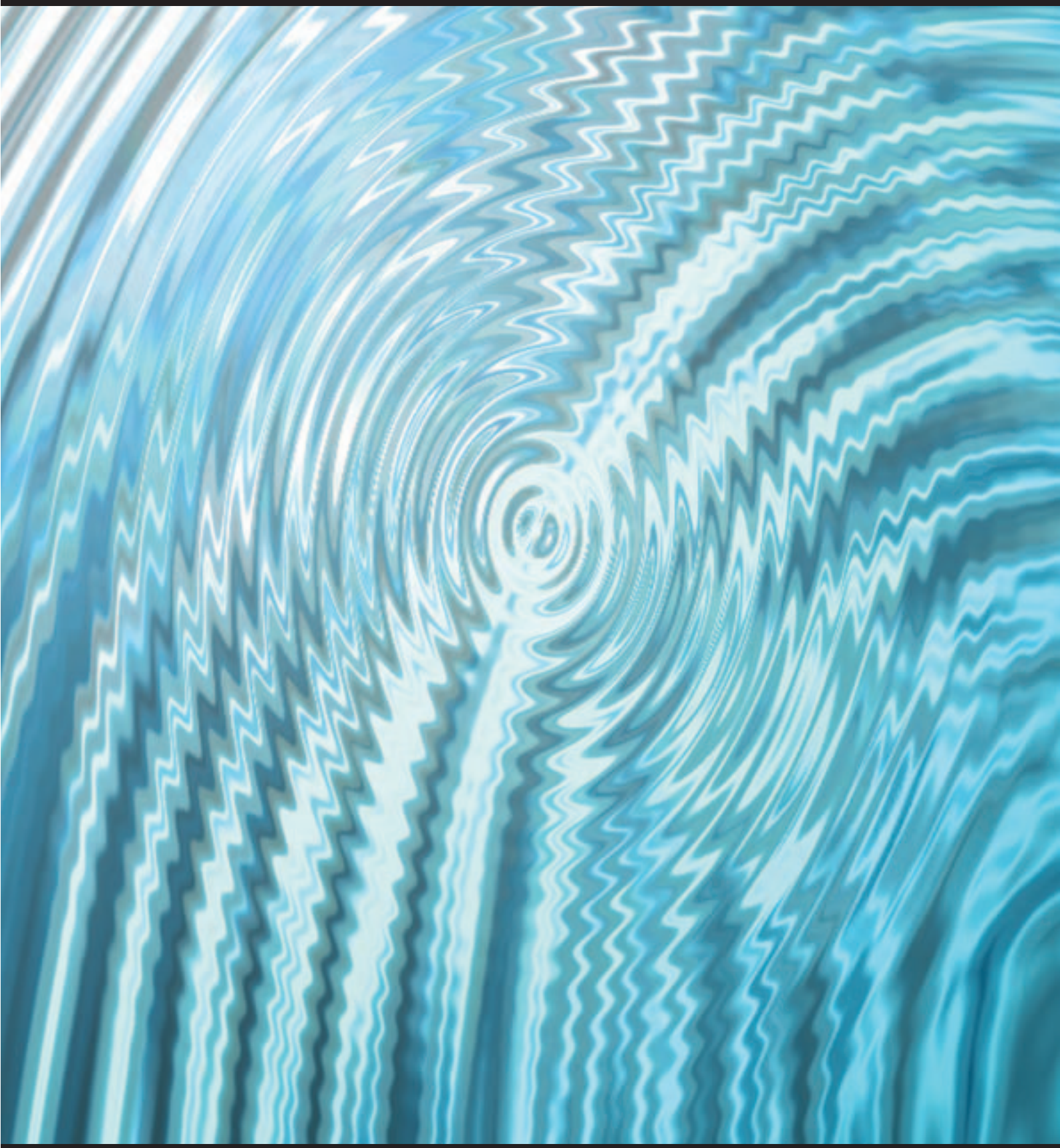
Understanding AIDS Vaccines

An Anthology of Primers from *VAX*



A publication of the *IAVI Report*

The world needs an AIDS vaccine

AIDS has been called the Modern Plague, and that description is no exaggeration. More than 20 million children, women and men have already lost their lives to this devastating disease, and over 40 million more are currently infected. AIDS is now the number one killer in sub-Saharan Africa and burgeoning epidemics threaten many parts of Asia. Around the world, 14,000 people are newly infected each day. The brunt of the pandemic is felt in developing nations, and is not only being measured in personal, family and community struggles but also gravely threatens the economic and political stability of whole regions of the world.

There has been recent progress in making antiretroviral (ARV) drugs available in these regions, with sweeping pledges made to improve global access to these powerful drugs that can greatly improve the quality of life of HIV-infected people. When these drugs do become more widely available it will be a great stride forward that will alleviate much human suffering. But ARV drugs will never be the whole answer; people will continue to become infected with HIV. The history of public health shows us that there is one crucial facet of an effective response to a pandemic like AIDS: a preventive vaccine.

Scientists alone cannot find an AIDS vaccine. Communities, policymakers, government leaders and AIDS activists all have important roles to play in this urgent mission. Whether you are new to AIDS vaccines or seeking additional tools for education and outreach, *Understanding AIDS Vaccines* is designed to deepen and broaden your grasp of key concepts, from immunology to vaccine manufacturing to the clinical trials process.

