaccine</b>	<b>132</b>
• Conducting AIDS vaccine trials in the developing world	133
• Challenges to introduction, access and use	134
– Challenge 1: Global funding, finance mechanisms, and pricing	
• Box: Tiered pricing: An effective strategy for access	135
– Challenge 2: Acceptability	
• Efficacy	
• Condom migration	
• Product characteristics	
• Stigma and risk perception	
• Myths and rumours	
• Box: Why promote risk reduction education with a vaccine?	138
– Challenge 3: Estimating Demand & Use	
– Challenge 4: Delivery	
– Challenge 5: Regulatory Approval/Licensure	
– Challenge 6: Manufacturing	

<b>Appendix 1: Glossary of AIDS Vaccine Terms</b>	<b>142</b>
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152

<b>Appendix 2: Reference materials list</b>	
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## Objective of the VaxLit Core Content



### **Vaccine Literacy Core Content**

The Core Content contains basic information about AIDS vaccines, 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 and testing, as well as future access and use.

### **Vaccine Literacy Toolkit**

The Vaccine Literacy **Core Content** is one component of the Vaccine Literacy **Toolkit**, and serves as the technical basis for the other components. The Toolkit contains educational and training materials on AIDS vaccines 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 is relevant in resource-poor settings.

The Toolkit (in development as of late 2004) will contain the following components:

- Core Content
- Prototype educational materials
- Training manual
- Electronic presentations based on Core Content chapters

## Audience of Core Content



The Vaccine Literacy Toolkit is targeted to a broad range of stakeholders involved in HIV/AIDS and AIDS vaccine-related work. While all of the Toolkit materials can be adapted for use at the local community level, they are generally written for individuals who work in AIDS-related areas, or who may be familiar with the AIDS vaccine research and development agenda.

The Core Content is meant for use by individuals and organisations that are providing AIDS vaccine-related information and education. It is not meant for distribution to the general public.



Groups that may use this material include, but are not limited to:

- Clinical AIDS vaccine trial site staff
- Non-Governmental Organisation (NGO) staff, to incorporate vaccine messages into their existing work
- Medical professionals or institutions, to provide vaccine information to patients or to incorporate into advocacy efforts
- Voluntary Counselling and Testing (VCT) centers, to provide clients with vaccine information
- Academic or religious leaders, to provide information and/or informed advice to advisees

## Use of the Core Content



The Core Content is designed for multiple uses to serve a variety of needs. For certain audiences, it may be used as reference information, such as background reading for training workshops. It can also be used as a reference document to develop educational materials or tools, or to incorporate AIDS vaccine information into existing tools. Examples include:

- Fact sheets on specific AIDS vaccine topics
- Brochures to be given to potential vaccine trial participants
- Informational videos to be shown in community settings
- Street plays to be performed in community settings
- Radio programmes

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

## Developing Educational Materials



The Core Content provides information that can be incorporated into educational materials and other tools. The development of quality materials requires that certain steps be taken on a formal

or informal basis. The following outlines some basic steps for developing materials.

## ➔ **1 Define audience and aim**

Identify characteristics of the target audience and the aim of the material for that audience:

- Determine what the audience already knows about AIDS vaccines
- Prioritize information needed or primary questions audience has about AIDS vaccines
- Determine appropriate and applicable methods of message delivery (e.g. print material vs. street play or drama)
- Assess audience's ability to read and understand print material, and 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 and design message**

In order to develop and design 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 help focus in on the most relevant messages for your audience.

## ➔ **3 Design the tool**

Production of a print material involves careful design and layout of information and illustrations defined in step #2. The following tips will help produce a quality material:

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

#### ➔ **4 Pretest and revise**

Before materials are finalized, it is advisable to pretest them among the target audience. The audience’s reaction and feedback is then used to revise the material before it is finalized 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. Pretests can be conducted on an individual or group basis. Generally, “open-ended” and “probing” questions are used in pretests.

#### ➔ **5 Print, disseminate, and evaluate**

There are several important considerations for printing materials, including number of copies needed, size and number of pages, number of colours in the material, type of paper.

A careful dissemination plan should be in place for the finalized and produced material. Dissemination should also include evaluation by end-users.

See *Developing Materials on HIV/AIDS/STIs for Low-Literate Audiences*<sup>1</sup> (PATH/FHI), for more detailed guidance on the steps listed above.

### **Additional resources for materials development**



**Documenting and communicating HIV/AIDS Work – a toolkit to support NGOs/CBOs**, International HIV/AIDS Alliance (October 2001).  
<[http://www.aidsalliance.org/\\_res/civil\\_society/technical\\_support/Documentation/Documentation\\_Toolkit\\_Eng.pdf](http://www.aidsalliance.org/_res/civil_society/technical_support/Documentation/Documentation_Toolkit_Eng.pdf)>

O’Sullivan GA, Yonkler JA, Morgan W, and Merritt AP. **A Field Guide to Designing a Health Communication Strategy**, Baltimore, MD: Johns Hopkins Bloomberg School of Public Health/Center for Communication Programmes, March 2003. <<http://www.jhuccp.org/pubs/fg/02/>>

## Acknowledgement of IAVI and materials review



As described, the Core Content is designed primarily as a reference on AIDS vaccines that can be used to develop or adapt materials or messages.

If IAVI has not been involved in production of materials or tools based on the Core Content, no review by IAVI is required. IAVI does request that appropriate acknowledgment of the AIDS Vaccine Literacy Toolkit be given, but the IAVI logo should not be used.

IAVI requests that it be notified of any tools or materials produced, in order that they be added to the Vaccine Literacy Resource Center, which is a public resource serving the entire AIDS vaccine field. Proper credit will be given for all resources included in the Resource Center.

## Navigating the Core Content



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



### **In This Chapter**

A short introduction to the chapter outlining by bullet point, the topics that will be covered in the ‘Key Concepts’ section.



### **Summary Points**

An ‘executive summary’ of the chapter, listing the major facts, which are explained in more depth in the body of the chapter.



### **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 1) 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 on the concepts that are most important to communicate to stakeholder audiences, or on 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**

References to other documents for more in-depth information. In general, the list includes all references used to write the chapter.

**Foot notes** 1 Information is based on *Developing Materials on HIV/AIDS/STIs for Low-Literate Audiences* by PATH/FHI. Please reference for more in-depth information and guidance. Links to this material can be found at <http://www.path.org/materials/materials-areas.php?kc=iec%20materials%20development>

# 1

## Vaccines and the Global Response to HIV/AIDS

**In this chapter** **HIV/AIDS presents one of the worst pandemics the world has seen. This introductory chapter places AIDS vaccines in the context of the AIDS pandemic and the global response to AIDS.**

### **This chapter discusses**

- The HIV/AIDS pandemic
- The effect of the HIV/AIDS pandemic on women and men
- The global response to HIV/AIDS
  - Approaches to prevention
  - Treatment, care and support
  - New technologies: vaccines and microbicides
- The need for a comprehensive prevention-to-care continuum

## Summary points

- 1** The effects of the AIDS pandemic globally are devastating. Sub-Saharan Africa is the region most affected; the epidemic 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** The pandemic has devastated many countries, particularly in the developing world, where the resources to undertake prevention efforts and to provide care to infected people are limited.
- 3** Women are disproportionately affected by the epidemic in many places, probably because of biological vulnerability, gender inequalities and lack of social and economic power.
- 4** Prevention approaches (such as condom promotion) 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, infrastructure, limited treatment options, 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 technologies, now 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 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 HIV/AIDS epidemic.

**1.1**  
**The**  
**HIV/AIDS**  
**pandemic**

**Adults and children estimated to be living with HIV/AIDS, end 2003**

**Global estimates of HIV and AIDS as of end 2003**



Source: UNAIDS 2004 Report on the Global AIDS Epidemic

<b>1</b> <b>North America</b> 1 000 000 (520 000–1 600 000)	<b>2</b> <b>Caribbean</b> 430 000 (270 000–760 000)	<b>3</b> <b>Latin America</b> 1 600 000 (1 200 000–2 100 000)	<b>4</b> <b>Western Europe</b> 580 000 (460 000–730 000)	<b>5</b> <b>North Africa and Middle East</b> 430 000 (270 000–760 000)
<b>6</b> <b>Sub-Saharan Africa</b> 25 million (32.1–27.9 million)	<b>7</b> <b>Eastern Europe and Central Asia</b> 1 300 000 (680 000–1 900 000)	<b>8</b> <b>South and South-East Asia</b> 6 500 000 (4 100 000–9 600 000)	<b>9</b> <b>East Asia</b> 900 000 (450 000–1 500 000)	<b>10</b> <b>Oceania</b> 32 000 (21 000–46 000)

**Total number of adults and children living with HIV: 38 million (35–42)**

Number of people living with HIV

<b>Total</b> <b>37.8</b> million (32.7–39.8)	<b>Adults</b> <b>35.7</b> million (32.7–39.8)	<b>Women</b> <b>17</b> million (15.8–18.8)	<b>Children &lt;15 years</b> <b>2.1</b> million (1.9–2.5)
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**The  
HIV/AIDS  
pandemic**

The Joint United Nations Programme on AIDS (UNAIDS) estimates that globally there were almost 40 million people—36 million adults and 2.1 million children—living with HIV at the end of 2003. Five million new infections and three million deaths occurred in 2003 alone. This brings the cumulative number of people infected with HIV worldwide to over 70 million since the beginning of the epidemic.

The effects of the AIDS pandemic, globally, are devastating. An estimated 95% of the people living with HIV/AIDS are in developing countries where the resources to undertake prevention efforts and to provide care are limited.

Sub-Saharan Africa is the region most affected:

- The region has almost two thirds of the people (25 million) living with HIV/AIDS in the world.
- AIDS is the leading cause of death in the region—approximately 2.2 million people died from complications of AIDS in 2003.
- 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 2003, an average of 7.5–8.5% of the population in these countries was infected, with percentages in countries ranging from 1% to 40%.
- HIV prevalence among women 15–24 years of age is greater than that of men of the same age in sub-Saharan Africa (13 women infected for every 10 men); in South Africa, 20 women are infected for every 10 men; and in Kenya and Mali, 45 women are infected for every 10 men.
- Botswana and Swaziland have the highest HIV prevalence, with close to 40% among adults 15–49 years of age, and in Lesotho, Namibia, South Africa and Zimbabwe, more than 20% of adults 15–49 years of age are infected with HIV.
- In Kenya, approximately 700 people become infected with HIV daily and over 2.6 million Kenyans were already infected by 2002.
- In South Africa, as of 2002, an estimated 600–1,000 South Africans die every day from AIDS-related complications.

- Uganda has shown evidence of significant declines in HIV prevalence and incidence, mainly due to behavioural changes. Prevalence, which had been as high as 30% among pregnant women in Kampala, is now 8% in Kampala and is below 10% throughout most of the country. As of 2004, no other country has matched this achievement.

The epidemic is now growing rapidly in other regions of the world, including parts of Eastern Europe and Central Asia; newer epidemics are emerging in China, Indonesia, Papua New Guinea, Vietnam, several Central Asian Republics, the Baltic States and North Africa.

The epidemic is growing rapidly in the Asia and Pacific region. Although in Asia national prevalence rates may seem low, the national rates may obscure serious epidemics that are emerging in some states and provinces. 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 has an HIV prevalence rate of between 0.4% and 1.3%, it had approximately 4 million (3.82–4.58 million) people living with HIV/AIDS nationally by the end of 2002 and at least 300,000 new cases in 2003.
- Serious epidemics are underway in several Indian states, although this may not be apparent from national statistics.
- Three Asian countries are already contending with serious nationwide epidemics: Cambodia (3%), Myanmar (1–2%) and Thailand (2%).
- It is estimated that the number of people with HIV/AIDS in Asia may grow larger than the total in Sub-Saharan Africa before 2010.

The AIDS epidemic has already devastated many countries, communities and families, affecting political, social and economic structures, particularly in the developing world. The effect of the epidemic is reversing many of the hard-won gains in development of 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.



**The epidemic is constantly changing throughout the world, and statistics will vary from year to year. For current statistics, please visit the UNAIDS website <<http://www.unaids.org/en/default.asp>>.**

### **Women, men and the HIV/AIDS pandemic**

The ratio of women to men living with HIV/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 57% of all infections in the region. Younger women, in particular, seem to be more vulnerable than men of their same age. Among those 15–24 years of age in sub-Saharan Africa, women are 2.5 times more likely to be infected than their male counterparts.

Women are disproportionately affected, probably because of greater biological vulnerability (HIV may pass more easily from a man to a woman than from a woman to a man). 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.

### **The global response to HIV/AIDS**

A range of interventions has been used to address the 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 the prevention of sexual transmission of HIV have relied thus far on limited available technologies: male condoms and female condoms. Research to develop new prevention technologies (vaccines and microbicides) is underway and progress has been made, but it is likely to be some time before these new technologies are available. HIV/AIDS-related treatment, including treatment for opportunistic infections and antiretrovirals (ARVs) for HIV infection itself, have had a dramatic role in decreasing AIDS death rates in places where medications have been economically accessible. The developing world is only just beginning to obtain access to ARVs. Other approaches for addressing the epidemic include care and support; stigma reduction; community education and mobilisation; 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 synergistically as components of a comprehensive response to the epidemic.



**We're losing three million people a year. Treatment will slow, but not eliminate the carnage. There are 14,000 new infections daily. 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, UN Secretary General's Special Envoy on HIV/AIDS in Africa

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### **Prevention approaches**

Despite the devastating effect of the 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 90% 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 cultural practices
- Management of sexually transmitted infections (STIs)

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 large 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
- Needle/syringe exchange for illicit drug use
- Prevention of mother-to-child transmission (PMTCT) (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 certain contexts. In particular, blood safety and the use of ARVs for PMTCT clearly reduce the risk of transmission. Despite these successes in prevention efforts, more than 20 years into the 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 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 continue to strengthen these existing prevention approaches while developing new prevention approaches and technologies, such as vaccines and microbicides, alongside them.

## **Treatment, care and support**

Treatments available for people living with HIV/AIDS 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. Until recently, these drugs were unaffordable for most people in resource-poor settings, but prices have come down significantly over the past several years.

ARVs are becoming increasingly available in developing countries because of community mobilisation and activism, recent 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 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 few people have access to free or low-cost drugs so far.
- *Infrastructure* – The infrastructure and the public health systems needed to ensure access to treatment and delivery of care are not yet in place in many resource-poor 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 in some patients of virus that is resistant to certain drugs.
- *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.

Care and support for people with HIV/AIDS at the community level has become an important component of HIV/AIDS 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/AIDS, medically, economically and socially, and to care for orphaned children.

### **New technologies: vaccines and microbicides**

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 or microbicide will be available, but both are likely to be important in HIV/AIDS prevention in the future. These new technologies will work together with other prevention, treatment and care approaches and alongside strategies to build health infrastructure and capacity to shift social norms and to address constraints on access to services, all forming part of the global effort to confront the AIDS epidemic.

Vaccines and microbicides, if proven effective, might both be important means of reducing women's vulnerability because it may be possible to use them without a partner's cooperation. Vaccines may 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 technologies now available. Both methods can potentially be used without a partner's knowledge in cases in which informing a partner would place the woman at risk of infection, violence or other consequences.

**Vaccines**— An AIDS vaccine is critical for stopping the AIDS epidemic. An effective AIDS vaccine is a substance that would be introduced into the body (usually by injection or orally) to stimulate the body's immune system to prevent or control HIV infection. Many vaccine candidates are being developed and tested, but none has yet been proven efficacious or is available for use outside of these studies.

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 is on the brink of being eradicated soon, also through immunization. When combined with existing prevention and treatment options, a vaccine is one of the best hopes for halting the epidemic.

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 development of 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 can at least initiate, if not control, and that possibly could be used without a partner's cooperation. There are many microbicide candidates now in various stages of development and testing, but it will probably require years of testing in animals and people before they can be proven safe and effective.

**The need for a comprehensive prevention -to-care continuum**

The availability of a vaccine or a microbicide will not eliminate the need for treatment and other prevention strategies. Treatment will be needed for those who are infected with HIV, and a range of prevention strategies, including vaccines and microbicides, is needed for those who are not infected. It is possible that the first vaccines and microbicides to become available will be only partially effective (see **Chapters 6** and **11** for a full explanation of partial **effectiveness/efficacy**), so it will be important to continue with other behaviour-change and risk-reduction efforts to ensure the success of a vaccine or a microbicide. People have different needs and preferences. Having a range of prevention tools and options, such as vaccines, microbicides or condoms, that can be used together can maximize 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 epidemic than a focus on any particular approach. This is often referred to as a comprehensive prevention-to-care continuum.



**Key messages**

pertaining  
to AIDS  
vaccines

**HIV/AIDS is one of the worst epidemics the world has ever seen. An AIDS vaccine, once developed, will have a major part 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/AIDS must be comprehensive and should include existing behavioural prevention strategies; new technologies, including vaccines and microbicides, once they are available; and treatment and care for those already infected.**

**For further information**

**Developing Vaccines to Prevent HIV and AIDS: An introduction for community groups 2nd edn** <<http://www.icaso.org/icaso/vaccines/Vaccine%20Primer,%202nd%20Edition-2002-web.pdf>>.

**Global Campaign for Microbicides** <[www.global-campaign.org](http://www.global-campaign.org)>.

**International Partnership for Microbicides** <[www.ipm-microbicides.org](http://www.ipm-microbicides.org)>.

**UNAIDS, and UNAIDS Best Practices Collection. AIDS Epidemic Update.** <[www.unaids.org](http://www.unaids.org)> (December 2003).

