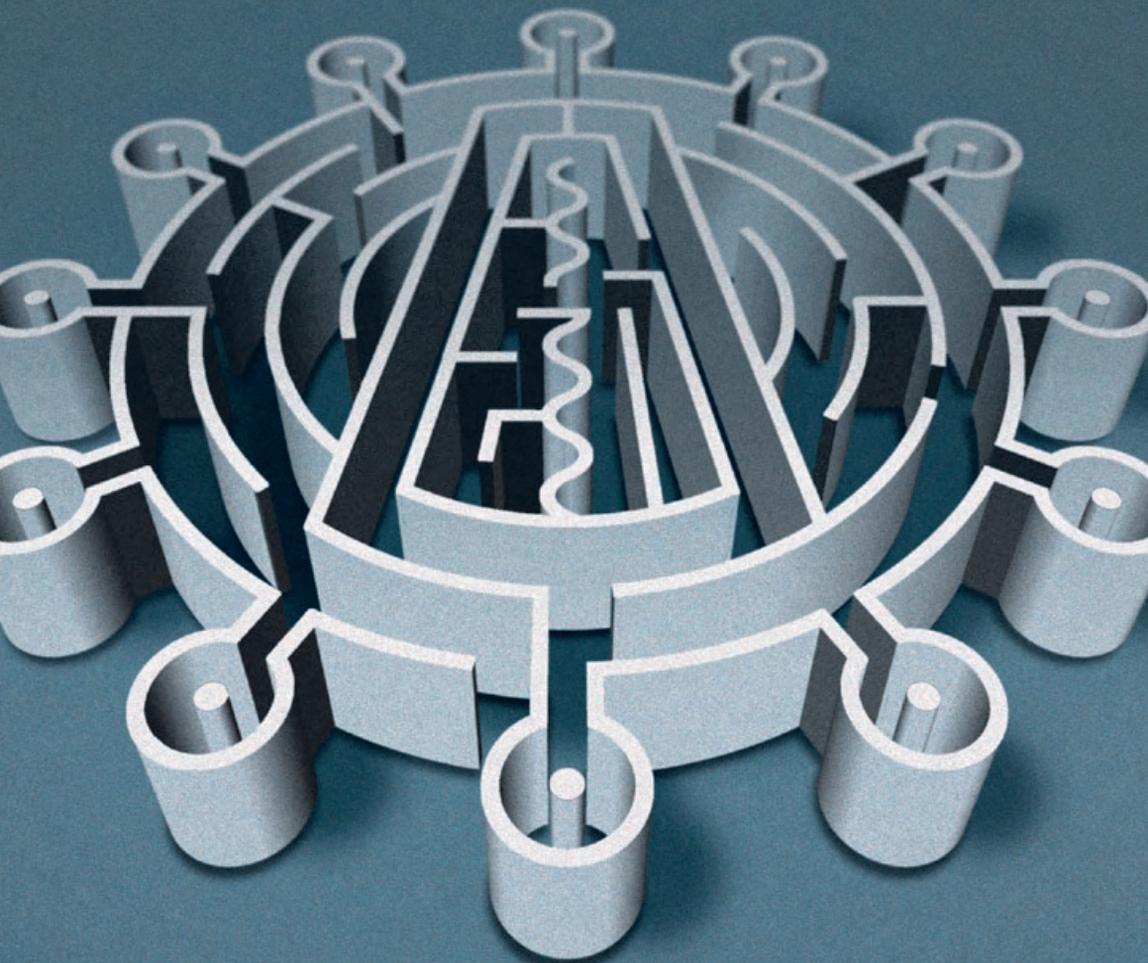


DECIPHERING AIDS VACCINES

AN ANTHOLOGY OF *VAX* AND *IAVI REPORT* ARTICLES EXPLAINING
KEY CONCEPTS IN AIDS VACCINE RESEARCH AND CLINICAL TRIALS



DECIPHERING AIDS VACCINES

After 25 years of battling the AIDS pandemic that has already claimed the lives of more than 25 million people, the need for an AIDS vaccine has never been greater. Last year marked the culmination of the most ambitious global program to date aimed at providing antiretrovirals (ARVs) to people with AIDS in developing countries. Although the World Health Organization's '3 by 5' program fell short of its target to place 3 million HIV-infected people on these life-saving medications by the end of 2005, the funding from this program and others—including the Global Fund to Fight AIDS, Tuberculosis and Malaria and the President's Emergency Plan for AIDS Relief (PEPFAR)—have helped provide ARVs to 20% of individuals in need in low- and middle-income countries.

This is a significant accomplishment and the momentum it has created is helping to bring hope to many communities devastated by HIV/AIDS. Importantly, these programs are also encouraging more and more people to be tested for HIV infection. But the pandemic shows little sign of abating. There are now about 40 million people infected with HIV around the globe, and 4 million of them were infected just last year. The soaring costs of treatment may soon make it unfeasible, perhaps impossible, to provide treatment to all in need.

New technologies to prevent HIV transmission remain an imperative and an AIDS vaccine offers the greatest hope of all for reversing the pandemic. There are still many scientific obstacles to the development of an effective vaccine, but important advancements have been made. Researchers now have a clearer understanding of the earliest immunologic events in HIV infection and are actively studying long-term nonprogressors to understand the mechanisms that allow some individuals to effectively control their HIV infection without ARVs. They are also gathering new insights on how to manipulate animal models to enhance the pre-clinical evaluation of vaccine candidates. These advancements, as well as the results from around 30 ongoing clinical trials of preventive AIDS vaccine candidates in more than a dozen countries around the world, will provide researchers with important clues on how to reach the ultimate goal—an effective AIDS vaccine.

The articles in *Deciphering AIDS Vaccines* originally appeared in *VAX* and *IAVI Report*, the only comprehensive publications on the AIDS vaccine field. We hope that you enjoy and learn from the articles in this anthology and that you will be intrigued to find out more. Visit www.iavireport.org for more information.

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The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996 and operational in 23 countries, IAVI and its network of collaborators research and develop vaccine candidates. IAVI's financial and in-kind supporters include the Alfred P. Sloan Foundation, the Bill & Melinda Gates Foundation, The John D. Evans Foundation, The New York Community Trust, The Rockefeller Foundation, The Starr Foundation; the Governments of the Basque Country, Canada, Denmark, European Union, Ireland, The Netherlands, Norway, Sweden, United Kingdom, and United States; multilateral organizations such as The World Bank; corporate donors including BD (Becton, Dickinson & Co.), Continental Airlines, Google Inc., Merck & Co., Inc. and Pfizer Inc.; leading AIDS charities such as Broadway Cares/Equity Fights AIDS, Crusaid, Deutsche AIDS-Stiftung, and Untill There's A Cure Foundation; other private donors such as The Haas Trusts; and many generous individuals from around the world. For more information, see www.iavi.org.

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...the early stages of HIV infection

How can studying what happens immediately following HIV infection help researchers design an AIDS vaccine?

By Kristen Jill Kresge

There are many reasons why HIV is such a difficult virus to combat (Figure 1). One is that HIV directly attacks the human immune system, the body's defense against pathogens like viruses and bacteria. The primary target of HIV is the CD4⁺ T cells, an important immune cell that directs the body's response to an infection. During HIV infection huge numbers of these cells are infected and killed each day, but new ones take their place.

Doctors or nurses can monitor the progression of HIV disease by CD4⁺ T-cell counts, which are a measure of the number of CD4⁺ T cells circulating in the blood. For many years after initial infection the quantity of these important immune cells can stay the same or drop only slightly, but in most people the virus will eventually take over and the total number of CD4⁺ T cells will start to dwindle.

A typical definition of AIDS is when the total number of CD4⁺ T cells in an HIV-infected person dips below 200 in a milliliter of blood (in people with healthy immune systems there are between 600-1200 CD4⁺ T cells in this same amount of blood) or when a person develops one of several AIDS-associated illnesses. Once

the CD4⁺ T-cell count is dangerously low, the immune system is incapable of defending the body from attack by other pathogens and a person also becomes susceptible to many opportunistic infections, which can be deadly.

Measuring the number of CD4⁺ T cells in the blood is a convenient way for researchers to estimate the damage HIV is doing to the immune system, since blood samples are easily obtained. But the majority of the body's CD4⁺ T cells aren't in the blood. Rather they are found in the mucosal tissues, such as those lining the respiratory, gastrointestinal, and genital tracts. Looking only at the blood may paint an inaccurate picture of what is really happening during HIV infection, so researchers have recently focused on studying the immune responses occurring specifically at these mucosal sites.



Jean-Marc Giboux/Getty Images

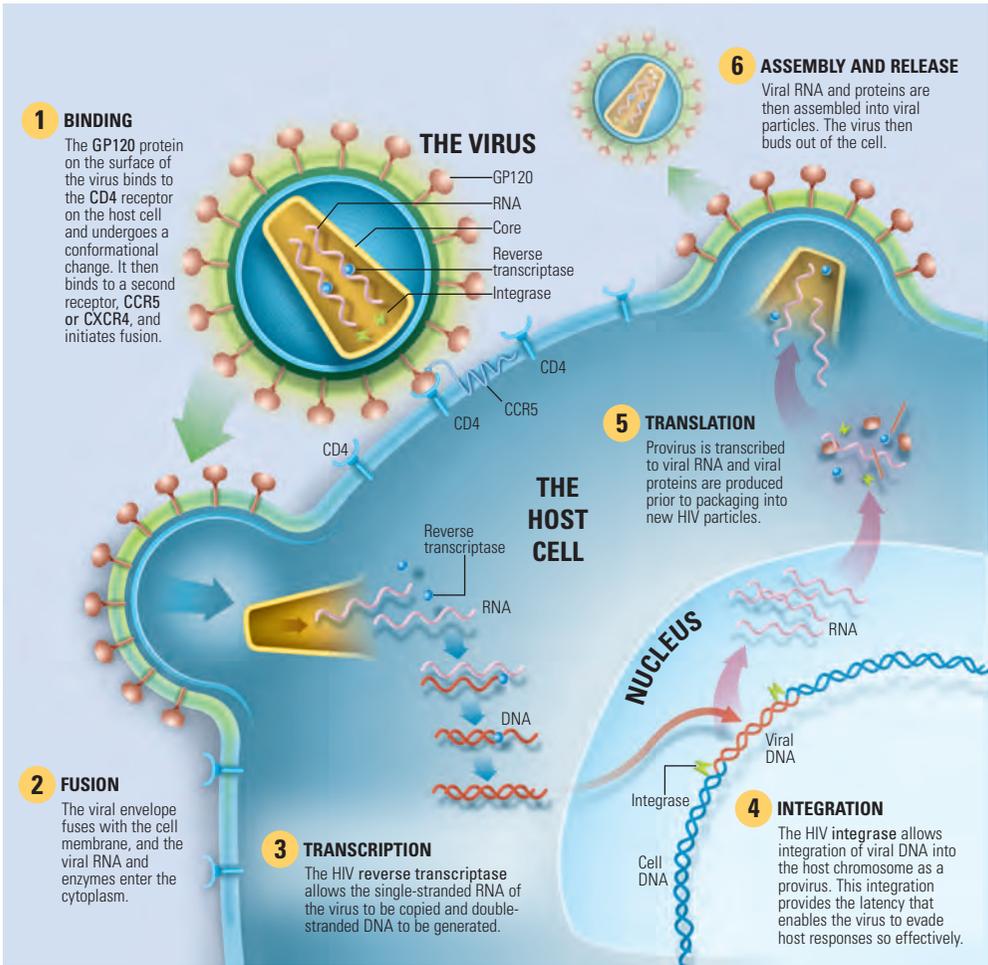


Figure 1. The HIV replication cycle. The virus first enters a human cell where it reverse transcribes its genetic material (RNA) into DNA that is then integrated into the cellular chromosomes. Once integration occurs the cell is permanently infected and throughout its lifespan it can produce new virus particles.

Looking at the gut

When researchers looked at mucosal tissues they found something very interesting. In both animal models and humans, researchers observed a massive killing of CD4⁺ T cells at mucosal surfaces in the intestine, or gut, very early in the course of HIV infection. For many years scientists were more concerned with the dynamics of the human immune system much later in HIV infection when it begins to fail. But research now suggests that a critical destruction of immune cells occurs long before a person exhibits symp-

oms or develops AIDS, and often even before an individual knows they are infected with HIV.

The bulk of CD4⁺ T-cell death in these tissues actually occurs within a few weeks after a person contracts the virus, during a period referred to as acute infection. Although the number of CD4⁺ T cells in the blood also decreases during this initial stage of HIV infection, researchers found that the greatest depletion is seen in the mucosal tissues of the gut.

Researchers have also found that the immune system has trouble repairing damage in these

mucosal tissues. CD4⁺ T-cell counts often rebound quickly in the blood once an individual starts taking antiretrovirals (ARVs), but the CD4⁺ T cells in the gut are restored much more slowly than in blood, even in HIV-infected individuals who have been receiving treatment with ARVs for several years.

This may mean that the loss of CD4⁺ T cells at the mucosal surfaces is a better predictor of disease progression than monitoring their quantity in the blood.

But it would be difficult to monitor HIV-infected individuals by repeatedly measuring CD4⁺ T-cell counts at mucosal sites. Testing these tissues requires a procedure known as a biopsy, which is a more invasive process than collecting a blood sample. Researchers are now looking for ways to analyze subtle differences between CD4⁺ T cells in the blood in order to more easily determine and predict what is happening in the gut.

Implications for vaccines

This research has many implications for AIDS vaccine design and research. If the critical battle between HIV and the immune system takes place in the earliest stages of HIV infection, as this research suggests, it is important to closely study the virus that is transmitted and to characterize the nature of the immune responses in the first weeks and months of infection.

Many organizations involved in developing AIDS vaccine candidates are therefore interested in studying recently HIV-infected individuals. IAVI is one group conducting this

type of epidemiological study with recently HIV-infected volunteers at several centers in Africa.

Other research organizations are working with collaborators to identify and follow newly-infected individuals at sites in many countries

Research now suggests that a critical destruction of immune cells occurs long before a person exhibits symptoms or develops AIDS, and often even before an individual knows they are infected with HIV.

around the world. Information collected from these studies may offer clues to help better define the target for a preventive vaccine.

Another important implication from this research is the need for AIDS vaccine candidates that induce strong immune responses at mucosal tissues, especially those lining the intestine. Several researchers think this will be necessary for a preventive vaccine to be effective and many methods are now being explored to enhance the mucosal immunity induced by existing AIDS vaccine candidates (see *Understanding mucosal immunity*, page 8).

Originally published in the April 2006 edition of VAX.

...mucosal immunity

How could the need to assess mucosal immunity affect AIDS vaccine trials?

By Kristen Jill Kresge

The most common way that HIV can be transmitted from person to person is through sexual contact with an HIV-infected partner. Researchers estimate that about 85% of HIV infections are caused by sexual transmission of the virus. HIV can enter the body during vaginal or anal sex, and also very rarely during oral sex, through the surface tissues (mucosae) of the genitals.

Since an effective preventive AIDS vaccine will primarily have to protect an individual from sexual transmission of HIV, researchers think it will probably be important for a vaccine candidate to induce strong mucosal immune responses.

The human immune system can be divided into several parts. One of these, referred to as the mucosal immune system, relies on immune cells and a specific class of antibody to prevent pathogens such as viruses or bacteria from penetrating and then replicating at mucosal surfaces—including those of the genital, intestinal, and respiratory tracts.

For sexually-transmitted viruses like HIV that enter the body through the genital mucosae, the mucosal immune responses are the first line of defense and play an important role in fending off a possible infection. Since an effective preventive AIDS vaccine will primarily have to protect an individual from sexual transmission of HIV, researchers think it will probably be important

for a vaccine candidate to induce strong mucosal immune responses.

So in recent years there has been an increased interest among researchers in developing vaccines that stimulate mucosal immunity. But there is still relatively little known about the events leading up to the sexual transmission of HIV or the immune responses necessary to prevent infection. Researchers are now beginning to study the mucosal immune responses induced by AIDS vaccine candidates in animal models and are also looking at ways to improve and optimize these responses.

Vaccines to induce mucosal immunity

One factor that affects the level of immune responses at the mucosal tissues is the route of vaccine administration. Most of the AIDS vaccine candidates that are currently in clinical trials around the world are delivered by intramuscular or intradermal injection. This route of administration can produce antibodies and cell-based immune responses in the blood (systemic immunity), but does not guarantee a robust immune response at the mucosal surfaces. Scientists think that mucosally-administered vaccines, including those by oral or nasal administration, will be more effective at producing responses in these tissues.

But the immune responses generated by mucosally-administered vaccines may vary greatly between the different mucosal surfaces in the body. Vaccines that are taken orally tend to produce the greatest immune responses at the mucosae of the intestinal tract, but are not very efficient at producing a specific class of antibody known as immunoglobulin A (IgA) at the vaginal mucosae, which could be necessary for protection against infections that can be sexually transmitted. Oral vaccines however are effective at preventing infections that primarily target

intestinal tissues. There are a few licensed vaccines that are administered orally, including one for polio and two for cholera, which is a diarrheal disease caused by bacteria that mainly infect the intestine.

Recent research suggests that vaccines that are administered to humans as sprays into the nasal passages can give rise to substantial IgA production in the mucosal tissues of the vagina, making this type of immunization appealing to AIDS vaccine researchers. However there are also possible safety issues with nasal immunization that will need to be fully explored before they are evaluated in human clinical trials.

Another way that mucosal immune responses can be optimized is by the choice of delivery system for the vaccine components. Several bacterial and viral vaccine vectors are currently being developed as AIDS vaccine candidates and some of these are known to generate strong mucosal immune responses, depending on how they are administered. Researchers are also studying how some factors, such as cholera toxin, which are known to be potent inducers of mucosal immunity, can be altered to make them safe for human administration.

Scientists are also looking at how substances called adjuvants delivered along with the vaccine candidate can be used to improve the mucosal immune responses induced. Adjuvants are already used with several licensed vaccines for other diseases to boost the level of immune responses and their duration. Now several research groups are looking at novel substances that can specifically increase the production of antibodies and immune cells at mucosal surfaces.

Measuring mucosal immune responses

Researchers are studying how AIDS vaccine candidates induce mucosal immunity in animals, but they are not sure how these responses will differ in humans who receive the vaccine

candidate in clinical trials. In the future they may need to actually measure in people the level of antibody or cellular immune responses at the mucosae during an AIDS vaccine trial. While systemic immunity can be measured by a simple blood test, measuring mucosal immunity will involve more invasive procedures that would need to be done repeatedly throughout the course of the trial.

While systemic immunity can be measured by a simple blood test, measuring mucosal immunity will involve more invasive procedures that would need to be done repeatedly throughout the course of the trial.

This could make AIDS vaccine trials more complex because it will involve fully and clearly explaining these procedures to all potential trial volunteers as part of the informed consent process. It would also require training the site staff on how to take mucosal samples and providing the trial sites with the equipment required to assess the level of mucosal immunity from the small quantity of cells obtained through such sampling.

It will be important that mucosal immune responses are measured in diverse populations of people during clinical trials because differences in nutrition, intestinal environment, and previous infections have been shown to affect the efficacy of mucosal vaccines.

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...AIDS vaccine pre-clinical development

How are AIDS vaccine candidates tested for safety and immunogenicity before they enter clinical trials?

By **Kristen Jill Kresge**

Clinical trials are a stepwise process to determine the safety and immunogenicity of AIDS vaccine candidates in human volunteers. The earliest trials (Phase I and II) are designed primarily to evaluate safety, while the later stage trials (Phase IIb and III) are when researchers determine if the vaccine candidate is effective. Each Phase involves a progressively larger number of volunteers and conducting clinical trials is a time-consuming and expensive process. The conduct of these trials is closely monitored by regulatory agencies, like the US Food and Drug Administration or the European Union's European Agency for the Evaluation of Medicinal Products, to ensure that a vaccine candidate meets necessary safety standards.

Prior to testing in humans, vaccine candidates are developed and tested extensively by researchers in the laboratory and then in different animal models. Data from these pre-clinical studies give researchers important information about how vaccine candidates might work in people and are carefully reviewed by regulators when they are granting approval to an organization or company to proceed with a Phase I clinical trial.

Vaccine development

Before a vaccine candidate is tested using animal models, researchers fully characterize the engineered vaccine in the laboratory—whether it is a viral vector, protein subunit, or DNA-based vaccine that will be used to present HIV protein to the immune system (Figure 2). For candidates that use viral vectors (see *VAX* September 2004 *Primer on Understanding viral vectors*), scientists will already have an extensive body of knowledge about how the naturally-occurring virus acts both biologically and immunologically so that they have an idea of how it will act in humans. This allows researchers

to generate a well-informed hypothesis about the types of immune responses the vaccine candidate might induce in humans.

Other pre-clinical evaluations

Even with a strong hypothesis, laboratory studies can only give researchers a vague idea of how the vaccine will work in the complex environment within the human body.

To try to gauge the safety and immunogenicity of a vaccine candidate, therefore, scientists have to conduct research in animal models. Usually the vaccine candidate will first be tested in mice and then in non-human primates, most often rhesus macaques.

Researchers start by administering the vaccine candidate to macaques and then characterizing the immune response it induces. This includes a detailed analysis of the cellular responses, especially in T cells, and measuring the level and type of antibody responses. Based on these results researchers can alter the vaccine candidate to try to enhance its immunogenicity and then re-test it in macaques. Working with animal models allows researchers to obtain extensive data that would be impossible to collect from human volunteers.

Next researchers usually use challenge studies to evaluate vaccine candidates. In these studies the vaccine candidate is administered to macaques that are later infected with simian immunodeficiency virus (SIV), which naturally infects many species of non-human primates. Challenge studies are only conducted in animal models, never in human volunteers. In this type of study researchers can determine how many macaques are protected by the vaccine candidate from becoming infected with SIV. They can also determine how long this protection lasts by challenging the macaques again later. Challenge studies may also provide clues on what type of

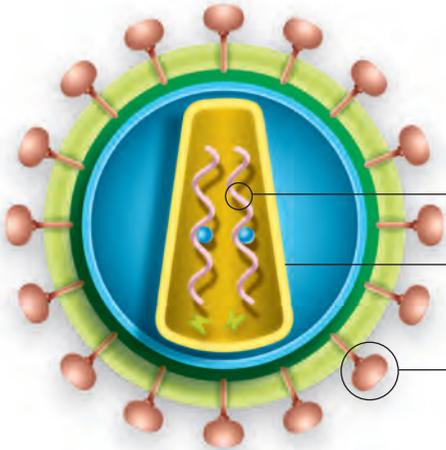


Figure 2. Different types of AIDS vaccine designs

VACCINES FROM HIV GENES

The vaccine uses HIV gene(s) as an immunogen. When taken up by human cells, these genes make HIV protein(s) that cannot cause disease but stimulate immune defenses.

Naked DNA
The vaccine consists of HIV gene(s).

Viral vectors
The vaccine consists of a weakened virus unrelated to HIV, into which HIV gene(s) are inserted. The virus delivers HIV gene(s) to human cells.

Bacterial vectors
HIV gene(s) are delivered via weakened bacteria.

VACCINES FROM HIV PROTEINS

Proteins
The vaccine uses HIV proteins (e.g., gp120 on HIV's surface) as an immunogen.

Peptides
The vaccine uses small pieces of HIV protein(s) as an immunogen.

immune responses (specific types of antibodies or cellular responses) are responsible for this protection, an idea referred to as correlates of protection.

This data gives researchers critical information about the vaccine candidate and helps them determine if it is safe and immunogenic enough to move into clinical trials involving human volunteers. Many of the vaccine candidates that are evaluated in pre-clinical studies never actually advance into clinical trials because they are not immunogenic enough to explore further.

Limitations

One important limitation with these animal studies is that the vaccine is not being tested against an HIV challenge. Researchers must evaluate the vaccine candidate's immunogenicity against SIV, which is a closely-related but different virus, because HIV does not infect non-human primates. To more closely mimic HIV infection in humans, researchers have tried running challenge studies with an engineered virus that contains both SIV and HIV genes—known as SHIV—but this is generally seen as an even less satisfactory model than SIV for predicting how a vaccine will work in humans.

Another limitation is that researchers have to also modify the vaccine candidate to carry SIV genes, rather than HIV genes, to match the virus being used in the challenge studies. Using a different challenge virus and a different vaccine candidate in a different animal species makes pre-

clinical evaluation more difficult. This is just one of the many complications researchers face in developing an effective AIDS vaccine.