The articles in *Understanding AIDS Vaccines* originally appeared in *VAX*, a monthly bulletin featuring short, nontechnical articles on AIDS vaccine research from the *IAVI Report*, the newsletter of the International AIDS Vaccine Initiative (IAVI). IAVI is a global organization whose mission is to ensure that an effective, preventive AIDS vaccine is developed as soon as possible and that it will be accessible to all throughout the world. As part of that mission we are committed to providing accurate, reliable, engaging and timely information about AIDS vaccine research, the scientific issues that make them such a complex challenge and the hurdles that have to be overcome to get vaccine candidates into human trials. To subscribe to or learn more about our publications and products, please see page 11 or visit our website (www.iavireport.org).

The development of an effective preventive AIDS vaccine is a daunting endeavor, but there are good scientific reasons to think that it will eventually be realized. It will require an effective combination of basic and clinical research, both laboratory work and testing vaccine candidates in humans. Right now there are about 30 clinical trials testing different AIDS vaccine candidates. But more needs to be done.

We hope you enjoy and are informed by this *VAX* Primer anthology.

Join us in the fight against AIDS. The world needs an AIDS vaccine.

The IAVI Report team

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HOW ARE AIDS VACCINES TESTED?

Contrary to some people's fears, AIDS vaccines are not tested by vaccinating people and then deliberately exposing them to HIV. This strategy is rarely used for tests of any experimental vaccine, and never for a vaccine against a disease as serious as HIV. Rather, vaccines are evaluated through a series of trials, called Phase I, Phase II and Phase III. While these trials serve different purposes, all of them involve volunteers who have been counseled about the vaccine being studied and the risks and benefits of trial participation. This is called the informed consent process, and it is designed to ensure that trial volunteers are well-informed of their rights and responsibilities.

Phase I trials

Phase I trials enroll small numbers of people who are at low risk for HIV. The primary goal of these first trials is to determine the safety of these products for human use. Vaccines in Phase I trials have already been through extensive testing in animals, which give a good indication of the products' overall safety and possible toxicities. Once vaccinated, the volunteers are monitored to determine whether or not the vaccine causes any side effects. They also periodically have their blood drawn, and scientists analyze these blood samples to see whether the vaccine has induced immune responses to HIV. It's important to remember that these responses may or may not protect against HIV—only later, larger trials can determine this.

Phase II trials

Phase II trials enroll larger numbers of people and may include some individuals who are at higher risk for HIV. They yield further data on safety and side effects, and on immune responses to the vaccine in this larger population. Phase I and Phase II trials also gather information on vaccine doses and the best schedule for a series of immunizations (most AIDS vaccines in development will require a sequence of immunizations delivered over several months or longer).

Phase III trials

Phase III trials are the true test of whether a vaccine provides any protection against infection or disease. These trials generally evaluate an experimental vaccine by comparing the rate of infection in individuals given the experimental vaccine with the rate of infection in a group given an inactive substance, called a placebo. Neither the trial staff nor the volunteers know who has been assigned to receive the vaccine or the placebo until the study is over. This is called a blinded study.

The trials make the assumption that some of them will be exposed to HIV, i.e., through unprotected sex, over the course of the study period. Prior to starting a Phase III trial, vaccine developers gather information on rates of infection, or incidence, in different regions and communities, since this is what determines how many volunteers will be needed and for how long they will have to be followed. The higher the incidence, the fewer volunteers and/or shorter the follow-up period required.

For HIV vaccine trials, these volunteers are usually followed for a period of 2-3 years. Throughout the entire trial, volunteers receive regular HIV/AIDS tests and risk reduction counseling, which reinforces the message that they should not consider themselves to be protected. Those who nevertheless become infected will be monitored to see whether the vaccine has an impact on viral load or $CD4^+$ T cell counts, which are markers of the stage of HIV disease. Once completed, the study is "unblinded" and scientists look for differences in infection rates between the vaccine and placebo groups and, in infected participants, in viral load and $CD4^+$ T cell counts. If differences are detected, statistical tests are performed to determine whether they are due to the vaccine, or whether they are coincidental. A "statistically significant" result is one which is very unlikely to arise by coincidence, and—if the trial was well designed and carried out—gives a solid scientific answer on whether, and how well, the vaccine works.

In an ideal scenario, a Phase III trial will yield clear answers. But in the real world there may still be open questions, so in practice there are sometimes multiple Phase III trials of the same product.

Once efficacy is proven, vaccines must then go through an approvals process before they are licensed for use. Even then, countries may need time to develop sites and strategies for delivering the vaccine. These steps can take as long as the trial itself. This is one reason why it is important to design and build these systems in advance in the countries where they are not already in place.

Primer
understanding
viral
diversity

WHY ARE THERE SO MANY DIFFERENT VERSIONS OF HIV?

Globally, more than 40 million people are infected with HIV. The vast majority of these people experience similar symptoms. Those people that have access to treatment have broadly similar responses to prescribed drug regimens, regardless of where they live. In these respects all HIV-positive people carry the same virus. But this does not mean that everyone is infected with an identical version of HIV. In fact there are many, many different versions of HIV. These can be thought of as members of a large family: they are different from, but related to, each other. The broad term for this phenomenon is viral diversity.

The usual way that researchers look at the differences between HIV strains is to examine the 'genome' or genetic code. All versions of HIV have similar but distinct genomes. Researchers can compare different HIV samples from different parts of the world using a technique called sequencing, which essentially "reads" the viral genome. The genome consists of a chain-like strand of building blocks called 'nucleotides.' There are four different nucleotides and long chains of these nucleotides make up a genome. The HIV genome contains all the information HIV needs to infect cells, make millions of copies of itself and cause disease. The sequence of nucleotides in a strand identifies the virus, like a fingerprint.