# 2

## Building a Supportive Environment for AIDS Vaccines

**In this chapter** **AIDS vaccine research is an important component of the global response to the AIDS epidemic.**

**Vaccine research is not only a scientific pursuit, however. It is also important to involve and 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 developing countries
- Country advocate and stakeholder groups
- Role of in-country stakeholder groups
- Influence of stakeholder support on trial recruitment

## Summary points

- 1** The conduct of AIDS vaccine trials in developing countries often raises valid concerns from the developing countries' perspectives.
- 2** AIDS vaccine trials cannot be conducted without making country stakeholders integral partners in the efforts.
- 3** In-country stakeholders include policy makers, nongovernmental organisations (NGOs) and 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.
- 4** Building support at the country level means raising levels of awareness and education so people are familiar with the idea of AIDS vaccines and the clinical trials that are conducted; in-country advocates and stakeholders can also be strong allies in increasing willingness of community members to learn more and consider volunteering for trials.
- 5** Advocates should be well versed in the work carried out in their own countries (and elsewhere), to manage expectations, fears and/or misconceptions about the research.

## Key concepts



### Conducting AIDS vaccine research in developing countries

It is important that AIDS vaccine candidates be tested in countries that are hard hit by the epidemic. The best way to know if a vaccine will be safe and efficacious in a particular population is to include that population in vaccine research and development from the beginning.

Although researchers aim to develop a vaccine that will be used worldwide, it is still unknown whether this goal is achievable. The most ideal goal is to design one vaccine that will protect against all HIV **subtypes**, but several different vaccines may need to be designed to protect against different subtypes (see **Chapter 5** for more information about subtype). In this case, the vaccines should be tested in areas where those subtypes are common.



## **Is subtype important in deciding where an AIDS vaccine should be tested?**

It is important to note that 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 where different subtypes are common.

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Conducting AIDS vaccine research in developing countries may raise concerns by some individuals or groups about the motivations behind such research and whether the trials would be beneficial or harmful to their country or community. To counter any false impressions, it is important to work closely with communities and stakeholder groups and to emphasize 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 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. 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.

Many in-country researchers, government leaders, nongovernmental organisations (NGOs) and other community groups have created strong partnerships with trial sponsors and other researchers to ensure sound conduct of trials in their countries. The partnership is a major benefit for trial sponsors because in-country partners have specific knowledge about local circumstances that can greatly ease trial conduct. Specific benefits of such partnerships include the following:

- Communities benefit from increased knowledge around AIDS vaccines, AIDS vaccine research and issues associated with AIDS vaccine trials.
- In-country researchers, investigators, site teams and other groups who become involved are an integral part of the research and development effort.
- Trial sponsors from developed countries work to ensure that training and transfer of knowledge is a part of the process of conducting a trial and will help leave the community better off than it was before the trial began by doing the following:
  - Improving health care infrastructure
  - Building laboratory capacity
  - Building capacity of regulatory review systems
  - Building skills of in-country scientists and other professionals, trial site teams, NGOs and other groups that may join in the research effort
- Communities in which trials are conducted will most likely be prioritised to receive the vaccine that is being tested, if it is proven safe and efficacious after all phases of testing are completed.

It is also important to remember that communities hardest hit by the epidemic have many needs, some of which are much more immediate than vaccine research. It is important that vaccine research 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 technologies.

**Country  
advocate and  
stakeholder  
groups**

**NGOs, CBOs and FBOs**

Leaders of NGOs, community-based organisations (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. To gain their support and seek their advice, trial site teams should reach out to these groups to inform them about clinical vaccine trial design and procedures and should 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 communication in local languages, building and sustaining community interest, dispelling myths about vaccines and trials and managing expectations. They can facilitate community participation, ensure 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 prevention education, media work and translations.

### **Parliamentarians, policymakers and ministries of health**

Policymakers have important roles 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 be made partners at a very early stage in planning for trials and eventual 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 provided a long-standing commitment to and strong support for AIDS vaccine development. The Ministry of Public Health plays a large 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 establishing and providing a major source of funding for the South African AIDS Vaccine Initiative (SAAVI), an organisation that coordinates the research, development and testing of HIV/AIDS vaccines in South Africa.
- 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 for over a decade. 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. Researchers 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 AIDS, AIDS vaccines and clinical trial participation. In communities in which trials are being conducted, it is 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. They also have influential power in shaping opinions, as they are often well respected by community members. 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 (US) and Europe demanded that researchers and regulatory authorities move more quickly to find medications to fight HIV. Some of these activists educated themselves about scientific research and HIV and demanded that they have an opportunity to comment on trial proposals. Through protests, letter-writing and lobbying the US government, activists succeeded in changing the US drug approval process. This activity also led to the formation of Community Advisory Boards (CABs) composed of nonscientists who review protocols, monitor trials and help educate and inform the rest of the community.

CABs were well established in the US by the early 1990s and were involved in some of the initial US HIV vaccine work. Some of the first CABs, especially in the US, were made up mostly of people living with HIV and AIDS, and in some communities this is still the case. Now, CABs are made up of leaders and other individuals representing various parts of the community, such as religious groups, schools or universities, media and NGOs/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 in both developed and developing countries. They are generally made up of no more than 20 people who serve as primary liaisons between the community and the trial researchers. Often a senior scientist or physician and/or other 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
- Support for volunteer recruitment by disseminating information about the trial
- 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 committee) for participants' rights
- Representation 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. As the CAB acts as a liaison between the researchers and the community, researchers may hold consultations with CABs about an upcoming 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 in the community.

**AIDS vaccine  
education  
in advance  
of trials**

Country and community stakeholders play a primary role in providing education to various audiences on both a national and a local level. 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/AIDS issues as a basis for AIDS vaccine education. Some trial site 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/AIDS knowledge, including understanding of and access to voluntary counselling and testing (VCT), before addressing more complex issues of clinical research and the specifics of AIDS vaccines.

Stakeholder groups can play a role in AIDS vaccine education beyond the trial site community by doing the following:

- *Integrating knowledge about vaccine development into HIV/AIDS prevention messages* – Vaccine development should be viewed as one part of a broader HIV/AIDS prevention effort. Where appropriate, existing community outreach networks should be used to discuss HIV vaccine development.
- *Assessing and shaping current attitudes and awareness about AIDS vaccines* – They can discuss AIDS vaccines with people, helping them understand the part vaccines might have in controlling HIV/AIDS 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, policy makers, 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 vaccines.
- *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/AIDS prevention and care networks and trial sites, and publishing in newsletters and on websites are good ways to share information. It is important to make sure that local media are well informed about vaccines.

**The role of advocates and stakeholders in the trial site community**

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 are 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 vaccines
- Helping to lay the foundation for access to and delivery of a vaccine once available

Community leaders can help educate potential trial participants about the trial. They can also educate the trial site 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 to 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.

**Mobilising volunteers**

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 HIV/AIDS and vaccine research, and they must be motivated to seek VCT to learn their HIV status (see box).

**VCT services:** To enter into an AIDS vaccine trial, an individual must know his or her HIV status. Voluntary counselling and testing (VCT) can be a primary entry point into vaccine trials.

**Key entry point and support for AIDS vaccine trials** The presence of high-quality VCT services in the area surrounding an HIV vaccine trial site can be helpful in several ways. It may help ‘off-load’ demand at the trial site, as the trial site might become extremely overwhelmed if it is the only place people can get HIV counselling and testing. Also, it may prevent people from coming to the trial site only to obtain counselling and testing services—something the site is not intended for.

Ensuring that the community around a trial site has access to and accepts VCT services will help minimize stigma and provide a large pool of potential volunteers who already know their status. Even where high-quality services exist and treatment for HIV-infected people is available, stigma and fear of HIV can be major barriers to VCT. Stakeholder groups can help improve access to VCT by reducing fear and stigma and helping individuals recognize the benefits of knowing their status, receiving risk-reduction counselling and accessing medical services if they are HIV infected. Certain vaccine trial stakeholder groups may also help establish VCT services.

See **Chapter 7** for more information on voluntary HIV counselling and testing in the context of vaccine trials.

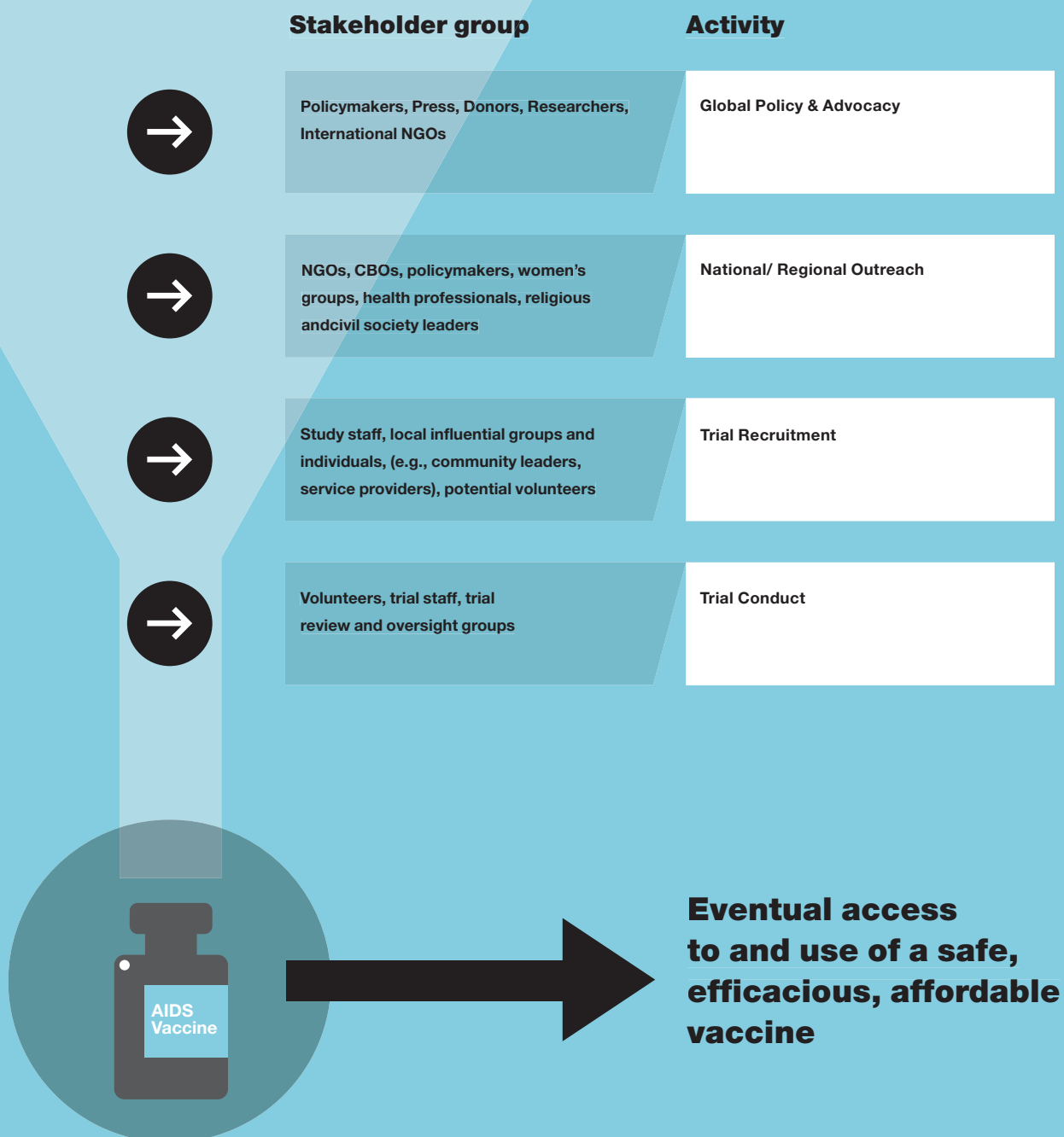
NGOs, CBOs, the media and government programmes working in the area of HIV/AIDS can be strong allies in helping to mobilise volunteers. These partners can help to assess and shape attitudes and awareness about AIDS vaccines, help people understand the role vaccines might have in controlling the epidemic 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.

## 2.1 Stakeholder funnel

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.

Source: IAVI



## 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 global/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.



Source: IAVI

**Managing expectations** 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 a highly efficacious vaccine will become available quickly after the trial is over. However, if the vaccine 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 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 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(s) being tested in their particular country, as well as about the global picture of AIDS vaccine research. This information will help people understand the ‘big picture’ of AIDS vaccine research as well as the important lessons that will be learned from individual trials.

**Key messages that will help in managing expectations include the following:**

- **AIDS vaccine research is a very slow process; research has been going on since the mid-1980s and will likely continue for another 10 years or more (after 2004).**
- **Many different types of vaccines are being tested around the world; researchers do not know yet 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 an AIDS vaccine (or vaccines) is (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 one has gone all the way to the Phase III trial stage (see Chapter 5); even when the results of a trial indicate that a vaccine candidate does not to protect against HIV infection, this does NOT mean that the trial was a failure. No matter what the outcome is, important lessons are learned from any trial; even learning that the particular vaccine does not work helps scientists decide which research to do next.**
- **If the history of vaccines for other diseases and for AIDS 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**

pertaining  
to AIDS  
vaccines

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 so that they become allies. It is their 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.

Communities in which 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/AIDS prevention and care.

There are very important reasons to conduct AIDS vaccine research in the developing world, 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.

**For further information**

AIDS Vaccine Advocacy Coalition (AVAC) Report 2004: AIDS Vaccine Trials – Getting the Global House in Order <[http://avac.org/pdf/reports/2004AVACReport\\_High.pdf](http://avac.org/pdf/reports/2004AVACReport_High.pdf)> (May 2004).

AIDS Vaccine Handbook: Global Perspectives. Second Edition, the AIDS Vaccine Advocacy Coalition (AVAC). Edited by Patricia Kahn, 2004. <<http://www.avac.org/primer.htm>>.

Developing Vaccines to Prevent HIV and AIDS: An Introduction for Community Groups 2nd edition <<http://www.icaso.org/icaso/vaccines/Vaccine%20Primer,%202nd%20Edition-2002-web.pdf>>.

Public health considerations for the use of a first generation HIV vaccine. Report from a WHO-UNAIDS-CDC Consultation, Geneva, 20–21 November 2002. AIDS 17, W1–W10 (2003).

# 3

## The Immune System and HIV/AIDS

**In this chapter** **This chapter describes the immune system in relation to HIV/AIDS and AIDS vaccines. It is not meant to be a comprehensive overview of immunology.**

### **This chapter discusses**

- Types of immune response
- Key components of the immune system, defined
- The immune system as it relates to HIV/AIDS

## Summary points

- 1** The immune system is the set of organs, tissues, and cells that 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 CTLs); 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**, 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.

## Key immune concepts and how they relate to HIV

Concepts	Explanation/definition	Relation to HIV
<b>Immune system</b>	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 pathogens.	<p>HIV damages the immune system, the very system that should defend the body against HIV.</p> <p>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.</p> <p>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’.</p>
<b>Pathogen</b>	Foreign, harmful organisms that cause disease in the human body; the most common pathogens are viruses, bacteria and parasites such as worms.	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).
<b>Opportunistic infections (OIs)</b>	Illnesses, caused by various organisms, which occur less frequently or less severely in people with healthy immune systems.	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 get sick 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.

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

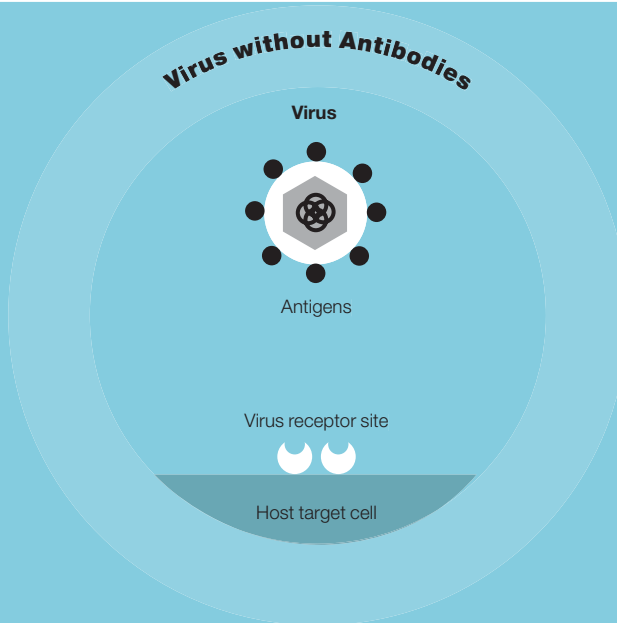
Concepts	Explanation/definition	Relation to HIV
		Pneumocystis pneumonia (PCP) and thrush are examples of common opportunistic infections. Other infectious diseases may be more serious in HIV-infected people, such as tuberculosis or genital herpes.
<b>Immune response</b>	When a pathogen enters the body, the immune system's first responders ( <b>macrophages</b> and <b>dendritic cells</b> ) pick up the invader, package some of its components or pieces (called <b>antigens</b> ) and present these parts on their outer surfaces, so that other immune cells ( <b>lymphocytes</b> ) can 'see' the pathogen and respond against it.	<p>HIV has many ways of avoiding the immune response.</p> <p>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.</p> <p>It is also capable of 'escaping' from immune cells that are designed to attack it by changing certain aspects of its form.</p> <p>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.</p> <p>These are some reasons why it is so difficult to develop an effective HIV/AIDS vaccine.</p>
<b>Antigen</b>	A piece or fragment of a pathogen (usually a protein) that is taken up and changed, or 'processed', by certain immune cells and parts of it presented to the rest of the immune system so that it can make an immune response.	<p>The immune system responds to many different parts of HIV. HIV is capable of changing some of these parts to avoid immune responses, sometimes referred to as "immune evasion".</p> <p>One key challenge for AIDS vaccine design is to identify the best possible antigens that will stimulate strong defences against HIV. Some of the HIV antigens used in AIDS vaccines are gp120, p24, gag, pol and nef.</p>
<b>Macrophages/ Dendritic cells/ Phagocytes</b>	These are the cells that look out for pathogens. When they encounter a pathogen, they alert other immune cells. Macrophages can also act as <b>antigen-presenting cells</b> (APCs).	Dendritic cells and macrophages are thought to have a key role in the early stages of HIV infection.