For many years, therefore, researchers have sought ways to improve their ability to evaluate candidates in pre-clinical studies and find a better animal model for HIV infection. Recently researchers have developed an engineered mouse model where human cells are transplanted into mice that have their own immune systems depleted. This allows mice to grow human immune cells that can be infected by HIV. With refinement this type of model may be useful to researchers as an initial screen for AIDS vaccine candidates to help determine if a candidate is immunogenic enough to pursue in human clinical trials.

Scientists are also studying the genetic factors that allow non-human primates to fend off HIV infection. This research might one day enable scientists to engineer an HIV strain that can productively infect an animal model and therefore more closely mimic human infection.

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...pre-existing immunity

What is pre-existing immunity to a vaccine vector?

By Kristen Jill Kresge

When a person is infected with any disease-causing agent (or pathogen, such as a virus) the immune system makes antibodies and immune cells that recognize the pathogen and control the infection. Many of these antibodies and immune cells disappear after the infection is over. But a group of immune cells remain that are called memory cells. These cells stay inactive in the body until the person is exposed to that same virus again. The memory cells can then quickly recognize the virus and make more antibodies or immune cells to limit and clear out the infection.

Researchers are trying to design a vaccine so that the protein of HIV will cause an immune response strong enough to protect people if they are later exposed to HIV.

A vaccine tries to get your immune system to produce the same immune response as in a natural infection by using immunogens (pieces of viral protein). These small pieces of virus generate memory cells that can rapidly respond if the person is later exposed to that virus.

In order to generate an immune response against HIV, an AIDS vaccine will have to contain some immunogens that are copies of pieces of the genetic material of HIV. Because only a part of the HIV genetic material is used, this type of vaccine cannot cause HIV infection. Researchers are trying to design a vaccine so that the protein of HIV will cause an immune response strong enough to protect people if they are later exposed to HIV.

First, the immune system must 'see' the vaccine. Many current AIDS vaccine candidates use a vector as a carrier to get to the immune system. The vector is a weakened virus (or bacterium) that is safe for use in humans. Sometimes the vector is developed from a vaccine against another disease. Scientists are working with a number of different vectors for AIDS vaccines (see *VAX* September 2004 *Primer on Understanding viral vectors*). Vectors made from other viruses are called viral vectors.

When a common virus or vaccine is used as a vector, some people will have been previously exposed to this virus either naturally or through immunization. Some people will have an immunity to the vector; this is called pre-existing immunity.

When someone has pre-existing immunity to a virus or to a harmless vector, they have immune memory cells or antibodies specific to that pathogen or vector stored in their body. If the vaccinated person's immune response is directed towards the vector, it might limit the immune response to the HIV immunogens. This could make the vaccine less effective. So for each vector it is important to figure out whether preexisting immunity to it could prevent the vaccine from working.

Current vectors

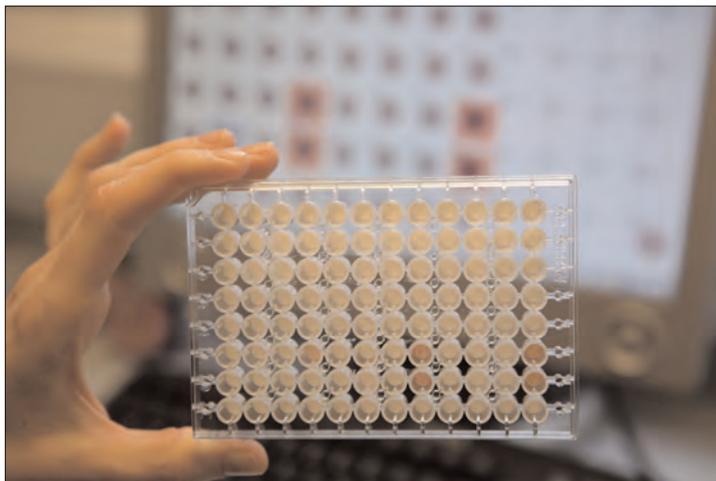
Several promising AIDS vaccine candidates are using a modified human adenovirus called Ad5 as a vector. Human adenoviruses naturally cause severe colds. After the infection is cleared the infected person has memory cells and antibodies specific to that adenovirus. There are about 40 different groups (called serotypes) of human adenoviruses. About 35% of people in Europe and the US, and as many as 90% of people in some countries (South Africa, Zambia, Botswana, and Thailand), have previously been

infected with Ad5. So pre-existing immunity to this vector is common.

An important AIDS vaccine trial is now ongoing with Merck's Ad5 vector, called MRKAd5. This trial will test the ability of the vaccine to either prevent infection with HIV or control disease progression in people who do later become infected with HIV. Researchers hope that the vaccine will stimulate the immune system to produce killer T cells that can kill HIV-infected cells. This is called a cellular immune response.

This vaccine is being tested in 1500 volunteers in eight countries. Only people with a low level of pre-existing immunity to Ad5 are enrolling in this trial. Without the problem of pre-existing immunity, researchers can fairly assess how effective the vaccine candidate is against HIV. But the results of this trial are not due for about four years. In the meantime researchers are exploring different approaches to improve the adenovirus vector. Some of these approaches include using higher doses of vaccine or using more than one vaccination (what is called a prime-boost strategy). Another approach would be to use a different serotype of adenovirus for which there is less pre-existing immunity, like Ad11 and Ad35. These serotypes are currently being developed as vectors for AIDS vaccines and could be used to get around the problem of pre-existing immunity to Ad5 if the current trial shows promise.

Other viral vectors now being used or developed for preventive AIDS vaccines may also face the problem of pre-existing immunity (such as measles or polio vaccine viruses) but each new vector must be studied to determine the importance of pre-existing immunity.



A researcher examines an ELISPOT assay and compares it with an automated readout on the computer screen.

Jean-Marc Ciboux/Getty Images

Researchers are yet to determine whether pre-existing immunity will be a problem for the different vectors being developed as AIDS vaccine candidates.

The Modified Vaccinia Ankara (MVA) vector is one example where pre-existing immunity does not seem to be a problem. This vector is part of several ongoing trials, including one that began in January. MVA is similar enough to the virus used for smallpox immunizations that pre-existing immunity to the smallpox vaccine could possibly affect the efficacy of an MVA-based AIDS vaccine candidate. But this vector may have less trouble with pre-existing immunity because smallpox vaccinations ended in most countries in the mid-1970s. People enrolling in vaccine trials are typically aged 25-40 and therefore pre-existing immunity will be unlikely. It is also no longer a naturally-circulating virus because of the successful worldwide immunization campaign. So far no effect of pre-existing immunity has been seen for MVA vectors but more information is needed.

Until researchers have more data on pre-existing immunity this is just one of the many considerations that vaccine developers must face.

Originally published in the February 2005 edition of VAX.

...long-term nonprogressors

What can AIDS vaccine researchers learn from studying people who are HIV infected but progress more slowly to AIDS?

By Kristen Jill Kresge

It takes, on average, about a decade for an HIV-infected individual to develop AIDS. This progression occurs gradually as the virus attacks and destroys CD4⁺ T cells, a subset of immune cells that are an essential component of the body's immune response to pathogens such as viruses and bacteria. Other mechanisms are also implicated in the gradual depletion of these cells. Many CD4⁺ T cells are initially replenished by the immune system and as a result most HIV-infected individuals remain healthy with few, if any, symp-

AIDS vaccine researchers are particularly interested in determining the type of immune responses that are responsible for slowing disease progression because mimicking these responses might be the key to producing an effective vaccine.

toms for several years. But eventually the immune system begins to fail and the number of CD4⁺ T cells slowly declines. This is often accompanied by an increase in the HIV viral load, which physicians measure by quantifying the number of copies of virus in a sample of blood.

A person with a healthy immune system has between 600-1200 CD4⁺ T cells in a milliliter of blood. When the number of CD4⁺ T cells falls below 200, a person is clinically defined as having AIDS. At this point it is recommended that individuals begin taking antiretrovirals (ARVs)

that can suppress the virus. Typically a person's CD4⁺ T cell count begins to rebound soon after starting ARV therapy and their viral load drops dramatically, often falling below the limit detectable by routine tests.

But some HIV-infected individuals are able to control the virus for much longer than a decade without ever taking ARVs. Researchers have even identified people who have been HIV infected for as long as 28 years and have never progressed to AIDS. These individuals are known as long-term nonprogressors, and they maintain very low viral loads and either don't progress to AIDS or do so much more slowly. Researchers estimate that 1% of all people who are HIV infected are long-term non-progressors.

Just what makes these individuals able to control HIV for longer than others is still something of a mystery, and it is further complicated because it could be due to different factors in different people. Several characteristics of the virus or the individual's genetic makeup could be partly responsible for this difference and researchers are actively studying long-term nonprogressors to determine exactly what enables them to control their HIV infection. AIDS vaccine researchers are particularly interested in determining the type of immune responses that are responsible for slowing disease progression because mimicking these responses might be the key to producing an effective vaccine.

This could be especially true for a partially-effective vaccine, one that would most likely not prevent HIV infection entirely but could lower viral load in people who do become infected. This lowered viral load would reduce the risk of them transmitting the virus to others, so a partially-effective vaccine could signif-

icantly reduce the number of new HIV infections. Long-term nonprogressors may hold important clues about what type of immune responses an AIDS vaccine would have to induce to keep HIV viral load under control.

Possible explanations

Researchers began studying long-term non-progressors more than 15 years ago and they have identified several possible explanations for why some people have the ability to control HIV more effectively than others. One is that the virus that these individuals are infected with is weaker and therefore less able to infect and kill CD4⁺ T cells. Some people are infected with a strain of HIV that is missing a key viral protein, known as Vpr, which limits its ability to infect cells.

Another possible explanation is that people have CD4⁺ T cells that are resistant to HIV infection. Individuals have been identified who lack a receptor on the surface of these immune cells that is normally used by HIV to gain entry into and subsequently infect the cell. Researchers think there are probably also other genetic properties that allow a person's immune cells to target and kill HIV more effectively.

But there are also many individuals who are long-term nonprogressors who are not infected with a weakened version of HIV or who do not have any of the known genetic properties that bolster their resistance to the virus. Researchers have studied these individuals to see if their immune systems are somehow able to mount more effective immune responses against HIV. So far none of the immune responses they've studied in long-term nonprogressors are any different than in people who progress to AIDS more quickly.

Elite controllers

To try to solve this puzzle and identify the particular immune response that might be impor-

tant in controlling HIV infection, a team of scientists are now collaborating on a project to study specific subsets of long-term nonprogressors known as elite or viremic controllers. Elite controllers are HIV-infected individuals not taking ARVs who maintain viral loads that are considered undetectable (<50 copies of virus per ml of blood). About 1 in every 300 HIV-infected people is considered an elite controller. Viremic controllers are infected people not taking ARVs whose viral load remains below 2000 copies/ml of blood.

Long-term nonprogressors may hold important clues about what type of immune responses an AIDS vaccine would have to induce to keep HIV viral load under control.

Bruce Walker and colleagues at the Harvard Medical School are now working with other AIDS vaccine researchers to identify a group of 1000 elite and viremic controllers around the world—they estimate there are about 2000 in the US alone, most of whom don't know it. They plan to analyze the immunologic and genetic characteristics of these individuals utilizing the information collected by the Human Genome Project that successfully mapped the thousands of human genes. By comparing this information across a larger cohort of controllers, researchers are hopeful that they will be able to identify the specific genes or immune responses that allow some people to control their HIV infection. Hopefully this will yield important clues for the future design of AIDS vaccines.

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...HIV clades

How does the genetic diversity of HIV affect AIDS vaccine design?

By Renata Rutman

A key concern for AIDS vaccine researchers is the tremendous genetic diversity of HIV. The majority of global HIV infections are caused by a single group of virus, which is divided into nine different subtypes, or clades, designated by the letters A through K. Further complicating matters are the viral recombinants that occur when viruses from different clades combine segments of their genome, forming a hybrid. These occur in several regions of the world where more than one HIV clade is circulating.

The advent of clades

The diversity of HIV and the development of clades stems from the ability of HIV to produce billions of viral particles daily (Figure 3). The enzyme involved in viral replication, reverse transcriptase, is not precise and sometimes incorporates mistakes into the viral genome, resulting in genetic mutations. The more HIV replicates, the more likely it is to make mistakes, increasing the potential for genetic variation.

Each of HIV's genes develops mutations at a different rate. The genetic sequence of the envelope gene (*env*), for example, which encodes the HIV surface protein that attaches the virus to human cells, can vary by as much as 35% in virus samples from different clades. Others, such as the *gag* gene that encodes the internal core of the virus, remain more conserved, varying by less than 10% from one clade to another. Overall, the genetic makeup between all clades deviates by approximately 30%.

HIV clades also vary in prevalence throughout the world. For example, HIV clade B is found mostly throughout North America and Europe, while the epidemic in South Africa and India is due to HIV clade C. Researchers are therefore trying to develop an AIDS vaccine candidate that offers the broadest possible protection.

But there are still many unanswered questions about the significance of viral diversity for AIDS vaccine design. Scientists do not yet know whether immune responses induced by a preventive AIDS vaccine would be able to protect against only one particular HIV clade or against several. Most clinical trials of AIDS vaccine candidates have occurred in communities where the antigen in the vaccine comes from the same HIV clade as the one circulating in the region, a concept known as clade or genetic matching. The key for an effective AIDS vaccine is to elicit the kind of immune response that would be effective against the circulating virus in the region, but this is not well predicted by clade alone. Clade classification refers to the different protein sequences that distinguish the circulating viruses and not the way the human immune system recognizes or reacts to HIV, so the importance of such matching is still in question. Scientists are also still trying to determine the type and magnitude of immune response required for protection, so clinical trials to determine the immunogenicity of vaccine candidates in relevant populations remain critical.

Implications for vaccine design

When the first AIDS vaccine trials were initiated, vaccine development efforts focused mostly on candidates from isolates of HIV clade B, found in North America, parts of South America, Western Europe, and Australia, and currently responsible for approximately 12% of global infections. Later, candidates with antigens from clades A and D, both common in parts of Africa, were brought to clinical trials. Several others were also developed based on clade C, the subtype circulating in Southern Africa, India, and China, which is responsible for over 50% of all HIV infections worldwide.

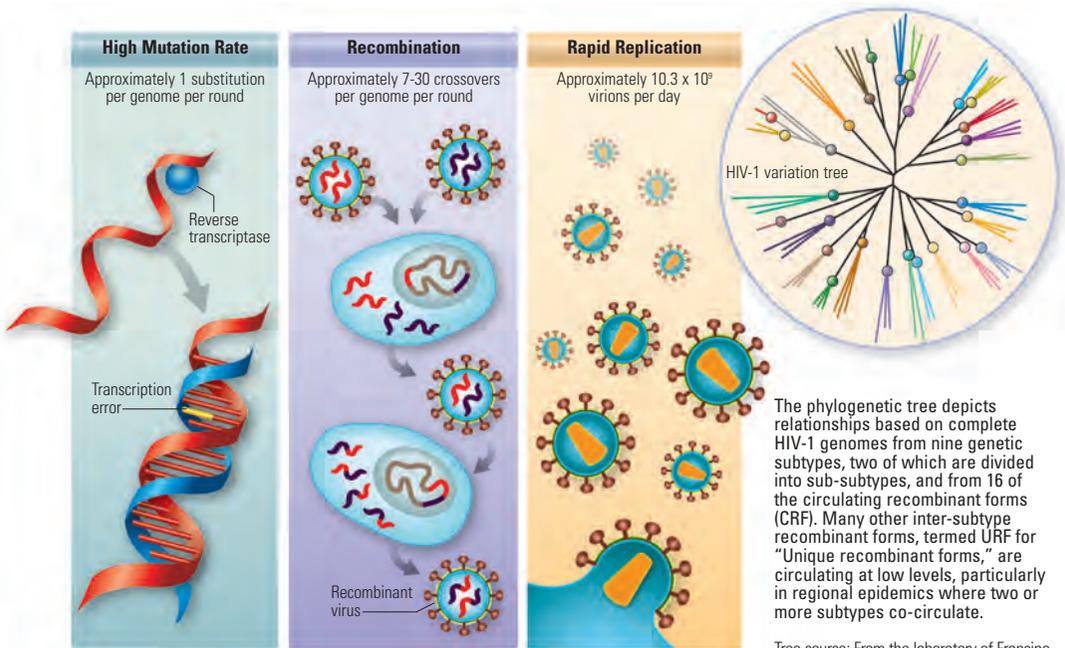


Figure 3. Causes of HIV variability and impact on the circulating virus

Tree source: From the laboratory of Francine McCutchan, Henry M. Jackson Foundation

As more candidates entered clinical testing different approaches to vaccine development have emerged to tackle HIV diversity. One strategy aimed at eliciting cellular immune responses involves the use of the most conserved regions of HIV or widely recognized protein pieces from different parts of HIV to develop an AIDS vaccine candidate.

A different vaccine strategy that aims to elicit broadly-neutralizing antibodies against several clades uses a combination vaccine with *env* genes from several clades. A third approach, which is not yet in clinical trials, compares the sequences of HIV genomes from different clades to create a computer-generated sequence that best matches the highest number of strains, with the hope that any protective immune response that the vaccine elicits would confer protection against infection by different HIV clades.

Informing the field

Merck and the HIV Vaccine Trials Network (HVTN) are now completing site preparations in South Africa for a second Phase IIb “test of concept” trial with the company’s clade B-based ade-

novirus serotype 5 (Ad5) vaccine candidate, known as MRKAd5. The candidate is currently being evaluated in another Phase IIb trial in North America, South America, the Caribbean, and Australia. The addition of a South African trial marks the first time this candidate will be evaluated in a population where the circulating clade of HIV, clade C, does not match that in the vaccine.

In 2003 the African AIDS Vaccine Programme came out strongly in favor of planning trials to give clear answers about protection across different clades as long as there is evidence that the vaccine candidate induces immune responses against the most commonly circulating virus, regardless of clade classification. Preclinical data for MRKAd5 show reactivity between the vaccine antigens and the predominant virus found in South Africa. The Merck trial therefore offers an opportunity to test this in a “proof of concept” trial that may provide preliminary answers about a vaccine’s efficacy while answering crucial questions for vaccine design.

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José Esparza



HIV vaccine developments

José Esparza MD, PhD has been a leader in the international HIV arena for almost two decades and for much of that time has been a consistent champion for AIDS vaccines, particularly for developing countries. He currently wears two hats, one as Senior Advisor on HIV Vaccines at the Bill & Melinda Gates Foundation, as well as head of the interim secretariat for the Global HIV Vaccine Enterprise.

Esparza began his research career at the Venezuelan Institute of Scientific Research in Caracas, Venezuela, where he rose from graduate student to full professor. During that time he completed his PhD at Baylor College of Medicine, Houston, Texas, and managed a two-year spell as a visiting professor at Duke University, North Carolina. His research interests have encompassed epidemiology to molecular biology in human virology, including herpes simplex viruses, Venezuelan equine encephalitis virus, and rotaviruses.

In 1986 he joined the World Health Organization (WHO) in Geneva, and soon became a leader in that organization's HIV/AIDS programs, with an emphasis on vaccines. Esparza then moved in 1996 to the Joint United Nations Programme on HIV/AIDS (UNAIDS) to lead their HIV vaccine programs. In 2004 he joined the Bill & Melinda Gates Foundation and has been an important figure in establishing the nascent Vaccine Enterprise.

IAVI Report Editor Simon Noble spoke to Esparza in December 2005 about the Gates Foundation, the Vaccine Enterprise, and recent developments in the field of AIDS vaccines.

The Gates Foundation is now a leading global health organization. Consequently it now has a very wide scope of activities—in comparison to other diseases, what emphasis does the Foundation place on HIV?

The Gates Foundation is a family foundation and our mission—which reflects the vision of Bill and Melinda Gates—is to help address fundamental inequities in the world, something that Bill has referred to as the random geography of birth: A child born in the US or Europe has a totally different perspective in relation to access to health, education, housing, the future in general, when compared to a child who is born in, say, the middle of Africa. They have identified that two of the major factors of this inequity has to do with lack of access to education and healthcare. Because of that, global

health—the emphasis is to develop interventions that can be used in developing countries—takes about 60% of our funding at this time.

When AIDS appeared 25 years ago, it not only created major inequities but also helped to identify existing major inequities, including inequities to do with access to education that helped prevent many people in the North from becoming infected but that wasn't widely available in the South. And that inequity between the haves and the have-nots was then increased when antiretroviral drugs were developed.

I hope that once an HIV vaccine is developed it will not contribute to further increasing the gap between the North and the South. If the vaccine that is developed is not appropriate for developing countries because of the cost, because of the regimen for

administration, because of the sub-type specificity, or for some reason it's not available in developing countries, then that would be the ultimate tragedy.

About \$1.1 billion of the \$6 billion in global health grants to date have gone towards HIV. This proportion may change as we find where the strategic opportunity arises, so we can move there and make a difference.

How much emphasis is placed on HIV prevention versus treatment?

Today, in 2006, we don't see a dichotomy between prevention and treatment. Both are important components of our response to AIDS, they have to go hand in hand. But 10 years ago, there was confrontation between prevention and treatment. When I was at the WHO I remember making the point that an organization that focuses on prevention can't disregard those who are infected.

We're very encouraged by the recent progress on treatment, but there's still a long way to go on prevention. We are developing a broad prevention portfolio, including microbicides, vaccines, pre-exposure prophylaxis, behavioral components like the Avahan initiative in India to empower disenfranchised populations, and others. We work with other partners to ensure that the response to the epidemic is not skewed in any direction but remains comprehensive, rational, and durable.

There have been major efforts in the last three years, like the President's Emergency Plan for AIDS Relief (PEPFAR) and the '3 by 5' program, to increase access to therapy. That's wonderful, and it has facilitated the work of organizations like IAVI that focus on prevention.

You used to work on rotavirus, it must be exciting to finally see an effective vaccine come to market. Does this example have lessons for AIDS vaccine development?

Yes, I started working with rotavirus soon after it was discovered, in 1974. The ultimate goal was the development of a vaccine, and I am thrilled that now we have one, or maybe even two. I often use rotavirus as a paradigm for HIV vaccines. The development of the vaccine took over 30 years of hard work, with multiple efficacy trials conducted

in industrialized and developing countries. A key strategic decision was when the end point to measure vaccine efficacy was changed from prevention of infection to prevention of disease, which is a current discussion in the HIV vaccine community, although there are important differences.

In rotavirus, there is not natural immunity after infection, children who are infected with rotavirus can be re-infected and re-infected. Conventional wisdom will tell you that if there is no post-infection immunity, forget about a vaccine. The eureka moment came when Al Kapikian at the US National Institutes of Health (NIH) and others realized that the primary infection was the more pathogenic, and when a child was re-infected the disease was generally very mild. That actually led to a change in the paradigm: A vaccine may not be able to prevent infection, but let's measure instead the severity of disease. And voila—there was a clear difference.

There are other parallels with HIV vaccines. There are many rotavirus types—although the problem of rapid mutation does not apply—and one vaccine is based on one type, and the other vaccine on four types. How much cross-protection between types exists? With correlates of protection, the rotavirus vaccine protection seems to be better than the level of circulating and mucosal antibodies would predict. So the immune correlates of protection are not very clear. Also, the rotavirus vaccine was developed without a good animal model.

The other lesson for HIV vaccines of course is the need to conduct multiple, multiple Phase III trials. To some extent, it was an empirically-developed vaccine. It wasn't this approach that scientists tend to have, that you do a trial or an experiment to prove that your hypothesis was correct. It was actually a very exploratory, empirical approach to vaccines that they learned by doing. Overall, the rotavirus vaccine gives us some good lessons for HIV, including the need to maintain a balance between rational development and empirical testing. There is no substitute for clinical trials.

Do you think that within the AIDS vaccine field people are seeing that prevention of infection, sterilizing immunity, is such an elevated goal that perhaps we

have to lower the bar and go for prevention of disease? Do you think that's being tacitly agreed upon?

I don't think so, or at least for me it's not clear. I think that the intermediate goal of a vaccine may be prevention of disease rather than infection. But we don't have the information to conclude that this should be the ultimate goal of a vaccine. Experience is that people who become infected will, sooner or later, progress to disease. And accepting this intermediate goal too early could actually prevent the research that is needed to see if we can develop a vaccine that confers sterilizing immunity. There are many, many opinions in this field and I think we need more than opinions; we need facts. Science is not what you believe but what you know.