By sequencing pieces from thousands of viral genomes, researchers have been able to map out the "family tree" of HIV. At the root of the tree, there are three 'groups' called M, N and O. Group M is responsible for the current AIDS pandemic.

Where did these groups come from? The answer lies in the origins of HIV itself. HIV is a relative of a virus called SIV (simian immunodeficiency virus) found in non-human primates, like chimpanzees and monkeys. Researchers think that some time in the first half of the 20th century SIV was passed from a non-human primate to a human, perhaps through a bite from a chimpanzee or through eating 'bushmeat.' The virus crossed from one species (chimpanzee) to another (humans). It was able to adapt to the human body and became what is now called HIV. Animal-to-human transmission is thought to have happened several times in different locations. Today's groups probably arose from these separate events of 'cross-species transmission.'

Over time additional genetic diversity has developed within each group. Viruses in Asia have developed differently from those in Africa. These regional subgroups are called clades, or genetic subtypes. Viruses within the same clade have genetic sequences that are more similar to one another than they are to sequences from other clades. Group M is split into nine clades. These clades have geographic distribution patterns. Clade C circulates in South Africa, India and parts of China. Clades A and D are common in east Africa and clade B is common in North America and western Europe.

HIV diversity is still increasing due to several processes. One process is called mutation. HIV reproduces (or replicates) in an infected person by making more copies of its genome. When it copies itself it frequently makes errors, called mutations. Mutations are the main reason why each person's viral population is slightly different, even from the HIV that he or she was originally infected with.

The other process, recombination, can happen if a person is infected with two different versions of HIV. It is possible for people who are repeatedly exposed to HIV to become infected with more than one virus—including viruses from different clades. (In some geographic regions there is a major clade plus smaller proportions of other clades.) Then these viruses can sometimes exchange portions of their genomes to form a new 'recombinant' virus that has parts of genes from each parent virus. Recombinant strains can be passed from one person to another. In some regions the major circulating HIV is a recombinant virus.

A problem for vaccines?

Viral diversity poses challenges for vaccine design. HIV vaccines are constructed using small pieces of the virus, called 'immunogens.' When a person is given a vaccine, these immunogens are "seen" by the immune system. This causes an immune response that creates defenses against the pieces of HIV. The goal of an AIDS vaccine is to get the immune system to create strong defenses that stop infection or disease if the person is later exposed to the complete virus [HIV].

One key question is: will fragments from one clade cause immune responses that protect against other clades? The same question applies to viruses within the same clade that have mutated, and are now very different from the original virus used to make the candidate vaccine.

Vaccine researchers are trying a number of different strategies to address these questions. One approach involves making vaccines that are not based on a single virus. Instead hundreds of HIV genomes are compared and an HIV sequence is artificially created based on the most common features of all the genomes. The result is a 'consensus' HIV sequence that bears a closer genetic similarity to all the circulating viruses than does an HIV sample taken from a single person. Another approach is to make vaccines that include HIV genes from multiple different clades. For example, one candidate vaccine that is being studied includes HIV genes from clades A, B and C.

There is ongoing debate about how to best organize, or classify, the different versions of HIV. For vaccine design it may prove more useful to organize HIV diversity using categories other than clades. One approach is to organize the different versions of HIV by the immune responses they cause in people. This is called organizing viruses by 'immunotype' and may give better clues about how to raise strong immune defenses against HIV.

Primer
understanding
routes
of
transmission

WHY DO VACCINES NEED TO BE TESTED IN DIFFERENT POPULATIONS?

Instead of conducting one large trial to see if an AIDS vaccine is successful, most vaccine developers plan on multiple trials of vaccines. One important reason for this strategy is that there are several different ways that people can become infected with HIV. HIV is passed or 'transmitted' from one person to another through close contact with body fluids that contain the virus (blood, semen, vaginal secretions or breast milk). Only certain types of contact with these fluids can lead to infection. These include unprotected vaginal or anal sex (sex without a condom); breastfeeding; and the use of a needle that has been contaminated with HIV-infected blood, as can happen when illegal drugs, such as heroin, are injected into the blood. This is called 'intravenous' (IV) drug use. The particular way that HIV enters and infects the body is known as the 'route of transmission.'

A route of transmission can be thought of as a pathway that the virus takes from one place in the body (the site of exposure) to another (the bloodstream that then carries HIV throughout the body). Each pathway has immune defenses that try to act against HIV and other infections. These can be thought of as border checkpoints and patrols designed to protect against foreign invaders.

Each route of HIV transmission has a different set of physical barriers and immune defenses, including immune cells and antibodies. These are tailored to different locations in our body. We can see and feel the differences in the physical barriers. The lining of our mouth, for example, is different from the skin on our arm. The differences we can't see with the naked eye include variations in the type and amount of immune defenses located at different sites in the body. There are also variations in the immune defenses found in women and men, and adults and children. By themselves, these defenses are not enough to prevent HIV infection every time a person is exposed to the virus. This is why there is an urgent need for an effective, preventive AIDS vaccine.

Implications for vaccines

The ultimate goal is to develop an AIDS vaccine that prevents HIV infection no matter how someone is exposed to HIV. This is a challenging task since it is possible that the route of transmission will have an effect on how well a vaccine protects against HIV infection and disease.