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

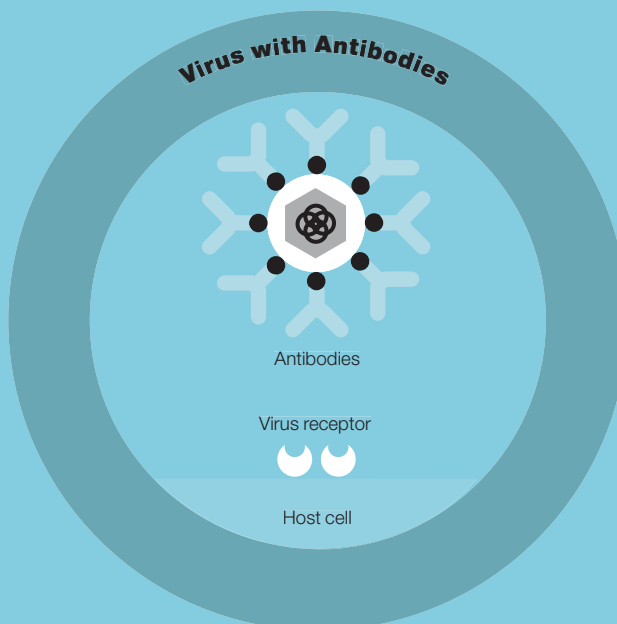
Concepts	Explanation/definition	Relation to HIV
<b>Antigen-presenting cells</b>	<p>APCs engulf the antigens and process them, and present the antigens on their own outer surface in a way that can be 'seen' by other immune cells called <b>lymphocytes</b>. This process stimulates the lymphocytes to function. Immune cells that act as APCs:</p> <ul style="list-style-type: none"> <li>• B cells (see below)</li> <li>• Macrophages</li> <li>• Dendritic cells</li> </ul>	<p>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.</p>
<b>Lymphocytes</b>	<p>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 <b>T cells</b> and <b>B cells</b>.</p>	<p>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.</p>
<b>T cells</b>	<p>T cells are the immune cells that can recognize 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: <b>CD4+ lymphocytes</b> and <b>CD8+ lymphocytes</b>.</p>	<p>HIV needs to be inside (or infect) human cells to make more copies of itself. T cells can recognize and attack these infected cells.</p> <p>CD4+ T cells are also vulnerable to HIV infection, as they are primary targets of HIV.</p>
<b>CD4+ cells</b>	<p>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'.</p>	<p>HIV prefers to attack and kill 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.</p>
<b>CD8+ cells</b>	<p>These T cells kill cells or slow down activity of cells that have been infected with the pathogen; therefore, they are called <b>cytotoxic T lymphocytes</b> (CTLs) or 'killer T cells'. They do this through 'cytotoxic' activity, a process that kills the infected cell.</p>	<p>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.</p>
<b>B cell</b>	<p>The B cell response fights the pathogens that have not yet infected a human cell.</p> <p>B cells direct the production of <b>antibodies</b>, 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.</p>	<p>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.</p>

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

Concepts	Explanation/definition	Relation to HIV
<b>Plasma B cell</b>	These cells will produce the <i>antibody</i> that is specifically shaped to fit with the antigen.	
<b>Antibody</b>	Antibodies are proteins dissolved in serum or lymph fluid that 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.	<p>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 (neutralize it) but many antibodies are not protective.</p> <p>Once a person has been infected with HIV, that person's immune system will make antibodies against HIV, to protect against disease.<sup>1</sup> A common way of diagnosing 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'.</p>
<b>Memory B cells and memory T cells</b>	<p>Helper T cells, killer T cells and plasma B cells form responses to many infections, such as chickenpox, tuberculosis or malaria (previously explained). Once the individual has recovered from the infection, a small population of <i>memory T cells and memory B cells</i> remains; these cells can quickly start a response if the pathogen ever returns.</p> <p>Memory cells 'remember' the pathogen and are prepared start an appropriate response more quickly and more vigorously the next time the body encounters the same pathogen.</p>	<p>It is not known how important memory cells are in the course of HIV disease.</p> <p>AIDS vaccines 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.</p>



This diagram shows a virus and a host target cell the virus will try to infect. The circular structures on outer surface of the virus are antigens. The virus infects the host when the antigens lock into the virus receptor site on the host target cell.



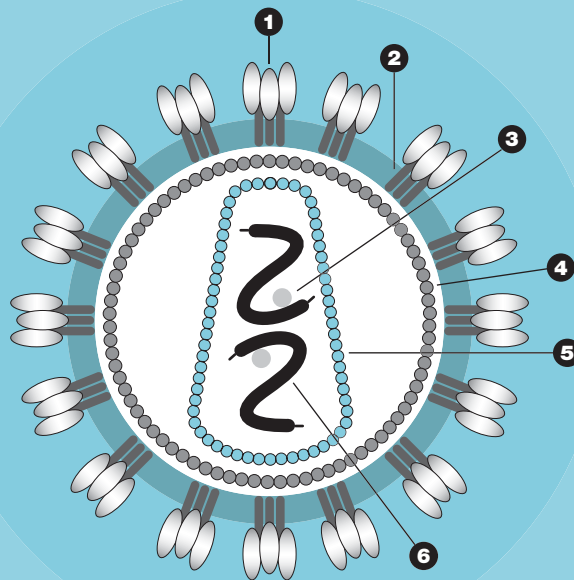
This diagram shows antibodies, represented by the Y-shaped structures. The antibodies have locked onto the virus antigens, coating the outer surface of the virus. This makes it impossible for the virus antigens to lock into the virus receptors on the host cell. Therefore, the virus cannot infect the host.

### How this relates to HIV

When an antibody protects a host cell from infection by a virus, it is sometimes referred to as a 'neutralizing antibody' because it neutralizes the effect of the virus. Neutralizing antibodies against HIV, those that will protect the host cell from HIV infection, have been very hard to identify by scientists.



## Structure of HIV



Source: Adapted from NAID

- 1** gp 120 glycoprotein
- 2** gp41 glycoprotein
- 3** Reverse transcriptase
- 4** p17 protein
- 5** p24 protein
- 6** Viral RNA

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**Definition of terms**


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- **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
-

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**Key  
messages**

pertaining  
to AIDS  
vaccines

**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 disease after infection.**

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**For  
further  
information**

Djomand, G., Peiperl, L. & Keefer, M. Introduction to HVTN Vaccine Portfolio for Non-Scientists. Online PowerPoint presentation from HVTN. <[http://www.hvtn.org/pdf/community/Non-ScientistsPres\\_FGM.ppt](http://www.hvtn.org/pdf/community/Non-ScientistsPres_FGM.ppt)> (2001).

Essential Medical Immunology <<http://www.roitt.com>>.

International Council of AIDS Service Organisations. The Science of HIV/AIDS: An introduction for community groups <<http://www.icaso.org/icaso/vaccines/Science%20Primer%20-%20E%20-%20Web.pdf>>.

Kuby, J. Immunology, fourth edition (W.H. Freeman and Company, New York, 2000).

NIH HIV Vaccine Glossary <<http://www.niaid.nih.gov/factsheets/GLOSSARY.htm>>.

NIH Publication 03-5423. Understanding the Immune System, How it Works (US Department of Health and Human Services, National Institute of Allergy and Infectious Diseases) <[http://www.niaid.nih.gov/publications/immune/the\\_immune\\_system.pdf](http://www.niaid.nih.gov/publications/immune/the_immune_system.pdf)>.

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**Foot notes**

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”.



A

# 4

## Vaccines

**In this chapter** **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 discusses**

- Definition of 'vaccine'
- How preventive vaccines work
- Idea 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 one specific disease or 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 ‘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 (intra-dermal or subcutaneous); by application to the skin (transdermal); by application to the inside of the nose (nasal); or by being swallowed (oral).

Vaccines are used to prevent many diseases in humans (and in animals). A few examples are polio, tetanus and measles vaccines, but there are many others. Each vaccine protects only 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. 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/AIDS.**

- How preventive vaccines work**
- The following steps outline how a preventive vaccine protects an individual from infection or disease:
- 1** The vaccine introduces a small piece or a non-harmful form of the pathogen into the body. This is called the foreign antigen ('foreign' indicates that it is not from the person's own body).
  - 2** The immune system in the body produces an immune response to the pathogen by making antibodies, killer cells or both.
  - 3** The immune system has memory B cells (producing antibodies) and memory T cells (helping the production of antibodies or killer T cells) (see **Chapter 3**). The next time the real pathogen is encountered, the immune system remembers it and mounts a much larger and quicker response than it would have if the person had never received the vaccine. This is called 'immune memory'.
  - 4** This larger and quicker immune response can act in several ways to fight infection and/or disease:
    - By stopping replication of the pathogen, so it cannot infect more cells
    - By producing antibodies that attach to the pathogen, rendering it harmless (antibody response)
    - By producing immune cells that attack and kill other cells that have been infected with the pathogen (killer cell response)

**Preventive versus therapeutic vaccines**

Preventive vaccines are the traditional type of vaccine, defined above. They are intended for people who have not yet been infected. 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 now marketed throughout the world are preventive vaccines, although a few can work if given immediately after exposure (such as a rabies vaccine given right after a dog bite or a tetanus 'booster' vaccine given after a wound, provided that the patient has been vaccinated before and has immune memory). 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 would be to start an immune response after a person has been infected with HIV; this would be called a therapeutic, or 'treatment', vaccine. Right now, there is no HIV vaccine that works this way, although some scientists are trying to develop one. Scientists are also trying to develop therapeutic vaccines for cancer.

**Common vaccine types** There are many ways to design vaccines, each of which uses a different approach to produce a response from the immune system. The table below 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.

### Common vaccine types

Vaccine type	General description	Relation to AIDS vaccine
<b>Whole-killed/ Whole-inactivated vaccines</b>	<ul style="list-style-type: none"> <li>• Uses the entire pathogen to stimulate an immune response</li> <li>• Pathogen is killed or is made inactive so that it is not alive and cannot cause infection</li> <li>• Vaccine causes the body to make an immune response that will protect against a live pathogen</li> </ul> <p>Examples: injectable polio vaccine (Salk), cholera vaccine, injectable influenza vaccine</p>	<p>Whole-killed vaccines are not being tested in clinical trials as preventive AIDS vaccines.</p>
<b>Live attenuated vaccines</b>	<ul style="list-style-type: none"> <li>• Uses a weakened form of the pathogen</li> <li>• Pathogen is changed in a particular way so it will not be harmful</li> <li>• Introduction of this form of the pathogen into a human will mimic true infection (without causing disease) and will enable the body to produce an immune response</li> </ul> <p>Examples: measles vaccine, oral polio vaccine (Sabin), intranasal live influenza vaccine</p>	<p>Live attenuated vaccines are not currently being developed for use in humans because of safety concerns.</p> <p>Scientists have studied live attenuated vaccines against HIV in animals, where they show high levels of protection. These studies are helping scientists understand the mechanism of protection provided by live attenuated HIV vaccines. Once they fully understand the mechanism, they will try to develop vaccine strategies that produce similar results and are also safe for use in humans.</p> <p>There are no current plans to test a live attenuated HIV vaccine in human trials.</p>

## Common vaccine types (continued)

Vaccine type	General description	Relation to AIDS vaccine
<b>Subunit vaccines</b>	<ul style="list-style-type: none"> <li>• Most subunit vaccines contain a small protein or piece of the pathogen; the protein acts as the foreign antigen (see <b>Chapter 3</b>), which will start the immune response</li> <li>• B cells of the immune system will produce antibodies against the antigen</li> <li>• Antibodies lock on to the antigen/protein of the pathogen</li> <li>• When the entire pathogen enters the body, the antibodies will attach to the proteins on the outer shell of the pathogen, coating it and making it harmless, or 'neutralizing' it</li> <li>• Certain subunit vaccines are made from smaller pieces of proteins called peptides</li> </ul> <p>Examples: hepatitis B vaccine, tetanus toxoid</p>	<p>The first AIDS vaccines developed and tested were designed using the subunit concept. The first AIDS vaccine to go through complete testing in humans, the AIDSVAX gp120 vaccine, was a subunit vaccine (see <b>Chapter 5</b>).</p> <p>This vaccine failed to protect against HIV infection in an efficacy trial, which is one of the reasons scientists are working to discover better vaccine concepts.</p>
<b>DNA vaccines</b>	<ul style="list-style-type: none"> <li>• 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)</li> <li>• Genes enter into human cells and use the cell's 'equipment' to produce some protein(s) of the pathogen encoded by the gene(s)</li> <li>• When the protein is produced, the immune system sees it as a foreign or harmful antigen and produces an immune response</li> <li>• The immune system remembers this response, which will prepare a response against the whole pathogen</li> </ul>	<p>This is a common strategy being used for AIDS vaccine development, and many of the current AIDS vaccine candidates are DNA vaccines (see <b>Chapter 5</b>).</p> <p>DNA vaccines will not cause HIV infection, because the vaccines do not contain all the genes of the live pathogen.</p>
<b>Recombinant vector vaccines</b>	<ul style="list-style-type: none"> <li>• Use same strategy as DNA vaccines, but the genes are carried by a harmless or very weakened bacterium or virus, called a <b>vector</b></li> <li>• Genes are attached to the DNA of the vector, carrying the genes into the human cell</li> <li>• Once in the human cell, genes produce protein(s) to which the body</li> </ul>	<p>This is a common strategy being used for AIDS vaccine development, and many of the current AIDS vaccine candidates are vector vaccines (see <b>Chapter 5</b>).</p> <p>Recombinant vector vaccines will not cause HIV infection because it contains copies of only one or several HIV genes, not all of them. Many scientists believe that the addition of a vector will allow the vaccine to be more effective in creating an immune response than a DNA vaccine alone.</p>



**Additional Adjuvant**

**vaccine concepts** 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 Phase III clinical trial conditions.

Efficacy is shown by comparing the rate of infection or disease in the vaccine group to that in a **placebo** group<sup>1</sup> (see **Chapter 6**). This is done by monitoring infection and disease in the two trial groups for a long period of time. In the case of HIV vaccine trials, it will take about 2–4 years. If the vaccine group has less infection or disease, the vaccine is said to have efficacy or to be efficacious. No vaccine is 100% protective. Some vaccines, like the hepatitis B vaccine, have an efficacy of over 95% if all three injections are received, and this protection can last for up to 10 years. Some vaccines do not protect as many people against disease but may still be able to stop epidemics. People who are vaccinated may be less likely to pass on the infectious organism to others, so protection can be greater for the group.

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, malnutrition, etc. It also is important to find out how long the protection lasts (see **Chapter 6**).

**Effectiveness**

**Effectiveness** describes how well the 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 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.

**Characteristics  
of an ideal  
preventive  
vaccine**

**Safe – does not cause any serious side effects (for example, fever, headache, soreness at injection site)**

**Efficacious – must show that people who are vaccinated have significantly less infections or disease**

**Available – should be able to be produced in large quantities and be deliverable to everyone who needs it**

**Effective – must decrease the disease in the general population**

**Stable – can last for a long time in various conditions or environments**

**Accessible – should effectively reach the populations in need quickly and easily**

**Affordable – should be affordable by governments or individuals who need it most**

## Key messages

pertaining  
to AIDS  
vaccines

Traditionally, vaccines are made to prevent healthy people from getting infection or disease; this is also the goal in developing a preventive AIDS vaccine.

No existing vaccine works on all people 100% 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 not eliminate the risk of HIV infection. Even after people receive the vaccine, they will still need to take other prevention precautions (such as using condoms and microbicides).

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 vaccines. Using these techniques, there is no chance that an AIDS vaccine will cause HIV infection.

## For further information

HIV Preventive Vaccine Fact Sheet (US Department of Health and Human Services, National Institute of Allergy and Infectious Diseases) <<http://www.aidsinfo.nih.gov/other/whatisvac.pdf>> (March 2003).

International Council of AIDS Service Organisations. The Science of HIV/AIDS: An introduction for community groups <<http://www.icaso.org/icaso/vaccines/Science%20Primer%20-%20E%20-%20Web.pdf>>.

NIH HIV vaccine glossary <<http://www.niaid.nih.gov/factsheets/GLOSSARY.htm>>.

NIH Publication 03-4219. Understanding Vaccines, What They Are, How They Work (US Department of Health and Human Services, National Institute of Allergy and Infectious Diseases) <<http://www.niaid.nih.gov/publications/vaccine/pdf/undvacc.pdf>>.

Vaccines 4th edn (eds Plotkin, S.A. & Orenstein, W.A.) (WB Saunders, 2004).

Vaccine Concepts and Designs, NIAID Division of HIV Vaccine Site, Feb 2003 <<http://www.niaid.nih.gov/daids/vaccine/concepts.htm>>

### Foot notes

1 In HIV vaccine trials, all participants receive continuous counselling to reduce their risk for HIV infection; despite this, some participants will inevitably become infected through blood or sexual exposure. The experimental vaccine itself cannot cause or transmit HIV infection.