I think that debate is still ongoing. I would caution against premature agreement in the scientific community that the goal should be a vaccine that just prevents disease. This is work in progress; we don't yet know the limitations.

An effective rotavirus vaccine was introduced into the US in 1999 but was subsequently associated with intussusception (a folding of the intestine) in fewer than 1:10,000 children given the vaccine, leading to its withdrawal. In industrialized countries rotavirus is a fairly innocuous infection but in developing countries almost half a million children die each year from dehydration caused by rotaviral diarrhea. Do you think this has any relevance for AIDS vaccines, that perhaps we have to look at the risk-benefit analysis of a vaccine in the context of a particular country?

I'm very familiar with the intussusception story, and we lost an opportunity there. The strategy for introducing most vaccines, still in use today, is introduction first in industrialized countries to try to recoup some of the development costs and then move it to developing countries. The conversation about rotavirus vaccine took place after the intussusception issue was identified in the US, when the vaccine was not actually in use in developing countries.

There is a very, very heavy political component to this. It's very difficult for decision-makers in

developing countries to justify using a vaccine that was found not to be safe enough for the US. I've seen all the calculations of how many lives will be saved, because intussusception, as you say, is a very rare phenomenon, but from the very beginning I knew that it would be too much to ask for decision-makers in developing countries to accept a vaccine that had been found unsafe.

Now, had the rotavirus vaccine been simultaneously tested and introduced into industrialized and developing countries, I think the discussion would have been different. Developing countries may have different risk-benefit decisions than industrialized countries. A risk-benefit analysis takes into account burden of disease, the cost of the product, its ease of use, and many other factors that typically differ from country to country. But the value of life is the same anywhere in the world, and if the perception is that you are proposing a substandard vaccine in developing countries, that will not fly.

So that's a lesson to learn for HIV vaccines: Simultaneous testing and simultaneous introduction of the vaccine in developing countries, and allowing developing countries to make their own risk-benefit analysis. A major priority for the Foundation is helping to ensure that health products that could save lives reach the people who need them the most as quickly as possible.

Given those provisos, do you think there is a global perception now that HIV/AIDS within developing countries has become such a crisis that perhaps these conversations can now be broached again?

Yes, I think so, and the reason is that there is far greater research literacy in developing countries today than ten or 15 years ago. Then it was very difficult because basically you went to developing countries to ask them 'Please trust me. Trust the NIH. Trust the WHO.' It's very difficult to have a rational and pragmatic discussion when you're asking people to trust you. Today, I think that thanks to the work of many people, IAVI included, vaccine literacy is much higher.

What do you think sets apart the Enterprise's way of doing business? What

does it offer above and beyond the collaborative efforts already underway?

I have been observing the field of HIV vaccines for many years, and I saw a major strategic shift after the results from the recent Phase III trials. On one hand, the research community realized that developing an HIV vaccine was one of the major scientific challenges we were confronting and that a much more intense and rational effort was needed to complement the more or less empirical approach taken up till then. The other shift was what I call from the “solitary hunting approach” to “pack hunting,” as prehistoric man did when he shifted from hunting small animals to mammoths. If we want to succeed on this hunt, we need to reorganize ourselves in a more purposeful and targeted way, as that proposed by the Enterprise. Collaborative efforts should expand beyond exchanging reagents and talking in meetings, to a more structured and accountable way—perhaps we should look at how collaboration is structured in industry.

But I want to clarify that the Enterprise does not propose to replace the creativity of individual investigators, which we consider essential. The Enterprise proposes to supplement that creativity with systems and structures that provide the critical mass, a clear blueprint for research that may lead to discovery and product development, access to information and resources, a supportive political and community environment, and the financial resources to achieve success.

I recently had a conversation with Rino Rappuoli, who for me is the quintessential, practical vaccinologist, and he thinks the industrial model is very much an engineering approach. If you want to put a man on the moon, you know the laws of physics that will govern how a rocket will fly from the earth to the moon, so it's an engineering problem, an industrial problem. The problem we have with HIV vaccines is that we are to some extent in a pre-industrial stage, because we don't have a solution, and we have to explore many avenues, we have to build many small space probes rather than one big spaceship. However, if the industrial model means a more targeted effort with clear milestones, with clear go-no go decisions, in which the different partners are accountable for

their contribution, then I like the industrial model.

A number of people believe there is a strategic gap in the field of HIV vaccines. We can divide the vaccine development process, from an idea to injection into the arms of people, through four phases. The first is the discovery phase, creation of new knowledge, and the NIH is the driving force. Most NIH-funded scientists stop at that level, publication is basically their goal. The second is the translational or, as I like to call it, maturation phase. The third phase is the manufacturing phase, the typical industrial approach, the engineering phase. And the fourth phase is the delivery of the vaccine; we have a vaccine, how do we make it available to people around the world?

My feeling is that we have a strategic gap in the second phase, and that is one of the areas where the Enterprise can make a major contribution and help mature ideas so that they become interesting leads for industry to follow, and then work together with industry as real partners, because we need industry for their process development and manufacturing expertise.

What are your initial impressions of how the Center for HIV-AIDS Vaccine Immunology (CHAVI) is developing?

I think that the success of CHAVI is related to the success of the Enterprise: We need to improve the way scientists interact with each other and CHAVI represents a new model for increased collaboration. CHAVI and the NIH decided to first identify the core leaders and then asked those leaders to develop the network. The foundation is taking a similar approach, although we first identified the members of the network, and now we are working with them to establish a collaborative group.

What I see from CHAVI is that they are making a very serious effort to do two things. One is to bring new partners to the field. Now, of course many of the leaders are veterans of the HIV vaccine effort, because you have to go to those people who have the knowledge that we need to tap. The trick is getting the same players to play a different game, a more cooperative game. But CHAVI is also making an effort to bring in new players, and in their list of collaborators you see more people from developing

countries, more strategic alliances being created with people who are actually newcomers to the field.

The second is to bring new money to the field, and the NIH has pledged up to US\$350 million for CHAVI. That is additive money, and hopefully it'll create a culture of more collaborative work than the typical NIH R01 grants. We are eager to see CHAVI's progress: I'm very optimistic that CHAVI is a critical contribution to the Enterprise.

It seems that the Enterprise's strategic scientific plan has been quite a step forward, and that at least the broad scientific questions, have been agreed upon.

I'm going to say something you may not be expecting: While the plan is important, in fact what's more important is the process that led to the development of the plan. That's a process of bringing people together and challenging them to identify the key questions and potential ways to address those questions, and I think that discussion between 150 scientists from around the world was very helpful.

The plan was agreed upon by everybody. Why? Because it basically represents what we would call the current paradigm. I wrote an article (*International Microbiology* 8, 93, 2005) on the Enterprise where I address the issue of group think versus individual thinking, and I refer to one of my favorite philosophers, Thomas Kuhn, who said that in the scientific community knowledge moves not by gradual increment but by scientific revolutions.

Thinking within the scientific community is defined by the current paradigm because the individual thinking that the scientific community values so much is constrained by preexisting data and available tools, but also by the ability of getting grants or getting published, by the peer review system in general. If you are a very innovative, creative person, maybe you will not get the grants and your papers will not be published. So the scientific plan that we have today is mostly a current paradigm plan, but still have to explore harder how to bring in new paradigms, real innovative ideas.

Kuhn proposed that when the current paradigm doesn't provide a solution to a scientific problem, then the scientific community jumps to a new paradigm. Now, when you try to jump to

a new paradigm, you're trying to jump with ideas that are not supported by data, because they are new. Most of the time those new ideas outside of the paradigm are wrong. So jumping to a new paradigm will require taking risks to a level that most organizations cannot accept.

Although the solution for an HIV vaccine may come out from the current paradigm we need to be constantly looking at innovative research, how to bring really new science, not only theoretical knowledge but also even instrumentation and bioengineering tools.

What do you see as the next big step in the Vaccine Enterprise?

A year ago the Gates Foundation issued a Request for Proposals, inviting the scientific community to submit innovative ideas and approaches to accelerate HIV vaccine development focusing on vaccine discovery, both antibody and T-cell inducing vaccines, and laboratory standardization. We're planning to make an announcement within the next few months. We're structuring these projects as an interactive and collaborative network that shares information, reagents, and ideas, not only among themselves but with other key partners of the Enterprise, including CHAVI, IAVI, and others.

Our major priority is expanding the research agenda to implement the scientific priorities identified in the Enterprise plan. Also, the Enterprise is almost ready to appoint its first Chief Executive and to establish its permanent secretariat. In the short term, our other priorities are to update the current scientific plan and establish approaches to monitor its implementation by the Enterprise partners, start the implementation of activities in the areas of clinical trials capacity, have a reality check on our approaches to working with industry in areas of process development and future manufacturing, fine-tune our investment menu—a list of financial needs to implement the priorities identified in the scientific plan—and use it to raise the necessary funds for the Enterprise partners and for the secretariat.

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...the benefits and risks of participating in clinical research

What are the major considerations influencing the decision to volunteer for an AIDS vaccine trial?

By Kristen Jill Kresge

Making the decision to participate in an AIDS vaccine clinical trial is a complex and personal process and it is important that all potential volunteers fully understand what is involved in the trial when making this choice. Researchers and staff conducting AIDS vaccine trials take several measures to ensure that, to the best of their ability, any possible benefits and risks of trial participation are identified. These are then reviewed before the trial begins by local and independent groups known as ethical review committees (ERC) or institutional review boards (IRB) and sponsors to ensure the list is complete. The ERC is committed to ensuring that the trials are run to the highest safety and ethical standards. All of the possible benefits and risks are also explained carefully to each interested volunteer during the informed consent process (see *Understanding informed consent*, page 29).

Benefits

There are several ways that clinical research, including AIDS vaccine trials, can benefit the countries and communities in which the trials take place even if the vaccine candidate being tested is eventually found to be not effective. Before AIDS vaccine trials are conducted, educational campaigns take place to raise awareness within the community about HIV transmission and prevention and these can benefit all community members, not just those who choose to volunteer for the trial. Many of these outreach programs also promote voluntary counseling and testing (VCT) for community members to find out if they are HIV infected, which can influence future decisions about their health and help reduce the stigma associated with HIV testing.

There are also several possible benefits for those who decide to participate in an AIDS vaccine clinical trial. They include the VCT services and risk-reduction counseling that the volunteers will receive regularly throughout the course of the trial (see *VAX August 2005 Primer on Understanding risk-reduction counseling*). Volunteers will also have continuous access to the best available prevention measures in their community, including male and female con-

There are several ways that clinical research, including AIDS vaccine trials, can benefit the countries and communities in which the trials take place even if the vaccine candidate being tested is eventually found to be not effective.

doms. Participants in AIDS vaccine trials also benefit from the rewarding feeling of being involved in medical research that may benefit others. Altruism, or concern for the welfare of others, is one of the most common reasons trial volunteers give for their participation.

Other possible benefits include the basic medical care that volunteers receive during the trial. People interested in volunteering for AIDS vaccine trials who are found to have malaria or tuberculosis can receive referrals to treatment

programs in their community, therefore improving their overall health. This is also true for people who are found to be HIV infected or who become HIV infected during the course of the trial through exposure in their community. These individuals can be referred to treatment programs, as well as to support groups.

Volunteers in AIDS vaccine trials might also receive reimbursement for transportation to and from the trial site or for food if they are expected to be at the site during a mealtime. A reasonable amount is determined, with input from the community advisory board, before the trial begins and is reviewed and approved by the ERC.

Researchers and trials staff are dedicated to making sure that AIDS vaccine trials are run safely and ethically and that these trials contribute to the overall health and welfare of the communities that participate in AIDS vaccine research.

Researchers and the ethics committees take these considerations seriously because they don't want the compensation or the health care provided at the trial sites to be the reason that people join the study. All trial organizers and approval bodies work carefully to avoid undue inducement. To prevent this, some trial sites may strive to provide a level of care that is consistent with what is available in the broader community. Other sites try to extend some basic healthcare services as much as possible to the wider community, which can be difficult at urban sites.

Volunteers should not feel pressured by the trial staff into enrolling in a trial but should make a decision only after weighing all of the potential benefits and risks. Ethicists are also

studying how to ensure that adolescents fully understand the risks and benefits of participation in medical research before agreeing to enroll. This may be an important issue in the future as researchers consider the possibility of testing AIDS vaccine candidates in this age group.

Risks

It is equally important that all volunteers understand the potential risks of participating in AIDS vaccine clinical trials. All vaccine candidates are tested extensively before they enter human clinical trials, but there is still the possibility that there will be side effects or adverse reactions caused by the vaccine candidate. Often these are mild and can include headaches, fever, and inflammation at the injection site, but these effects should be explained to all volunteers clearly during the informed consent process. However, researchers can't predict each individual's response to the vaccine.

It is also critical for volunteers to understand that there is a possibility that the vaccine candidate will not be effective or that they will be randomly selected at the start of the trial to receive an inactive substance known as a placebo. Either way, the volunteers won't be protected against HIV infection by participating in the trial, emphasizing the need to practice risk-reduction behaviors.

Other potential risks include the possibility of receiving a false-positive HIV test result in the future (see *VAX* November 2005 *Primer on Understanding HIV testing*), being unable to donate blood after participation in the trial, and social risks such as facing possible stigma or discrimination.

Despite these inherent risks, researchers and trial staff are dedicated to making sure that AIDS vaccine trials are run safely and ethically and that these trials contribute to the overall health and welfare of the communities that participate in AIDS vaccine research, especially in developing countries.

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...community advisory boards

What role do community advisory boards have in vaccine trials?

By Kristen Jill Kresge

An important part of preparing for clinical trials of preventive AIDS vaccine candidates is engaging policymakers, government leaders, non-governmental organizations (NGOs), and members of the community where the trial is taking place. Each of these groups has a role in ensuring that trials are run ethically and that the entire community benefits from having access to information about AIDS vaccines and other prevention strategies.

The involvement of members of the local community is vital to a successful trial because they are the people who will be volunteering. Community advisory boards (CABs) are one way for members of the community to be closely involved in the process of planning and running vaccine trials.

CABs became part of the clinical trials process in the US and Europe in the early 1980s when AIDS activists urged researchers and regulatory groups, including the US Food and Drug Administration (FDA), to quickly find and approve treatments for HIV infection. Many community activists educated themselves about HIV and demanded that they be involved in the design of treatment trials. The community activists were successful in changing the drug approval process in the US so that essential drugs could be approved faster. Activists were also part of CABs that met with pharmaceutical companies and the FDA to review how trials were being run. The CAB members then shared this information with others, making them the liaison between the researchers and the community.

CABs were also part of the first AIDS vaccine trials that took place in the US and Europe and are now an important part of trials that are run throughout developing countries. Uganda formed one of the first CABs in Africa in the late 1990s, a year before the first AIDS vaccine trial

began on the continent. The goal of CABs is to build a strong relationship between the researchers running vaccine trials and the local community where the vaccine candidates are being tested to ensure that the community has input into the process.

Who attends CAB meetings?

Participation in CABs is voluntary but in some communities members are asked to remain committed to the group for a set amount of time. The CABs for vaccine trials usually include community leaders like nurses,

The goal of CABs is to build a strong relationship between the researchers running vaccine trials and the local community where the vaccine candidates are being tested to ensure that the community has input into the process.

teachers, members of the media, or NGO staff. Many may also involve local religious leaders. CABs try to be as diverse as the local populations they represent so that all members of the community can benefit. The members of a CAB will have different educational backgrounds and concerns. Some members may understand medical or scientific issues while others may just be interested in HIV prevention. The early CABs in the US included mostly people who were HIV infected because the trials were testing HIV treatments. For vac-



Many public health campaigns, like this one in Nairobi, Kenya, focus on vaccination.

cine trials, CABs may include people who are current or past volunteers in a trial and want to help improve the process in the future.

There are typically around 20 members in each CAB who meet regularly to discuss the trial process. A researcher or investigator from the trial site will often attend the meetings to provide updates on trials that are in progress or to explain those that are starting soon.

What does the CAB discuss?

CAB members are often asked to provide comments on the way trials are designed, including how volunteers are recruited for the trial. Members of the CAB can help recruiters by giving them culturally-specific advice on how to reach local populations that are important to include as trial volunteers. This may include where the best locations are to recruit volunteers or how the trial staff can use gender-specific approaches to encourage women to enroll in vaccine trials. The CAB also encourages other members of the community to volunteer by giving them information about the trial. For example, CAB members can explain that you cannot

become infected with HIV from the vaccine candidate, which may ease some of the worries people have about participating in a trial.

CABs are also asked to share their questions and concerns about the informed consent process that all volunteers must participate in before joining a trial. This process includes a description of the trial, details of what participation in the trial entails, and explains the possible side effects of the

vaccine candidate. Informed consent is one area where CABs can have a direct influence on trial protocols. CABs can advise the trial coordinators about what information to include in the process to ensure that volunteers understand the aim of the trial. They can also help researchers understand how to explain the process of informed consent to volunteers in a way that is culturally acceptable. Other issues a CAB may address include the compensation for volunteers in vaccine trials, the community's fears about participating in research, the stigma involved with HIV research, and understanding the results of vaccine trials.

The CAB meeting is a place where the members can ask questions and comment on any part of the trial process and where there is an exchange of information between the community and the research staff. This creates a supportive environment for vaccine trials because CAB members can be certain that researchers are considering the perspective of the participants.

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...capacity building at vaccine trial sites

How can AIDS vaccine trials help build infrastructure and capacity in developing countries?

By Kristen Jill Kresge

In order to determine whether an AIDS vaccine candidate is effective it must be tested in the populations that are most affected by the disease. Clinical trials have to take place in communities where there is a high enough incidence of HIV infection for researchers to determine positive benefits from the vaccine. This often requires running trials in developing countries, where there is the highest HIV/AIDS burden. It is also essential that vaccines be evaluated in the communities that need them the most.

Many organizations involved in AIDS vaccine research, including the Global HIV Vaccine Enterprise and the European & Developing Countries Clinical Trials Partnership (EDCTP), have recently published reports emphasizing the importance of developing both the physical infrastructure and the human resources at clinical trial sites in developing countries. This is the strategy used by organizations like Walter Reed Army Institute of Research, the US Centers for Disease Control and Prevention, and IAVI that have been running vaccine trials in Africa and Asia. The idea of building trial site capacity involves both establishing clinics and laboratories and training medical professionals. Both of these steps help ensure that the research site is sustainable over the long term and can be used for future clinical trials. Developing these sites also benefits the community by providing career opportuni-

ties for healthcare workers that can serve the community long after the trial ends or by attracting other medical services to the area, such as HIV treatment programs (see *Understanding the benefits and risks of participating in clinical research*, page 23).

Infrastructure

The first step in building an AIDS vaccine clinical trial site involves constructing the actual buildings that will serve as clinics and laboratories or modifying those that already exist. These facilities are then equipped with the instruments necessary to process laboratory samples obtained from volunteers during the trial and preparing these specimens for storage or shipment. Some sites may even develop sophisticated HIV immunology and virology laboratories that can analyze samples and process the data from the trial in the country where it takes place.

India recently started an AIDS vaccine trial sponsored by IAVI in partnership with the



James Onyango in a Kenya AIDS Vaccine Initiative (KAVI) laboratory in Nairobi, Kenya.

Jean-Marc Gihou/Getty Images

Indian Council of Medical Research and the National AIDS Control Organization at the Tuberculosis Research Center (TRC) in Chennai. The TRC, a newly-established center of excellence for the clinical evaluation of vaccines in the country, features a safety and immunology laboratory where all laboratory tests will be run.

Human capacity

Once the clinics and laboratories are established it is also important to build human capacity at AIDS vaccine trial sites. Sponsor organizations spend significant amounts of time hiring and training medical professionals in developing countries to handle the activities associated with the trial.

Developing these sites also benefits the community by providing career opportunities for healthcare workers that can serve the community long after the trial ends or by attracting other medical services to the area, such as HIV treatment programs.

This occurs through a series of instructional workshops that cover all aspects of the clinical trial process, from screening and enrolling volunteers to collecting and analyzing data, and are based on a set of work practices developed specifically for each site. All trials are certified according to a set of international guidelines, known as Good Clinical Practice (GCP). Compliance with GCP guidelines ensures that the trial is run properly, that the rights and needs of the volunteers are protected, and that the data collected during the trial is of high quality.

Counselors and nurses are trained to work with potential volunteers and to administer the informed consent process (see *Understanding informed consent*, page 29). These individuals may also receive

specialized training on enrolling women in AIDS vaccine trials and other gender-related issues.

For the staff working in the laboratories the training includes how to handle and process the laboratory samples and the procedures for data management. All tests run in the laboratories are verified by quality control processes to ensure that the results of the trial are meaningful.

The process of site development continues even after the trial has started. Many organizations continue working to enhance the site's ability to deliver HIV prevention and treatment services and to provide referrals to other clinics in the community. This can involve additional training sessions or meetings arranged with the staff from other AIDS vaccine clinical trial sites in order to learn from shared experiences.

Providing the site staff with such extensive training helps strengthen the human resources in that community. Once the trial is complete, these medical professionals can work in many other areas, including research, nursing, or in conducting other clinical trials.

Sustainable trial sites

Developing both the physical infrastructure and human capacity at a site are necessary steps for conducting an AIDS vaccine clinical trial in developing countries, but once established these sites can continue to function well beyond the end of the current trial. The staff's expertise in HIV could make the site suitable for other types of HIV prevention trials, including trials of microbicides, or for clinical research studies that contribute to the understanding of the HIV/AIDS epidemic in that country. These sites may also attract HIV treatment programs or other healthcare services that can continue adding benefit to the community. Keeping these sites active is also of great interest to organizations sponsoring AIDS vaccine trials, since many vaccine candidates will need to be evaluated in the future and these trials will require experienced sites and surrounding communities that have successfully conducted past trials.

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...informed consent

How does the informed consent process work in vaccine trials?

By Kristen Jill Kresge

AIDS vaccine candidates must be tested in human volunteers to evaluate their safety and efficacy. A vaccine trial can only be successful if people in the community are willing to volunteer for the trial, receive the vaccination, and return to the trial site for follow-up visits. An essential part of running ethical research is assuring that the rights of these volunteers are protected.

To ensure that the volunteer enrollment in vaccine trials meets high ethical standards there is a process known as informed consent. During this process trial investigators must fully explain the details of the trial and the vaccine candidate that will be tested, make sure that the volunteer understands the information, and allow the potential volunteer to freely decide if they wish to participate. The informed consent process must be completed for each person before he or she can enter the screening process for the trial. During the screening process all volunteers undergo research voluntary counseling and testing (see *Understanding research voluntary counseling and testing*, page 31) for HIV infection because only people who are not infected with HIV can enroll in a preventive vaccine trial.

At the end of the informed consent process, everyone who chooses to join the trial is asked to sign the informed consent document that has all this information in writing. The document shows that they want to participate in the trial, but informed consent involves much more than simply signing a paper. The United Nations Joint Programme on HIV/AIDS (UNAIDS) established a set of guidelines that recommends cooperation between researchers, community representatives in the form of Community Advisory Boards (see *Understanding community advisory boards*, page 25), and regulatory bodies to design and implement the informed consent process at AIDS vaccine trial sites throughout the world. The protocol for a vaccine trial, including the informed consent

document, must receive approval from a local ethics committee and national regulatory authority before that trial can begin.

Information

Community outreach is the first step of the informed consent process and aims to prepare a community for a vaccine trial. All the educational materials about HIV and AIDS vaccines are a necessary first step in getting people informed and interested in participating in a trial. This general information includes what HIV is, how it is transmitted, and how an AIDS vaccine might work. When members of the community who may be interested in volunteering come to the trial site, they are educated about the trial and the vaccine candidate being tested.

The nurse or counselor at the trial site begins by explaining any general background information about HIV and then explains why the vaccine candidate is being tested, what participation in the trial involves, and how the trial is being conducted. For example in some trials, not every person in the trial will receive the vaccine candidate. Some volunteers will receive an inactive substance known as placebo, so that the researchers can compare the vaccine being tested to something they know will have no effect. In most trials, neither the volunteers nor the researchers will know who receives the vaccine candidate or placebo until the end of the trial (this is called a double-blinded study). The nurse or counselor explains that the person can't be infected with HIV from the vaccine candidate and also emphasizes that the vaccine being tested may not provide any protection against HIV infection and so all volunteers must avoid risk behaviors.