A comparison of sexual versus IV routes of transmission shows why this is possible. Sexual transmission occurs across 'mucosal surfaces.' These mucosal surfaces are the boundaries between the outside world and the inside of the body, and include the inside of the mouth and nose, the lungs, the lining of the stomach, the vagina and the rectum. For infection to happen during sex, HIV must pass the physical barrier of the mucosal surface as well as the immune cells and antibodies that patrol that surface. Breastfeeding transmission of HIV also happens across mucosal surfaces—the lining of the baby's mouth and stomach.

A syringe that pierces the skin bypasses the physical barrier and immune defenses designed to keep out foreign invaders. When intravenous drug users (IDUs) share syringes that contain HIV-infected blood, a small amount of the virus is injected directly into their bloodstream. Once the virus is in the bloodstream it can spread rapidly throughout the body.

"We cannot assume that vaccines which prevent or reduce sexual transmission will necessarily work as well against spread through IV drug use," says Chris Beyrer, a researcher on vaccines and IDUs at Johns Hopkins University (US). This is not because IDUs will make different immune responses from other people. Most people who are vaccinated with an effective AIDS vaccine will make similar types of immune defenses. But these defenses may be more or less able to block HIV infection depending on the route of transmission of the virus.

There may also be variations in vaccine effects with different types of sexual exposure, such as anal and vaginal sex. The only way to find out how routes of transmission affect vaccines is to test AIDS vaccines in communities where HIV-negative people are likely to be exposed to HIV through different routes, such as gay men exposed through anal sex and IDUs exposed through drug use. This strategy was used in the two large-scale 'Phase III' trials of an AIDS vaccine called AIDSVAX. In the US, Canada and Europe the trial tested the vaccine in just over 5,400 people: 5,108 HIV-negative men who have sex with men, and 309 HIV-negative women who were at high risk of heterosexual exposure. In Thailand the trial tested a closely-related version of the vaccine in roughly 2500 HIV-negative intravenous drug users. (The vaccine provided no overall protection in either trial.)

Today the need for vaccines that protect against sexual and IV transmission is greater than ever. There is a serious epidemic underway in intravenous drug users in Eastern Europe and Central Asia and the rate of new infections remains high in sub-Saharan Africa, where heterosexual contact is the most common route of transmission. It is crucial to conduct trials in people at risk for infection either via sexual contact or IV drug use. To do this, trial sponsors, governments and communities will have to work together to create research environments that are safe and welcoming to all people, including individuals who are discriminated against because of their behaviors, such as drug users and commercial sex workers. These trials will bring the world closer to the ultimate goal of a universal AIDS vaccine.

Primer
understanding
trial
approval

HOW DOES AN AIDS VACCINE TRIAL GAIN OFFICIAL APPROVAL AND COMMUNITY SUPPORT?

OFFICIAL APPROVAL

Before an AIDS vaccine is tested in people, review committees from the countries and institutions involved in the research must approve the trial. This official review process is designed to ensure that trials are conducted ethically. A simple definition of ethical research is that it upholds the safety, human rights and well-being of the volunteers involved in the trial. Review committees also provide guidelines for trial staff, and monitor the trial once it has begun. This review process is not unique to AIDS vaccines. It is part of all ethical research projects involving humans.

Who is involved in the official approval process?

All developed countries and a growing number of developing countries have official 'regulatory' committees that are trained in evaluating research proposals. These committees are made up of scientists, ethicists, community members and other experts who are independent from the trial sponsors and investigators. They provide an unbiased evaluation of the study proposal.

The names and composition of these review committees vary from country to country. However, in general there is an ethical review committee (ERC) and/or an institutional review board (IRB), and a scientific review committee. The main concerns of the IRB or ERC are the safety and human rights of trial participants and the ethical conduct of the trial. The scientific committee ensures that the trial is asking legitimate scientific questions and that the study is well designed to answer these questions. A few countries like Uganda and South Africa have AIDS vaccine committees that have been created specifically to review AIDS vaccine trials. All of these committees follow internationally agreed-upon guidelines such as the Declaration of Helsinki, which gives 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.

However, just because a trial has been approved in one country it does not mean that it will be approved in another. A 'multi-site' trial that is being conducted in more than one country must be reviewed and approved independently by each country.

What trial materials are reviewed?

All of these committees review the trial 'protocol,' a detailed document that defines exactly how the trial will be carried out. A trial protocol contains in-depth information on every aspect of the trial such as the vaccine candidate that will be tested, the goals and design of the study, standards for including or excluding volunteers, the number of visits that volunteers will be asked to make to the trial site, the procedures to be done at each visit, the type of information that will be collected and how it will be analyzed.

ERCs and IRBs assess other trial documents too. These include advertisements that may be used to recruit volunteers and the forms and plans for obtaining 'informed consent', a crucial part of ethical research. Informed consent is an agreement signed by all volunteers that indicates their understanding of the purpose and goals of the trial; what will be done during the trial and for how long; the risks and benefits of participation; and their rights and responsibilities as research volunteers. ERCs and IRBs look at all available information about the vaccine candidate and the potential risks of trial participation to be certain that all of this information is provided to volunteers in ways that they can readily understand. They also review documents such as brochures, videos and short quizzes that may be used in the informed consent process.

These committees also consider the package of benefits that will be offered to volunteers during the trial and compensation such as travel costs to and from the trial site. They ensure that the benefits are fair but do not have an inappropriate or 'undue' influence on a volunteer's decision to participate.