# 5

## AIDS Vaccine Development

**In this chapter** **A vaccine is the best way to stop an epidemic. With the exception of clean drinking water, no other effort has the effect that vaccination has had on reducing infectious diseases. Overall, it is the most cost-effective way to improve public health.**

**Given the extent and severity of the HIV/AIDS epidemic, the world urgently needs an AIDS vaccine. AIDS vaccine research started in the 1980s and is now underway worldwide. As of 2004, most experts agree that the development of an effective AIDS vaccine will require many more years of work.**

### **This chapter discusses**

- Basic facts on 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** No vaccine has yet been proven to prevent HIV/AIDS.
- 2** Many experimental vaccines for preventing HIV/AIDS are being developed and tested; they involve new vaccine ideas such as recombinant DNA, recombinant vectors and subunits (copies of parts of the HIV virus).
- 3** As of 2004, AIDS vaccine research has been underway for almost 20 years; it is likely to take many more years until one or more HIV vaccines is proven safe and effective.
- 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.

## 5

## Key concepts



### Basic facts about AIDS vaccine science

- There is at present no HIV/AIDS vaccine that has been proven efficacious in clinical trials. Many vaccine candidates are in various stages of research, development and testing (see **Chapter 6**).
- As of 2004, AIDS vaccine research has been underway for almost 20 years. It takes many years to develop and test vaccines, and most experts agree that it will take at least 8-10 more years to develop one or more safe and effective AIDS vaccines.
- 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 already 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 in the future
  - Modifying the course of HIV infection so that even if it were not successful in preventing HIV infection, the vaccinated person would have mild course of disease and AIDS would develop more slowly or not at all

The most common type of AIDS vaccines being developed contains copies of small, non-harmful portions of HIV genes. 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 enters the body. There is no risk that they will cause HIV infection.

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### **What does the term 'copies of genes' mean?**

This term is used when describing AIDS vaccines 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 ensures that the vaccine cannot cause HIV infection.

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#### **Types of AIDS vaccine candidates**

##### **DNA vaccines**

DNA vaccines have *copies* of small segments of DNA (genetic material), or genes, that resemble those of HIV. When the DNA vaccine is injected, the genes are picked up by the body's own cells. Then, the cells are able to produce certain proteins that will create a **cellular** and/or **antibody immune response** (see **Chapter 3**).

The segments of the DNA that can change the least may be chosen to be made in the lab and put into the vaccine. The particular genes are also chosen because they have been shown to induce (or cause) a good immune response in animals.

##### **Vector vaccines**

Vector vaccines use the same basic concept used in DNA vaccines with the addition of a **vector**, or delivery system, that carries the vaccine's genetic material into the human cell. A vector is usually a different virus, which is naturally harmless to humans or which has been made harmless by scientists. The man-made genes 'piggy-back', or get carried on the vector, and this helps them enter into human cells more efficiently.

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 the virus, such as a protein. Most subunit vaccines use 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.

**Additional concepts related to AIDS vaccine candidates**

#### **'Prime-boost'**

This is a series of immunizations 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 general term to describe much of the technology used in developing AIDS vaccines.

## 5.1 Timeline

### Major points in the history of AIDS vaccine research





**Status of  
AIDS vaccine  
research as  
of January  
2004**

- Since clinical trials started in 1987, over 30 different AIDS vaccine candidates have been tested in over 70 clinical trials around the world, including Africa, Asia, the Americas and Europe.
- In the early years of vaccine research, most vaccines were developed for clade/subtype B vaccines, the clade now most common in North America and Europe.
- Since the mid- to late 1990s, more emphasis has been placed on the creation of vaccines for the developing world, focusing on clades common in Central and South America, Africa, Asia.
- Experts agree that many different types of vaccines will need to be tested in different regions of the world before an AIDS vaccine will be approved and licensed.

**AIDS vaccine trials database**

IAVI maintains a database of all completed and ongoing AIDS vaccine trials, available at <<http://www.iavireport.org/trialsdb/>>.

This database allows users to search for any vaccine that is being tested or that has been tested in any part of the world. The site also maintains a poster, which details all current ongoing trials.

For a current version of this poster, go to <<http://www.iavireport.org/specials/OngoingTrialsofPreventiveHIVVaccines.pdf>>.

For a map showing locations and other key information on AIDS vaccine trials that began immunizations in 2004, go to <<http://www.iavireport.org/Vax/vax.dec.jan2005.map.web.pdf>>.

**Results of the first AIDS vaccine Phase III efficacy trial**

Only one vaccine candidate has been tested in large-scale Phase III trials (see **Chapter 6**) to evaluate whether it is effective. Subunit gp120-based vaccine (AIDSVAX B/B and AIDSVAX B/E, VaxGen Inc.) was found not efficacious in two Phase III trials completed in 2003, the first in the US, Canada and Netherlands and the second in Thailand. Results showed that the vaccine was not efficacious in preventing HIV infection or in modifying the progression of HIV infection.

The AIDS Vaccine Advocacy Coalition (AVAC) has written reports detailing the important lessons of this trial. The article gives a full explanation of why the trial was a success for the AIDS vaccine field, even though it proved that the vaccine did not work.

Multiple references can be found in the 'AIDSVAX EFFICACY TRIAL RESULTS' at <[www.avac.org](http://www.avac.org)>.

Despite the disappointing results of the AIDSVAX trials, these trials provided invaluable information about the conduct of AIDS vaccine efficacy trials. A phase III trial of a prime-boost combination vaccine (canarypox or ALVAC vector, boosted by AIDSVAX B/E) was initiated in November 2003.

**Challenges of  
AIDS vaccine  
development**

**How to make the vaccine**

Many of the proven ways of making vaccines against other diseases produce a strong immune response because the whole pathogen, either in killed or attenuated (weakened) form (see **Chapter 4**), is used in the vaccine. This strategy has not been practically applied when developing an AIDS vaccine for use in humans. If a vaccine were made from a whole pathogen, it would be very hard for scientists to be absolutely sure that the vaccine would not cause HIV infection. Likewise, 'killed' HIV vaccine would be difficult to produce in large quantities.

Because of these concerns, HIV vaccines are not made using the whole virus. Instead, vaccine candidates contain only copies of parts of HIV that are made in a laboratory. The vaccine could contain structural materials like proteins or peptides, or it could contain genetic material that resembles pieces of the HIV genome. These vaccines cannot cause HIV infection.

The AIDS vaccines now being developed and tested in humans *cannot cause HIV infection* for the following reasons:

- Vaccines being tested in clinical trials do NOT contain the entire virus.
- The vaccines contain either a protein that resembles the outer coat or other part of HIV, or they contain manufactured copies of small segments of genetic material resembling that of HIV; no single protein or gene could cause HIV infection.
- The genes contained in the vaccines are *copies* of HIV genes, meaning scientists have produced them in laboratories, so the final genes put into the vaccines have never been part of an actual virus.

**Lack of a known predictive animal model**

Before being tested in humans, all vaccines must go through testing in

animals. Normally, an ‘animal model’ is used, such as a mouse, rabbit or monkey. This testing in the animal is designed to give scientists a good idea of what effects (safety and immune response) the vaccine may have in humans.

Animal testing may not be predictive of the human immune response to an experimental vaccine. Animal testing is useful, however, in providing information about the safety of the vaccine and general information about the type and amount of immune responses generated.

No animal model is known to predict vaccine protection against HIV/AIDS, making vaccine research and human trials more difficult to design. For this reason, however, clinical (human) trials are the only way to answer questions relevant in humans.

### **Insufficient knowledge about immune correlates of protection**

For infectious diseases in general, ***correlates of protection*** are biological markers (such as a sufficient level of antibodies or killer T-cells) that seem to indicate that a person is protected against infection. Because no population exists that has naturally recovered from HIV infection, or that has been protected against HIV infection by a vaccine, scientists do not know the exact biological markers that would indicate vaccine-induced protection against HIV. This makes vaccine design more difficult, but not impossible.

### **Complexities related to mutation and subtype**

HIV is a virus. This means that it survives by invading a ‘host’ (in the case of HIV, the host is a person) and making many copies of itself inside that host. As viruses continue to make copies of themselves, some of the copies may become slightly different from the original virus. This process is called *mutation*.

When new forms of the virus are better able to copy themselves and survive in one host, these mutations are passed on to other hosts, and the virus evolves. The different forms of HIV that have evolved over time can be thought of as members of a large family: they are different from but related to each other. The different branches of the family tree are called subtypes, also referred to as ‘clades’. Each clade is about 30 percent different in its genetic makeup from any of the others. Scientists have given the clades letters as names. Sometimes viruses are a combination of two clades; these are called ‘recombinant’ forms. Clade C is common in Southern Africa, Ethiopia, China and India, for

example, while clade B is most common in the US, Europe, Caribbean and South America. However, they do not always stay where they are. For example, right now the clade that is most common in East Africa, clade A, is becoming increasingly widespread in the Ukraine and parts of Eastern Europe. In the early days of vaccine testing, most candidates were based on Clade B. Now, however, many vaccines are being developed and tested for other clades that exist. It is not yet clear whether it will be necessary to develop vaccine candidates that 'match' the most common clade in the country or region where the candidate is likely to be used. An ideal preventive HIV vaccine would protect people against infection of all clades of HIV. How to make a vaccine or mixture of vaccines that can induce broad protection is the question all HIV vaccine designers are attempting to answer.

More than nine different clades have been identified worldwide. The map on the right shows how these clades are spread throughout the world.



### **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 a change in the genes. 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 virus forms but still allow a few of the viruses to 'escape' the immune response. In a similar way, the HIV in a person may mutate to become resistant to some antiretroviral drugs. Researchers do not know if an HIV vaccine would be protective against different forms of HIV in an individual.

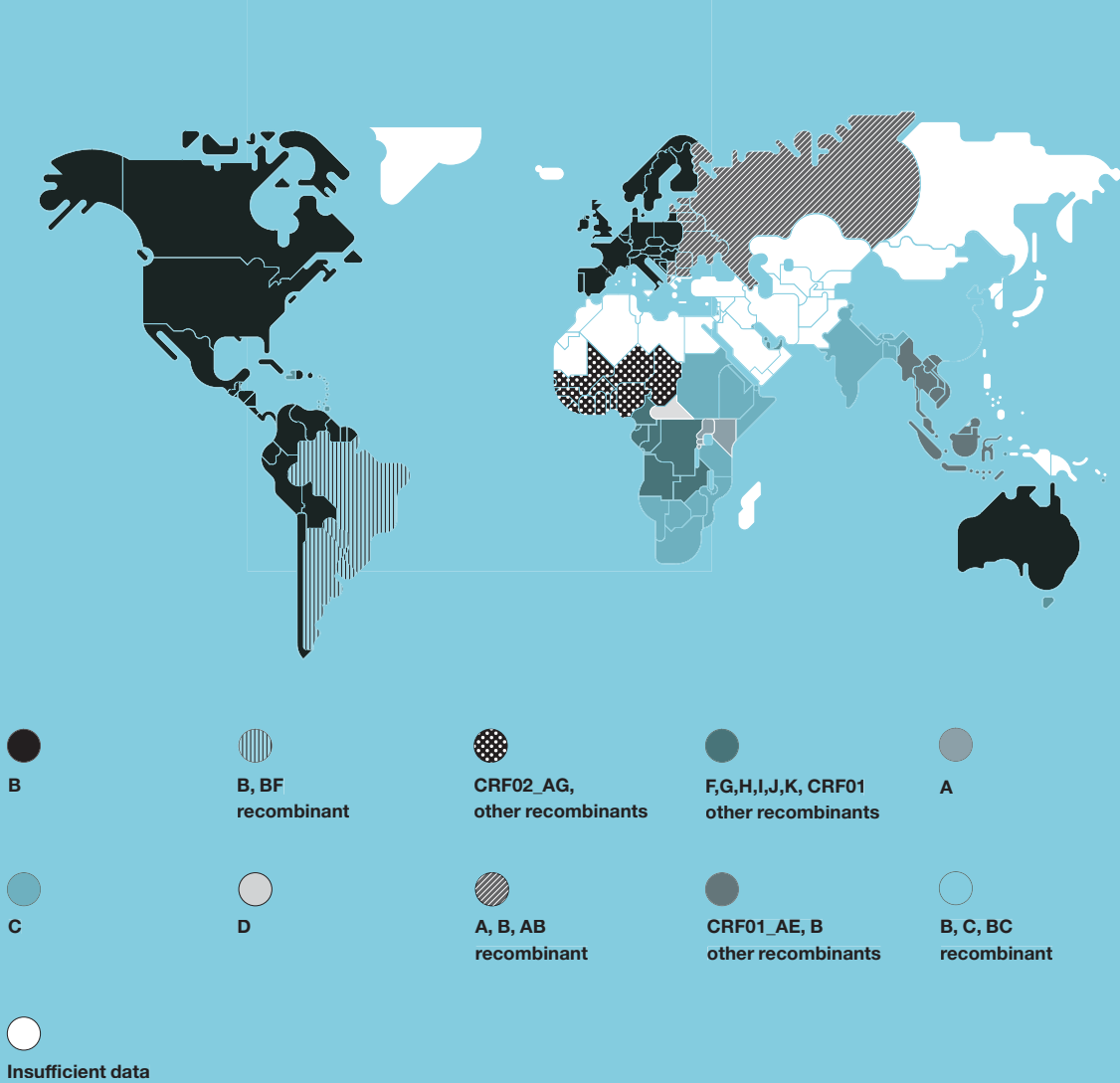
#### **Different forms of HIV throughout the world**

Because of mutation, different clades exist in different parts of the world. Researchers do not know yet if a vaccine designed for a clade in one part of the world will work for clades in other parts of the world.

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**5.2**  
**Global**  
**distribution**

**HIV-1 subtypes and recombinants**



Source: Adapted from: Fanchine E. McCutchan, Henry M. Jackson Foundation (Rockville, Maryland); McCutchan and colleagues who helped develop the data used to generate this map.

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

## Organisations involved in international AIDS vaccine research

Name	Brief description	For further information
<b>African AIDS Vaccine Programme (AAVP)</b>	Established in 2000 by the WHO-UNAIDS HIV Vaccine Initiative (HVI). 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.”	<a href="http://www.who.int/vaccine_research/diseases/hiv/aavp/en">http://www.who.int/vaccine_research/diseases/hiv/aavp/en</a>
<b>AIDS Vaccine Advocacy Coalition (AVAC)</b>	Nonprofit organisation founded in 1995 to speed the ethical development and global delivery of HIV/AIDS vaccines. Does not conduct AIDS vaccine research itself but instead engages in advocacy, educational outreach, and building awareness both in the US and internationally.	<a href="http://www.avac.org">http://www.avac.org</a>
<b>AIDS Vaccine Integrated Project (AVIP)</b>	European-based programme whose mission is to develop novel vaccines to be tested collaboratively in trials in Europe and developing countries and to foster training, technology transfer and community involvement among European and developing countries.	
<b>Canadian Network for Vaccines and Immunotherapeutics (CANVAC)</b>	A Canadian network of scientists working with other institutions towards the development of safe and effective vaccines to protect Canadians and people around the globe from cancer and life-threatening viral infections, including HIV.	<a href="http://www.canvacc.org/publik/frameset.htm">http://www.canvacc.org/publik/frameset.htm</a>
<b>European Vaccine Effort Against HIV/AIDS (EUROVAC)</b>	A European cluster working to test preventive AIDS vaccines by bringing together 21 European laboratories and moving vaccine candidates into clinical trials. Funded since 2000 by the European Union.	<a href="http://www.eurovac.net/index1.htm">http://www.eurovac.net/index1.htm</a>

## Organisations involved in international AIDS vaccine research (continued)

Name	Brief description	For further information
<b>HIV Vaccine Trials Network (HVTN)/National Institutes of Health (NIH)</b>	<p>Formed in 1999 from two existing groups, 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 US National Institutes of Health (NIH). Mission is to “develop and test preventive HIV vaccines.”</p> <p>Research is done through multicentre clinical trials conducted simultaneously in the US and international sites.</p> <p>Research is done through multicentre clinical trials conducted simultaneously in the US and international sites.</p>	<a href="http://www.hvtn.org">http://www.hvtn.org</a>
<b>Institute for Human Virology (IHV)</b>	<p>The Institute of Human Virology 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.”</p>	<a href="http://www.ihv.org/">http://www.ihv.org/</a>
<b>International AIDS Vaccine Initiative (IAVI)</b>	<p>Nonprofit organisation formed in 1996. Mission is to “ensure the development of a safe, effective, preventive AIDS vaccine for use throughout the world.” 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. Has regional offices in New Delhi, India; Nairobi, Kenya; and Amsterdam, the Netherlands.</p>	<a href="http://www.iavi.org;">http://www.iavi.org;</a> <a href="http://www.iavi.org.in">http://www.iavi.org.in</a>
<b>Kenya AIDS Vaccine Initiative (KAVI)</b>	<p>Mission is to “contribute to a world without AIDS by developing a safe, effective and affordable preventive HIV vaccine.” Formed by partnership between the University of Nairobi, Oxford University and IAVI.</p>	<a href="http://www.kaviuon.org/">http://www.kaviuon.org/</a>
<b>South Africa AIDS Vaccine Initiative (SAAVI)</b>	<p>Formed in 1999 as a programme of the Medical Research Council (MRC) of South Africa. Established to coordinate the research, development and testing of HIV/AIDS vaccines in South Africa. Based at the MRC; works with key national and international partners to produce an affordable, effective and locally relevant preventative HIV/AIDS vaccine in as short a time as possible.</p>	<a href="http://www.saavi.org.za">http://www.saavi.org.za</a>

## Organisations involved in international AIDS vaccine research (continued)

Name	Brief description	
<b>IAVI at Uganda Virus Research Institute (UVRI)</b>	Partnership between IAVI and UVRI formed in August 2001. Conducts clinical trials in Entebbe in partnership with IAVI and the Government of the Republic of Uganda.	<a href="http://www.iavi.org/uganda">http://www.iavi.org/uganda</a>
<b>US Military HIV Vaccine Research Program (USMHRP)</b>	HIV Research Program is a division of the US Army. Main focus is on the US Army, but does conduct international HIV vaccine research on vaccine candidates that are designed specifically for HIV subtypes found in their own regions. Works in East and West Africa and partners with government and academic institutions in Uganda, Kenya, Tanzania, Cameroon and Thailand. Affiliated with Walter Reed Army Institute of Research.	<a href="http://wrair-www.army.mil/">http://wrair-www.army.mil/</a> ; <a href="http://www.hivresearch.org">http://www.hivresearch.org</a>
<b>Vaccine Research Center (VRC)</b>	Established by the US NIH to facilitate vaccine research, as part of an initiative by former US President Bill Clinton to develop an AIDS vaccine. The VRC conducts research for vaccines against a variety of human diseases.	<a href="http://www.niaid.nih.gov/vrc/">http://www.niaid.nih.gov/vrc/</a>

### Key messages

pertaining  
to AIDS  
vaccines

**No AIDS vaccine that has been proven to be safe and effective currently exists. As of 2004, it may take many more years of research to identify one.**

**There is no chance that any of the AIDS vaccine candidates could cause HIV infection.**

**Developing an AIDS vaccine is very difficult for many scientific reasons. First, the virus is extremely effective at evading the immune system because it can mutate within an individual, meaning that HIV can learn how to avoid the effects of a vaccine. Second, mutation leads to different subtypes of the virus throughout the world, which may react differently to different vaccines.**



**For  
further  
information**

**AIDS Vaccine Advocacy Coalition 2004 Report: Getting the Global House in Order** <[http://www.avac.org/pdf/reports/2004AVACReport\\_High.pdf](http://www.avac.org/pdf/reports/2004AVACReport_High.pdf)> (May 2004).