The information provided also includes specifics about the trial process, including the length of the trial, the number of visits to the site, and what medical tests (such as the collection of blood samples) will be required. Potential volun-

teers will also be informed about the type of general healthcare they will receive during the trial, any reimbursement they will receive for traveling to the site, and most importantly, their right to leave the trial at any time.

The way this information is provided varies based on the trial site, but informed consent documents used in developing and developed countries are very similar. At some sites the informed consent process can extend over several visits, allowing the volunteers to take the information home and discuss it with their family. Once the trial site staff are trained, it is their responsibility to carry out informed consent process according to international and local standards.

When members of the community who may be interested in volunteering come to the trial site, they are educated about the trial and the vaccine candidate being tested.

Researchers may use videos or flip charts to explain complex issues like the benefits and risks of participation in the trial. The possible benefits include the medical attention that volunteers receive, as well as the rewarding feeling of participating in research that will benefit the community. Potential risks of participating in a vaccine trial include the possibility of side effects of the vaccine candidate or the possibility of temporarily having a false positive HIV test in the future, even though they are not HIV infected. A false positive can occur because the vaccine may cause the person's immune system to make antibodies to HIV, which is what the standard tests measure.

Cultural considerations

Investigators at the site do their best to explain terms in a way that is easy for the individual to understand and should try to answer all ques-

tions to the best of their ability. This is an important part of obtaining "true" informed consent. Researchers must be able to explain complicated terms to potential volunteers in a way that is relevant to the community and can easily be understood, sometimes even in languages that have no translations for these words.

The local ethics board as well as Community Advisory Boards have input into the informed consent process before the trial protocol is implemented and can therefore influence this process. Leaders in the community can provide the investigators with culturally-specific ways to explain key concepts. But it is still very important that researchers uphold the standards of the informed consent process, while trying to make it more sensitive to the beliefs of the community.

Understanding

The final step of the informed consent process involves ensuring that each individual fully understands the information provided. At some sites investigators may use written tests to verify their understanding. The investigators also try to ensure that each person's decision to participate is truly voluntary. The potential volunteer must not be pressured into enrolling by anyone at the trial site, or anyone in their family or community. This can be difficult in some cultures where, for example, women are unable to make decisions without consulting their husbands or community leaders. The nurses or counselors at the trial site should do their best to find out if each person's decision was made independently.

After they are certain the choice was made independently and based on a firm understanding of the trial, the informed consent document can be signed. If the volunteer cannot write, he or she may be identified in another way, such as a thumbprint. Volunteers that complete this step can enter the screening process, where they are examined and tested to see if they are eligible for the trial.

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...research voluntary counseling and testing

How is voluntary counseling and testing provided to volunteers in clinical research or vaccine trials?

By Kristen Jill Kresge

Before a clinical trial of an AIDS vaccine candidate or a clinical research study takes place in a community, the essential components of a research and healthcare system must be in place. These components include infrastructure for a study site, training researchers and healthcare workers at study sites to counsel and test people for HIV, and a place to refer those in need for proper treatment. This is sometimes referred to as the three Ts (Training, Testing, and Treatment); without these there can be no trial.

Eligibility for enrollment in a vaccine trial or a clinical research study will hinge upon whether a potential volunteer is infected with HIV, so everyone must have an HIV test. For AIDS vaccine trials potential volunteers can not be HIV-infected, but for other types of clinical research studies only HIV-infected individuals can enroll. HIV testing prior to joining a study is voluntary and the process is referred to as research voluntary counseling and testing (RVCT). These programs serve as the gateway to enrollment in studies. Other types of community-based VCT programs involve similar procedures but do not share the goal of enrolling people in a trial. The primary aim of community VCT programs is getting people to know their HIV status and undergo risk-reduction counseling so that they can protect themselves and their partners against HIV infection or be referred for care and treatment.

Like VCT, RVCT is confidential and seeks to help the volunteers understand the risk behaviors associated with HIV infection, the implications of the test results, and how they can reduce their future risk. RVCT also involves explaining what participation in a trial involves and getting the potential volunteer's informed consent to participate in a clinical research or vaccine trial. During

this process researchers ensure that volunteers understand what is involved in the trial before enrolling and that their participation is voluntary.

Different models are used to recruit people into RVCT programs where they can find out their HIV status and learn about how studies are conducted. Several methods of recruitment may be used from general community awareness, focus group discussions, and one-on-one interactions. All approaches involve strong community participation through community advisory boards—groups of people in the community that are familiar with the trial or study.

Pre-test counseling

All volunteers meet with a trained counselor before having an HIV test. In this session the counselor provides each volunteer with basic information about HIV/AIDS and asks questions to determine the understanding of how HIV is transmitted and what methods of protection are available. An important part of RVCT is also explaining what type of research is being conducted at the specific site and informing the volunteer that they may be able to participate.

During pre-test counseling background information is discussed with each volunteer. Information is collected about the volunteer's risk behaviors including sexual behavior, condom use, history of sexually-transmitted diseases, and use of injection drugs. Based on the information provided, the counselor will give explanations and recommendations on how to avoid and reduce the risk of HIV infection. If the volunteer joins the study this information may also be used to determine how his/her risk behavior may change over time. This will be analyzed by researchers at the site.



Vials of blood that are being collected for HIV testing. Samples are bar coded to protect the anonymity of those being tested.

For volunteers considering joining an AIDS vaccine trial, the counseling session also covers the study procedures. These include regular HIV testing, use of contraceptive methods, duration of the trial, and the necessity of making all scheduled study visits. In an RVCT session the counselor will explain that some volunteers in the trial will receive an inactive substance, called a placebo, instead of the candidate vaccine. Most vaccine trials are double-blinded, which means that neither the doctor nor the volunteer knows who is receiving vaccine or placebo. RVCT counselors will also emphasize that the researchers do not know whether the vaccine candidate is protective or not, and that until Phase III efficacy trials show otherwise the vaccine candidate should be considered as not protective.

A volunteer may choose not to be tested for HIV after receiving pre-test counseling.

Testing

The type of HIV testing that is used may vary by site. Many sites now use the rapid HIV tests that require only a finger prick to collect a blood sample and test for the presence of antibodies against HIV. Results from these tests are available in just 15 minutes. Some trial sites will do two rapid tests at the same time so they can be more assured of the results. At sites where rapid tests are not available it is very important to ensure that volunteers return for their

test results so they can receive the post-test counseling and be referred to healthcare facilities for HIV care and treatment should they be HIV-infected. For AIDS vaccine trials, more sophisticated HIV tests may be used in addition to the classic rapid tests to ensure accuracy.

Post-test counseling

Once the results are available the counselor will inform each person whether or not they are HIV infected and help

them to understand the results. If the volunteer is not HIV infected the counselor will explain that there is a period of time (called a window period) between when a person gets infected and when the body makes antibodies against HIV. Though they usually appear in three weeks, it can take up to three to six months for these antibodies to register on the test. If the volunteer reports risk behaviors in this window period then they may be asked to return for a repeat test.

Counselors will review ways for volunteers to reduce risk behaviors in the future, regardless of the test results. For volunteers who are HIV infected the post-test counseling will provide the volunteer with the opportunity to discuss their concerns. The counselor will help the volunteer set a plan of action, including notifying their partners or families finding ways to stay healthy, and referral for care and treatment available in the community.

RVCT has many benefits for communities. Research studies have shown that HIV incidence often declines in areas where extensive testing and public health campaigns promoting HIV education take place. People who know their HIV status are also likely to encourage other members of their community to be tested. This helps support enrollment in vaccine trials or clinical research studies.

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...couples voluntary counseling and testing

Why is voluntary counseling and testing for couples an important process for recruiting women into vaccine trials?

By Kristen Jill Kresge

Voluntary counseling and testing (VCT) is the process used by community-based clinics and trial sites to offer HIV testing, education, and counseling to individuals who want to know whether they are HIV infected or not. The VCT process involves learning about how HIV is transmitted and what behaviors put a person at risk for infection, in addition to the meaning and implications of the individual's test results.

There are several different types of VCT depending on whether the service is administered at a community clinic, as an initial screening for participation in an AIDS vaccine trial, or before joining a research study (see *Understanding research voluntary counseling and testing*, page 31). There are also different types of VCT used to target specific populations. One involves testing and counseling couples that are married or living together, rather than individuals, and is therefore referred to as couples VCT (CVCT).

What is different about a CVCT session?

During a traditional VCT session a person is given information on what can put them at risk for HIV infection. In a couples session the counselor works with the couple to find out how their behaviors work together to influence their risk. This involves opening a dialogue between partners about their sexual activities and empowering them to communicate their shared risks, which can be complicated in countries where such discussion may be taboo. Nurse counselors encourage each person to take responsibility for their behaviors and inform them about ways they can limit their risk, such as using condoms. CVCT is a complex process because counselors are working with the needs and emotions of two people whose risks for

HIV infection can involve others outside of their relationship.

A couple will go through the entire process together, including completing the consent documents (see *Understanding informed consent*, page 29), pre-test counseling, HIV testing, and post-test counseling. The consent for participation in CVCT requires that the partners agree to receive their HIV test results together, but these results remain confidential outside of the couple.

Dependent on their test results, the nurse or counselor will work with the couple during the post-test counseling to help them make a plan for

Counselors can work closely with discordant couples to create an atmosphere where the partners support each other, both through this process and in the future, while limiting the uninfected partner's risk of becoming HIV infected.

the future. In testing and counseling couples there are three scenarios: both partners are HIV infected, both are uninfected, or one is infected and the other is uninfected. This last case is what researchers refer to as a discordant couple. Counselors can work closely with discordant couples to create an atmosphere where the partners support each other, both through this process and in the future, while limiting the uninfected part-



Entrance to a medical center in Ggaba, Uganda, where IAVI is working with the Uganda Virus Research Institute (UVRI) on research studies in preparation for future vaccine trials.

ner's risk of becoming HIV infected.

Working with couples rather than individuals has been shown to have many positive effects, including increased condom use and a lower rate of new HIV infections between partners.

Why is CVCT an important recruitment tool for AIDS vaccine trials?

To find out if an AIDS vaccine candidate is effective at blocking HIV transmission, researchers must administer the vaccine candidate to groups or cohorts of people who are at high risk of becoming infected with HIV. This requires testing the vaccine in countries or communities where there is a high prevalence of infection. In Africa, couples are at the highest risk for HIV infection and researchers estimate that between 60-70% of HIV transmission occurs within couples that are married or living together.

African couples are therefore an important cohort for evaluating the efficacy of AIDS vaccine candidates and CVCT is one way to enroll volunteers that are at high risk of HIV infection from heterosexual transmission. This may not be true on other continents like Asia, where HIV transmission is still mainly occurring in the more traditional high-risk groups such as sex workers or injection drug users.

How can CVCT be used to recruit women for vaccine trials?

CVCT is an important way for researchers to reach out to more women about accessing counseling and testing services as well as possibly joining a vaccine trial. In recent years the number of people utilizing VCT services in some areas of sub-Saharan Africa has increased dramatically, mainly because of new treatment programs that offer people life-saving drugs if they are found to be HIV infected.

Despite being more vulnerable to infection, women remain underrepresented at many VCT sites.

Counseling and testing partners together can empower women to access VCT services, while avoiding discrimination or even possible violence from their husbands or communities. At some sites counselors will invite couples who have received CVCT to come for focus groups to see how they feel about possibly enrolling in a trial. Couples can learn about the vaccine candidate being tested and find out what it is like to volunteer for an AIDS vaccine trial.

One of the earliest centers to implement CVCT was a clinic in Kigali, Rwanda run by Projet San Francisco and Susan Allen, a researcher from Emory University who has established one of the largest couples counseling centers in Africa. This site started screening couples because women requested that their husbands also be tested. Of the original 1500 women that were seen at the Kigali center, 1000 were able to convince their husbands or partners to join them. The nurse counselors are now preparing for the site's first AIDS vaccine trial.

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...home-based voluntary counseling and testing

How can home-based or mobile services for HIV counseling and testing improve community responses?

By Kristen Jill Kresge

Voluntary counseling and testing (VCT) services are a key component of HIV prevention, treatment, and care programs. Individuals learn about behaviors that put them at risk of HIV infection and how they can reduce this risk through the counseling process, and this information can be a catalyst for people to alter their behaviors.

Individuals who undergo VCT also find out whether or not they are HIV infected (see *VAX* November 2005 *Primer on Understanding HIV testing*). VCT services, therefore, are often the primary entry point for infected individuals into treatment and care programs. These important outcomes make VCT programs a critical part of the community's response to HIV/AIDS.

There are various types of VCT services, including those given before enrollment in a vaccine trial or research study or sessions specifically tailored for couples (see *Understanding research voluntary counseling and testing*, page 31, and *Understanding couples voluntary counseling and testing*, page 33). These almost always occur at community health clinics or clinical trial sites, but the stigma associated with HIV in many communities, as well as the distance people are required to travel to clinics in rural areas, can prevent people from seeking these services on their own. Since VCT is such a powerful tool in getting people information on HIV and access to treatment if needed, researchers have looked for ways to maximize the number of people utilizing these services. One of these approaches is taking VCT services directly to people in their homes or neighborhoods. Such home-based or mobile VCT services, while limited, have been successful in getting more people to be tested for HIV infection.

The process

The VCT services administered in people's homes are conducted similarly to those in clinics. Community healthcare workers are trained to provide HIV counseling and testing and must obtain consent from all individuals before administering VCT. The only difference is that these healthcare workers go door-to-door offering these services.

Since VCT is such a powerful tool in getting people information on HIV and access to treatment if needed, researchers have looked for ways to maximize the number of people utilizing these services.

Some organizations, such as The AIDS Support Organization (TASO) in Mbale, Uganda, couple their home-based VCT services with at-home care programs. So when field officers deliver antiretrovirals (ARVs) directly to the homes of infected individuals they also offer VCT services to other family members in the household.

Others, like the AIDS Information Centre (AIC) in Uganda, have implemented a stand alone home-based VCT program in an effort to increase the number of people being tested for HIV. National surveys in the country reported that although 70% of people want to be tested for HIV infection, only about 10% have actually participated in VCT.

A pilot project, funded by the US Centers for Disease Control and Prevention (CDC) was started by AIC in 2004 in the districts of Tororo and Busia



A housing community in Uganda. Organizations like TASO are implementing home-based VCT programs in the country.

in Uganda in an attempt to reach as many people as possible in these districts and offer them home-based VCT services. Trained outreach teams visited each home and offered all family members information so they could decide if they wished to participate. Adults in the household were given the choice to receive these services individually, or as couples. Anyone who was found to be HIV infected during this process received referrals to treatment and care programs in their community.

Judging success

Many organizations have found that offering home-based VCT programs is an effective way to increase access to treatment and prevention services. The AIC program lasted for one year and during this time over 5000 individuals received VCT services in their homes, which was more than double the study's target. The outreach teams visited more than 2000 homes in these two districts of Uganda and in 65% of them at least one household member agreed to participate in VCT.

The results of this program were presented at the International AIDS Society meeting on HIV Pathogenesis and Treatment, which took place last year in Rio de Janeiro, Brazil, and the CDC plans to use this program to create guidelines that will allow additional home-based VCT programs to be started in Uganda.

The AIC concluded that stigma seemed to be

much less of an influence on a person's decision to undergo HIV testing when VCT services are administered in the home, instead of in clinics. Home-based VCT services could also be a promising strategy for reaching disempowered individuals, especially women.

Another option is providing just the test results and post-test counseling at home. In settings where rapid tests are unavailable, people sometimes do not

return to the clinic to find out the results of their HIV test. In a study conducted by the Medical Research Council in Entebbe, Uganda, researchers found that offering test results in a person's home was an effective way to ensure that people received them.

Mobile units

Another method for bringing VCT services directly to communities is to utilize mobile VCT units. The Foundation Agency for Rural Development, a non-governmental organization in Nairobi, Kenya, uses bicycles to bring VCT to local communities. Four mobile sites are set up in different areas throughout the city and each week several individuals undergo VCT. Like home-based services, these mobile units can reach people who may be unable to travel to a clinic to receive VCT.

From community to country

The most ambitious home-based VCT program is currently taking place in Lesotho, where on World AIDS Day last year the president announced plans to take VCT services door-to-door in an effort to reach every household in the country by 2007. To meet this challenge the government trained 6500 healthcare workers to provide VCT services. Prior to this universal HIV testing initiative, it was estimated that only 1% of the population had accessed VCT.

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...test of concept trials

Why are Phase IIb trials an important step in evaluating AIDS vaccine candidates?

By Kristen Jill Kresge

AIDS vaccine candidates are evaluated in a stepwise manner in a series of clinical trials known as Phase I, II, and III. Phase I and II trials generally involve a small number of volunteers and provide researchers with critical information about the safety and immunogenicity of the vaccine. It isn't until Phase III trials that the efficacy of the vaccine is assessed. These trials test the ability of the candidate to prevent infection and/or slow progression of disease. These trials require large numbers of volunteers, are extremely expensive (can cost more than a hundred million dollars), and take a long time to set up and complete. Phase III efficacy trials are the final step before a vaccine can get approval for licensure from a regulatory body like the Food and Drug Administration in the US or the Agency for the Evaluation of Medicinal Products in Europe.

What is a test of concept trial?

As the name implies, a test of concept trial is about finding out if the vaccine concept or the type of vaccine being tested will be effective. A test of concept trial is not designed to establish the efficacy of a particular candidate but rather to help researchers decide if this candidate is worth testing in larger Phase III trials. These intermediate studies are also referred to as "proof of concept" or Phase IIb trials.

The number of volunteers required for such trials is smaller, only around 2000-5000 volunteers as compared to over 10,000 for Phase III trials. Phase IIb trials are therefore much easier to design and manage, and are less costly. Since fewer doses of vaccine are required, these trials are also much faster to implement because the manufacturing process is limited. Very importantly, they may also provide researchers with the immune correlates of protection, or the immune

response generated by the vaccine that cause it to be effective. This can often be difficult to do in large Phase III trials.

However because Phase IIb trials are run in smaller populations, the precision of the trial is less. Therefore a vaccine can not be licensed based on the results of Phase IIb testing. If the results of a Phase IIb trial indicate that this approach is promising, a Phase III efficacy trial will be required before licensing and use of the vaccine. This means that the decision to run a

A test of concept trial is not designed to establish the efficacy of a particular candidate but rather to help researchers decide if this candidate is worth testing in larger Phase III trials.

Phase IIb trial will extend the total amount of time it takes to complete the clinical trials process. Phase IIb trials are an important screening step for different vaccine candidates and help organizations determine which ones to move forward into Phase III trials, without expending more time and money.

The idea of using Phase IIb studies is more than a decade old but the first one involving an AIDS vaccine candidate began just last year. Test of concept trials have already been done for other vaccines as well as for other preventive technologies. US-based Merck and GlaxoSmithKline Biologicals in Europe tested their respective vaccine candidates for human papilloma virus in Phase IIb trials. These candidates are now both being tested in Phase III efficacy trials. The HIV



A researcher prepares to analyze polymerase chain reaction samples on a gel.

Prevention Trials Network is also testing a microbicide candidate known as Buffergel PRO2000 in an ongoing Phase IIb trial to see if this agent can block transmission of HIV.

Why are test of concept trials especially useful for AIDS vaccines?

Because the challenge of developing an effective AIDS vaccine has proven so difficult and the need remains so great, researchers must evaluate several candidates as quickly as possible. This requires testing several candidates at the same time.

Researchers are also using new approaches to try to find an effective AIDS vaccine. Test of concept studies are one way to find out quickly if these new candidates can be successful. An example of this is the first Phase IIb trial of an AIDS vaccine candidate, which is being conducted by Merck and the HIV Vaccine Trials Network. This ongoing study is testing the company's lead vaccine candidate known as MRKAd5 in approximately 3000 volunteers. The MRKAd5 candidate primarily generates a cellular immune response, but scientists are unsure if this type of vaccine will be sufficient to protect people from HIV infection. Merck decided to test this type of vaccine in a Phase IIb trial to

find out if this strategy will be able to prevent HIV infection or to slow the progression of disease in people who do become infected through exposure in their community. The results of this trial will influence the company's decision to go ahead with a Phase III trial and will provide the entire AIDS vaccine field with critical information about the importance of cell-mediated immune responses in vaccine efficacy.

Another advantage of a Phase IIb trial is that it allows researchers to evaluate a candidate in a more confined study population. The MRKAd5 candidate is based on a particular strain of a human virus that naturally causes the common cold (adenovirus serotype 5). This candidate may not work as well in people who have already developed immunity to this strain of natural adenovirus, due to what is called pre-existing immunity (see *Understanding pre-existing immunity*, page 12). Initially Merck's Phase IIb trial was designed to include only people who had low levels of pre-existing immunity, so that they could find out if the vaccine concept was even feasible under optimal conditions. The trial has since been amended to include a more diverse population of volunteers.

The use of test of concept studies to evaluate AIDS vaccine candidates is also being considered by other organizations and more may be conducted in the future. For trial volunteers, communities, and health policymakers it is important to understand that a vaccine will not be approved based on the results of these studies even if the investigators are able to draw preliminary conclusions about its efficacy.

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AIDS vaccines for adolescents

By **Kristen Jill Kresge**

As HIV continues to infect millions of people throughout the world, more and more of the newly infected are between the ages of 15 and 24. Young people in this age group now account for almost half of all new HIV infections, with nearly three million becoming HIV infected each year. Despite these startling statistics, AIDS vaccines have so far not been tested in adolescent volunteers.

“The epidemic is becoming more youth-driven,” says Linda-Gail Bekker of the Desmond Tutu HIV Centre in Cape Town, who is preparing for AIDS vaccine trials involving adolescents in South Africa. Research shows that despite increased efforts to reach adolescents and provide them with information about HIV prevention, young people in many communities are having sex and pursuing injection drug use at an earlier age. This makes the optimal age for vaccination even younger, since adolescents should ideally receive a preventive AIDS vaccine before they become sexually active. “That’s our big motivation,” adds Bekker.

But before AIDS vaccine trials with promising candidates can be initiated in adolescents, researchers must tackle potentially thorny legal, ethical, and regulatory issues, and make sure they adequately address the concerns of parents about their children participating in research. Many organizations are currently working to develop guidelines and protocols that will enable future trials to be conducted successfully with adolescent volunteers. Progress in these areas will help guarantee that an effective AIDS vaccine, when available, will reach both adult and adolescent populations as quickly as possible, offering the greatest chance for curbing the pandemic. “I think we need to keep the pressure on,” says Bekker. “As we move closer to more promising candidates, we don’t want to be caught short.”

An adolescent epidemic

In the US, 40% of all new HIV infections are now occurring in individuals younger than 25. Although the risk facing teenagers varies greatly from place to place, in many countries, especially in Africa, the situation facing young women is particularly dire. Young women in South Africa continue to be at very high risk of HIV infection, with studies showing that HIV prevalence rates approach 16% among girls between age 15 and 24, four times the infection rates seen in boys of the same age. In Botswana nearly 25% of girls between the ages of 15 and 19 are already HIV infected.

“...when you look at the epidemic in Africa, adolescents are the highest incidence group and if you’re going to make headway in dealing with the epidemic you need to involve them.”

– Michael Robertson

Statistics like these are helping to fuel discussions amongst researchers, sponsoring organizations, and regulatory agencies about how and when to test AIDS vaccine candidates in younger volunteers. “Everyone has been cautious about moving into adolescents with AIDS vaccines,” says Michael Robertson, a lead investigator on Merck’s Phase IIb AIDS vaccine trial. “But when you look at the epidemic in Africa, adolescents are the highest incidence group and if you’re going to make headway in dealing with the epidemic you need to involve them.”

Researchers were given some guidance recently on adolescent trials by the US Food and Drug Administration (FDA). In a document issued in May 2006 (Development of Preventive HIV Vaccines for Use in Pediatric Populations, www.fda.gov/cber/guidelines.htm) the agency provided vaccine trial sponsors with direction on the requirements for licensure in adolescent populations. Most regulatory agencies like the FDA that oversee the approval and licensure of medicines and vaccines require that experimental products are tested in the population in which they will be used. For most vaccines this is in infants, who are susceptible to many diseases that they would normally catch during early childhood. Infants are also at greatest risk of developing life-threatening symptoms from viral infections because their immune systems haven't fully developed. Extensive childhood immunization programs have been implemented in many countries where sufficient healthcare infrastructure exists, and have drasti-

cally reduced mortality rates.