When can a trial begin?

All of these committees have the opportunity to review the protocol, make suggestions, and recommend or require changes. Trial sponsors make required changes to the protocol or other documents and re-submit them. A trial can only begin after all of the committees have given their approval.

What happens once a trial has started?

After an AIDS vaccine trial begins, ERCs, IRBs and other groups receive regular updates that allow them to determine whether the trial is safe and ethical and that trial sponsors 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.

BUILDING COMMUNITY SUPPORT

For a trial to be successful it is also important for trial site investigators and sponsors to inform and obtain general support from the countries and communities that will be involved in the research. (The agencies and scientists who have designed and funded the trial (the sponsors) are often separate from the clinics and staff (the investigators) who will conduct the trial.)

Site investigators often conduct meetings with community leaders and people who might volunteer for the trial. These consultations are not part of the formal approval process but they help to ensure that communities have accurate information and that their concerns are addressed. Sponsors may make changes to the trial protocol so that it reflects community input.

Trial sponsors frequently meet with political leaders, national AIDS organizations and other partners to build national and local support for AIDS vaccine research.

Many sites also establish community advisory boards (CABs). For AIDS vaccine trials these are usually committees composed of community representatives such as religious leaders, teachers, journalists, and people living with HIV and AIDS. CABs have a variety of duties that may include informed consent documents and educational materials, monitoring trials, and helping to inform and educate the rest of the community.

Primer
understanding
the
immune
system

HOW DO VACCINES INTERACT WITH THE IMMUNE SYSTEM?

The immune system and protection from disease

The immune system is the set of defenses in the body that protects us from becoming ill. It is made up of many different types of cells and substances, all of which work together to help us heal when we have been injured, get well when we have become ill, and avoid some illnesses altogether.

The immune system can do this because it is able to recognize, fight and remember foreign invaders, like bacteria or viruses, which can cause illness when they enter the body. Such invaders are called "pathogens." A common cold is caused by a pathogen (a cold virus). HIV is the pathogen that causes AIDS.

When a new pathogen enters the body, the immune system uses a variety of defenses to control or get rid of it. One of the first responses comes from B cells. These cells can recognize foreign invaders soon after they have entered the body, but before they have entered and infected any of the body's cells. Many pathogens, including HIV, enter cells and infect them in order to multiply.

B cells produce antibodies which coat the surface of the pathogen to stop it from multiplying itself or infecting cells. This process is called "neutralization." Antibodies also label the pathogen so that other immune defenses can "see" and attack it.

Another initial response comes from other immune system cells called dendritic cells and macrophages. These cells patrol the body and pick up the pathogen. They then carry the pathogen to the lymph nodes, which are the hubs of the immune system. Lymph nodes can be found under the jaw, under the arms, in the gut and in the groin. When we start becoming ill, our lymph nodes often become swollen or sore as immune cells gather in the nodes to fight the infection.

In the lymph node, the patrolling cells show or "present" the pathogen to $CD4^+$ T cells. These "helper" $CD4^+$ T cells coordinate the activities of a set of "killer" cells called $CD8^+$ T cells. $CD4^+$ and $CD8^+$ T cells work together to eliminate cells that have been infected by pathogens.

HIV infects and kills $CD4^+$ T cells, which is why doctors sometimes count these cells when people are infected with HIV. Our immune systems try to fight off HIV by sending $CD8^+$ T cells to kill off the HIV-infected $CD4^+$ T cells. Unfortunately the immune system cannot eliminate HIV from the body. Over a period of time, HIV infection exhausts the body's immune defenses. This leaves HIV-infected people vulnerable to a variety of other infections. Antiretroviral drug treatment can suppress multiplication of the virus in the body and so reduce HIV-related illness, prolonging the life of the infected person. But this treatment cannot rid the body of HIV completely.

Immune memory

Although the immune system cannot control HIV, it can control or get rid of many other infections. This is why we become well after many illnesses. After a pathogen has been controlled, most of the immune cells and antibody that fought the infection disappear. However a small group of "memory" immune cells remains in the body. These memory cells have already fought the pathogen once before and so if the pathogen ever enters the body again they can very quickly start a strong immune response. Memory cells "arm" the body against future infections from the same pathogen. There are some infections, such as chickenpox or measles, which we generally get only once. This is because memory cells from the first infection effectively fight the pathogen if we are ever exposed to it again.

Vaccines and immune memory

Immune memory is a key reason why vaccines protect us from disease. An effective vaccine safely introduces the immune system to a pathogen that it has never seen before. It arms the immune system so that it can effectively control the pathogen if it ever invades the body. Vaccines use safe forms or fragments of pathogens to mimic the actual pathogen and trick the body into generating immune responses. The fragments or safe forms of pathogens that are used in vaccines are called "immunogens." This word reflects the fact that vaccines cause immune responses, *not* disease.

When the vaccine enters the body, the immune system sees it and responds to it just as it does to any foreign substance. T cells and B cells react to the vaccine. Some of these cells become memory cells. These cells are ready to respond to the real pathogen if it ever enters the body.

All of the AIDS vaccines in development today use small fragments of HIV as their immunogens. These fragments cannot cause HIV infection. The goal of these experimental AIDS vaccines is to produce memory cells that will be able to mount a rapid, strong immune response against HIV if a person is ever exposed to whole, live HIV through high-risk contact such as unprotected sex.