**AIDS Vaccine Fails to Show Efficacy in Thai Trial** <<http://www.avac.org/AIDSVAXthai.htm>> (12 November 2003).

**AIDS Vaccine Handbook: Global Perspectives. Second Edition, the AIDS Vaccine Advocacy Coalition (AVAC).** Edited by Patricia Kahn, 2004. <<http://www.avac.org/primer.htm>>.

**Challenges in Designing HIV Vaccines** <<http://www.niaid.nih.gov/factsheets/challvacc.htm>>.

**Chang, M.L., Vitek, C. & Esparza, J.; WHO-UNAIDS-CDC.** Public health considerations for the use of a first generation HIV vaccine. Report from a WHO-UNAIDS-CDC Consultation, Geneva, 20–21 November 2002. *AIDS* 17, W1–W10 (2003).

**Djomand, G., Peiperl, L. & Keefer, M.** Introduction to HVTN Vaccine Portfolio for Non-Scientists. Online PowerPoint presentation from HVTN. <[http://www.hvtn.org/pdf/community/Non-ScientistsPres\\_FGM.ppt](http://www.hvtn.org/pdf/community/Non-ScientistsPres_FGM.ppt)> (2001).

**Do Clades Matter for HIV Vaccines? IAVI Report 7 (2), May–August 2003** <<http://www.iavi.org/iavireport/Issues/0803/IAVIRportMay-August2003.asp>>.

**Heyward, W.L., MacQueen, K.M. & Goldenthal, K.L.** HIV vaccine development and evaluation: realistic expectations. *AIDS Res. Hum. Retroviruses* 14, S205–S210 (1998).

**The Science of HIV/AIDS Vaccines: An introduction for community groups** <<http://www.icaso.org/icaso/vaccines/Science%20Primer%20-%20E%20-%20Web.pdf>>.

**Understanding the Results of the AIDS VAX Trial** <<http://www.avac.org/pdf/UnderstandingAIDS VAX.pdf>> (14 May 2002).

# 6

## Vaccine Development and Clinical Trials

**In this chapter** **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 experimental AIDS vaccines are now in clinical trials. 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, effectiveness.

## Summary points

- 1** 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.
- 2** A new vaccine must pass through a series of trial phases; all phases determine if the vaccine is safe and works well in humans, in increasing numbers of people.
- 3** Phases I and II determine the dose (how much), the regimen (how many times and how far apart), the route (by mouth, skin, injection and so on) and the strength and type of immune response it produces in the body.
- 4** Phase III trials, which test the vaccine in thousands of people, determine how efficacious the vaccine is in preventing infection and/or disease.
- 5** All clinical trials involve both risks and benefits for trial volunteers.
- 6** 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 answer specific questions about a new vaccine or drug; while undergoing testing, new 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.

### Clinical vaccine trials examine the following main issues:

- **Safety** – establishing that the vaccine does not cause adverse events (see definitions below), which would prevent its use.  
**Adverse events** (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 not caused by the vaccine is an auto 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 (1 in 1,000,000) or uncommon (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 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 experimental 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 experimental vaccine.

Vaccines are expected to be safe when used in humans. Many marketed vaccines can 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 to give the vaccine such as by mouth, through the skin, by injection in the muscle, and so on (route).
- *Immunogenicity* – the ability, strength and type of immune responses in humans. These 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 HIV 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 being used in the general population (see section on Phase IV studies, below). See **Chapter 4** for further information on effectiveness.



### 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 in a significant number of people or to a significant or severe degree in any person.

Testing for safety does not mean testing to see if the vaccine causes HIV infection. Before a vaccine goes into clinical trials, researchers already know that there is no chance it will cause HIV infection in humans (see **Chapter 5**). No vaccine that could cause HIV infection would be put into preventive AIDS vaccine trials in humans.

Finally, people may think safety means safe from HIV infection, as in ‘safe sex’. But people who join a clinical trial should never count on the experimental product protecting them! When the degree of protection the vaccine provides in the trial is being tested, this concept is referred to as **efficacy** (see previous definition). Safety means that the vaccine itself is not harmful.

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#### Phases of clinical trials

No matter how promising it 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 to work. A series of carefully conducted trials is the fastest way to see if a new vaccine protects people from infection or disease. This series involves three or more phases and several trials before an application for licensure to distribute the vaccine is made.

### **Phase I**

These trials are the first human tests of an experimental vaccine. They measure *safety* and *immunogenicity* in a small group (20–60) 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 12–18 months.

### **Phase II**

These trials measure *safety* and *immunogenicity* in a larger group (50–500) of healthy volunteers. Here the goal is also to find the best *dose* and *regimen*. Phase II trials may last up to 2 years or longer.

In some cases, a larger group of volunteers that represent the population at risk for the disease is asked to join a trial; these trials are known as Phase IIb trials. These trials can provide important data about safety of the vaccine and may give some information about whether the vaccine truly works, or has efficacy.

### **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 range from 2,000 to 20,000, depending on the number of infections per year in the population) who are at significant risk of infection. 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 (3–5) 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 immunocompromised), 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 adverse events are primary goals of Phase IV studies.

**6.1**  
**Summary of**  
**vaccine**  
**studies**

**Summary of Phases of Clinical Vaccine Trials**

Source: JAVI

<b>Phase</b>	<b>Volunteers</b>	<b>Length</b>	<b>Objective</b>
<b>I</b>	20 - 60	12 - 18 months	Safety, dose, regimen, route
<b>II</b>	50 - 500	2 years	Safety and immunogenicity with selected dose, regimen, route
<b>III</b>	2,000 - 10,000	3 - 4 years	Safety, efficacy
<b>IV</b> Expanded access	5,000 - 50,000	Varies	Safety
<b>IV</b> Surveillance studies/field studies	50,000 - millions	Ongoing	Safety, effectiveness





## What are the benefits and risks of participating in an AIDS vaccine trial?

### 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 for others
- Medical evaluation during the trial with referral for care and treatment if needed
- Compensation for the effort of participation – 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 to receiving the vaccine, such as headache, fever, soreness; in clinical research there is always a possibility that the experimental vaccine 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 the volunteer is not infected with HIV (see **Chapter 7**); this may or may not happen, and if it does happen, it is not certain how long it will last

Researchers and other authorities on the trial must balance the potential *risk* and potential *benefit* for volunteers.

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### Regulation of clinical vaccine trials

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 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 Committee on Harmonization (ICH) of Good Clinical Practices (GCP) and Good Laboratory Practices (GLP).

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**.

**Key vaccine  
trial concepts**

**Placebo**

Many (but not all) vaccine trials involve the use of a *placebo*, which is a harmless, inactive substance that looks like the vaccine. Sometimes this 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/placebo 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 may be unfairly divided and may not be 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) according to whether they received vaccine or 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 have 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 2–4 years, to see how many people become infected in each group.<sup>1</sup> 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.

The formula used for calculating efficacy is as follows

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

The degree of efficacy may be important as well. No vaccine is 100% efficacious. 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.

## Mathematical modeling for efficacy

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 at different levels of efficacy on a population. 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

### 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 is safe and if it works. Trials must be completed and the data must be analysed and reviewed by researchers and regulatory authorities before the vaccine can become available. Experimental or candidate vaccines are not available to the general public. Additionally, there may be 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 vaccines and malaria vaccines.

Licensed vaccines are those that have been through 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 vaccine, the measles vaccine and the hepatitis B vaccine.

### 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 get, especially in developing countries. However, it is very important to distinguish between interventions given in clinical trials and those given in 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, as this has not yet been proven. Furthermore, volunteers always have the chance of receiving a placebo (inactive substance) during the trial, and they do 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 that have previously been proven in clinical trials.

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## Key messages

pertaining  
to AIDS  
vaccines

**Before a Phase III 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.**

**As do all clinical trials, AIDS vaccine trials have benefits and risks for volunteers; however, there is no risk that the 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.**

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## For further information

**Code of Federal Regulations and ICH Guidelines as adopted by the FDA, 2002–2003. Online, searchable version <<http://www.access.gpo.gov/nara/cfr/cfr-table-search.html> - page1>.**

**Developing Vaccines to Prevent HIV and AIDS: An Introduction for Community Groups 2nd edition <<http://www.icaso.org/icaso/vaccines/Vaccine%20Primer,%202nd%20Edition-2002-web.pdf>>.**

**International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Copyright ICH Secretariat, Geneva, Switzerland.**

**Clinical Research Resources <<http://www.clinicalresearchresources.com>>.**

**National Institutes of Health website on Clinical Trials <<http://www.clinicaltrials.gov/ct/info/resources>>.**

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### Foot notes

<sup>1</sup>For HIV vaccine trials, it is important to remember that while all trial participants are counselled to reduce their risk for HIV infection, some participants will likely become infected through blood or sexual exposure. The experimental vaccine itself cannot cause HIV infection.



# 7

## Participation in AIDS Vaccine Trials

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

### **This chapter discusses**

- General criteria for participation
- Flow chart of steps involved in trial participation
- Description of the participation process
- Volunteer protection and confidentiality
- Treatment and care for trial volunteers



## Summary points

- 1** Participation in any clinical trial is voluntary, and enrollment 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 site 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 consultation with community advisory boards (CABs).

# 7

## Key concepts



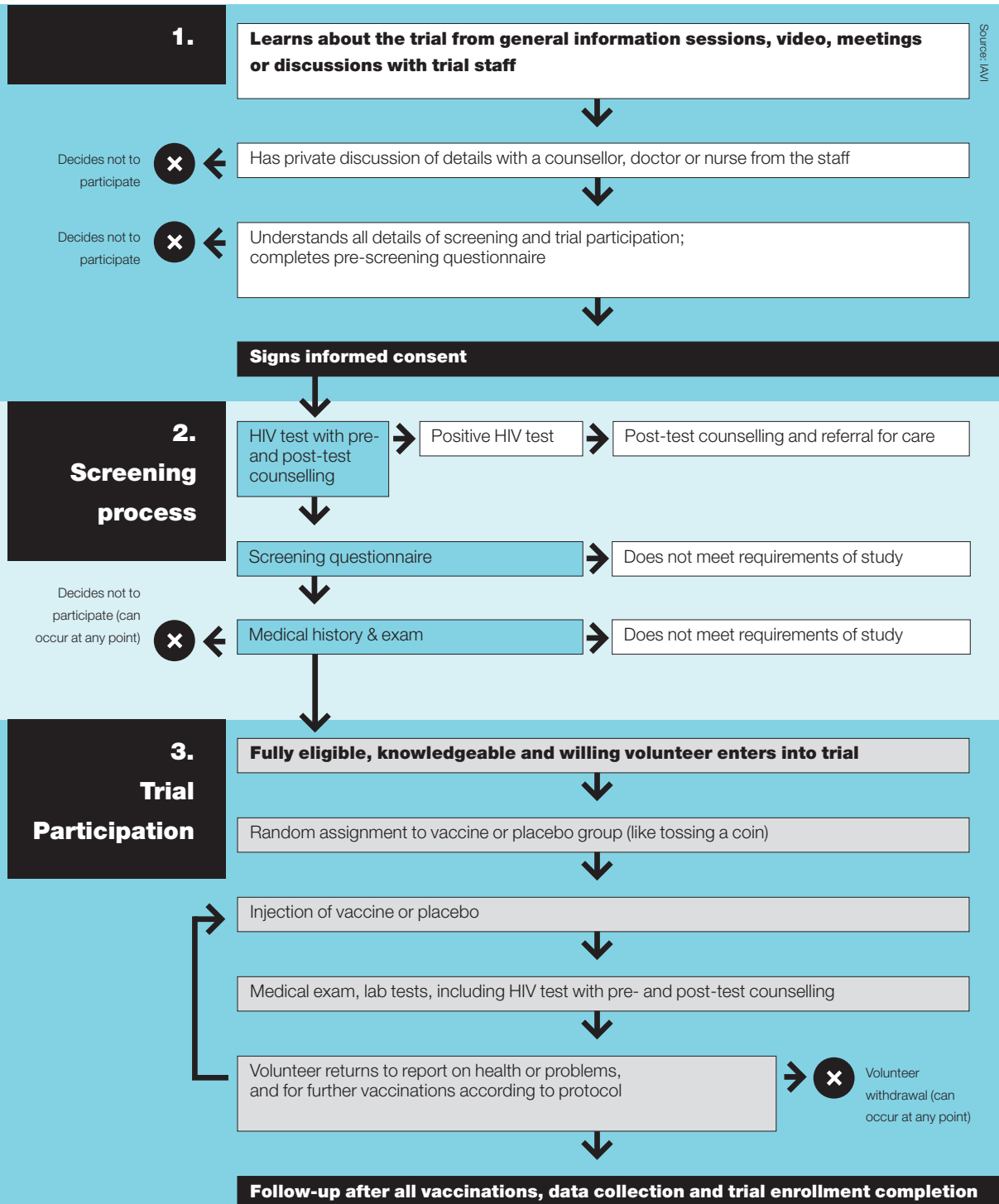
### General criteria for participation

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 be 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 pregnant and must use an effective contraceptive method for the period defined in the protocol
- Agree to HIV testing until a certain time has passed after the last injection and to risk-reduction counselling to prevent HIV

# 7.1 Trial participation

## Flow chart of steps involved in trial participation



**Trial participation process** The flow chart above depicts a generic flow of trial participation. The exact details will vary according to country, community and trial site. 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**

The study team provides information about the trial and answer any questions. 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 site.

### **Informed consent**

Each trial participant must give informed consent (indicated by a signature, finger print, 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, to build a general understanding and preparedness among the community at large. Building general education in a community about AIDS vaccine trials enhances individual knowledge and decreases the stigma attached to finding out about the trial, both of which ensure that individuals in the community are free and 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 gaining informed consent, potential participants will get details of the screening process, including HIV testing. Researchers may test individuals to make sure they fully understand key information about participation. After signing or making his or her mark in the informed consent form for the study, the volunteer enters into the screening process, which may involve a complete medical history and 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 he or she is 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 talk between the study team and volunteers. A counsellor will be available and able 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 will explain the test, conduct a risk assessment, discuss risk-reduction strategies and safer sexual practices, explain the meaning of positive and negative results and what the test results mean to the volunteer, and obtain informed consent. After the test results are ready, the counsellor will meet with the volunteer again for a post-test counselling session. During this session, the counsellor will give the volunteer the test results, discuss the meaning of those results, talk about feelings, review risk-reduction plans and make referrals for any services needed. If the test is positive, the counsellor will address the volunteer's emotional response to the news, explain treatment and support options and discuss self-care, choices for how to inform the volunteer's partner(s) and how to prevent transmission of HIV to others. It is important to note that test results and all information revealed during these counselling sessions be 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***, below.

## **The trial vaccine and vaccine administration**

Most AIDS vaccine candidates are injected into the muscle of the upper arm (intramuscular), under the skin (subcutaneous) or in the skin (intradermal). Some day, newer AIDS vaccines may be given via mouth (oral) or nose (intranasal).

Volunteers are ***randomised*** to receive either the experimental vaccine OR the placebo; this is 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', or ***blinded***.



### 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 AIDS (UNAIDS) has standardized 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 standardized process described above. The process is in fact voluntary, and the individual will also receive quality counselling before and after being tested and receiving test results. The process, however, does not necessarily fit the standard model of VCT as it exists in VCT centers that may be available in the community, where people attend only to determine their HIV status. First, counselling includes trial-specific issues, and the visit includes trial-related follow-up. Also, risk-reduction counselling and HIV testing is done several times during the course of the trial. Because of this ongoing nature, 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.

**Double-blinded** means that the research staff also does not know which volunteers got the vaccine or placebo, to be sure that the study is fair. In this case, the vials of vaccine and the inactive placebo look just alike except for a code that is kept sealed 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 one half hour or 1 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 'right' to pay volunteers to be in vaccine trials. However, they may be paid back for the costs of participating in the trial; for example, for travel costs to get to the clinic. Food and/or child care may 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 site decides what is fair.