But there is much less of a precedent for adolescent vaccination. A vaccine against hepatitis B virus (HBV) was the only one to target this age group until a vaccine for human papillomavirus (HPV) was recently licensed by the FDA for girls aged 9 to 26 (see *Cervical cancer vaccines*, page 70). The large efficacy trials for the HPV vaccine involved thousands of adolescent (age 12-18) and pre-adolescent girls, and many researchers are closely monitoring the acceptance and inclusion of this new vaccine into immunization programs to help gauge the response to vaccines still in development that aim to prevent other sexually-transmitted infections, including HIV and herpes simplex virus type 2. "It's an excellent model for AIDS vaccine researchers," says Jeffrey Safrin of the Elizabeth Glaser Pediatric AIDS Foundation.

Results from HPV and HBV vaccine trials also give researchers good reason to be opti-



A group of young people gather at a health clinic in Cape Town, South Africa.

mistic that adolescents may respond even better to vaccination than adults. Clinical trials with both vaccines induced stronger immune responses in younger volunteers. The primary concern will be establishing safety data in these populations rather than immunogenicity, says Robertson.

The guidance document issued by the FDA suggested that strong safety and immunogenicity data for AIDS vaccine candidates should be collected in adults before adolescent trials begin. The agency also emphasized that efficacy data collected in adults could only be extrapolated to adolescents if researchers could successfully identify the immune responses that are predictive of protection, also known as correlates of protection. Establishing which immune responses correlate with protection is not a simple task and for both HPV and rotavirus vaccines (see *Rotavirus: Vaccines enter battle against an intestinal virus*, page 77) correlates of protection have not been identified even after large Phase III efficacy trials.

For AIDS vaccine candidates it may therefore be necessary to run large efficacy trials in adolescents. It is unlikely that these can only be done in the US since HIV incidence rates there are generally too low among adolescents to support a conclusive Phase III trial, says Audrey Smith Rogers, an epidemiologist at the US National Institute of Child Health and Human Development. The guidance document by the FDA recommends that trials sponsors discuss AIDS vaccine efficacy trials planned in other countries to ensure that this data can be applied to adolescent approval in the US.

Researchers in South Africa and Botswana are leading the charge due to the high prevalence of HIV infection among adolescents in these countries. The South African AIDS Vaccine Initiative (SAAVI) is currently collaborating with the HIV Vaccine Trials Network (HVTN) to prepare a protocol for an adolescent trial. The World Health Organization (WHO) and the African AIDS Vaccine

Program (AAVP) also sponsored a meeting earlier this year in Gaborone, Botswana, to address some of the challenges of including adolescent volunteers in AIDS vaccine trials. And Merck is now considering testing its lead vaccine candidate in adolescents in South Africa as part of a Phase IIb trial that will start there later this year in cooperation with the US National Institutes of Health and the HVTN. “The plans are very much in the discussion phase,” says Robertson. “We’ve discussed expanding the planned trial and amending the age cutoff to include adolescents, or adding another small safety and immunogenicity trial there just for adolescents.”

Key challenges

But before an actual trial begins these groups are working to overcome some of the key challenges that are unique to adolescent trials. Chief among these is the need to obtain

Involving adolescent organizations and community advisory boards that can offer peer support to volunteers could greatly improve the experience of adolescent volunteers.

informed consent from both the adolescent and their parent or guardian prior to enrollment (see *Understanding informed consent*, page 29). US and South African law both require that parental consent be provided for any trial involving minors where the vaccine isn’t guaranteed to provide some benefit, and Bekker predicts that many parents may be reticent, at least initially, to allow their children to participate, necessitating education and counseling for both adolescents and parents. “Once you give them the statistics, you can

easily change people's perception," she says. "Parents are very aware that their children are in danger."

Parental consent also requires striking a balance between involving parents and protecting the confidentiality and privacy of the volunteer. Adolescents may be uncomfortable disclosing their potential risk behaviors to a parent or guardian. This may become even more complicated in efficacy trials, where enrollment is dependent on the volunteer being sexually active and therefore at some risk of HIV infection, says Rogers.

Including adolescents in trials is viewed as a necessary step in making an eventual AIDS vaccine available to this population.

This raises legal and ethical issues about involving adolescents in trials before they have reached the legal age for sexual consent, which varies from country to country. "The implication is that you're saying the age of consent isn't applicable," says Bekker. "I'm a bit squeamish about that, even though I've been a great protagonist." A possible solution to this dilemma is including in efficacy trials only adolescents over the age of sexual consent and reserving Phase I and II trials for younger volunteers.

Regardless of these sexual consent issues, trial protocols are being developed to protect these adolescent volunteers by tailoring the informed consent process and counseling sessions to specifically address their concerns, as well as those of their parents. "These are the same issues we faced with our HPV program," says Robertson. The experiences in running these efficacy trials are helping the company plan future AIDS vaccine trials in teenagers.

Another concern for parents when making the decision to allow their child to participate is

the potential that volunteers in AIDS vaccine trials may test positive on HIV tests without actually being HIV infected (see *VAX* November 2005 *Primer on Understanding HIV testing*). And researchers will also face obstacles, including the retention of adolescent volunteers who tend to be more mobile than adults. "I don't think these are insurmountable problems," says Rogers.

For these trials to be successful, expertise must come from outside the vaccine field. Involving adolescent organizations and community advisory boards that can offer peer support to volunteers could greatly improve the experience of adolescent volunteers. "My take has always been that this can be done, but it can't be done by everyone," says Bekker. "You have to have groups who are used to working with adolescents."

Preliminary research indicates that many adolescents are eager to participate in AIDS vaccine research. Results from a feasibility study conducted by Bekker in South Africa indicate that 53% of 256 adolescents (age 11-19) were willing to participate in a trial. However the most common reason given for participation was the perception that it would offer them protection from HIV infection. This raises the concern of behavioral disinhibition in trials, where volunteers feel a false sense of protection from a vaccine candidate that hasn't yet proven effective. As a result they may continue or increase behaviors that put them at higher risk of HIV infection. Disinhibition is an important consideration in any prevention trial, but may be even more critical for adolescents. "It's a valid concern but I don't know that there's data out there to support it," says Bekker.

Including adolescents in trials is viewed as a necessary step in making an eventual AIDS vaccine available to this population, but the need to protect this vulnerable group from stigma and other social harms is imperative during the conduct of the trials.

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Zackie Achmat

Facing a prevention crisis

Zackie Achmat is one of the best known and most important AIDS activists in the world. He co-founded the Treatment Action Campaign (TAC) in 1998, which is now one of South Africa's preeminent AIDS organizations as well as one of the most influential activist groups anywhere. Since their inception TAC has been a critical proponent for affordable generic antiretrovirals (ARVs) and has challenged the South African government in and out of the courtroom over their slow response in making these medicines available.



For several years Achmat refused to take ARVs to treat his own HIV infection in protest of the government's failure to provide treatment to all citizens in need. His candor about his own struggles with the disease—he is most often seen in a tee shirt that reads "HIV Positive"—has helped create an open and supportive movement for the country's more than five million HIV-infected individuals.

Achmat was an activist long before turning his attention to HIV/AIDS. He was born in Johannesburg in 1962 and by the late 1970s he was leading student protests against apartheid. Later he began advocating for gay rights and eventually founded the National Coalition for Gay and Lesbian Equality.

In 2003 he was awarded both the Nelson Mandela Award for Health and Human Rights and the Jonathan Mann Award for Global Health and Human Rights. The following year he was nominated for the Nobel Peace Prize. Achmat remains a persistent and spirited champion for the rights of people infected with HIV, but as the epidemic in his country continues to grow—there were 500,000 newly-infected individuals last year alone with a prevalence rate among adults now around 25%—he is now also turning his focus to HIV prevention efforts. TAC is organizing a prevention march for early 2006 in Cape Town during the biannual international Microbicides conference. Achmat hopes it will create the same momentum for prevention as the treatment protest held at the 2000 International AIDS Conference in Durban, which is often referred to as a turning point in the battle for ARV access in developing countries.

VAX and IAVI Report Science Writer Kristen Jill Kresge spoke with Achmat in November 2005 about HIV prevention advocacy and how activists can ensure that communities understand the research and development of new prevention technologies like vaccines and microbicides.

What are the key challenges you still face as a treatment activist in your country?

Unfortunately there are still many challenges in South Africa regarding treatment. In our country about 800,000 people currently need treatment and fewer than 110,000 are receiving it. Of these, fewer than 70,000 are in the public sector. That's quite sad. There is also the need to

establish second- and third-line regimens for people who fail their initial treatments and provide access to ARV treatment for children.

All of these problems are worsened by some serious mixed messages from our government, including denial by some of the science of HIV infection. This political and scientific denial really reinforces very deep, personal denial for many

South Africans. The government isn't utilizing the strong and open HIV-positive movement, which doesn't exist in many other countries, to create further progress and that makes all of our tasks as activists much bigger. It's particularly difficult for the individual who discovers they have HIV and then doesn't have access to a doctor or nurse who understands what the issues are.

What is the situation with HIV prevention efforts in South Africa?

We don't simply have a crisis of treatment; we also have a critical crisis of prevention. Our country had 500,000 new HIV infections last year and it's critical that we act on that. It's critical that we look at why the ABC [abstinence, be faithful, use a condom] message has failed. You cannot reduce prevention of HIV to a simple slogan. It is a caricature of what needs to be a comprehensive prevention program that is linked to serious treatment and care issues.

I think all of us know that prevention is the key to ending the epidemic and that means we have to find new tools, like vaccines and microbicides. But there isn't a magic bullet and there's not going to be one for a long time so we have to use the array of tools that we have at the moment, whether it is barrier methods like male and female condoms or programs to prevent the mother-to-child transmission of HIV. We have some decent programs on prevention, but currently we're not doing enough to scale them up or to encourage openness about their use.

Why haven't activists done more prevention advocacy?

For many activists their inhibition is discussing basic science. Unfortunately all of us that have worked in prevention haven't developed the scientific literacy that needs to go along with a serious understanding of the social problems and inequality that inhibit behavior change. There is now some understanding of how gender and economic inequality hamper prevention efforts and put people at risk, but there isn't a scientific understanding of prevention tools and how they can be used.

I remember when we were first starting to do

HIV work and all we worried about was giving out condoms. We never said how the condom prevented transmission of the virus and it's a tragedy that it took politicians and the Catholic Church to make us explain exactly how these tools work and get us to think about the science of prevention in a way we didn't before.

There are numerous prevention service organizations with people who talk about condoms or voluntary counseling and testing, but I am yet to come across someone in those programs who actually understands the science. It's just a simplistic ABC message, which is why these messages are so counterproductive because they actually stop people from thinking. Our first job as activists in South Africa was actually on the prevention of mother-to-child transmission and many of us who started TAC actually began in HIV prevention and human rights work. Now it's sort of coming full circle as we are trying to make sure that what we learned in treatment goes back into prevention.

According to the latest report from UNAIDS and WHO on the status of the global epidemic, the HIV prevalence rates among pregnant women in Kwazulu-Natal, one of the hardest hit provinces in South Africa, is around 40%. Is there still debate about the use of single-dose nevirapine as a way to prevent mother-to-child transmission?

I have never believed in having one standard for the north and another for the south, but you have a situation in many countries where there are no antenatal services for poor women and so single-dose nevirapine is a first step. It provides an entry point for building the antenatal and treatment services that are needed. To automatically say that this regimen is third class and you either have to have the best or nothing at all is not practical. Even single-dose nevirapine is reaching less than 10% of people who need it. That frustrates me. We're still delaying both prevention and treatment significantly.

Presumably it's even more difficult to explain the basic science involved in the

research and development of vaccines and microbicides. How can this be accomplished?

South Africa is one of the few countries where there is a relatively good understanding of microbicides among activists and increasingly within civil society because there are some really good researchers in the country. And all of us who are activists, whether in prevention or treatment, now have a much clearer understanding of what we need to do to ensure that there is access to information about microbicide and vaccine development. It's difficult to explain the science of microbicides and vaccines, but no more difficult than treatment. HIV treatment has allowed us to become engaged in science and it's time that we became a lot more scientifically literate about HIV prevention.

We need to find a way to reach out to a broader community and find people who love to talk about basic science and then bring them into the HIV movement so that we get to the point where the conversation about HIV vaccines, microbicides, and new medicines is an informed scientific conversation. There has to be a certain level of scientific literacy within communities because otherwise they can be exploited by either quacks or people who wish to misuse science for commercial or political ends.

I also believe it's important that we as activists don't try to undermine the outcomes of science. Whether it's favorable to what we believe or not, we have to support the integrity of the scientific process.

Recently there has also been a great deal of discussion about male circumcision to prevent HIV infection in men based on the results of a study in South Africa. How do you think the international community should react to this?

As soon as there's a scientific consensus we need to move with rapidity. But first we have to be aware of and prepared for every single pitfall. You have to consider situations where young men will go and get circumcised in a bush with unclean implements, without having been tested for HIV.

It's really critical that there be a global and urgent summit to discuss an appropriate way to respond to this. If the reduction is valid, then it will be an important intervention and it should be offered to every man who wishes to do it, along with condoms and other means of protection.

Many African countries face problems with infrastructure and lack of medical centers or trained physicians. Is this a problem in South Africa?

It's not South Africa's major problem but there is a problem with human resources. I was just looking at some research that said 12,000-16,000 of our nurses and doctors work outside South Africa. There are also 55,000 trained nurses inside the country who are working outside the healthcare system. So there's a huge potential pool of people who just need better pay, improved conditions, and minor retraining to be brought back into the system.

You were in New York City recently to attend a Global Health Summit sponsored by TIME magazine. Do you think it is important for the international media to keep global health issues in the news?

I think it is a major step forward that the US media in particular is talking about global health problems and raising it as an issue to inform Americans. Now this needs to be matched with the mobilization of civil society in the US on health, both locally and globally. It's very important to raise the issue of global public health and not just in terms of economic consequences or cost-effective strategies, but on what Helene Gayle [director of AIDS programs at the Bill & Melinda Gates Foundation] referred to as the policy of being a good neighbor and if my neighbor is sick then I should do something about it.

In that sense we still have a long way to go. We have to create a consensus that everyone has the right to life and everyone has the right to health care. And that includes understanding that the right to life is about a life with dignity.

What role has the South African media had in covering the country's epidemic?

The media in South Africa has played a critical role in discussing HIV. They raised awareness on the government's delay on providing treatment and on a range of other issues. There's still a lot more the media can do, but it's much better than almost anywhere else that I've seen. They've been dealing with the issues in a non-sensationalist and non-judgmental way and clearly laying out what still needs to be done.

South Africa is now hosting a Phase II vaccine trial and a Phase III microbicide trial. Do vaccine and microbicide trials in general receive much attention in the South African media?

Microbicides and vaccines get coverage, but the problem with the publicity has been with talking about them as magic bullets. This causes a degree of skepticism, both in the public and the activist community, about the potential for microbicides and vaccines. Skepticism is good for most things, but I think we need to eliminate this type of skepticism because it can paralyze us from taking action or wanting more information about these important strategies. There's no way we can proceed with an infection of this nature that continues to infect millions of people across the globe, and at least half a million people a year in our country alone, without educating ourselves.

We need to ensure that we understand the range of measures that need to be taken to end the AIDS epidemic. We can end the epidemic but there are at least two things we have to do: find a vaccine for tuberculosis (TB) and HIV. So I would like to see organizations like IAVI work closely with AIDS and TB activists. We have to end the solo approach to treatment and prevention and look at the broader impact and use of HIV as a way to promote really good medical care for everyone's benefit.

As the AIDS vaccine community begins discussing the possibility of testing vaccine candidates in adolescent volunteers there will undoubtedly be discussion about South Africa since there is such a high prevalence rate among 15-24 year

olds. Is there any momentum building for this type of trial?

There's no momentum for it and there's not enough talk about the young people. I think that's certainly an area where we need to do some work. There's obviously a range of consent and possible infection issues involved, but the fact is clear that if you stand at least a 1 in 10 chance of getting infected then there's a duty to prevent that. And just as we try to advocate for condoms in school, we should advocate for very good trial practices for adolescent volunteers.

What advice would you give to the activist community?

TAC is regarded as one of the strongest movements in the country and as one of the strongest movements of people living with HIV in the world, yet I don't believe we reach 1 in 100 people in our country, maybe a little more or a little less. But there are 46 million people in our country. And in any other country the burden of dealing with such a public health crisis would not fall on organizations like ours, it would fall on the state, so we have to reach more people. We have the capacity. In our organization more than half of our activists are under 25. I'm really one of the oldest and I think these young people are essential. But we don't have the resources to reach as many people as we want.

Still we all must continue to educate ourselves, spread the message, and ensure that there's money available. But then also start looking three, five, even ten years ahead. What happens when a vaccine or microbicide becomes available? Do we have the systems ready for it? How do we make sure that access is once again not going to be limited? Discussion about vaccines allows us to talk about issues with intellectual property that rewards research and development and allows companies who want to make a profit to do so, while at the same time ensuring the widest possible access everywhere. Every person has the right to decent health care whether it's in the US, China, India, or South Africa.

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Cutting HIV transmission

Male circumcision as a potential HIV prevention strategy

By Sheri Fink, MD, PhD

While the ultimate hope for stopping the AIDS epidemic, a vaccine, remains years away there may already be a way to effectively cut the sexual transmission of HIV—male circumcision. Scientists in eastern and southern Africa have been studying whether the surgical procedure can protect against HIV infection, and also what it would mean to promote for medical reasons a practice that has long held cultural significance.

Results from the first of three major randomized, controlled trials of circumcision were announced at the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment in Rio de Janeiro in July. The French National Agency for Research on AIDS and Viral Hepatitis (ANRS) sponsored the study involving over 3000 volunteers in Orange Farm, an urban area within South Africa's Gauteng Province. The men were randomized to either receive circumcision immediately or defer the procedure for 21 months. Circumcision proved markedly protective. At the interim study evaluation three times fewer circumcised participants (18) had acquired HIV compared with control participants (51). The study's Data Safety and Monitoring Board halted the trial and offered circumcision to members of the control group.

The results did not surprise many HIV prevention researchers since an inverse relationship between circumcision rates and HIV prevalence had been noted for years. An analysis of more than 30 observational studies—cross-sectional, case-control and cohort—suggested that circumcision might reduce the risk of HIV infection by 42%. The suggestion made sense, biologically. “The foreskin has HIV target cells which make it easy for HIV

transmission and acquisition,” says Godfrey Kigozi, a co-principal investigator with the Rakai Health Sciences Program in southwestern Uganda, a body established in 1988 as the Rakai Project. “During sexual intercourse the foreskin is retracted, exposing a large surface area which is vulnerable to entry of HIV. Also, the foreskin is associated with genital ulcer disease (GUD), which makes entry of HIV into the body easy.”

“It is a procedure that a man undergoes once in their life; it would then provide some level of protection for the rest of their life.”

– Maria Wawer

Some researchers have likened circumcision for boys and men to a partially protective AIDS vaccine. “It is a procedure that a man undergoes once in their life; it would then provide some level of protection for the rest of their life,” says Maria Wawer of Johns Hopkins University in the US. “If circumcision is protective, its role in the fight against HIV could be really very dramatic.” An ongoing trial is investigating whether male circumcision can help prevent transmission of HIV from men to women. But even if there is no direct protective effect for women, if male circumcision can effectively lower transmission from women to men in a given population then eventually everyone will benefit—fewer transmitters mean that, overall, incidence rates will decline.

Kigozi and Wawer are two of the investigators leading an even larger randomized, controlled trial of male circumcision in progress in Rakai Province, Uganda, under the auspices of the Rakai Health Sciences Program. The US National Institutes of Health (NIH) sponsored the circumcision study because despite the considerable body of correlative research, the precise link between HIV infection and circumcision remained unclear. Public health experts have held back from recommending circumcision as an HIV preventive method because the observational studies had not established whether circumcised men were protected by circumcision itself or by other factors. For example, in many parts of Africa

Despite the considerable body of correlative research, the precise link between HIV infection and circumcision remained unclear.

circumcised men are much more likely to be Muslim, and previous research conducted by the Rakai Program showed that Muslim men in the province tended to have fewer extramarital partners than non-Muslim men. That raised the possibility that it was not circumcision that protected them but different sexual practices. “The only way you can really find out if circumcision protects men is to take a group of men who volunteer for a study and then randomly assign them to either get the circumcision right away or to delay the procedure,” says Wawer.

Putting circumcision to the test

Rakai is a province of rolling hills, red dirt roads, and simple mud and brick dwellings. It is a community on the socio-economic rise, but many inhabitants still live off subsistence farming and do not enjoy electricity or motorized transport. They share the land with cows, corn,

banana trees, and a profusion of birds. They also live close to the crossroads with Tanzania. The region was the site of considerable troop movements and unrest during Uganda’s civil war. In the 1980s Ugandan researchers including David Serwadda and Nelson Sewankambo of Uganda’s Makerere University were drawn here by reports of the mysterious illness they called “Slim Disease.” It later became known as AIDS. The researchers began studying the population and were joined by Wawer, Ron Gray, Tom Lutalo, and Fred Wabwire Mangen and others from the Ugandan Virus Research Institute (UVRI), Johns Hopkins University, and Columbia University.

Over the years the team has conducted many studies on HIV. The circumcision study is one of their latest. On a typical morning in the spring of 2005, around 40 potential study volunteers hiked or pedaled their bikes to the Rakai village of Kyawanyana. There they gathered under a blue and white striped tent and watched a video explaining the research. HIV prevalence is high in Rakai—one in eight adults—and the men were looking for ways to protect themselves. “I came here to learn how to avoid STDs,” says one.

After the video, the men were called one by one into small pup tents for individual counseling, physical exams and testing for HIV and other sexually transmitted diseases (STDs). They were urged to use condoms and practice safe sex. A day or two later, those who met the study criteria were invited to randomly select an envelope which informed them whether they would receive circumcision immediately or have to wait until the end of the two-year study period.

John Paul Wasa, a counselor, says that most men hope to receive immediate circumcision. “It might be STD/HIV prevention, it might be sexual prowess, it might be any other thing, but through the counseling process they get to know why we’d want them to remain in the arm in which they are randomized and the importance of that.” Rakai investigators know of only three cases where volunteers in the control group went

elsewhere to obtain circumcisions prior to the end of the study.

The Rakai Program performs the circumcisions in a series of new, technically-advanced operating rooms in the small town of Kalicizo. Patients undergo circumcisions under local anesthesia. As of the spring of 2005 nearly 3000 men had been circumcised, and a roughly equal number had been randomized to serve as controls. Only about 400 more surgeries remained.

Once they are enrolled, circumcised and uncircumcised men are followed closely for two years and regularly tested for HIV infection. “We are also looking at women to see whether circumcision in the male partner might reduce transmission of HIV and STDs to the woman partner,” says Wawer. This latter research is part of a separate, concurrent study funded by the Bill and Melinda Gates Foundation. Rakai is the only one of the three sites to include analysis of male circumcision’s effect on HIV transmission to women.

This is just one of the reasons the Rakai Program investigators believe it is essential for their study to continue, even in light of the South African group’s finding that circumcision had a powerful protective effect against female-to-male HIV transmission. “There’s always a need to have more than one trial before you implement findings into policy,” says Kigozi.

Officials with the Joint United Nations Programme on HIV/AIDS (UNAIDS) agree. “The two other randomized controlled trials, currently ongoing in Uganda and Kenya with a combined total of nearly 8000 participants, remain important to clarify the relationships between male circumcision and HIV,” said an agency statement. “The potential for negative or uncertain results in the other two trials cannot be ruled out at this stage.”

Challenges and suspicions

Now that at least one of the randomized controlled studies has shown that circumcision might help prevent HIV infection, public health experts are considering whether the

practice should be promoted widely, and how. In Uganda some experts fear that if the demand for circumcision grows, villagers seeking to avoid the typical charge of roughly 50,000 Ugandan shillings—US\$30—might turn to unqualified practitioners. If they re-use instruments between patients without proper sterilization they risk HIV infection. Every year, poorly-performed circumcisions lead to infections and disfigurement. Chief Rakai Program surgeon Dr. Stephen Watya, a consultant urologist at Makerere University’s Mulago Hospital, has treated the complications of some village circumcisers. “Recently I saw one young boy about five years with a severed glans, that’s the head of the penis being chopped off with the circumcision knife,” he says. “Occasionally that happens.”