Today the challenge for AIDS vaccine developers is to identify the best immunogens to create strong antibody and cellular responses that will protect against HIV infection and disease.

Primer
understanding
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HOW DO AIDS VACCINES PREPARE DIFFERENT PARTS OF THE IMMUNE SYSTEM TO FIGHT HIV?

The goal of an AIDS vaccine is to produce immune defenses that try to stop HIV infection and disease. There are different ways to try to achieve this goal. This is because the immune system uses several different types of defenses to fight HIV or any other foreign invader or "pathogen" that infects the body. The unique features of these different defenses are helping to guide the design of AIDS vaccines.

Innate and acquired immunity

Our immune system is divided into two broad categories: "innate immunity" and "acquired immunity." Innate immune defenses are the first to respond to any foreign invader that enters the body. These defenses are also called "non-specific" or "non-adaptive" defenses; they are like a security force that patrols the body looking for unusual activity, but not a particular intruder.

Innate defenses can protect the body against some infections, but in many cases additional help is needed from acquired immunity. Acquired immune defenses are activated only after our immune system has "recognized" a particular pathogen. These specific defenses are like police tracking down a known criminal; all of their activities are directed towards a single, specific intruder.

There are two branches or "arms" of the acquired immune system: humoral (or antibody-mediated) immunity and cellular (or cell-mediated) immunity (see Immune System *Primer,* page 7). These two sets of defenses reinforce each other, and they use different strategies to try to prevent infection or rid the body of foreign invaders.

AIDS vaccines are designed to prepare our immune systems to fight HIV. Since a single vaccine may not be able to stimulate both cellular and antibody defenses, scientists are trying to develop the best possible candidates to stimulate each arm of the acquired immune system.

AIDS vaccines and humoral immunity

Many of today's licensed vaccines, including measles, polio and hepatitis B vaccines, cause the humoral immune system to produce large amounts of antibodies. These defenses are molecules that stick to pathogens and prevent them from infecting cells or doing other damage to the body. It is thought that the antibodies produced by these vaccines play a crucial role in protection from disease.

Humoral defenses are coordinated by B cells which have "receptors" on their surface that allow them to connect with and capture pathogens as they circulate freely in the blood. These receptors also connect B cells to other immune cells, and tell the B cells that there is a new pathogen in the body. The B cell starts to multiply itself and also produce antibodies against the pathogen.

An antibody is shaped so that it attaches perfectly onto a pathogen—the way that a key fits into a lock. There are antibodies that bind to many parts of HIV. Some are called "neutralizing" antibodies because they effectively block the activity of HIV before it infects other cells.

Scientists are now trying to design vaccines that resemble antibody "binding sites" (locks) on HIV. These vaccines aim to teach B cells how to produce HIV-specific neutralizing antibodies that will then be ready to fight HIV if it ever enters the body.

Creating a vaccine that leads to the production of neutralizing antibodies against HIV is a very difficult task. The binding sites on HIV that induce neutralizing antibodies are very well hidden. Some of these sites are exposed briefly, at the moment the virus is infecting a cell; others are masked by an outer protective layer on the surface of the virus. This difficulty is the reason why only a few of the vaccines currently in clinical trials have been designed to stimulate production of neutralizing antibodies.

AIDS vaccines and cellular immunity

Every cell in the body has an outer coating or "membrane." This membrane is studded with small bits of chemical information about the cell, such as what it does or what part of the body it comes from. This information is like a business name on the outside of a building; you can tell what is happening inside the building without entering it.

When a cell has been infected by a pathogen, it puts warning signals on its outer coating—similar to the way a person might lean out of a window and call for help if a building was on fire. Cellular immune defenses respond to these warning signals.

This response starts with $CD4^+$ T cells, which are sometimes called the "generals" of the immune system because they direct many other defenses. $CD4^+$ T cells use chemical messengers called "cytokines" to activate $CD8^+$ "killer" T cells that identify and kill pathogen-infected cells.

Many of the AIDS vaccines in clinical trials today have been designed to prepare cellular immune defenses. Each of these experimental vaccines is designed differently, but all use the same basic strategy: scientists start by manufacturing small molecules that mimic fragments of HIV but cannot cause HIV infection or disease. These fragments are packaged into a vaccine which is delivered into the body (usually via injection). Antigen presenting cells, including dendritic cells (see Immune System *Primer*, page 7), patrol the body and pick up the synthetic fragments and display them on their surfaces, causing $CD4^+$ T cells to respond. The goal is to create cellular defenses that will react quickly and powerfully if HIV ever enters the body.

Primer
understanding
vaccine
development

HOW ARE VACCINES DEVELOPED?

Vaccine development is a lengthy process of testing ideas and candidates with the goal of identifying a safe, effective vaccine that can be reliably and affordably produced and distributed to all who need it. The development process can be divided into five overlapping stages. These stages are common to all medicines, vaccines and microbicides. Scientists, manufacturing experts, policy makers and advocates work on many of these stages simultaneously with different candidates. It can take 10 years or more for one candidate to complete the first three phases and even longer to identify an effective candidate for licensure and widespread use. The five stages are described below using AIDS vaccines as an example.