A benefit of being in the trial is medical examinations and care related to the trial. The volunteer can benefit by knowing about his/her health status. This cannot replace standard health care and specialized medical services that the volunteer may need or want to use on his/her own. Another benefit is the counselling and 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 feeling is often considered a personal benefit.

If a volunteer experiences a vaccine-related injury, the informed consent explains what will happen. In many trials, he or 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 positive. 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 for health or life insurance, travel or employment, they should get tested at the study site.
- Similarly, volunteers are asked not to donate blood, bone marrow or organs during the trial.

### **Becoming HIV infected while in the trial**

*The HIV vaccine candidates cannot cause HIV infection.* However, although volunteers receive HIV risk-reduction counselling, it is possible that some will become infected through blood or sexual exposure outside of the trial (for example, unsafe sex or injection drug use). Volunteers will be tested for HIV a few times during the trial. These tests will show if a volunteer has become infected. If a volunteer is found to be infected with HIV, he or she will no longer receive injections as part of the study. He or she, however, will be immediately 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**

Trial volunteers are informed that the vaccine may not protect them against HIV and therefore they should practice safer sex. They receive counselling to help them reduce their risk of infection and, in some trials, condoms as well. Counselling reinforces the need to practice safer sex to avoid both sexually transmitted infections, including HIV/AIDS, 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 4 months after receiving the last vaccination. Female volunteers will have pregnancy tests at the time of screening, before each vaccination and at some additional times. Male volunteers should also use condoms for at least 4 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 until the end of the pregnancy, and her baby will be examined during the first month of life to ensure that the baby is healthy.

## **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 will be discussed.

## **Study conclusion**

Phase I and II AIDS vaccine trials last anywhere from 1 to 3 years; Phase III trials may last up to 5 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.

## **Volunteer protection and confidentiality**

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. It is therefore the responsibility of researchers to make sure volunteers are protected, for example, by meeting the following standards:

- Upholding strict respect of confidentiality of their participation and their medical files<sup>1</sup>
- Avoiding stigma and discrimination due to their participation in the vaccine trial
- Providing treatment for vaccine-related injuries



- Help 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**.

**Treatment  
and care  
for trial  
volunteers**

Volunteers have access to some health care and HIV prevention services from the trial site 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, as agreed with national and local stakeholders. 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 on the horizon in many countries, which may affect trial-related policies.

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**Key messages**

pertaining  
to AIDS  
vaccines

**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 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 pressure someone into participating.**

**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 infected with HIV through sexual or blood exposure is provided with or linked to available health care; he or she continues to be monitored to find out if the vaccine affects HIV.**

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**For further information**

**Bass, E. Ethics, antiretrovirals and prevention trials: An online debate. IAVI Report 7 (3), September 2003–January 2004 <<http://www.iavi.org/iavireport/Issues/0104/EthicsAntiretroviralsandPreventionTrials.asp>>.**

**Bass, E. Raising hopes and many questions: Vaccine trial sponsors' new approaches to providing antiretrovirals for trial volunteers. IAVI Report 7 (3), September 2003–January 2004 <<http://www.iavi.org/iavireport/Issues/0104/NewApproachestoProvidingAntiretrovirals.asp>>.**

**Ethical Considerations in HIV Preventive Vaccine Research <[http://www.unaids.org/html/pub/Publications/IRC-pub02/JC765-EthicalCons-Repr\\_en\\_pdf.htm](http://www.unaids.org/html/pub/Publications/IRC-pub02/JC765-EthicalCons-Repr_en_pdf.htm)> (May 2000).**

**Finding the Way: Community and science working towards a vaccine for HIV. Produced by South African HIV Vaccine Action Campaign (SAHIVAC), funded in part by South African AIDS Vaccine Initiative (SAAVI) (2001).**

**HIV Vaccine Trial in Uganda – Frequently Asked Questions <<http://www.iavi.org/uganda/pdf/brochure.pdf>>.**

**UNAIDS. Voluntary counselling and testing (VCT): UNAIDS technical update <<http://www.unaids.org/en/in+focus/topic+areas/counselling+and+voluntary+counselling+and+testing.asp>> (UNAIDS, Geneva, May 2000).**

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**Foot notes**

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 site.



# 8

## Gender Issues in AIDS Vaccine Trials

**In this chapter** **This chapter provides an overview of gender issues related to HIV/AIDS, vaccines and AIDS vaccine trials.**

### **This chapter discusses**

- The concept of gender (versus sex)
- The effect of gender on 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, 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 women to be involved in AIDS vaccine trials to detect trends in the effect of the vaccine on men and women.
- 4** Gender can affect trials in many ways: it may be more difficult to recruit women into trials; ensuring informed consent can be difficult because women are often vulnerable to coercion; women are 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 participate 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.

## Key concepts



### The concept of gender

The terms 'gender' and 'sex' sometimes cause confusion and debate. The terms are often used interchangeably, but they are also used with very distinct meanings. In this chapter, we have used distinct meanings for the words, recognizing their inter-relationship.

*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 men's and women's 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 socialized within gender roles.

We often collapse the two terms and simply use 'gender'. We do so 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.

**Effects of gender on women's vulnerability to HIV infection**

Nearly half of all infections worldwide now occur among women, and in certain countries with generalized 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, who have less-mature tissues, may be more vulnerable to microlesions (and may 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 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 socialized to be self-reliant and to not seek help.
- Men may also face social and economic pressures to reproduce.

**Role of vaccines in reducing women's vulnerability to HIV**

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 the behaviour 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. 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 in which 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 in vaccine trials to detect differences between men and women in effect of the vaccine. There are ethical reasons for the inclusion of women in trials, as well as the need to collect data that will ensure that the vaccine is approved 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 women and enough men in clinical trials. Any 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. Past clinical trials have not always 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. Enrollment of women 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. HIV 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.



**The potential effect of gender on AIDS vaccine trials**

**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 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 voluntary counselling and testing (VCT) and to participate in a trial if the 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 the 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 be able to physically travel to a trial site 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 male 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 safe 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.

**Strategies  
for making  
clinical trials  
gender  
equitable and  
for ensuring  
women's  
participation**

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.

**Preparing the site**

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 patient 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) 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 a 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 community advisory boards. 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 through community advisory boards to develop solutions, and conduct social research to determine barriers and facilitating factors.

### **Effect of gender on future access and use of an AIDS vaccine**

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 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 the needs, desires and perceptions of different audiences.

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### **Key messages**

pertaining  
to AIDS  
vaccines

**Although the AIDS pandemic is affecting women at greater rates than men in many places, current prevention options are not feasible for many women. There is an urgent need for new prevention options that are more easily used and controlled by women.**

**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 easily without men’s cooperation, if necessary, as it is separate from the sexual act.**

**It is important that women participate in vaccine trials to determine whether a vaccine works for them, but they often find it difficult to participate for social, cultural and logistical reasons. Efforts should be made to support involvement of women in trials and to ensure that they make voluntary, independent and well-educated decisions to participate.**

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**For  
further  
information**

**Developing Vaccines for HIV and AIDS: An Introduction for Community Groups.** <<http://www.icaso.org/icaso/vaccines/Vaccine%20Primer,%202nd%20Edition-2002-web.pdf>> (The International Council for AIDS Service Organisations (ICASO), Canada, 2002).

**Ethical Considerations in HIV Preventive Vaccine Research, UNAIDS guidance document.** <[www.unaids.org](http://www.unaids.org)> (UNAIDS, Geneva, 2000).

**Kapoor, S. Gender considerations in HIV vaccine trials** (position paper, IAVI, 2004).

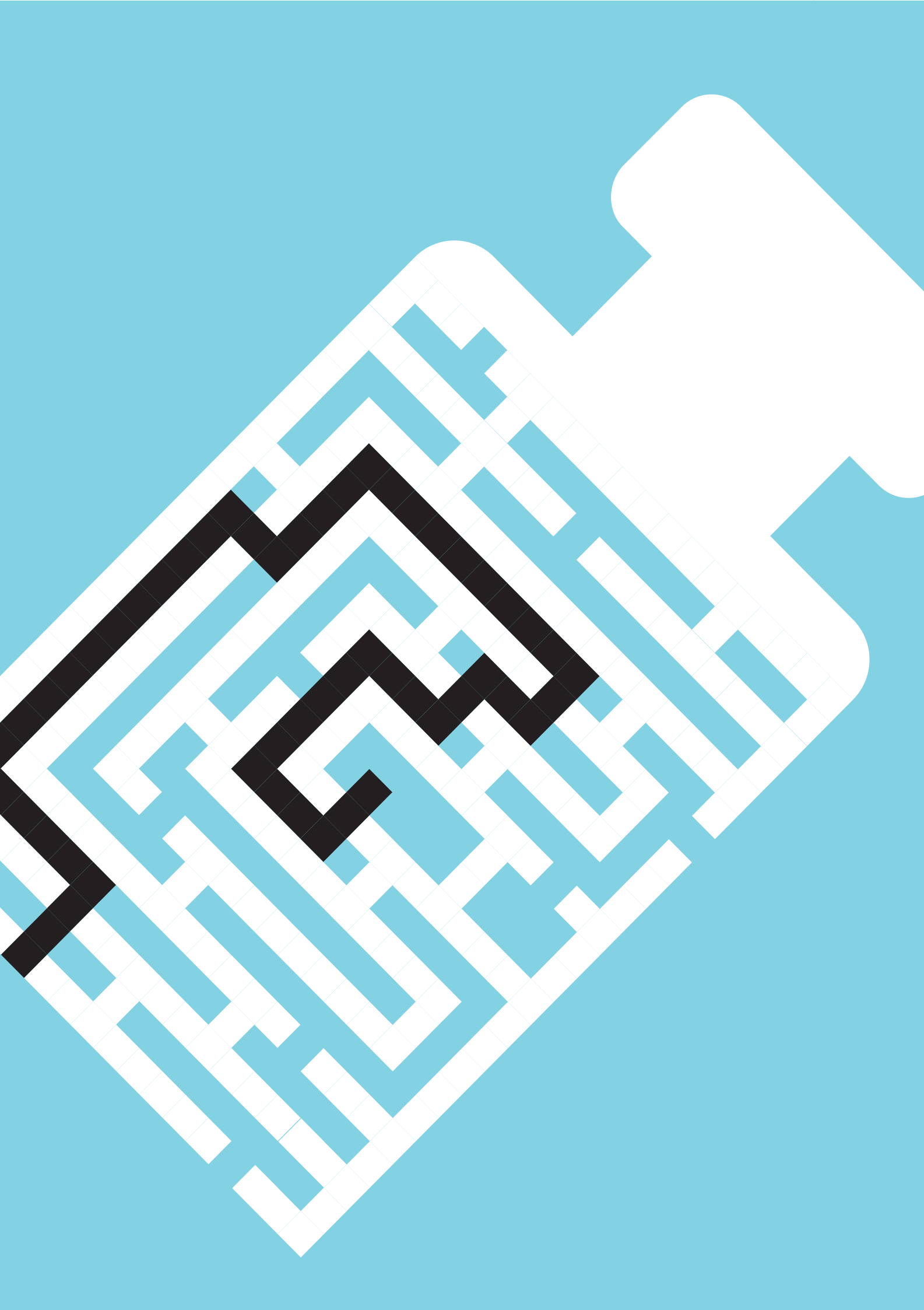
**Nath, M.B. Gender, HIV and Human Rights: A Training Manual** (UNIFEM, 2000).

**Parker, R. & Aggleton, P. HIV/AIDS-related Stigma and Discrimination: A Conceptual Framework and an Agenda for Action** <[www.popcouncil.org](http://www.popcouncil.org)> (The Horizons Programme, Population Council, 2002).

**Richter, Lindegger, Karim & Gasa. Guidelines for the development of culturally sensitive approaches to obtaining informed consent for participation in HIV vaccine-related trials** (paper commissioned by UNAIDS). <<http://www.hs.unp.ac.za/mind/icunaids.htm>> (1999).

**Special Report: Women and AIDS vaccines. IAVI Report 5 (8), July–September 2001.**

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# 9

## Ethical Issues in AIDS Vaccine Trials

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

### **This chapter discusses**

- Primary principles of ethical research
- Informed consent process
- Informed consent document
- Risks versus benefits of participation
- Volunteer rights and protection
- Ethical review of trials
- The Joint United Nations Programme on AIDS (UNAIDS) Guidance Document on AIDS vaccine research



## 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 the volunteer makes his or her own decision to participate; 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; The Joint United Nations Programme on AIDS (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, practical design and methodology
- 3** Fair participant<sup>1</sup> selection – volunteers should be selected in a fair manner, based on scientifically and ethically sound factors
- 4** Favourable risk/benefit ratio – risks of participating should be kept to a minimum and should be justified by benefits of participating and of knowledge gained by the study

- 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 – rights and welfare of participants must be protected throughout the entire trial, conclusion and follow-up

**The informed  
consent  
process**

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 trial sites, 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 trial 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 minimize stigma that may be attached to community members who participate or who even ask for information about the trial.

Most AIDS vaccine trial sites 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 trial site will sometimes offer general information sessions, at which anyone interested can learn about AIDS vaccines and the vaccine trial. There may also be one-on-one counselling sessions, at which potential volunteers learn about the trial in more detail. Finally, some studies require that before signing the informed consent, potential volunteers complete a questionnaire containing a checklist, narrative or combination of both, to test comprehension.

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 trial, including 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 to not participate or to 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**

The **informed consent** document is the paper signed by anyone who decides to volunteer in a trial 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 trial
- 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 the trial
- 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

**Risks versus benefits of participation**

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 to make an informed choice of whether he or she feels that the benefits outweigh the risks of participation.

When researchers plan a study, they must make sure that the risks and benefits of participation balance. If the relative balance of risks and benefits is not reasonable, the trial will be not 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.

### **Examples of risks and benefits**

**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 risks include:**

- **Physical side effects of the experimental vaccine, such as a sore arm, headache or fever, and possible serious adverse events (SAEs)**
- **Social risks such as stigma or discrimination that may be associated with participating in a vaccine trial**
- **False sense of protection from the vaccine, which may cause participants to be less careful about exposure to HIV, or risk behaviour**
- **False-positive HIV antibody tests (in a person who received vaccine but is not infected with HIV; see Chapter 7); the risk of this happening and the time it might last are as yet unknown**
- **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**

**It is important to note that the vaccines now being tested cannot cause HIV infection. Hence, infection from the vaccine is NOT considered a risk of participation (see Chapter 5).**

**Benefits vary from place to place and person to person. Some potential benefits that have been cited include the following:**

- **Rewarding feeling of being involved in the clinical trial team – some participants report feeling that the staff becomes a ‘family’ or the study clinic, a place of comfort**
- **Rewarding feeling of 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 health care, it may be attention an individual would not receive otherwise; for example, HIV counselling and testing, routine blood analysis/monitoring**
- **Receiving food at clinic visits or monetary compensation for travel to clinic visits**

**Volunteer rights and protection**

Participating in a trial 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 it is the duty of researchers to make sure volunteers are taken care of. Protection of trial volunteers is a human rights issue and has become a defining factor in the conduct of AIDS vaccine trials.

**Examples of protection include the following:**

- Strict respect of confidentiality before, during and after the trial
- Adequate time and information to understand study information 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 given 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, that they give informed consent without inducement and that the protocol 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, the participant may disclose to people of his or her own choice at a time he or she chooses.

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 want 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 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 science review.

**Trial guidelines** 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 International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP). These are fully discussed in **Chapter 10**.

**UNAIDS guidance document: Ethics of AIDS vaccine research** In May 2000, UNAIDS issued a guidance document to specifically address the issues involved in AIDS vaccine development, including the conduct of trials. This reference can be found at <[http://www.unaids.org/html/pub/Publications/IRC-pub02/JC765-EthicalCons-Repr\\_en\\_pdf.htm](http://www.unaids.org/html/pub/Publications/IRC-pub02/JC765-EthicalCons-Repr_en_pdf.htm)> Some of the issues addressed include AIDS vaccine development throughout the world, vaccine availability, vulnerable populations and special measures for obtaining informed consent. Additionally, UNAIDS reviews some protocols for ethics and science considerations.

**Key messages**

pertaining to AIDS vaccines

**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 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 are not unfairly influenced to participate.**

**For  
further  
information**

**AIDS Vaccine Handbook: Global Perspectives. Second Edition, the AIDS Vaccine Advocacy Coalition (AVAC). Edited by Patricia Kahn, 2004. <<http://www.avac.org/primer.htm>>.**

**Developing Vaccines to Prevent HIV and AIDS: An Introduction for Community Groups 2nd edn<<http://www.icaso.org/icaso/vaccines/Vaccine%20Primer,%202nd%20Edition-2002-web.pdf>>.**

**DHEW publication (OS) 78-0012. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 18 April 1979. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research <<http://www.fda.gov/oc/ohrt/irbs/belmont.html>> (Washington, D.C.: U.S. Government Printing Office).**

**Ethical Considerations in HIV Preventive Vaccine Research <<http://www.unaids.org/html/pub/Publications/IRC-pub02/JC765-EthicalCons-Representative.pdf>> (May 2000).**

**National Institutes of Health. Ethical Framework for Clinical Research <<http://www.bioethics.nih.gov/research/humanres/ethicsframework.pdf>>.**

**Richter, L.M., Lindegger, G.C., Abdool Karim, Q. & Gasa, N. Guidelines for the development of culturally sensitive approaches to obtaining informed consent for participation in HIV vaccine-related trials (Discussion Paper, University of Natal, 1999).**

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# 10

## Review and Approval for AIDS Vaccine Trials

**In this chapter** **Every clinical research project or 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 or vaccine or medical device proposed for use in humans.**

### **This chapter discusses**

- Review groups
- Review by a regulatory agency (or agencies)
- Review by ethics committee(s)
- Example of an in-country review process
- Standard guidelines on trial regulation

## Summary points

- 1** Before a trial can be conducted anywhere in the world, it must go through a scientific and an ethics review.
- 2** There are three primary types of review: regulatory, scientific and ethics.
- 3** Some bodies have been created specifically to review or give advice regarding the review of AIDS vaccine trials.
- 4** Official, standardized guidelines, laws and regulations exist for the regulation of trial conduct throughout the world.