“I think we have shown that circumcision can be acceptable, given the compliance we are seeing, given the overwhelming numbers that are coming to us to participate in this.”

– Godfrey Kigozi

The contrast between the Rakai Program’s state of the art operating theaters and the clinics where many African men receive circumcisions is remarkable. Just a few miles away traditional Muslim circumcisers perform their operations at a spartan clinic, the Kyotera Muslim Health Unit. A single bulb dangles from the ceiling of the circumcision room, which is nearly barren except for a bed. Each circumciser brings his own tools. “This room is small and there are no special facilities here. If you compare it with the [Kalicizo] theater, this is far below required standards,” says Sheik Badru Matovu who heads this clinic. Still, long-time circumciser Sheik Abudusamir

Abudalazake Kakooza says that with education, many traditional and religious circumcisers in Uganda have modified their practices in order to decrease the risk of complications and contaminated equipment. Kakooza says his rate of complications is low. But no matter how advanced the facility, circumcision is never performed without risk: Rakai researchers report a 0.7% rate of serious complications, and about 1 in 20 patients overall experiences at least minor complications.

Even if circumcision is made relatively safe and affordable, how willing will men be to undergo the procedure? After all, circumcision is more than just surgery. It is a cultural and religious practice, it is wrapped up in tribal and personal identity, and many myths about it remain.

“As a public health measure, it would have to be very carefully introduced into the communities with very, very strong education and would require a very significant paradigm shift.”

– Karusa Kiragu

Back in the Ugandan village of Kyawanyana last spring, a group of men gathered for their post-operative check-ups. They say they’ve endured the disapproval of their fellow villagers. “Most people in our villages, our village men, tell us that you just want to stop us from having more children, as a form of family planning,” says one. Another agrees. His friend told him “these people just bring out the program so that they can castrate you.” A third shares a similar story. “People tell us in the villages there that we’re just wasting our time. That AIDS, all the same, whether we get circumcised or not, AIDS is going to kill us. So all in all they tell us ‘you’re just wasting

your time, you’ll just be like us, you’ll still be wiped out!”

Father Joseph Kato, a Catholic priest with the Matala parish in Rakai Province has been privy to another concern among his parishioners: that circumcision might turn them into Muslims. “They came with that kind of fear. And I told them this has a medicinal purpose, preventing against HIV, rather than being something conversational.” Other men express worries that their penis size will be reduced, or that they won’t be able to resume intercourse. In the US some anti-male-circumcision activists argue that circumcision reduces sexual sensation in men and that this could lead to even lower rates of condom use.

Still, the Rakai researchers say that men have been remarkably willing to undergo circumcision, even before knowing whether it was protective. “One of our secondary endpoints was to find out whether circumcision could be acceptable in these communities,” says Kigozi. “I think we have shown that circumcision can be acceptable, given the compliance we are seeing, given the overwhelming numbers that are coming to us to participate in this.” The South African team also studied the acceptability of circumcision and found that 70% of uncircumcised men expressed a willingness to undergo the procedure if it would reduce the risk of contracting HIV infection. Other acceptability research has yielded similar results, including a large Harvard AIDS Institute study in Botswana in which over 80% of uncircumcised men said they would undergo circumcision if it was performed safely and affordably.

False sense of security?

The scientists have another concern, though. Might circumcision change the men’s sexual behavior? Perhaps they would feel immune from HIV and engage in more risky, unprotected sex, increasing their likelihood of acquiring—and passing—HIV infection. These questions are identical to those that would be raised by the development of a partially protective

AIDS vaccine.

Jennifer Wagman heads up behavioral research at the Rakai Program. She is looking at how men perceive circumcision and whether circumcised men engage in practices that might put them at risk for HIV. One of those potential practices is known as ‘sexual cleansing.’ “After they’re circumcised they have to go out and have sex with as many women as they can who are not necessarily their wives or main sexual partners,” says Wagman. “We don’t know if it’s happening, so we want to find out.”

Public health experts will have to take practices like this into consideration in any widespread effort to introduce circumcision. After the South African results were released, UNAIDS released a statement calling it “premature to recommend male circumcision services as part of HIV prevention programmes.”

Karusa Kiragu is a behavior change scientist with the Population Council in Nairobi, Kenya. “As a public health measure, it would have to be very carefully introduced into the communities with very, very strong education and would require a very significant paradigm shift,” she says. “The paradigm of the past was that upon circumcision in many communities, the boys then go on to become sexually active. From a public health point of view the paradigm would be that yes, you’re circumcised but no, it doesn’t mean that you now have permission to go and have sex. So, disentangling that for communities may be difficult.”

Difficult, yes, but possible, says Rakai Program principal investigator Fred Nalugoda. If circumcision is confirmed to be effective, he says, governments and other agencies should make an effort to provide the surgery to as many men as possible. “It would be unethical, once you learn something’s protective, to then with-

hold it from the people. I think what has to be combined with the provision is the intensive health education and counseling—telling people exactly what they have to do to counter their perception that maybe because it’s protective then they can do whatever they want with themselves.”

“We have all been looking for additional tools to use against this epidemic for the last 20 years. And it has been very disappointing how difficult it has been to come up with new tools.”

– Maria Wawer

So far, the men in the Rakai Program study are not reporting higher risk behavior. The potential that circumcision might provide a whole new approach to stemming the tide of HIV has many scientists feeling hopeful, including Wawer. “We have all been looking for additional tools to use against this epidemic for the last 20 years. And it has been very disappointing how difficult it has been to come up with new tools.” An estimated five million people worldwide contracted HIV last year alone, and even a partial reduction in HIV risk could save thousands, perhaps millions, of lives.

Sheri Fink, MD, PhD, is a freelance writer whose work has appeared in such publications as The New York Times and Discover Magazine, and the author of War Hospital: A True Story of Surgery and Survival.

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Treatment as prevention

Researchers are studying the use of licensed drugs to prevent—rather than treat—HIV infection

By Kristen Jill Kresge

When AIDS was first described in the medical literature 25 years ago, there was not a single medicine to treat people infected with this new human virus. Since then more than 20 antiretrovirals (ARVs) have been licensed by the US Food and Drug Administration for the treatment of HIV/AIDS. These drugs have dramatically improved the health of millions of HIV-infected people around the globe and are now becoming increasingly available in developing countries where the need is still the greatest.

“The concept of using an antiretroviral as a preventive has been tested and proven successful in preventing mother-to-child transmission of HIV.”

– Jim Rooney

But with 4.9 million new HIV infections last year alone, new ways to stem the spread of HIV are more urgent than ever. In response researchers have turned their attention to novel approaches to HIV prevention. One of these involves giving the ARVs usually used to treat HIV infection to try to protect people from contracting the virus in the first place. The idea of healthy people popping pills to stay HIV free may seem strange, but it isn't without precedent. Travelers headed to countries where malaria is endemic will often take drugs to protect them from becoming infected with this parasitic disease. Researchers hope that giving ARVs to individuals at high risk of HIV infection could have the same effect. This idea is known as pre-exposure prophylaxis, or PrEP,

and is being tested in five ongoing clinical trials. “We urgently need new types of prevention tools and PrEP is one of many promising strategies, like microbicides and vaccines,” says Albert Liu, an investigator for one of the PrEP trials in the US.

Researchers first thought that PrEP might be an effective approach more than a decade ago but the complexities of conducting clinical trials to test the idea has placed them at the forefront of debate. Many researchers harbor concerns that giving drugs that are known to be effective for treating the disease could encourage people to participate in more risk behavior, an idea known as behavioral disinhibition, which could lead to a higher risk of infection. But investigators involved in clinical trials insist that measures are in place to limit this effect. And if found effective PrEP may have the greatest benefit for people who are unable to negotiate use of traditional barrier methods and therefore have few options when it comes to HIV prevention. “We desperately need PrEP to protect women in resource-poor settings,” says Joep Lange of the University of Amsterdam.

If the idea of PrEP is borne out in clinical trials, many other questions may arise about implementing this strategy on a global basis. Researchers will confront issues of long-term drug toxicity when ARVs are taken outside the controlled environment of a clinical trial. Other issues like drug pricing and the community outreach and educational campaigns needed to introduce this concept to communities may present further obstacles. “PrEP is not a universal panacea,” says Lange, who emphasizes that an AIDS vaccine is “still an absolute priority” since its impact will be far greater.

Preparing for PrEP

The concept of PrEP is not altogether new. “The concept of using an antiretroviral as a preventive has been tested and proven successful in preventing mother-to-child transmission of HIV,” says Jim Rooney of Gilead Sciences, the company that manufactures both drugs currently being tested in PrEP trials. Over the last 12 years countless children have been spared from HIV infection because mothers and babies received ARVs during labor or for a short time following birth (see *VAX* February 2005 *Spotlight* article, *Preventing mother-to-child transmission*).

Administering ARVs to laboratory or health-care workers after accidental needle-stick exposure to HIV is also a common practice, known as post-exposure prophylaxis (PEP). But in both of these situations the window of exposure to the virus is known and healthy individuals only need to take ARVs for a limited time. The premise of PrEP is that ARVs could be taken on a daily (possibly less frequent) basis for years in order to protect against the possibility of multiple exposures to the virus either through sexual activity or injection drug use. Giving ARVs, even if their toxic effects are minimal, to otherwise healthy people over a long period raises safety concerns.

The choice of ARV is therefore paramount. Tenofovir, licensed for the treatment of HIV infection, was the first drug that researchers considered for PrEP. Tenofovir has been on the market since 2001 and has a relatively good safety profile. It also has several other characteristics that make it favorable for PrEP, including once-daily dosing.

An initial study by Gilead showed that tenofovir was able to protect macaques from infection with simian immunodeficiency virus (SIV) when given just before or after exposure to the virus. However in subsequent studies when animals were treated with tenofovir and exposed repeatedly to a similar virus, the results weren't as promising.

Trials and tribulations

Still, researchers knew the ultimate answers on the efficacy of this approach will come from studying tenofovir PrEP in humans and clinical trials are now underway (Table 1). The CDC started a Phase II safety study in February 2005 in the US with tenofovir in 400 men who have sex with men (MSM) and two larger Phase IIb/III trials with tenofovir PrEP with 1600 injection drug users (IDUs) in Thailand and 1200 heterosexual volunteers in Botswana.

Ongoing or Planned PrEP Trials

Location	Sponsor	# of Volunteers	Population Being Studied	Drug
Botswana	CDC	1200	heterosexual men and women	tenofovir/Truvada
Ghana	FHI	800	high-risk women	tenofovir
Peru	NIH/UCSF	1400	MSM	Truvada
Thailand	CDC	1600	IDUs	tenofovir
United States	CDC	400	MSM	tenofovir

Table 1. Ongoing trials to evaluate the safety and efficacy of daily tenofovir or Truvada in preventing HIV infection. All trial participants are healthy, HIV-uninfected individuals. **FHI:** Family Health International; **CDC:** US Centers for Disease Control and Prevention; **NIH:** National Institutes of Health; **UCSF:** University of California, San Francisco; **IDUs:** injection-drug users; **MSM:** men who have sex with men

Family Health International, a US-based non-profit public health organization, also launched a series of tenofovir PrEP trials in Malawi, Nigeria, Cameroon, Cambodia, and Ghana, with funding from the Bill & Melinda Gates Foundation, but only the Ghana trial is still ongoing. Some of the trials were stopped or suspended after activist protests regarding the lifetime provision of ARV treatment for volunteers who become infected during the trial. Others were halted for concerns about the ethical or biological parameters of these trials. In Malawi the government halted the trial due to concerns that it would foster HIV resistance to tenofovir, which they are now using in treatment. In response to these events the International AIDS Society held a global consultation on PrEP research last year where researchers and activists discussed the issues regarding these trials (www.iasociety.org/images/upload/1025.pdf).

Questions linger about why PrEP is just now entering clinical trials, but disinhibition was one concern that kept researchers away from these studies.

Another PrEP trial, conducted by the US National Institutes of Health (NIH) and the University of California, San Francisco (UCSF) is in the process of getting approval from local institutional review boards to begin recruiting 1400 MSM in Peru. This study is expected to start later this year, according to IMPACTA, a Peruvian non-governmental organization.

Questions linger about why PrEP is just now entering clinical trials, but disinhibition was one concern that kept researchers away from these studies. Many hesitated to dive into PrEP research because of fear it could actually encourage volunteers to abandon other proven methods of HIV prevention like condoms or

increase their number of sexual partners.

Others like Lange are not as concerned about disinhibition. As in any clinical trial, volunteers in PrEP trials will be tested frequently for HIV infection and counseled on how they can reduce their risk. “Usually people are better off in a clinical trial than on the outside,” he says. Volunteers will also have easy access to condoms. “We want to test the efficacy of PrEP on top of what we know already works,” Liu adds.

Several studies have analyzed the behaviors of volunteers during prevention trials and the results have been mixed. During the Phase III AIDS vaccine trial run by VAXGEN, researchers found that injection drug users did not increase their risk behavior during the trial. But Mayer warns that this may not be a fair comparison. “We can’t say that what happened in a vaccine trial will happen with PrEP.” Volunteers in vaccine trials may receive at most three inoculations. “It’s very different taking a pill every day,” he adds, which researchers fear could reinforce a false sense of protection among volunteers on a regular basis.

All of the ongoing clinical trials are placebo controlled so that researchers can be sure to detect any protective effect the drug may offer. The trial Liu is coordinating in San Francisco is also attempting to evaluate the effects of disinhibition by staggering when volunteers start receiving pills. Only half of the volunteers will receive a daily pill of either tenofovir or placebo for the first nine months of the study, while the others receive nothing. This will allow the study investigators to compare the reported behaviors of volunteers who are taking pills and those who aren’t. This information will be valuable to researchers, but the true impact of disinhibition isn’t likely to be realized until PrEP is administered widely. Then educational campaigns will be critical in describing both the promise and limitations of this approach.

One is the loneliest number

Researchers have always speculated that a combination of ARVs, like that used for HIV treatment, may work even better for PrEP. At a major scientific meeting in the US earlier this year,

researchers from the CDC presented results from an animal study with the drug Truvada, a single pill containing tenofovir and another drug called FTC, which supports this hypothesis. This idea, now being called combo-PrEP, may be even better at fending off infection than tenofovir alone and sparked great interest among prevention researchers. In response, some of the ongoing or planned PrEP trials have been modified to test Truvada.

The NIH/UCSF trial that will start later this year has been altered to include combo-PrEP instead of tenofovir alone and the CDC plans to add an additional site to the US safety trial where volunteers will receive Truvada rather than tenofovir. New volunteers in the CDC trial in Botswana will also receive Truvada, while the 70 who were already enrolled will continue on tenofovir.

Non-viral challenges

Results from these trials are still several years away but some investigators are already considering the next steps. All of the current trials are testing daily doses of drug but the next round of studies will evaluate more sporadic use of PrEP drugs, according to Lynn Paxton who is running the PrEP trials at the CDC.

Others are considering how this approach could be implemented if found effective and one of the first considerations on everyone's mind is cost. "The access question is very important to start thinking about now," says Liu. Both drugs are only available from Gilead and a year's supply costs on average US\$4800 for tenofovir and \$7800 for Truvada. Gilead has provided free drugs for all of the trials but otherwise has stayed out of PrEP research altogether.

The company does have an access program for treatment, offering the drug at no-profit

pricing in 97 developing countries. But even at this drastically reduced price of about a dollar a day it is expensive for governments struggling to treat those already HIV infected. The company does seem willing to negotiate. "If data suggest that tenofovir or Truvada is safe and effective in preventing transmission of HIV, we would continue to work to ensure access at the lowest feasible cost," says Rooney.

In developing countries it may be more difficult to educate communities on PrEP and to give out drugs to healthy individuals who are at high risk for HIV infection if they aren't accustomed to seeking medical care.

Distributing drugs to those most in need would be another challenge for PrEP programs. In developing countries it may be more difficult to educate communities on PrEP and to give out drugs to healthy individuals who are at high risk for HIV infection if they aren't accustomed to seeking medical care. "This is going to have to be a team effort," says Paxton, "but there's no reason to think that it couldn't be done with proper planning."

Regardless of these questions, researchers and activists alike eagerly await the results of the ongoing PrEP trials and the public health opportunities this prevention strategy may hold.

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Capping infection

An ongoing clinical trial is testing whether the contraceptive diaphragm can help lower women's risk of HIV infection

By Sheri Fink, MD, PhD

An old-fashioned birth control method, the diaphragm, could one day soon make a comeback as a woman-controlled HIV prevention method. That's the hope of researchers conducting a randomized, controlled HIV prevention study funded by the Bill and Melinda Gates Foundation and known as Methods for Improving Reproductive Health in Africa (MIRA) that has enrolled women in Harare, Zimbabwe and in Durban and Johannesburg, South Africa. Investigators from the University

Findings suggest that shielding the cervix with a diaphragm might lower the risk of a woman contracting the virus.

of California at San Francisco (UCSF), University of Zimbabwe, Ibis Reproductive Health, Medical Research Council of South Africa, and the Perinatal HIV Research Unit of South Africa are assessing whether latex diaphragms used during intercourse can protect women from contracting HIV.

"Biologically, it's very plausible that it will work," says MIRA Principal Investigator Nancy Padian. Contraceptive diaphragms cover the cervix, the lower opening of the uterus, and prevent access to the upper genital tract, both thought to be key sites of entry for HIV. Cervical tissue is much thinner than vaginal tissue and observational studies have suggested that other sexually-transmitted pathogens, including those causing gonorrhea and chlamydia, preferentially infect cervical as opposed to vaginal cells and that diaphragms used with

spermicide can prevent the transmission of some sexually-transmitted infections (STIs). Analogous to the male foreskin, the cervix also contains some of the same target cells for HIV; Langerhans cells, a type of antigen-presenting dendritic cell. A recent prospective study in South Africa showed that male circumcision may significantly reduce men's chances of acquiring HIV (see *Cutting HIV transmission*, page 47).

Although women can still acquire HIV after hysterectomy, these other findings suggest that shielding the cervix with a diaphragm might lower the risk of a woman contracting the virus. In addition, because relatively high amounts of HIV are shed by cervical cells, covering the cervix during intercourse might decrease a woman's infectiousness if she already has HIV.

Current prevention methods fall short

With effective AIDS vaccines and microbicides still years away, male and female condoms remain the most reliable method for HIV prevention. But condom use remains extremely low—one study in the US found that condoms were used consistently during heterosexual intercourse only about 19% of the time. Female condoms, comparable in efficacy to the male condom in preventing STIs other than HIV and on the market for more than a decade, have been inadequately supplied and adopted—in 2005, only 14 million female condoms were available worldwide, compared with 6-9 billion male condoms.

Male circumcision is showing some promise in trials as an HIV prevention method but, even if proven effective, will require years to implement widely. Female-initiated methods are seen as particularly important in light of the fact that

young, married women are the fastest-growing group of new HIV infections in many countries, and they often have difficulty negotiating condom use. Both HIV professionals and at-risk populations have shown a keen interest in expanding HIV prevention options, particularly those that are woman-controlled and already approved for use.

The diaphragm fits both of these criteria but its low usage worldwide and its labor-intensive initial fitting process cast doubt on whether women and health care providers will find the method acceptable. In the US and other countries where oral hormonal contraceptives are affordable and widely available, diaphragms have fallen out of favor as a birth control method. In 1995 only 2% of contraceptive users between the ages of 15 and 44 in the US used the method. Standard diaphragms come in nine different sizes and must be fitted in a health clinic and inserted prior to intercourse. Many health care providers stopped recommending them. “There’s somewhat of a provider bias,” says Padian. “Health care providers assume women won’t use them.”

Padian’s recent research, however, has been finding the opposite. “They’re highly acceptable,” she says. Her group conducted a six-month diaphragm acceptability study in Zimbabwe prior to the launch of the HIV prevention study. Nearly all of the 186 participants reported having tried the diaphragm during the study period. At the study’s conclusion 96% had used the diaphragm during the previous two months, however consistent diaphragm use between visits was low—only 13-16%.

Zimbabwe study

On a recent afternoon at the MIRA study site in Epworth, a densely-populated suburb of Harare, Zimbabwe, a dozen or so women arrived for their final study visit. Outside in the dusty sunshine, music blared from a saloon next door and peddlers squatted before small piles of tomatoes and carrots. Here in Zimbabwe the researchers have enrolled 2503

women ages 19-49, randomized them into diaphragm and no-diaphragm arms (both receive condoms and prevention education), and are following them for at least 12 months. During quarterly visits the researchers test the participants for HIV and STIs and ask them about their experiences with the diaphragms. The women fill out computer surveys and meet with counselors and clinicians. All women completing their final visits are offered a diaphragm. “Most women are accepting it,” says Project Director Agnes Chidanyika. “They look forward to using it, especially those in the

Those championing the diaphragm claim that its great advantage over the condom is the fact that women can typically use it without their partners’ knowledge.

condom arm who haven’t used it.”

In a counseling room at the clinic, a young woman in the diaphragm arm of the study demonstrated diaphragm use on a plastic pelvic model. She grasped the latex, cup-shaped diaphragm by its firm, springy lip, squeezed it in two, and inserted it easily into the model. “To be eligible to be in the study you have to be able to insert the diaphragm within five attempts,” says Chidanyika. “We had one or two out of those 2500 women who couldn’t insert the diaphragm in five attempts. It was fairly easy once they knew how it was done for them to be able to insert it.”

The young woman said she found her own diaphragm comfortable and had used it throughout the study period except when she tried to get pregnant. As with all barrier methods, the importance of child-bearing in many societies may be an obstacle to widespread adoption of the diaphragm as an HIV prevention method.

Those championing the diaphragm claim that its great advantage over the condom is the fact that women can typically use it without their partners' knowledge. Chidanyika said that was only partly true in the MIRA study, because participants are asked to use Replens gel when inserting their diaphragms. "There's this myth about dry sex in African countries, so we were worried they might not want to use the diaphragm because they would have to use the gel to ease the insertion," she says. "But we actually found the gel became quite popular." Chidanyika says the diaphragms were acceptable among the male partners of most women, who were happy to let their female partners use

"I don't think anyone thinks diaphragms will be more effective than condoms, but we're doing the study in the situation where many women cannot use condoms."

– Nancy Padian

a potential HIV prevention method that their partners were responsible for and they could not feel. However, this sentiment was not universal, says Chidanyika. "The problem we did have with some women is the partner would say if she can use it without me knowing, then she can be unfaithful."

Challenging study environment

The MIRA study is being conducted at the epicenter of the HIV epidemic. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2006 Report on the Global AIDS Epidemic, HIV prevalence among adults ages 15-49 in Zimbabwe is 20.1% and in South Africa it's 18.8%. If diaphragms prove to be acceptable and effective against the transmission of HIV and STIs at these sites, chances are that they will prove use-

ful in other countries hit hard by HIV/AIDS.

In Zimbabwe in particular, researchers could scarcely have chosen a more challenging situation in which to conduct their study. The country is currently experiencing epic inflation and joblessness. The Epworth study site sits just a few feet away from the rubble of countless shanties destroyed by order of the Zimbabwean government in the summer of 2005 in a campaign called Operation Murambatsvina or "Drive out Trash." According to a UN-Habitat study, an estimated 700,000 people lost their dwellings or businesses in the campaign.

Over a quarter of the MIRA study participants in Zimbabwe were displaced by Operation Murambatsvina. This could have devastated the study, but MIRA researchers temporarily stopped enrolling new participants and channeled all of their energy and resources into tracking participants in order to keep them in the study. "We went to everybody, regardless of whether we just saw them yesterday or we last saw them last year," says Chidanyika. "We just tried to find out if they were going to be evicted by Murambatsvina and, if they were, which places they were most likely to move to."

The researchers managed to retain a stunning 99% of the participants by visiting homes, villages, and displaced persons camps, reaching out to alternative contacts, and launching a radio and poster campaign. The researchers now provide many participants with bus fare to reach the study site from their new locations. Chidanyika says the high retention rate also reflects the enthusiasm of the diaphragm study participants. "The participants themselves, they were very interested in participating in the study and coming back," she says.