Idea generation and basic science

Vaccine development begins with "basic science," which includes experiments on and observation of various aspects of HIV and the immune system. Basic science research is carried out in laboratories in universities, research institutes and private companies. Scientists use various techniques to isolate the virus and human immune cells and to study the types of cells HIV infects, how it kills those cells, and what effects this has on other cell types. One general term for these studies is "*in vitro* assays." (*In vitro* means "in glass" in Latin and it is used for studies that are conducted outside of a living organism.) *In vitro* assays give scientists a chance to observe processes that usually happen inside the human body. Some basic science experiments study immune responses to HIV in small animals like mice. Basic science provides clues about how to develop better vaccines.

Pre-clinical development

Pre-clinical tests include tests of the purity and composition of the candidate, as well as very early measures of vaccine effects against HIV. Some of these tests are done *in vitro* and some have to be done in animals. (Tests in animals or humans are called "*in vivo*" experiments.) For example, scientists might try to design a vaccine that causes immune responses that effectively control HIV growth in cells. This can be tested by immunizing mice, then testing their immune cells *in vitro* to see if they stop HIV from growing. These and other experiments are used to gather early information about "immunogenicity," which is a measure of the types and strength of the immune response caused by the vaccine. If the candidate appears promising, additional tests are done in monkeys. Researchers give the monkey the experimental vaccine and later "challenge" the animal with a monkey version of HIV called simian immunodeficiency virus (SIV) to see whether the vaccine provides any protection. Pre-clinical studies also gather extensive information on product safety. Only a small percentage of the vaccines that make it to the pre-clinical development stage move forward to the next stage.

Clinical trials

A clinical trial is a research study in humans used to answer a question about an experimental drug, vaccine or other medical intervention. Clinical trials are conducted in sequential steps or "phases," each answering a different question. Small Phase I safety trials of AIDS vaccines ask: Is the vaccine safe in a small group of HIV-uninfected people who have undergone an extensive health screening process? Phase I trials may also look at vaccine immunogenicity. Phase II AIDS vaccine trials ask: Is this vaccine safe and immunogenic in a group of hundreds of HIV-uninfected people, who are known to be generally healthy?; and What is the best dose, dosing schedule, and route of immunization for the vaccine? Phase III AIDS vaccine "efficacy" trials usually enroll thousands of volunteers to ask: Does this vaccine provide protection against HIV infection, or reduce the severity of illness in people who receive the vaccine and later become infected with HIV through high-risk contact? If a Phase III trial shows that a candidate has either benefit then it may advance to the licensing and approval stage. The trial sequence may sometimes include large Phase IV trials after licensure.

Licensing and approval

If a Phase III vaccine trial shows that the candidate has positive effects, then vaccine developers may submit an application to regulatory agencies for licensure. In the US the regulatory agency is the Food and Drug Administration; in the European Union it is the European Agency for the Evaluation of Medicinal Products; in South Africa it is the Medicines Control Council.

Regulators review everything about a product: all of the details of the manufacturing process, what it is made of, the benefits and risks of use, and the label and packaging that will be used to inform the public about the product. It is their task to determine whether the product is safe and of sufficient benefit to be made available to the public.

Several factors could influence decisions about whether to license AIDS vaccines. These include the level of benefit or efficacy observed in the Phase III trial, and the type of population that was enrolled in the trial. Some regulatory agencies may require a second "confirmatory" Phase III trial that may test the product in a different population, perhaps in a different age range or different part of the world.

Policy makers and health advocates are now working to develop and strengthen expertise in the regulatory agencies in the developing nations and to identify strategies for rapid licensing and approval processes.

Manufacturing and delivery

Once an effective vaccine has been developed, it must be made in sufficient quantities to meet the global need. These supplies can only be made in large-scale manufacturing facilities which are costly and time-consuming to build. This is why vaccine developers begin planning manufacturing facilities long before they have a licensed product and even before they have results from a Phase III trial.

It is also essential to have systems and strategies to deliver the vaccines to people who need them. These systems require storage facilities and equipment and trained personnel who can safely administer the vaccine. The strategies include outreach and education campaigns to explain to people how the vaccine works, who should use it, and why the vaccine should not replace condoms or other strategies to avoid HIV, since all of these strategies must be used together.

Adapted from the December 2003-March 2004 Uganda AIDS Vaccine Update*, the newsletter of the Uganda Virus Research Institute-IAVI HIV Vaccine Program. For more information or a copy of the newsletter: www.iavi.org/uganda*

Primer

understanding

partial efficacy

WHAT IS A PARTIALLY EFFECTIVE VACCINE?

It is widely thought that receiving a vaccine against a particular disease-causing agent or "pathogen" provides life-long protection against that disease. Many vaccines do indeed provide high levels of long-lasting protection against disease caused by many pathogens. However, there is no such thing as a vaccine that provides 100% protection, 100% of the time. In this sense, all vaccines are "partially effective." It is important to remember that vaccines are still highly beneficial for individuals and communities. They are the most powerful tools we have for preventing disease worldwide. Understanding "partial efficacy" can help to understand current goals for AIDS vaccines.

What could a partially effective AIDS vaccine do?

The phrase "partial efficacy" can be used in two different ways. The first definition describes a vaccine which does not completely prevent infection by a particular pathogen but does help reduce the severity of disease caused by the pathogen. An AIDS vaccine with this type of efficacy would reduce the severity of HIV disease in vaccinated people who later became HIV-infected through blood or sexual exposure.

The second definition of a partially effective vaccine is one that can protect some people in a population but not others. This is possible because a variety of factors affect our immune systems and, by extension, our ability to respond to a vaccine. Most licensed vaccines are actually partially effective, although they may work for 80 or 90% of a population. Others, like oral cholera vaccine and BCG (against tuberculosis) have lower levels of efficacy but are still beneficial.