## Key concepts



### Review groups

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**.

### Review by a regulatory authority

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 a 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, an NRA from each country must give approval. Every 6 months or year, a report of 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 (EMA), and it establishes some overall regulations for the NRAs and reviews products when the sponsor asks for a product to be licensed.

**Review by an independent ethics committee**

Before an AIDS vaccine is tested in people, independent ethics committees (IECs), also called ethics review committees (ERCs) or institutional review boards (IRBs)<sup>1</sup> 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 8** 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 IEC?**

These committees are made up of several members including scientists, ethicists, community members and other experts who are independent of the trial sponsors who evaluate the science, medical aspects and ethics of the proposed trial. In the United States (or if the trial is funded by the United States (US) government) the committee should include at least one member whose interest is nonscientific 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 IEC is responsible for reviewing the qualifications of the trial investigator according to relevant documentation.

The investigator may provide information about the trial to the IEC, 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 IEC.

**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 IEC for review and approval:**

- 1** The trial *protocol*, which defines exactly how the trial will be carried out; a 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
  - Objectives and design of the study
  - Criteria for including or excluding volunteers
  - Number of visits that volunteers will be asked to make to the trial site
  - Procedures to be done at each 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
  - 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** Informed consent document (see **Chapter 8** 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 (see **Chapter 8** for further information on informed consent process)
- 5** Plans for compensation, if any, such as travel costs to and from the trial site, to ensure that they do not unfairly influence on a volunteers’ decision to participate, and that risks do not outweigh 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 Regulatory Authority

### **How the IEC approves and monitors a trial**

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 site'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 (SAEs) 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.

#### **Ethics and scientific advisory committees**

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 WHO/UNAIDS HIV Vaccine Initiative (HVI). This is an independent body, made up of a rotating group of 10–20 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 protocols. It makes recommendations to governments of countries where trials are proposed.

**Summary of types of review** In general, there are three types of review processes for any given trial: regulatory, scientific and ethics.<sup>2</sup> 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.

## Ethics and scientific advisory committees

	Regulatory	Scientific	Ethics
<b>Focus of information reviewed</b>	Package for review includes all relevant information about the product, including all previous tests (preclinical and clinical) done on the product and how it will be tested in humans, including protocol for testing the product, and the Investigator's Brochure.	Scientific committee review ensures that the trial is asking legitimate scientific questions and that the study is well designed to answer these questions.  NOTE: Scientific review may be carried out by an ethics committee.	Package for review includes all relevant information about the <b>protocol</b> , focusing on one study of the product to be conducted at a specific institution. Some also include review of the product, usually based on the Investigator's Brochure.
<b>Level of committee</b>	Country/national, appointed by government; sometimes regional	Institution/university or country/national	Institution/university in most cases; national in some cases
<b>Materials reviewed</b>	Product specific materials—entire package of information on preclinical and clinical testing of the product, its safety and its 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, advertisements for study recruitment, informed consent document
<b>Examples</b>	US Food and Drug Administration (FDA); National Council of Science and Technology of 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

**Example  
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 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 (WHO/UNAIDS) may be requested by the Government of Kenya to review the protocol
- Authorities responsible for other sites if it is a multicentre trial; for example, if the study is also conducted at St. Thomas’s Hospital in London, the study is reviewed by the ERC at St. Thomas’s 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, multisector 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<sup>3</sup>
- National Technical Committee on Bio-safety (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<sup>4</sup>
- The National AIDS Program has its own Research Committee, formed by AIDS researchers and community representatives, that often has access to and provides input for AIDS vaccine research proposals, although its role is more of an advisory one and it is not mandatory that it review a project

**Guidelines  
for trial  
regulation  
and conduct**

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, to provide global representation. The purpose of the project was to come to consensus on regulations for worldwide conduct of clinical research and for eventual licensure of pharmaceutical products.

### **Good Clinical Practice**

Official guidelines for Good Clinical Practice (GCP) were established by the US Food and Drug Administration (FDA), in agreement with the ICH. The purpose of the guidelines are 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 recognized 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/operation at each of the trial laboratory sites. It is a comprehensive checklist that will be invaluable to laboratory management and staff in their quest for accreditation.

## **Code of Federal Regulations**

The Code of Federal Regulations (CFR) was developed specifically for clinical studies regulated by the US 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 US, the CFR is used in conjunction with ICH/GCP guidelines, which are accepted worldwide.

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### **Key messages**

pertaining  
to AIDS  
vaccines

**All clinical trials, including AIDS vaccine trials, are carefully reviewed before they receive approval to begin, to make sure 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.**

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**For  
further  
information**

Code of Federal Regulations and ICH Guidelines as adopted by the FDA, 2002-2003. Online, searchable version <<http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>>.

DHEW publication (OS) 78-0012. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 18 April 1979. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research <<http://www.fda.gov/oc/ohrt/irbs/belmont.html>> (US Government Printing Office, Washington, DC).

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Linked at <<http://www.ich.org/cache/compo/276-254-1.html>>. (Copyright ICH Secretariat, Geneva, Switzerland, 1996).

OECD principles of good laboratory practice in Annex II of the decision of the council concerning the mutual acceptance of data in the assessment of chemicals. (C(81)30 (final)) <<http://www.oecd.org/env/glp>>.

UNDP/Worldbank/WHO. Good Laboratory Practice: quality practices for regulated non-clinical research <<http://www.who.int/tdr/publications/publications/>>.

Report of the WHO/UNAIDS Vaccine Advisory Committee <[http://www.who.int/vaccine\\_research/diseases/hiv/policy/en/vac\\_2001\\_nov.pdf](http://www.who.int/vaccine_research/diseases/hiv/policy/en/vac_2001_nov.pdf)>.

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**Foot notes**

1 Elsewhere in the Vaccine Literacy Core Content, IECs may be informally referred to as 'ethics committees'.

2 In some cases in certain countries, additional types of review may include biosafety 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 it is mandatory for it to be reviewed by both the IRB and the CONEP. International projects also need to have been approved by an ethics committee in their country of origin.

4 This is a technical analysis of the safety of the product and not an ethics review process, but it's nonetheless mandatory, and often the CONEP requests for their technical input before approving a project that involves some kind of GMO.

# 11

## Preparing for Access and Use of an AIDS Vaccine

**In this chapter** **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 can be quickly distributed to and used by the people who need it most throughout the world.**

### **This chapter discusses**

- Conducting AIDS vaccine trials in developing countries
- Challenges to introduction, access, and use of a vaccine

## Summary points

- 1** Historically, vaccines have taken up to 20 years from approval and licensure to reach developing countries, where they are most needed.
- 2** Vaccines should be developed for countries that are hardest hit by HIV/AIDS, and therefore need to be tested in those countries.
- 3** Addressing potential barriers to access during vaccine development and clinical trials can potentially make access faster once licensure has been achieved.
- 4** Potential barriers to immediate access include: acceptability, regulatory capacity for licensure financing mechanisms, ability to match demand and supply, sensible delivery systems, and manufacturing capacity.
- 5** The level of acceptability of an AIDS vaccine among both stakeholders and potential users could depend upon its level of efficacy; concerns about behaviour change; product characteristics; stigma and risk-perception; and myths and rumours.

# 11

## Key concepts



### Conducting AIDS vaccine trials in developing countries

AIDS vaccine trials are conducted in both developed and developing countries. There are various factors that may affect how a vaccine works that differ from place to place. It is logical to test AIDS vaccines in various regions where they are likely to be used – including developing countries – to ensure that they are appropriate for those settings. Testing vaccines in these countries will provide data needed to speed approval and access where AIDS vaccines are needed most. Other vaccines that have been developed and tested in the US and Europe have taken up to 20 years to become available in developing countries, and often at prices that limit their use. For example, while a vaccine against hepatitis B virus has been available since 1981, about 60% of the world's children still do not receive the vaccine. The urgency of the AIDS epidemic makes it crucial that no such delay occurs with an AIDS vaccine.

Testing vaccines in developing and developed countries at the same time will help 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 specific type of HIV that the population encounters. 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 between 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 it is appropriate to local conditions* - Conducting clinical trials in-country may demonstrate that the vaccine can be delivered effectively in the local conditions.
- *Facilitating national regulatory approval* - Conducting trials in developing countries will provide relevant data to support vaccine approval.
- *Raising awareness and preparing communities* - The process of conducting a clinical trial will help increase knowledge and awareness of AIDS vaccines among key stakeholders and communities, which will help ready communities for a vaccine when one is available.



**Future global access to AIDS vaccines is fundamental to the goal of AIDS vaccine development.**

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**Challenges to introduction, access and use**

There are many challenges to introducing a new vaccine into a country, making it accessible to the populations that need it, and ensuring that it is used. It is important to begin to address these challenges and to prepare for access well before a vaccine is proven efficacious or licensed. Such advance planning can help accelerate access to and uptake of a new vaccine.

### **Tiered pricing: An effective strategy for access**

**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. Developing countries would receive the vaccine at a lower price, made possible by higher prices paid by developed countries. The system allows developing countries to receive favourable prices, but will also provide commercial firms with a reasonable profit on vaccine production.**

### **Challenge 1: Global funding, finance mechanisms, and pricing**

Financial mechanisms must be set up to ensure that vaccines are affordably priced and 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, especially in wealthy countries, as well as multinational funding bodies like the Global Fund to Fight AIDS, TB, and Malaria, and organizations like the World Bank.

To help guarantee sufficient funding, mechanisms for purchase and delivery can be put into place including, for example, “advance purchase commitments” from funders. If such commitments are made, governments will likely be more willing and able to create systems for delivery. Ensuring demand may also encourage investment by pharmaceutical and biotech firms who may be reluctant to invest in developing a product that might only have a small profit.

### **Challenge 2: Acceptability**

Acceptability of an AIDS vaccine is important on various levels. If it is acceptable to policy makers 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 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**

Just as no vaccine that is currently available for other diseases provides absolute protection to everyone who receives it, an AIDS vaccine will not offer full protection for everyone (see **Chapter 4** for more information on 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 effectiveness may influence acceptability on all levels. Governments, for example, may consider the vaccine's efficacy level in decisions to make vaccines a public health priority, medical providers in their decisions to promote and/or recommend its use, and individuals in their decisions to use a vaccine. 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 the epidemic in high incidence countries if given to a large segment of the population.<sup>1</sup>

An AIDS vaccine, as with any vaccine, must be combined with other prevention efforts and treatment programs.

### **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. Some policy makers or medical providers might be concerned that if partially effective 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 needle sharing or other use of contaminated needles. 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 the existing prevention and risk-reduction strategies and integrate vaccines and microbicides 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



multiple doses; an oral vaccine might be more acceptable than an injected vaccine for some people. Unfortunately it is unlikely that scientists will have 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 access to and use of AIDS vaccines. First, stigma can affect risk perception. People often believe that only certain stigmatized 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 stigmatized 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.

### ***Myths and rumours***

Undue fears, myths and rumours 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 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 with a vaccine?**

Since an AIDS vaccine will most likely be partially effective it will be very important not to create 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, abstinence, and clean needles 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 & Use**

In order to plan for manufacturing and delivery of a vaccine it is important to predict the number of people who will be willing to be vaccinated as well as 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 predicted level of efficacy of the vaccine
- Length of time a vaccine offers protection
- Number of doses required for protection
- Acceptability and likelihood of use (see above)
- Affordability and predicted price of the vaccine
- Country capacity for vaccine or service delivery

Information about the demand for an AIDS vaccine can help plan for production, delivery, education programmes, and financial needs.

**Challenge 4: Delivery**

Unlike current vaccination programmes, most of which benefit children, AIDS vaccines will first be available for adults and adolescents who may be difficult to reach through current vaccine delivery systems. Efforts to reach the highest-risk populations such as sex-workers or injection drug users may be even more difficult. Strategies for delivery should be well planned and placed within the broader national AIDS prevention agenda. They should also be compatible with national vaccine programmes.

A delivery strategy should address:

- Transportation
- 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

**Challenge 5: Regulatory Approval / Licensure**

In order to make a vaccine available in a country it must be licensed or approved by national regulatory authorities, such as a country's Ministry of Health or the Food and Drug Administration (FDA) in the United States. Historically, there have been delays of several years between initial licensure in an industrialized country and widespread approval in developing countries. Vaccine developers often seek approval first in those places where there is a more profitable market, which is usually in industrialized or developed 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 assure a smoother approval process. Efforts to better coordinate and standardize regulatory processes across regions and internationally may facilitate approval.

Approval in some developing countries usually relies on prior approval by regulatory agencies in industrialized countries. Stronger regulatory review mechanisms are needed in developing countries, and should be better coordinated internationally. One potential approach is to pool expertise and resources across regions and link with more experienced regulatory bodies for technical support.

### **Challenge 6: Manufacturing**

Manufacturing a novel AIDS vaccine will require hundreds of millions of dollars (US) 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 create incentive for large companies to work on scale-up for manufacturing or to provide small biotechnology companies or academic developers with the resources to do this work. One effective way to achieve these goals is by creating partnerships between the public and private sectors.

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### **Key messages**

pertaining  
to AIDS  
vaccines

**Historically vaccines have taken up to 20 years after approval and licensure in developed countries to be available to people in countries where they are most needed. This delay must not happen in the case of an AIDS vaccine.**

**There are concerns 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.**

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**For  
further  
information**

**AIDS Vaccine Advocacy Coalition (AVAC) Report 2004: AIDS Vaccine Trials – Getting the Global House in Order** <[http://avac.org/pdf/reports/2004AVACReport\\_High.pdf](http://avac.org/pdf/reports/2004AVACReport_High.pdf)> (May 2004).

**AIDS Vaccine Handbook: Global Perspectives. Second Edition, the AIDS Vaccine Advocacy Coalition (AVAC).** Edited by Patricia Kahn, 2004. <<http://www.avac.org/primer.htm>>.

**Developing Vaccines to Prevent HIV and AIDS: An Introduction for Community Groups, 2nd edition (ICASO):** <http://www.icaso.org/icaso/vaccines/Vaccine%20Primer,%202nd%20Edition-2002-web.pdf>

**Esparza J, Bhamarapravati N. Accelerating the development and future availability of HIV-1 vaccines: why, when, where, and how? Lancet 2000; 355: 2061-2066.**

**Global Campaign for Microbicides:** [www.global-campaign.org](http://www.global-campaign.org)

**IAVI Access Blueprint: AIDS Vaccines for the World: Preparing Now to Assure Access:** <http://www.iavi.org/access/blueprint.htm>

**International Partnership for Microbicides:** [www.ipm-microbicides.org](http://www.ipm-microbicides.org)

**Public health considerations for the use of a first generation HIV vaccine. Report from a WHO-UNAIDS-CDC Consultation, Geneva, 20-21 November 2002. AIDS 2003, 17: W1 – W10.**

**For a complete list of literature on demand and acceptability, please see “Demand for a preventive HIV vaccine: A review, Policy Research Working Paper, February 2005”, available at <http://www.iavi.org>**

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**Foot notes**

**1** BCG, the vaccine against Tuberculosis, has proven only partially effective. The vaccine, however, is recommended for countries where TB is endemic since it will at least reduce the incidence of TB in the population. Another example of a common vaccine that is partially effective is the influenza vaccine.

## A

**adjuvant:** a substance sometimes included in a vaccine formulation to enhance or modify the immune-stimulating properties of a vaccine.

**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 standardized skin tests. A small amount of solution containing an antigen known to cause a response, such as tetanus, mumps, or candida, 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, neutralizes, 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**.)

**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

**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**.)

**CD:** abbreviation for “cluster of differentiation,” referring to cell surface molecules that are used to identify stages of maturity of immune cells, for example, CD4+ T cells.

**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 immunized 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 immunity (correlates of protection):** 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**.)

## D

**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.

## E

**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 colour 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.

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

**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.

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## F

**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.

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## G

**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<sup>+</sup> 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.

**gp160:** glycoprotein 160, a precursor of HIV envelope proteins gp41 and gp 120.

# H

**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.

**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.

**immunization:** 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:** memory cells are 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. (See also **anamestic response**.)

**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**.)

**microencapsulated:** surrounded by a thin layer of biodegradable substance referred to as a microsphere. A means of protecting a drug or vaccine antigen from rapid breakdown. Microencapsulation may also enhance an antigen's absorption and the immune response to that antigen.

**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 recognizes 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.

## N

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**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 recognize 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.

## O

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**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.

## P

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**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, it's 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 closely monitored clinical trial of a vaccine conducted in a small number of healthy volunteers. A Phase 1 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 2 trials enroll some volunteers who have the same characteristics as persons who would be enrolled in an efficacy (Phase 3) trial of a vaccine. Phase 2 trials enroll up to several hundred participants and have more than one arm.

**Phase III vaccine trial:** large controlled 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 3 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.

**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:** a vaccine designed to prevent HIV infection.

**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).

**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.

**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.

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## R

**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 and other viruses that carry their genetic material in the form of RNA rather than DNA and have 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.

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## S

**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.

**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 so heterogeneous, 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<sup>+</sup> T cells per cubic millimeter of blood is often used as a surrogate marker.