A look to the future

Results from the MIRA study are expected in 2007. If diaphragms prove effective at lowering HIV transmission, however, those wishing to promote wide-scale adoption of the method will need to contend with several difficulties.

The major fear with diaphragms and indeed all female-controlled methods is that they will lead to lower condom usage. “I don’t think anyone thinks diaphragms will be more effective than condoms,” acknowledges Padian, “but we’re doing the study in the situation where many women cannot use condoms.” There is also a fear that behavioral disinhibition will result from women believing that they can stop worrying about contracting HIV if they are using a diaphragm, but this is a consideration with all HIV prevention mechanisms and even HIV treatment. The potential problem will need to be countered by education.

Perhaps the most serious obstacle to future use of diaphragms is the possibility that they will be less acceptable in real settings than they are in the research environment. Over-optimism about the prospects of the female condom, another woman-controlled contraceptive and HIV prevention method, is an important cautionary case. While evidence suggests that the female condom is effective and easy to use, it has taken a long time to increase uptake for this unfamiliar contraceptive method.

On the positive side, however, female condoms have been successfully marketed in some high-prevalence countries. Furthermore, the diaphragm may be more attractive economically for some women; a single diaphragm, though initially more expensive than a female condom, may be used for several years.

The main problem with traditional diaphragms is the cumbersome way they are fitted. The traditional, labor-intensive method uses rings. The MIRA study, instead, has used a method that its directors term a “modified fitting scheme.” All women start with one size of diaphragm, then the fit is assessed using digital examination and other sizes are tried as necessary.

Even this simpler method, however, requires a health clinic attendance for a diaphragm fitting, a potentially costly prospect that may be associated with stigma. This limitation has led developers to pioneer alternate forms of cervi-

cal barriers. Maggie Kilbourne-Brook, program officer with the group Program for Appropriate Technology in Health (PATH), says a single-sized device is the main improvement needed. “It needs to be ‘one size fits many,’” she says, “which will reduce the procurement cost, the training cost, and has the potential to become an over-the-counter device.”

This conclusion is based on detailed research that PATH, in conjunction with the Contraceptive Research and Development

The diaphragm may be more attractive economically for some women; a single diaphragm, though initially more expensive than a female condom, may be used for several years.

Program (CONRAD), has conducted on the acceptability of cervical barriers. Women who had used barriers were asked what they did and did not like about them. Providers, too, were asked why barriers were not being used in their clinics and what it would take to bring them into wider use. Donors and those in charge of procurement were also surveyed. The goal was to uncover the roadblocks to greater use of cervical barriers, opening the possibility to create better products. “They’d been around 100 years and hadn’t really been improved in that time,” says Kilbourne-Brook. “We now understand much more about vaginal anatomy. Manufacturing practices have changed. New materials have been developed.”

In addition to needing a one-sized product, the researchers concluded that several other modifications would make diaphragms much more acceptable. “What we need to be able to achieve is to make a device that is easier to insert and remove than standard products, and easier to use and learn to use than the cur-

rently available product,” says Kilbourne-Brook. “It needs to be comfortable for both partners.”

The PATH researchers used this information to develop an improved diaphragm. Their development process was further informed by user feedback from women and their partners in Thailand, South Africa, and the Dominican Republic. The resulting product, SILCS, is a single-sized silicone diaphragm with a nylon or polymer spring that fits most women across all of these countries. The researchers expect to begin testing the product for contraceptive effectiveness in late 2006.

If both microbicides and diaphragms prove to be partially effective at preventing HIV transmission then combining them could well offer higher protection.

A number of other cervical barriers are also in the process of being developed and approved. The single-sized Lea’s Shield is a silicone cervical barrier contraceptive already FDA approved for up to 48 hours of continuous use in the US and Europe. Another product being tested, the BufferGel Duet, is a disposable, one-size diaphragm pre-filled with the candidate microbicide and contraceptive BufferGel.

Indeed, if both microbicides and diaphragms prove to be partially effective at preventing HIV transmission then combining them could well offer higher protection. “We’re interested in evaluating whether the use of a physical barrier like a diaphragm could advance the effec-

tiveness of a microbicide,” says Sharon Hillier, a microbicides researcher at the University of Pennsylvania. “Thinking of combinations of chemical agents like microbicides with physical barriers may present a real advance in effectiveness.”

Kilbourne-Brook believes it is important for advocates of various woman-controlled prevention methods, including cervical barriers, microbicides, and female condoms, to come together and devise strategic ways to look at research questions and procedural and regulatory hurdles. “Anything that we can do for one of these products will strengthen the future prospects for all of these products as well,” she says. “All of these products can offer a greater likelihood of protected sex for couples.” Padian agrees, “None of the methods we are looking at are 100% effective.”

If the MIRA study indicates that traditional diaphragms are protective against HIV transmission, Padian believes there will be ways to extend the results to the new forms of cervical barriers that are being developed. “We’ll be able to generalize somewhat,” she says. “It would be crazy if you had to do a complete other trial.”

Her hope is that even partial protection against HIV by diaphragms will have a powerful effect on the epidemic. “Even though it’s not perfect, it’s better than nothing,” she says, “especially when women can’t negotiate male condom use. For many women this is unequivocally one hundred percent out of the question.”

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HIV prevention in a pill?

Drugs that treat herpes may help reduce HIV transmission

By Kristen Jill Kresge

If ongoing clinical trials pan out, it's possible that one day people could be cutting their risk of HIV infection simply by popping a couple of pills per day. The pills are cheap, safe, and have been around for years. The catch? These drugs don't target HIV, they fight off herpes.

Simply suppressing genital herpes could be enough to substantially reduce an individual's risk of acquiring and transmitting HIV. Researchers have long known that sexually transmitted infections (STIs) play a role in HIV transmission. Now nearly a dozen clinical trials are investigating whether drugs that suppress a type of herpes virus (herpes simplex virus-2 or HSV-2) that causes genital herpes can reduce HIV transmission (Table 2).

Approaches to HIV prevention that aim to modify behavior are yielding only modest gains against HIV transmission, so many researchers are now looking into strategies that focus on biology rather than behavior. For example, earlier this year a clinical trial in South Africa found that male circumcision could reduce the risk of men acquiring HIV.

Ideally strategies that combine biology and behavior may provide greater gains in prevention than either would alone. "Aside from individual behavior change, we don't really have ways to prevent HIV transmission," says Anna Wald, an epidemiologist at the University of Washington School of Public Health and Community Medicine in Seattle. "That is the starting point of why we are looking at herpes."

The current trials will test whether drugs to suppress herpes can actually reduce HIV transmission in real world settings, says Jairam Lingappa, medical director of one of the studies organized by the University of Washington. "While epidemiologic studies show a relationship between HIV and genital herpes," he says, "we don't yet have a clear demonstration of the public health benefit."

Partners in crime

Herpes is a lifelong infection that causes recurring outbreaks of painful ulcers at the surface tissues (or mucosae) of the genitals. During the course of infection the virus moves between periods of latency and reactivation, when the ulcers appear. Numerous studies have found a strong association between herpes or other genital ulcer diseases and an increased risk of HIV transmission. An analysis of previously completed studies conducted by Esther Freeman and colleagues at the London School of Hygiene and Tropical Medicine (LSHTM) found that men and women with genital herpes are at three times greater risk of acquiring HIV.

Approaches to HIV prevention that aim to modify behavior are yielding only modest gains against HIV transmission, so many researchers are now looking into strategies that focus on biology rather than behavior.

Genital ulcers can help HIV establish an infection by disrupting the physical barrier of the skin and enabling the virus to more easily enter the body. Genital herpes also causes inflammation of the genital tissues, which in turn recruits activated CD4⁺ T cells, the primary cells infected by HIV, to the site. Dendritic cells are also recruited and can entrap HIV particles and carry them to CD4⁺ T cells in other areas of the body.

The elevated risk of acquiring HIV may be greatest in the first few months following infection with HSV-2, when severe outbreaks of gen-

ital ulcers are most common. So controlling these ulcers should reduce HIV transmission, especially in sub-Saharan Africa where genital herpes is the most widespread STI. In some regions of Africa about 80% of the population has acquired HSV-2 by age 35.

There are also other ways that herpes could increase the risk of becoming HIV infected. Even if actual genital sores are not present, HSV-2 can increase the risk of HIV transmission because the two viruses can interact in complicated ways that aggravate the effects of both diseases.

To demonstrate the possible public health benefit of knocking down herpes, researchers are running a number of clinical trials to evaluate if two types of treatments can reduce HIV transmission.

People infected with HIV and HSV-2 will often have frequent and prolonged outbreaks of genital ulcers because herpes takes advantage of HIV's ability to weaken the immune system. This increased expression of the herpes virus in turn allows for an increase in HIV replication. This vicious cycle between HIV and HSV-2 means that suppressing herpes could reduce both the risk of acquiring HIV (acquisition) and the risk of transmitting it to a sexual partner (infectiousness).

Herpes suppression on trial

To demonstrate the possible public health benefit of knocking down herpes, researchers are running a number of clinical trials to evaluate if two types of treatments can reduce HIV transmission. One type will assess the benefit of giving a drug to treat HSV-2 only during outbreaks of genital herpes when genital ulcers are present. The other will evaluate the benefits of suppress-

ing the herpes virus by continuous administration of the drug in order to keep it latent. All of these trials are using the drug acyclovir, an affordable, safe, and proven anti-herpes medication efficient at blocking HSV-2.

Some researchers, including Philippe Mayaud of the LSHTM, think providing acyclovir just when herpes flares up and ulcers appear could have a significant effect on HIV transmission. He is currently involved in three studies, one of which is looking at HIV transmission after acyclovir is given to women in Ghana and the Central African Republic who come to clinics seeking treatment for genital herpes. Women who consent to be in the study are HIV tested and offered acyclovir three times a day for five days or an inactive substance called placebo. Mayaud and his colleagues will take genital samples from all women and will monitor the interactions between the two viruses in women that are also HIV infected.

Mayaud and other research teams are also exploring providing volunteers with a continuous, suppressive regimen of acyclovir therapy. One study is testing this concept in female bar and hotel-workers in Tanzania. Either acyclovir or placebo is being given to 1000 HIV-infected and uninfected women in a trial led by Debby Watson-Jones at the LSHTM. The women that are HIV uninfected at the start of the trial are being monitored for HIV infection, while the HIV-infected women are being monitored to see if the suppressive acyclovir regimen decreases the amounts of HSV-2 and HIV present at the genital mucosae.

But researchers also want to know if giving continuous acyclovir to people with HSV-2 can reduce HIV acquisition. A large scale study to answer that question is being conducted by Wald and Connie Celum, also of the University of Washington. The study is following women in three African nations (South Africa, Zambia and Zimbabwe) and men who have sex with men (MSM) in the US and Peru to see if acyclovir can reduce their risk of becoming HIV infected. The researchers will also be looking at how well the drug controls the occurrence and frequency of

Ongoing Trials of HSV-2 Suppression

Population	Treatment	Regimen	Primary Outcome	Sponsor
1600 HIV-/HSV-2+ MSM in USA and Peru. 1600 HIV-/HSV-2+ women in Zambia, Zimbabwe, and South Africa	Suppressive	Acyclovir 400 mg twice daily for 18 months	HIV infection	National Institutes of Health; University of Washington (Coordinating Center)
2800 discordant couples in which one partner is HIV+/HSV-2+ in South Africa, Kenya, Tanzania, Uganda, Rwanda, Zambia, Botswana	Suppressive	Acyclovir 400 mg twice daily for up to 24 months given to HIV+/HSV-2+ partner	HIV transmission to non-infected partner	Bill and Melinda Gates Foundation; University of Washington (Coordinating Center)
60 HIV+/HSV-2+ MSM in USA	Suppressive	Valacyclovir 1.0 g daily for 8 weeks	HIV shedding	University of Washington; GlaxoSmithKline
40 HIV+/HSV-2+ MSM and women in Peru	Suppressive	Valacyclovir 1.0 g daily for 8 weeks	Plasma and mucosal HIV levels	University of Washington; GlaxoSmithKline
150 HIV+/HSV2+ women not needing ARV; 60 on ARV in Burkina Faso	Suppressive	Valacyclovir 1.0 g daily for 3 months	HIV and HSV-2 shedding	French National Agency for Research on AIDS and Viral Hepatitis
300 HIV+/HSV-2+ women in Johannesburg, South Africa	Suppressive	Acyclovir 400 mg twice daily for 3 months	HIV and HSV-2 shedding	Wellcome Trust
1000 female bar-workers (HIV+ and HIV-) in Mwanza & Shinyanga, Tanzania	Suppressive	Acyclovir 400 mg twice daily for 2 years	HIV seroconversion among HIV-; HIV/HSV-2 shedding in HIV+	Wellcome Trust
Population: 500 women (HIV+ and HIV-) with genital ulcer disease in Ghana, Central African Republic	Episodic	Acyclovir 400 mg 3 times daily for 5 days	HIV and HSV-2 shedding; HIV/HSV-2 seroconversion	French National Agency for Research on AIDS and Viral Hepatitis
500 men and women (HIV+ and HIV-) with genital ulcer disease in Lilongwe, Malawi	Episodic	Acyclovir 400 mg 3 times daily for 5 days	Ulcer healing and HIV/HSV-2 shedding; HIV seroconversion	Fogarty International Centre; UK Department for International Development
600 HIV+ men with genital ulcer disease in Johannesburg, South Africa	Episodic	Acyclovir 400 mg 3 times daily for 5 days	Ulcer healing, lesional HIV shedding; HIV seroconversion	Centers for Disease Control and Prevention; LSHTM
40 HIV+/HSV-2+ women in Cameroon	Suppressive	Acyclovir 400 mg twice daily for 8 weeks	Genital HIV shedding	Fred Hutchinson Cancer Research Center; Institute for the Development of Africa

Sources: Philippe Mayaud and Clinicaltrials.gov

Table 2. Ongoing trials to evaluate episodic or suppressive treatment of HSV-2 for the prevention of HIV acquisition or transmission. The trial participants are either HIV-infected (HIV+) or HIV-noninfected (HIV-) and HSV-2-infected (HSV-2+) or HSV-2-noninfected (HSV-2-). **ARV:** antiretroviral; **MSM:** men who have sex with men; **LSHTM:** London School of Hygiene and Tropical Medicine

genital ulcers and whether the participants can adhere to the regimen of two pills daily. “The trial of 3200 women and men is over 80% enrolled with excellent retention and adherence, so we are optimistic that we will get an answer about the degree to which genital herpes increases HIV susceptibility,” says Celum.

Stopping transmission

Researchers are also interested in studying how continuous HSV-2 suppression can limit the risk of an HIV-infected person transmitting the virus to their sexual partners. This question is being studied in a cohort of “HIV discordant” couples, where one partner is infected with both HIV and HSV-2 and the other partner is not

“Until the day comes when an effective AIDS vaccine is developed, researchers must try everything they can to stem the spread of HIV.”

– Pat Fast

infected with HIV. Nearly 3000 HIV discordant couples will participate in such a study at twelve sites in seven African countries. The HIV-infected, HSV-2-infected partner will be given either acyclovir or a placebo to see if they are at reduced risk of passing HIV to their non-infected partner, in the context of couples’ counseling (see *Understanding couples voluntary counseling and testing*, page 33), treatment of bacterial STIs, and condom provision.

If acyclovir proves capable of reducing HIV transmission, the trial results will benefit everyone—but none so much as the discordant couples themselves. HSV-2 is the leading cause of genital ulcers in married couples, says Susan Allen, a professor at Emory University’s Rollins School of Public Health and a pioneer in studying HIV-discordant couples. “This time period [when one partner is infected and the other is

not] is a critical window in which to implement a public health strategy to reduce transmission,” says Lingappa. “If we can enhance the number of families that maintain one healthy parent or adult, that is one of the things we should promote.”

While well-designed, no study can answer every question about HSV suppression. The couples study is meant to examine acyclovir’s role in preventing HIV transmission to the non-infected partner, but it does not test whether a greater reduction in intra-couple transmission could result if both members of the couple took acyclovir. By studying acquisition and transmission of HIV in two separate trials, the researchers run the risk of finding only weak associations in both. But Celum says the team carefully considered combining the trials and decided it would be better to separate the studies to determine the relative impact of acyclovir.

A medicine for the masses?

If Mayaud’s trials are successful, he hopes that acyclovir will be offered as a standard treatment for genital ulcers when people seek treatment at a clinic. But providing a suppressive therapy regimen—that is, a 400 mg pill of acyclovir twice a day for years—will be expensive and may be difficult to distribute. Although a year’s course of generically-produced acyclovir could cost as little as US\$40 per year in Africa, it could still be prohibitive in most settings. Valacyclovir, the newer form of the drug that can be taken just once a day, is not yet manufactured generically.

Despite these concerns most researchers argue that if there is a remedy on the shelf that can be used to reduce HIV transmission it should be made available. “Until the day comes when an effective AIDS vaccine is developed,” says Pat Fast, medical director at the International AIDS Vaccine Initiative, “researchers must try everything they can to stem the spread of HIV.”

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Stephen Lewis

Waiting for a breakthrough

Stephen Lewis is the Special Envoy to the United Nations (UN) for HIV/AIDS in Africa. He has served in this capacity for four years and has become an unwavering voice in the battle for the development of new prevention technologies like AIDS vaccines and microbicides that could help to slow or end the pandemic, as well as for the rights of women. Lewis was born in Canada and resides in Toronto, but the majority of his time is spent on the road or in a plane. Whether visiting with affected communities in Africa or at the UN headquarters in New York City, Lewis always commands attention.



Prior to his role as envoy, Lewis served as the deputy executive director of the UN Children's Fund (UNICEF) and also as the Canadian Ambassador to the UN. He spent the early part of his career entrenched in national politics and was once leader of the New Democratic Party in Ontario, Canada. His humanitarian efforts and outstanding oratory skills have earned him numerous honors, including more than 20 honorary degrees. Earlier this year Lewis was named one of the world's one hundred most influential people by US-based TIME magazine. And at 67, Lewis shows no signs of slowing.

Lewis recently gave a rousing speech at the opening ceremony of the HIV Pathogenesis and Treatment meeting held by the International AIDS Society in Rio de Janeiro, Brazil. He used the speech to criticize the recent meeting of the G8 nations for "getting caught up in celebrity." He leveled an abundant amount of praise on the '3 by 5' initiative of the World Health Organization, the progress of The Global Fund to Fight AIDS, Tuberculosis, and Malaria, and the continued dedication of UNAIDS, saying these efforts have made all the difference in the world. Lewis also emphasized the pressing importance of vaccine research.

VAX and IAVI Report Science Writer Kristen Jill Kresge spoke with Lewis in July 2005 about progress in battling AIDS in Africa and what new initiatives he thinks may help halt the epidemic's unchecked spread there.

As envoy for HIV/AIDS in Africa, you are reporting directly to the Secretary General on an entire continent's epidemic. How do you accomplish this and what do you see as your main activities as UN envoy?

The primary activities of my job are to visit African countries, meet with the political leadership, meet with groups of people living with AIDS, and spend time seeing projects in the field. I've always seen these last two activities as critical so that I can see how the diplomatic community can be of greater use. When I come back to New York I hold a media briefing so that

the international media has a sense of what I have found. Then I meet with the Secretary General and discuss with him what I've seen and together we discuss how that might influence the way in which he, and the UN more generally, responds.

In the process I have come to understand that advocacy is also a very important component of the envoy role. I've therefore spent a great deal of time speaking around the world at conferences and meetings in order to convey what is happening in Africa and why it is so desperately important for the world to respond.

How has the response to the HIV epidemic in Africa changed in your four years as envoy?

That's a difficult question. The envoy role has clearly evolved since the early days when I or anyone at the UN didn't have a substantial sense of what it would be. The sense of hope right now is more alive than at any time during the previous four years. The tremendous efforts by the World Health Organization to put millions of people on treatment and the evidence, although very slight, of increased resources has made people feel glimmers of hope in the midst of pervasive anguish. This

“Women are fighting more and more for their voices to be heard because they themselves are so appalled at the carnage.”

– Stephen Lewis

pandemic has been going on for over 20 years and we are only now, literally at this moment in time, beginning to come to grips with it. So the job has changed in the sense that I feel now more keenly than ever before that we must do something to subdue the pandemic. Unfortunately, on the ground things are as painful as they've always been because people are dying in such vast numbers.

How has your attitude changed during your tenure as envoy? Do you find it difficult not to get discouraged?

When I started as envoy I was swamped with despair. Now I live in a perpetual rage. I feel an even greater sense of urgency four years into it. At first I heard all these numbers about the situation in Africa and I was lost in the data. Now when I travel I just want to save individual lives. You reach a point where every single human life becomes a matter of obsession.

Instead of getting discouraged I get angry because when you are surrounded by death you can't get over it.

One example is the situation with orphans. Everyone understands that one of the single most important things for orphans is to eliminate all school fees so that these kids can get into school, have peers to play with, and gain some self-worth. And even though everyone knows that we should abolish school fees, nothing changes year after year. I'll never forgive those who have been indifferent, insensitive, and just paralyzed over such long periods of time. But there's no point in being discouraged because futility leads nowhere. Instead, I get neurotic.

I'm just one person out of thousands who are responding to this from within the UN family and when I think of all the people who are in the field, I don't know how they hold their emotional fabric together. It's so incredibly painful on a daily basis and I'm in a rage about it.

AIDS is now disproportionately affecting women. What is the situation like in Africa?

I feel more deeply now than I ever did before that the vulnerability of women is possibly the most terrifying component of the pandemic and about which the world is doing almost nothing. This is true in Africa, as well as in other regions of the world. The women are the core of the society—they do the farming, they carry the burden of care—yet they are really under siege. The disproportionate number of infections is huge and women are suffering so extensively. Women are fighting more and more for their voices to be heard because they themselves are so appalled at the carnage.

What is being done on the ground to address the vulnerability of women?

I see very little change on the ground. There is little progress in building a legal infrastructure and getting laws in place to protect the property and inheritance rights of women. It moves from inertia to paralysis. We need the toughest laws imaginable against sexual violence and marital

rape, and we need ways to enforce them. We need to encourage the social empowerment of women, whether it's putting girls in school or starting income-generating projects. But I just can't get over how slowly this is happening. What we have is an absolute vindication of the feminist analysis: when you're dealing with the inability of men to relinquish power and authority, then you are in real trouble.

So what do you think can be done to alter the course of the epidemic in women?

I've come to the conclusion that we must have an international women's agency rooted in the UN. There is a United Nations Fund for Women (UNIFEM) and it has a budget of around US\$20 million a year for the whole world. In comparison, UNICEF has a budget of over \$1 billion and the United Nations Development Program (UNDP) nearly \$2 billion. So more than half of the world's population gets a pittance of support from within the UN system. This is not the fault of the UN; it's the fault of the member states. And maybe you could get away with that until the dramatic expansion of the pandemic in women, but now there must be an international agency for women. This is the single most important reform that could happen within the UN as far as I'm concerned. It dwarfs all other development issues.

UNAIDS (the Joint United Nations Programme on HIV/AIDS) must also take on AIDS as a women's issue as though there were no tomorrow, because for the women of Africa there is no tomorrow.

The UK government recently released a report from their Commission on Africa. Did this commission's report confront the situation facing women?

The one major flaw in the Blair Commission report, an excellent report in all other respects, was that it is lousy on women. I just ask the question, how is it possible that they had 17 commissioners and only 3 were women? How do you strike a commission, where you can appoint anyone in the world, and only find three women?

What does that immediately say about what you think is important?

If we had a Commission on Africa with 14 women and 3 men, we would get a much more valid and significant view of the continent.

Research into new preventive technologies like AIDS vaccines and microbicides is seen as a critical way for women to become empowered and be able to protect themselves from HIV infection. Do you think there is enough political action into the search for an AIDS vaccine?

I remember the first time I met Seth Berkley of IAVI and he said to me the most obvious thing in the world—a vaccine is the ultimate answer. It's really strange that we don't integrate that into absolutely everything we say and do because it is the ultimate answer for women, and for everyone. But this urgency has not gripped everyone yet, and we're still not putting enough money, or energy, into it.

“...I love the sense that a vaccine and a microbicide are marching together and that these aren't separate initiatives as they have tended to be seen. You have to fight like hell on both fronts simultaneously.”