It is the first type of partial efficacy—protection against disease, but not infection—that is receiving the most attention in the AIDS vaccine field today. This is because most of the candidates being tested in clinical trials are designed to produce cell-mediated immune defenses (see *Primer*, page 8), which act against HIV only after the virus has entered the body and infected immune cells. Instead of preventing infection from happening at all, these "vaccine-induced" defenses are likely to improve the immune system's ability to fight HIV once infection has occurred. They would do this by helping to slow viral activity and protect immune cells, especially $CD4^+$ T cells, which are targets for HIV infection. These defenses could also help to control the amount of virus circulating in the body (viral load).

Such a vaccine could have several benefits for the individual. First, it could slow the rate of disease progression following HIV infection. By reducing viral load and helping people preserve their $CD4^+$ T cells the vaccine would allow people to live with HIV for longer periods of time without getting sick. It could also prolong the time until a person needed to start antiretroviral therapy (ARVs). ARVs are generally recommended for people with less than 200 $CD4^+$ T cells per mm^3 of blood. Each person reaches this point at a different time after infection; an AIDS vaccine could help extend this time period. ARV therapy must be taken every day for life and a vaccine that allowed people to remain healthy and off ARVs could simplify people's lives and avoid the side effects of daily therapy.

A vaccine that reduced the severity of HIV disease could also have positive effects at the community level. Studies have found that people with high viral loads are more likely to transmit the virus to their partners during unprotected sex or to their infants during pregnancy and childbirth. A partially effective vaccine that reduced viral load might reduce the likelihood that an HIV-infected person would pass the virus on. If enough people were vaccinated, this could help to slow the spread of an epidemic in a given country or community.

How do we find a partially effective AIDS vaccine?

Even without a vaccine, people with HIV usually do not get sick for five to seven years after infection. So to directly observe whether an AIDS vaccine affects disease, studies would have to be conducted for ten years or even longer. To get a more rapid answer, vaccine trial sponsors can look at markers of disease progression like viral loads and $CD4^+$ T cell counts in vaccine and placebo recipients who become infected through high risk contact. They can use these data as an early indication of whether or not the vaccine will have a long-term impact on disease progression or infectiousness.

A vaccine that improved health for people who became HIV-infected would be a major breakthrough. It is possible that such a vaccine would be licensed for use outside of a clinical trial. However even after licensure researchers would continue studies to answer open questions including: How long would vaccine-induced protection last? How much of a reduction in viral load is needed to translate into long-term health benefits for the individual? How much of a reduction in viral load is needed to reduce the risk of transmitting to another person?

Part of a comprehensive response

Once an effective AIDS vaccine has been developed, it will not replace or even reduce the need for comprehensive prevention and treatment programs for HIV. This will be particularly true for partially effective vaccines that reduce the severity of HIV disease in vaccinated people who later become HIV-infected. In fact an AIDS vaccine will be most effective when it is promoted as one of several strategies for fighting HIV. This can be compared to family planning methods such as condoms, hormonal contraceptives and diaphragms. No single method is 100% protective, but used in combination, these methods can provide very, very high levels of protection.

This Primer was adapted from the AIDS Vaccine Advocacy Coalitions' forthcoming AIDS Vaccine Handbook*; for more information or to order a copy: www.avac.org*

vax

IAVI Report Publications

The IAVI Report team publishes the *IAVI Report* and *VAX*, both of which are hosted on our website (www.iavireport.org) along with many additional features. Both publications are available free of charge—to subscribe please visit our website or e-mail: iavireport@iavi.org

IAVI Report

The *IAVI Report* provides comprehensive coverage of the AIDS vaccine field—from the latest scientific research to policy, advocacy and community perspectives, bringing news and analysis, adding context and underscoring trends and gaps in the search for an AIDS vaccine. Highlights include:

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The *IAVI Report* is published six times a year and has a global readership of over 8,500 subscribers in 140 countries, with thousands of additional readers accessing the online edition.

vax
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VAX is a monthly bulletin on AIDS vaccine research and news intended for non-technical readers, from advocates to policymakers to community leaders to vaccine trial volunteers. As well as presenting *IAVI Report* articles in a straightforward, easily-accessible style, each edition includes a Primer that communicates an AIDS vaccine related topic in non-technical format to enable non-scientists to broaden their understanding and become familiar with scientific terms and ideas. Each edition of *VAX* is currently available in five different languages—English, French, German, Portuguese and Spanish. To receive *VAX* by e-mail, please send a request (including language preference) to: vax@iavi.org

IAVI Report Online

The newly-launched IAVI Report Online is a one-stop resource for HIV researchers, advocates, policymakers, and anyone else with an interest in the progress towards an effective, preventive AIDS vaccine. In addition to hosting all the current *IAVI Report* and *VAX* content and archived editions, IAVI Report Online is a centralized source of information on all aspects of AIDS vaccine research and associated scientific disciplines—from basic science like molecular virology and immunology to more applied fields such as HIV prevention research. IAVI Report Online Early Edition now means that *IAVI Report* articles are published directly to the web as soon as they are available, ahead of print publication. Other highlights include:

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IAVI Report

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IAVI is a scientific organization founded in 1996 whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI focuses on four key areas: Accelerating scientific progress; education and advocacy; ensuring vaccine access and creating a more supportive environment for industrial involvement in HIV vaccine development.

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