**syncytia:** giant cells formed by the fusion of an HIV-infected blood cell with one or more uninfected ones.

## T

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**T cell:** white blood cell critical to the immune response. Among these are CD4<sup>+</sup> T cells and CD8<sup>+</sup> 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.

## V

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**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.

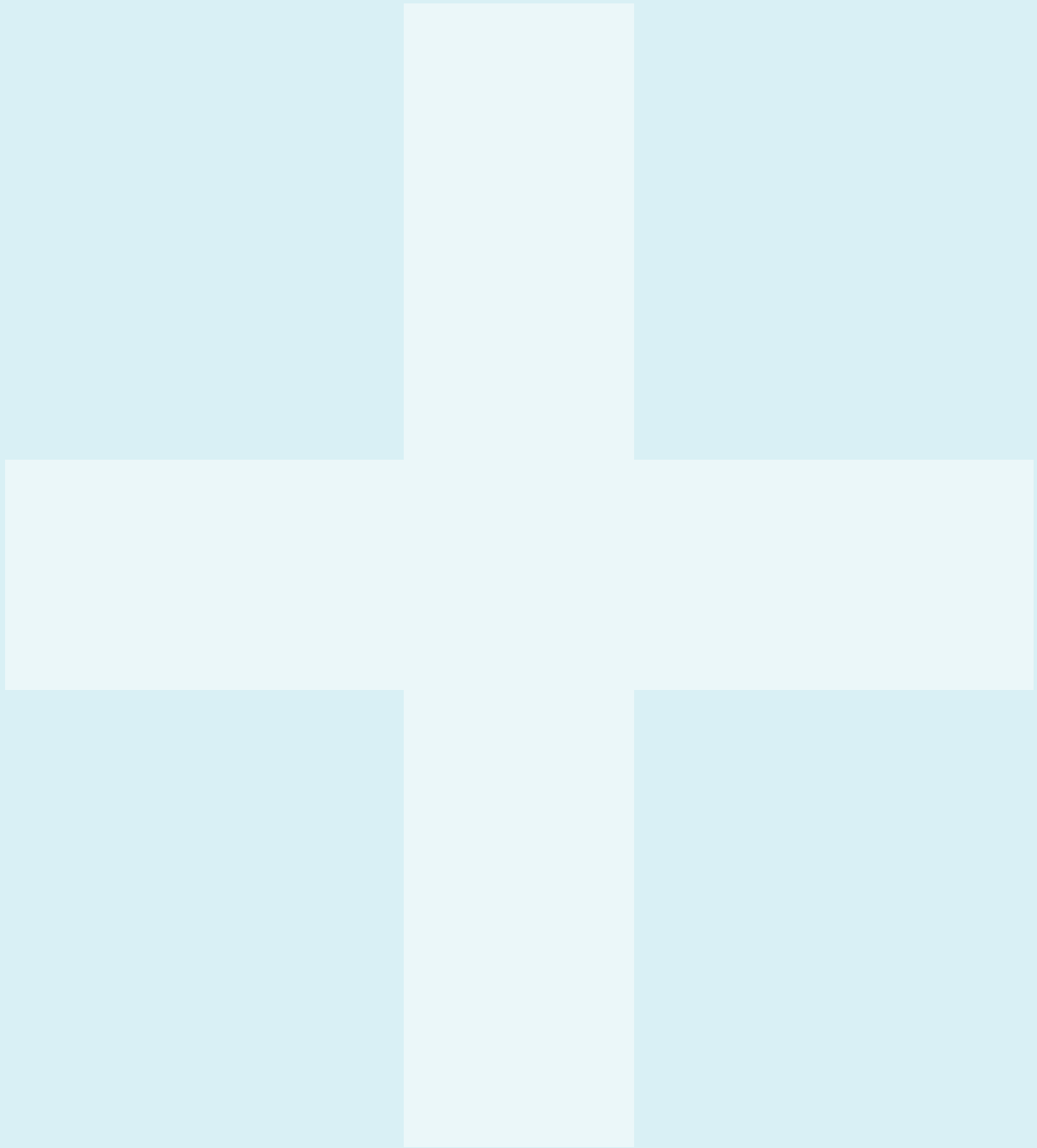
**virion:** a mature infectious virus particle existing outside a cell.

**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.

## W

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**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.



## 1

### Chapter

Developing Vaccines to Prevent HIV and AIDS: An introduction for community groups 2nd edn  
<<http://www.icaso.org/icaso/vaccines/Vaccine%20Primer,%202nd%20Edition-2002-web.pdf>>.

Global Campaign for Microbicides <[www.global-campaign.org](http://www.global-campaign.org)>.

International Partnership for Microbicides <[www.ipm-microbicides.org](http://www.ipm-microbicides.org)>.

UNAIDS, and UNAIDS Best Practices Collection. AIDS Epidemic Update. <[www.unaids.org](http://www.unaids.org)> (December 2003).

## 2

### Chapter

AIDS Vaccine Advocacy Coalition (AVAC) Report 2004: AIDS Vaccine Trials – Getting the Global House in Order  
<[http://avac.org/pdf/reports/2004AVACReport\\_High.pdf](http://avac.org/pdf/reports/2004AVACReport_High.pdf)> (May 2004).

AIDS Vaccine Handbook: Global Perspectives. Second Edition, the AIDS Vaccine Advocacy Coalition (AVAC). Edited by Patricia Kahn, 2004. <<http://www.avac.org/primer.htm>>.

Developing Vaccines to Prevent HIV and AIDS: An Introduction for Community Groups 2nd edition <<http://www.icaso.org/icaso/vaccines/Vaccine%20Primer,%202nd%20Edition-2002-web.pdf>>.

Public health considerations for the use of a first generation HIV vaccine. Report from a WHO-UNAIDS-CDC Consultation, Geneva, 20–21 November 2002. AIDS 17, W1–W10 (2003).

## 3

### Chapter

Djomand, G., Peiperl, L. & Keefer, M. Introduction to HVTN Vaccine Portfolio for Non-Scientists. Online PowerPoint presentation from HVTN. <[http://www.hvtn.org/pdf/community/Non-ScientistsPres\\_FGM.ppt](http://www.hvtn.org/pdf/community/Non-ScientistsPres_FGM.ppt)> (2001).

Essential Medical Immunology <<http://www.roitt.com>>.

International Council of AIDS Service Organisations. The Science of HIV/AIDS: An introduction for community groups <<http://www.icaso.org/icaso/vaccines/Science%20Primer%20-%20E%20-%20Web.pdf>>.

Kuby, J. Immunology, fourth edition (W.H. Freeman and Company, New York, 2000).

NIH HIV Vaccine Glossary <<http://www.niaid.nih.gov/factsheets/GLOSSARY.htm>>.

NIH Publication 03-5423. Understanding the Immune System, How it Works (US Department of Health and Human Services, National Institute of Allergy and Infectious Diseases) <[http://www.niaid.nih.gov/publications/immune/the\\_immune\\_system.pdf](http://www.niaid.nih.gov/publications/immune/the_immune_system.pdf)>.

## 4

### Chapter

HIV Preventive Vaccine Fact Sheet (US Department of Health and Human Services, National Institute of Allergy and Infectious Diseases) <<http://www.aidsinfo.nih.gov/other/whatisvac.pdf>> (March 2003).

International Council of AIDS Service Organisations. The Science of HIV/AIDS: An introduction for community groups <<http://www.icaso.org/icaso/vaccines/Science%20Primer%20-%20E%20-%20Web.pdf>>.

NIH HIV vaccine glossary <<http://www.niaid.nih.gov/factsheets/GLOSSARY.htm>>.

NIH Publication 03-4219. Understanding Vaccines, What They Are, How They Work (US Department of Health and Human Services, National Institute of Allergy and Infectious Diseases) <<http://www.niaid.nih.gov/publications/vaccine/pdf/undvacc.pdf>>.

Vaccines 4th edn (eds Plotkin, S.A. & Orenstein, W.A.) (WB Saunders, 2004).



## 5

### Chapter

AIDS Vaccine Advocacy Coalition 2004 Report: Getting the Global House in Order <[http://www.avac.org/pdf/reports/2004AVACReport\\_High.pdf](http://www.avac.org/pdf/reports/2004AVACReport_High.pdf)> (May 2004).

AIDS Vaccine Fails to Show Efficacy in Thai Trial <<http://www.avac.org/AIDSVAXthai.htm>> (12 November 2003).

AIDS Vaccine Handbook: Global Perspectives. Second Edition, the AIDS Vaccine Advocacy Coalition (AVAC). Edited by Patricia Kahn, 2004. <<http://www.avac.org/primer.htm>>.

Challenges in Designing HIV Vaccines <<http://www.niaid.nih.gov/factsheets/challvacc.htm>>.

Chang, M.L., Vitek, C. & Esparza, J.; WHO-UNAIDS-CDC. Public health considerations for the use of a first generation HIV vaccine. Report from a WHO-UNAIDS-CDC Consultation, Geneva, 20–21 November 2002. AIDS 17, W1–W10 (2003).

Djomand, G., Peiperl, L. & Keefer, M. Introduction to HVTN Vaccine Portfolio for Non-Scientists. Online PowerPoint presentation from HVTN. <[http://www.hvtn.org/pdf/community/Non-ScientistsPres\\_FGM.ppt](http://www.hvtn.org/pdf/community/Non-ScientistsPres_FGM.ppt)> (2001).

Do Clades Matter for HIV Vaccines? IAVI Report 7 (2), May–August 2003 <<http://www.iavi.org/iavireport/Issues/0803/IAVIRReportMay-August2003.asp>>.

Heyward, W.L., MacQueen, K.M. & Goldenthal, K.L. HIV vaccine development and evaluation: realistic expectations. AIDS Res. Hum. Retroviruses 14, S205–S210 (1998).

The Science of HIV/AIDS Vaccines: An introduction for community groups <<http://www.icaso.org/icaso/vaccines/Science%20Primer%20-%20E%20-%20Web.pdf>>.

Understanding the Results of the AIDSVAX Trial <<http://www.avac.org/pdf/UnderstandingAIDSVAX.pdf>> (14 May 2002).

## 6

### Chapter

Code of Federal Regulations and ICH Guidelines as adopted by the FDA, 2002–2003. Online, searchable version <<http://www.access.gpo.gov/nara/cfr/cfr-table-search.html> - page1>.

Developing Vaccines to Prevent HIV and AIDS: An Introduction for Community Groups 2nd edition <<http://www.icaso.org/icaso/vaccines/Vaccine%20Primer,%202nd%20Edition-2002-web.pdf>>.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Copyright ICH Secretariat, Geneva, Switzerland.  
Clinical Research Resources <<http://www.clinicalresearchresources.com>>.

National Institutes of Health website on Clinical Trials <<http://www.clinicaltrials.gov/ct/info/resources>>.

## 7

### Chapter

Bass, E. Ethics, antiretrovirals and prevention trials: An online debate. IAVI Report 7 (3), September 2003–January 2004 <<http://www.iavi.org/iavireport/Issues/0104/EthicsAntiretroviralsandPreventionTrials.asp>>.

Bass, E. Raising hopes and many questions: Vaccine trial sponsors' new approaches to providing antiretrovirals for trial volunteers. IAVI Report 7 (3), September 2003–January 2004 <<http://www.iavi.org/iavireport/Issues/0104/NewApproachestoProvidingAntiretrovirals.asp>>.

Ethical Considerations in HIV Preventive Vaccine Research <[http://www.unaids.org/html/pub/Publications/IRC-pub02/JC765-EthicalCons-Repr\\_en\\_pdf.htm](http://www.unaids.org/html/pub/Publications/IRC-pub02/JC765-EthicalCons-Repr_en_pdf.htm)> (May 2000).

Finding the Way: Community and science working towards a vaccine for HIV. Produced by South African HIV Vaccine Action Campaign (SAHIVAC), funded in part by South African AIDS Vaccine Initiative (SAAVI) (2001).

HIV Vaccine Trial in Uganda – Frequently Asked Questions <<http://www.iavi.org/uganda/pdf/brochure.pdf>>.

UNAIDS. Voluntary counselling and testing (VCT): UNAIDS technical update <<http://www.unaids.org/en/in-focus/topic+areas/counselling+and+voluntary+counselling+and+testing.asp>> (UNAIDS, Geneva, May 2000).

## 8

### Chapter

Developing Vaccines for HIV and AIDS: An Introduction for Community Groups. <<http://www.icaso.org/icaso/vaccines/Vaccine%20Primer,%202nd%20Edition-2002-web.pdf>> (The International Council for AIDS Service Organisations (ICASO), Canada, 2002).

Ethical Considerations in HIV Preventive Vaccine Research, UNAIDS guidance document. <[www.unaids.org](http://www.unaids.org)> (UNAIDS, Geneva, 2000).

Kapoor, S. Gender considerations in HIV vaccine trials (position paper, IAVI, 2004).

Nath, M.B. Gender, HIV and Human Rights: A Training Manual (UNIFEM, 2000).

Parker, R. & Aggleton, P. HIV/AIDS-related Stigma and Discrimination: A Conceptual Framework and an Agenda for Action <[www.popcouncil.org](http://www.popcouncil.org)> (The Horizons Programme, Population Council, 2002).

Richter, Lindegger, Karim & Gasa. Guidelines for the development of culturally sensitive approaches to obtaining informed consent for participation in HIV vaccine-related trials (paper commissioned by UNAIDS). <<http://www.hs.unp.ac.za/mind/icunaids.htm>> (1999).

Special Report: Women and AIDS vaccines. IAVI Report 5 (8), July–September 2001.

## 9

### Chapter

AIDS Vaccine Handbook: Global Perspectives. Second Edition, the AIDS Vaccine Advocacy Coalition (AVAC). Edited by Patricia Kahn, 2004. <<http://www.avac.org/primer.htm>>.

Developing Vaccines to Prevent HIV and AIDS: An Introduction for Community Groups 2nd edn <<http://www.icaso.org/icaso/vaccines/Vaccine%20Primer,%202nd%20Edition-2002-web.pdf>>.

DHEW publication (OS) 78-0012. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 18 April 1979. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research <<http://www.fda.gov/oc/ohrt/irbs/belmont.html>> (Washington, D.C.: U.S. Government Printing Office).

Ethical Considerations in HIV Preventive Vaccine Research <[http://www.unaids.org/html/pub/Publications/IRC-pub02/JC765-EthicalCons-Repr\\_en\\_pdf.htm](http://www.unaids.org/html/pub/Publications/IRC-pub02/JC765-EthicalCons-Repr_en_pdf.htm)> (May 2000).

National Institutes of Health. Ethical Framework for Clinical Research <<http://www.bioethics.nih.gov/research/humanres/ethicsframework.pdf>>.

Richter, L.M., Lindegger, G.C., Abdool Karim, Q. & Gasa, N. Guidelines for the development of culturally sensitive approaches to obtaining informed consent for participation in HIV vaccine-related trials (Discussion Paper, University of Natal, 1999).

## 10

### Chapter

Code of Federal Regulations and ICH Guidelines as adopted by the FDA, 2002-2003. Online, searchable version <<http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>>.

DHEW publication (OS) 78-0012. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 18 April 1979. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research <<http://www.fda.gov/oc/ohrt/irbs/belmont.html>> (US Government Printing Office, Washington, DC).

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Linked at <<http://www.ich.org/cache/compo/276-254-1.html>>. (Copyright ICH Secretariat, Geneva, Switzerland, 1996).

OECD principles of good laboratory practice in Annex II of the decision of the council concerning the mutual acceptance of data in the assessment of chemicals. (C(81)30 (final)) <<http://www.oecd.org/env/glp>>.

UNDP/Worldbank/WHO. Good Laboratory Practice: quality practices for regulated non-clinical research <<http://www.who.int/tdr/publications/publications/>>.

Report of the WHO/UNAIDS Vaccine Advisory Committee <[http://www.who.int/vaccine\\_research/diseases/hiv/policy/en/vac\\_2001\\_nov.pdf](http://www.who.int/vaccine_research/diseases/hiv/policy/en/vac_2001_nov.pdf)>.

# 11

## Chapter

AIDS Vaccine Advocacy Coalition (AVAC) Report 2004: AIDS Vaccine Trials – Getting the Global House in Order <[http://avac.org/pdf/reports/2004AVACReport\\_High.pdf](http://avac.org/pdf/reports/2004AVACReport_High.pdf)> (May 2004).

AIDS Vaccine Handbook: Global Perspectives. Second Edition, the AIDS Vaccine Advocacy Coalition (AVAC). Edited by Patricia Kahn, 2004. <<http://www.avac.org/primer.htm>>.

Developing Vaccines to Prevent HIV and AIDS: An Introduction for Community Groups, 2nd edition (ICASO): <http://www.icaso.org/icaso/vaccines/Vaccine%20Primer,%202nd%20Edition-2002-web.pdf>

Esparza J, Bhamarapavati N. Accelerating the development and future availability of HIV-1 vaccines: why, when, where, and how? *Lancet* 2000; 355: 2061-2066.

Global Campaign for Microbicides: [www.global-campaign.org](http://www.global-campaign.org)

IAVI Access Blueprint: AIDS Vaccines for the World: Preparing Now to Assure Access: <http://www.iavi.org/access/blueprint.htm>

International Partnership for Microbicides: [www.ipm-microbicides.org](http://www.ipm-microbicides.org)

Public health considerations for the use of a first generation HIV vaccine. Report from a WHO-UNAIDS-CDC Consultation, Geneva, 20-21 November 2002. *AIDS* 2003, 17: W1 – W10.

For a complete list of literature on demand and acceptability, please see "Demand for a preventive HIV vaccine: A review, Policy Research Working Paper, February 2005", available at <http://www.iavi.org>