– Stephen Lewis

I think the excitement that has been growing around a microbicide is pretty legitimate. It looks as though there may be something not that far down the road and, even with all the limitations, over time millions of lives could be saved. But I love the sense that a vaccine and a microbicide are marching together and that these aren't separate initiatives as they have tended to be seen. You

have to fight like hell on both fronts simultaneously. The traditional prevention vehicles, indispensable though they are, need a tremendous shot in the arm, and a vaccine or microbicide may be just that.

How important a role does debt relief play in reversing the trend of poverty on the African continent?

The cancellation of debt in the poorest developing countries is absolutely an obligation that the Western world should fulfill. If we were able to cancel over \$30 billion of Iraqi debt overnight just because the US wanted us to, then surely the world can come together on the cancellation of African debt. That would free a good deal of money, otherwise used for servicing debt, to invest in social sectors where the needs are great.

“The traditional prevention vehicles, indispensable though they are, need a tremendous shot in the arm, and a vaccine or microbicide may be just that.”

– Stephen Lewis

I think, however, that doubling the official development assistance to reach the famous target of 0.7% GNP [gross national product] is probably the single most important immediate response. And there we're in trouble because the US refuses to embrace the objective. We're surprisingly also in trouble because Canada refuses to set a timetable for that objective. The development assistance is so important because if the disease burden of a country is as high as it is in the case of these AIDS-afflicted countries, then you never get economic growth until you deal with the disease burden, and that requires resources. This is the argument that Jeffrey Sachs makes—once you've dealt with the disease burden you can start talking more vigorously about economic growth.

However even with debt cancellation and foreign aid, you don't build economies until you have fair international trading laws. There is not yet any substantive movement to give the producers in Africa a chance to compete fairly in the world, which would be the strongest way to repair the economies.

The UN general assembly recently held its special session on HIV/AIDS (UNGASS) in New York City. Were AIDS vaccines or microbicides high on the agenda? Was there discussion on the pressing needs of women?

I sat in on the “so-called” session on gender and AIDS and there was no meaning to that meeting, and I don't care who is offended by that. I would say it ranged from fatuous to non-descript. There was nothing in that meeting that would galvanize a response by governments to what is happening to women. There was a lot of rhetoric, which is symptomatic of what's happening—we're not responding. The Secretary General opened UNGASS by saying that although we have made some progress, most countries have failed to meet their promises. This isn't just Stephen Lewis being Cassandra; I'm just mirroring what others are saying.

In the materials on prevention produced for the meeting there was absolutely no mention about AIDS vaccines or microbicides. How is it humanly possible that the people who are responsible for setting out the details on prevention forget these important technologies? It just isn't rooted in the minds of those who have to respond.

You have become such a strong voice for women's rights that I wonder how your wife has influenced your work.

My wife, Michele Landsberg, has been one of the strongest feminist voices in print in Canada for a quarter of a century, and the feminist analysis has very much become part of my own ideology because of her influence. She's been an absolutely extraordinary and uncom-

promising voice and the power and force of her ideas has been unquestionably the greatest influence on my life.

We have been married for 42 years and Michele always says that it took her 20 years to turn me into a human being, and then the next 20 years were tolerable. I think that's probably accurate. I also inherited a lot from family, of course, and was deeply engaged in politics for a while, but in terms of what I think is and isn't important in this world, the benchmark for me has been my wife.

How important was your work in politics and how has it shaped your current position?

I love politics and I regarded it as a principled and useful profession. I served in parliament for more than 15 years and I am very sad that politics has now descended into such personal animus and vitriol in the US and in Canada. It's very different from the days when I was in politics, or when my father was in politics in the 60s and 70s. But I was very lucky, I got into politics when I was 25 and out when I was 40. My political experience has helped me most in the advocacy around AIDS.

What are the most critical steps the international community can take in advocating for a suitable response to AIDS?

Let me say something that is a trifle provocative. The world is now assessing questions of how the UN and the international community are responding to critical issues like Darfur, the way it responded to Rwanda, and the way in which it is failing to respond in Northern Uganda. And national governments have every right to disagree with the interpretation of the international community and say go to hell, but I think that with this pandemic everything changes. We can't allow ourselves the diplomatic privilege of always working behind the scenes and being silent.

If you think that treatment is rolling out too slowly in South Africa, the country with

the highest absolute number of infections in the world, then something has to be said about that. If in a country like Zimbabwe you see the pandemic eviscerating the population, there has to be a desperate effort made to confront the turbulent political situation. It just seems to me that the UN cannot be seen as complicit in the passivity and slowness that characterizes some of the responses, because people's lives are at stake. We have a responsibility, in a thoughtful way, to say to recalcitrant countries that this isn't good enough and we expect more because we're fighting for every life.

“...even though treatment is now being rolled out it's happening too slow, too late, and too incrementally. That drives me crazy.”

– Stephen Lewis

How do you get the world to realize the consequences of this pandemic?

You have to keep at it relentlessly by driving home your arguments, trying to persuade people, and never allowing your voice to be silenced. You have to be tenacious and indefatigable. We know that we can save lives because we have generic antiretroviral drugs at a low enough cost that they should be available to everyone. But even though treatment is now being rolled out it's happening too slow, too late, and too incrementally. That drives me crazy.

The criminal negligence on the part of the Western world has lasted for so long that we'll never be able to compensate for the deaths that have occurred. But you have to continue fighting, and one day, unexpectedly, you break through. That's what I'm waiting for.

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Cervical cancer vaccines

Introduction of vaccines for HPV may offer lessons for a future AIDS vaccine

By **Kristen Jill Kresge**

Cervical cancer is the leading cause of cancer-related mortality in developing countries and accounts for more than 290,000 deaths worldwide each year. Precisely how cervical cancer develops isn't fully understood but scientists now widely agree on the cause. Human papillomavirus (HPV), an incredibly common sexually-transmitted infection, is a necessary, although not in itself sufficient, step in the development of cervical cancer.

Routine tests like Pap smears that detect early-stage abnormalities in the cells of the cervix, which are the first signs of cervical cancer, have substantially reduced the rate of mortality due to this disease in the US. But regular gynecologic care is often not available to women in developing countries. For these women, a vaccine that can prevent cervical cancer is the ultimate solution—and it may soon be a reality.

GlaxoSmithKline's (GSK) HPV vaccine candidate was submitted to the European Commission for approval and licensure in the countries of the European Union earlier this year and another HPV vaccine developed by the US pharmaceutical company Merck already received approval and licensure in several countries, including the US, Australia, Canada, Brazil, Mexico, Peru, and the countries of the European Union. Both of the vaccines have proven highly effective in large clinical trials. However, even with one promising vaccine in hand and another on the way, researchers still face the difficult challenge of making these vaccines available in developing countries, where immunization against HPV could save the most lives.

Questions about pricing and the ease of administering a vaccine to adolescents loom large in many countries where the disease burden is the greatest and these may be obstacles to the global use of HPV vaccines. "It's very exciting to have this vaccine that

works so well, but there is still much work to be done," says Mark Feinberg, vice president of policy, public health and medical affairs at Merck. Many of these same issues may arise when an effective AIDS vaccine is developed and this has many closely watching how the debut of this important vaccine plays out. "This is a sort of test case for HIV vaccines and there will be a lot of lessons on acceptability and delivery," says Jessica Kahn, a pediatrician at Cincinnati Children's Hospital in Ohio.

Behind the virus

HPV is one of the most common sexually-transmitted infections (STIs) in the world and most studies suggest it infects at least 25% of sexually active adults—with one study reporting prevalence close to 80% in a cohort of adolescent women in the US. Exact prevalence is difficult to pinpoint in many parts of the world because of the varying sensitivity of the assays used to detect the virus.

There are nearly 120 types of the virus that infect humans and a third of these primarily cause genital infection. These HPV types are further classified as high and low risk based on their ability to cause cancer. HPV types 6 and 11 are responsible for 90% of cases of genital warts. Two of the high-risk HPV types, 16 and 18, are responsible for 70% of the cervical cancer cases worldwide, according to Kahn, but the predominant HPV types can vary geographically and these types are not as common in sub-Saharan Africa or Asia as they are in North America and Europe.

There is limited research on the epidemiology of HPV infection in developing countries but a study published in the *New England Journal of Medicine* in 2003 pooled data from 11 case-controlled studies in 2506 women with cervical cancer in Morocco, Mali, Colombia, Brazil, Paraguay, Peru, Thailand, the Philippines, and Spain. HPV

type 16 was the most common with an overall prevalence of 59%, reaching 70% in some countries. The second most common HPV type was 18, with an overall prevalence of 15%, followed by types 45, 31, and 35. The authors suggest that the predominant HPV type should be considered if vaccines are to be created for a specific geographic region. Philippe Monteyne, vice president of worldwide operations for GSK's cervical cancer vaccine program, acknowledges limited regional differences in HPV types but says his company's vaccine "is really useful on a worldwide basis."

The vaccines

Not every woman that is HPV infected will develop cervical cancer. Many infections with either the high- or low-risk HPV types can be temporary and cleared easily by the immune system. But HPV becomes dangerous when infection with a high-risk type isn't cleared. A persistent and active HPV infection can cause pre-cancerous lesions on the cervix known as cervical intraepithelial neoplasia (CIN) that may eventually lead to non-invasive and then advanced cervical cancer, which can be a life-threatening condition. An unresolved HPV infection is also associated with both anal and oral cancer in men and women.

Preventive HPV vaccines—like Merck's and GSK's—may help reduce the reliance on screening methods in the future. Both candidates consist of a single HPV protein that can self assemble into a virus-like particle (VLP), a non-replicating shell that resembles an actual virus particle closely enough to fool the immune system into thinking it is encountering a natural HPV infection.

Merck's vaccine, known as Gardasil, was approved and licensed by the US Food and Drug Administration (FDA) in June 2006 and the European Agency for the Evaluation of Medicinal Products in September based on data from multiple Phase III efficacy trials in over 25,000 women and men. Gardasil contains HPV proteins from four viral types, HPV 6, 11, 16, and 18. In one of their Phase III trials involving 12,167 women aged 16-26, 3 doses of the vaccine were able to prevent all cases of high-grade CIN or non-invasive cervical cancer associated

with the virus types included in the vaccine. "It's really hard to do better than that," says Feinberg.

The vaccine was also able to prevent cases of persistent HPV infection that caused high-grade CIN and non-invasive cancer associated with strains 16 and 18 by 97% in women who received at least one injection, a more "real world" example of the vaccine's efficacy since people may not return for all 3 inoculations.

Gardasil was approved for girls between the ages of 9 and 26, but ideally a preventive HPV vaccine would be administered prior to infection, which for such a common virus means vaccinating girls and boys before they become sexually active. Initially this created some controversy in the US with some groups arguing, as they do for HIV, that promoting abstinence is a better message. But the Advisory Committee on Immunization Practices, a sub-committee of the US Centers for Disease Control and Prevention, recently recommended that girls be routinely vaccinated at age 11 or 12.

...without a doubt introducing these vaccines in developing countries "could have a tremendous impact on mortality."

– Jessica Kahn

The other preventive HPV vaccine developed at GSK in Rixensart, Belgium, in collaboration with MedImmune was submitted to the European regulators earlier this year and approval and licensure is expected in 2007. The vaccine, known as Cervarix, is also a VLP vaccine but only includes HPV proteins from types 16 and 18. GSK has 5 ongoing Phase III efficacy trials with Cervarix in 28,000 female volunteers. Data show that 3 doses of the vaccine are 100% effective at preventing persistent HPV infection with the two types of virus in the vaccine. The vaccine was 95% effective at preventing persistent HPV infection and 93% effective at preventing CIN in women who received at least one injection.

GSK is only testing its vaccine in women, but Merck has chosen to evaluate the efficacy of Gardasil in both male and female adolescents, as well as in trials with men who have sex with men (MSM). Not only does HPV cause significant disease burden in males, says Feinberg, it is also likely that vaccinating both men and women will increase immunity levels on a population basis and therefore decrease overall the number of life-threatening infections in women. Merck has yet to report results on the efficacy of Gardasil in male volunteers and their license from the FDA only applies to women.

Implications for HIV

Since both HPV and HIV can be sexually-transmitted and enter the body through the same mucosal tissues, researchers have been studying the link between these two infections. The cervical lesions caused by persistent HPV infection can enhance women's risk of acquiring HIV because of increased bleeding and the recruitment of CD4⁺ T and dendritic cells to the mucosal tissues of the cervix, believed to be a target site for establishment of HIV infection in women. And a study presented at the 2005 International AIDS Society Conference in Brazil found that anal HPV infection was independently associated with HIV acquisition in a cohort of 1409 MSM (Abstract no. TuOa0403).

Several studies have also found that HIV-infected individuals are at greater risk for acquiring HPV and the two prove to be perilous partners. Co-infected individuals are more likely to develop severe cervical lesions than those only infected with HPV. It is estimated that HIV-infected women are three to five times more likely to develop cervical lesions due to HPV infection. HIV's ability to hinder the immune system may be at the root of this problem, either directly or indirectly, because it allows HPV to persist longer, making cancer development more likely. Even people on highly active antiretroviral therapy (HAART) for HIV infection are more likely to develop serious anal and cervical lesions.

Rollout plans

There are several significant challenges to implementing HPV immunization programs around the world. Before vaccination can begin

researchers must first work to educate communities about the cause of cervical cancer and this may be particularly difficult in some countries where discussion of sexually activity is uncommon or even taboo. Vaccinating early adolescents in some developing countries might also require new ideas for vaccine delivery since many young girls may not be attending school. "There really isn't any infrastructure in developing countries for administering vaccines to adolescents," says Feinberg, who attributes much of the progress made with immunization programs in developing countries to vaccine administered to infants.

Another obstacle to immunization will be cost. Gardasil is priced at US\$120 a dose and 3 doses are recommended for optimal protection. The final cost of GSK's HPV vaccine will not be released until after licensure. Both companies say they will use a tiered-pricing model for their vaccines, which means they will charge higher prices in the US and European markets and lower prices in developing countries.

The Program for Appropriate Technology in Health (PATH), an advocacy group in Seattle, is now exploring ways to make HPV vaccines available in developing countries, focusing on both pricing and implementing immunization programs. Initially the organization is working in countries that already have active vaccination programs and high levels of HPV disease burden, including India, Peru, Vietnam, and Uganda.

PATH will also work on a proposal to the Global Alliance for Vaccines and Immunization (GAVI) to explain why funding should be allocated for the purchase of HPV vaccines. "We expect to look at a range of strategies to encourage an affordable supply," says Jacqueline Sherris, program director at PATH.

New research into the epidemiology of HPV infection by region may also be an important consideration in the implementation of these vaccine programs, but without a doubt introducing these vaccines in developing countries "could have a tremendous impact on mortality," says Kahn.

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Malaria vaccines: Renewed promise

By **Kristen Jill Kresge**

Filip Dubovsky only treated a single case of malaria while working as a pediatrician in California, and his diagnosis of this case was entirely unexpected. While treating a young patient with appendicitis, he also noticed the tell-tale signs of malaria. Several years after this brief encounter with the parasitic disease, Dubovsky is the scientific director for a US-based nonprofit organization that is devoted to the development of a vaccine to help end the scourge of malaria in developing countries. Malaria, along with tuberculosis and HIV/AIDS, is among the most deadly communicable diseases, killing nearly 3 million people each year. The Malaria Vaccine Initiative (MVI), a division of PATH (Program for Appropriate Technology in Health) in Seattle where Dubovsky works, is trying to accelerate the discovery process for an effective malaria vaccine and the field may soon reap the benefits.

“This is the golden age for malaria vaccine research and we are going to see a lot of data coming in over the next few years,” says Dubovsky. “We now have real proof that a malaria vaccine is possible and that it can save the lives of children in Africa.”

This new evidence was a long time in coming. Vaccinologists and parasitologists have been trying for decades to develop a vaccine for malaria. But there were many scientific obstacles to overcome first, not the least of which was decoding the sequence of more than 5000 genes that make up the *Plasmodium falciparum*—the most lethal of the malaria parasites. After this was accomplished three years ago, the pace of vaccine research gathered speed. “The science is here, and finally the biotechnology is at a point where we can develop promising candidates,” adds Dubovsky.

There are now dozens of promising malaria vaccine candidates in various stages of clinical development. There are two main ways these

experimental vaccines can help control malaria. There is a critical turning point in the parasite’s development once it enters humans. Vaccines that act before this point would offer sterilizing protective immunity, because they would prevent immunized individuals from developing an established malaria infection. Other vaccines that act after this point would work by limiting the severity of disease. Scientists are currently faced with a similar situation in the pursuit of an AIDS vaccine.

“This is the golden age for malaria vaccine research and we are going to see a lot of data coming in over the next few years.”

– Filip Dubovsky

The malaria vaccine candidates that are the furthest along in development work by the second route and do not offer complete sterilizing immunity. This type of vaccine could still make great strides in reducing the mortality associated with malaria and could have immense social and economic benefits in the hardest hit areas. In countries where malaria is widespread, the parasite is responsible for up to one quarter of all deaths in children under the age of five. Malaria’s burden falls primarily on the younger generations that would eventually become important contributors to the welfare of both their household and community. Malaria is also increasingly linked with other diseases like AIDS. Children and women, particularly pregnant women that are HIV infected, are disproportionately affected by malaria and in many African countries the diseases overlap geograph-

ically. In people who are co-infected, both diseases can progress more rapidly and this can have grave implications.

Meanwhile researchers are continuing the search for vaccine candidates that could provide sterilizing protective immunity. “We have several candidates going forward now, and we’ve already eliminated a lot that don’t work. All this is great news,” says Dubovsky. However the ultimate challenge for the malaria vaccine field will come once a successful candidate progresses through clinical trials. Then the test will be getting the vaccine to those who need it most.

From mosquito to human

A malaria infection occurs when a female mosquito bites a human. In the process, the mosquito transmits parasites into the blood. At this point, the parasite is in an early stage of maturity known as a sporozoite. Once inside a human, the parasite goes through a complex growth process. To reach the next stage the

Newer and improved strategies for treating malaria involve taking combinations of drugs, as is the strategy with HIV infection.

sporozoites must make the journey to the liver, where they use liver cells to reproduce. This is the critical turning point where an established infection occurs. A sterilizing vaccine would stop the parasite before reaching the liver. To do this successfully it must block all of the parasites because even if just one sporozoite finds its way to the liver, it can rapidly multiply and still cause a lethal infection.

After replicating in the liver, the parasite is then released into the blood. This stage of the parasite is called a merozoite. The merozoite then enters red blood cells where it can produce even more parasites. Once huge numbers of

parasites form it causes the red blood cells to rupture resulting in shock, severe anemia, coma, and eventually death. A vaccine that acts after the parasite reaches the liver would hinder reproduction so that fewer parasites make it into the blood. This type of vaccine would reduce the severity of disease and lessen the likelihood of death. Researchers refer to a vaccine that does not offer sterilizing immunity as “leaky” because it allows some of the parasites to leak through the immune response. Designing this type of vaccine is now proving a simpler task than one that induces sterilizing immunity.

Although a leaky vaccine is not 100% effective it will allow children to slowly develop natural immunity to the parasite. In areas where malaria is prevalent, people are repeatedly bitten by infected mosquitoes and are continuously exposed to the parasites. This allows them to build up some immunity against malaria so that even though parasites are entering the liver, the immune system is controlling their numbers. By the time people reach adulthood, many of them have developed enough immunity to avoid severe symptoms and death. Children and infants are therefore at the highest risk for severe malaria and death, and 90% of severe disease occurs between the ages of 5 months and 3 years.

In the absence of a vaccine other simple interventions are effective at lowering rates of malaria infections. By reducing the number of mosquito bites, insecticide-treated bed nets can reduce the number of infections by 45% in areas where they are used regularly and properly. But as is often the case, the simplest interventions are often unavailable or not widely accepted.

There are also anti-malarial drugs that can be taken as prophylaxis before exposure to the parasite, but unfortunately these are of little use in developing countries because of increasing drug resistance in the parasite in many endemic areas. One popular anti-malarial to which there are now high levels of resistance is chloroquine. Newer and improved strategies for treating

malaria involve taking combinations of drugs, as is the strategy with HIV infection. Like anti-retrovirals, combination therapies for malaria also have high price tags and are not available in all areas, making them only feasible as treatments where the risk of disease is very high. The World Health Organization (WHO) just recently adopted these updated regimens for use in its Roll Back Malaria program after being criticized by researchers and activists for treating people with outdated and sub-optimal malaria therapies.

Progress in trials

Several malaria vaccine trials are currently ongoing in Africa with a robust array of candidates. There are four candidates in trials that aim to provide sterilizing immunity with an additional nine in earlier development. The selection of candidates that may limit severity of disease is even more expansive. Nine candidates are now in clinical trials and another 28 are still in the laboratory.

The field's lead candidate was developed by the pharmaceutical company GlaxoSmithKline (GSK) and is now being readied for a large-scale efficacy trial (Phase III) in approximately 13,000 children at 6 to 8 sites throughout Africa. This vaccine candidate, known as RTS,S, seems to limit disease progression and prevent childhood deaths. GSK started malaria vaccine research in 1984 and just recently completed a Phase IIb trial in Mozambique that enrolled more than 2000 children. Completion of this trial was a landmark in malaria research, according to Regina Rabinovich, the director of infectious diseases at the Bill & Melinda Gates Foundation.

The vaccine was 57% effective at preventing severe malaria through six months. The RTS,S candidate is composed of a single protein from the surface of the sporozoite attached to a hepatitis B virus protein and is delivered with an adjuvant known as AS02. The vaccine cannot cause malaria or hepatitis B and caused few side effects in the Phase IIb trial. Preparations for the Phase III trial are now underway and the

company is spending millions of dollars on refurbishing an existing manufacturing facility to produce the vaccine for the trial, according to Ripley Ballou, vice president of emerging disease at GSK. The company is also investigating the optimal dosing strategy for the trial. Ballou predicts that a prime vaccination followed by a booster shot will likely give the best response.

Several malaria vaccine trials are currently ongoing in Africa with a robust array of candidates.

Many other research groups are currently investigating ways to include other parasite proteins in a vaccine candidate to find one that induces sterilizing immunity. Stephan Kappe of the Seattle Biomedical Research Institute in the US is researching which of the parasite's 5000 genes are required for it to establish infection in the liver. Many of the vaccines now in development have relied on the same handful of proteins to induce an immune response to the parasite. Kappe's work is intriguing to many in the field who think additional proteins will need to be included in a vaccine for it to be completely effective at stopping the parasite.

Ensuring access

Although activity and funding in the search for a malaria vaccine has been increasing steadily, much of this work has been accomplished with a strikingly small budget. Dubovsky estimates that only US\$27 million this year will be spent on malaria vaccines. The partnerships between private companies like GSK and non-governmental organizations like MVI have helped keep malaria vaccine research on the agenda. Industry is reluctant to invest in research for products like malaria vaccines that would not be sold in the lucrative US or European markets. Drug prophylaxis

laxis is sufficient and available to travelers from areas where malaria is not prevalent to protect them from getting malaria. “For products like this, there needs to be some promise that someone is going to buy the vaccine in order for industry to make such a large commitment,” says Ballou.

“A vaccine can be licensed, but until someone steps up and says they are going to buy it for their country and start massive immunization campaigns, it doesn’t matter much.”

– Ripley Ballou

Discussions about potential strategies for making a malaria vaccine available at an affordable price are now being held between industry and organizations like the Gates Foundation and MVI. Similar planning and

discussions are taking place around AIDS vaccines and many in that field are looking at malaria vaccines as a model.

“A vaccine can be licensed, but until someone steps up and says they are going to buy it for their country and start massive immunization campaigns, it doesn’t matter much,” warns Ballou. “You can give the vaccine away for free, and there’s still a cost involved.”

To this end, MVI is planning to get a licensed malaria vaccine included in the WHO’s Expanded Programme on Immunization in developing countries. “It’s the best system we have and our goal is to get an effective malaria vaccine integrated into it,” says Dubovsky.

In a recent speech at the Brookings Institution (a US-based public policy think-tank) Nelson Mandela reminded policymakers that African countries need improved access to treatment and prevention resources for the three biggest killers: AIDS, malaria, and tuberculosis. “Freedom, after all, means nothing to someone left to die at the mercy of these preventable and treatable diseases.”

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Rotavirus: Vaccines enter battle against an intestinal virus

New vaccines prevent potentially deadly diarrheal disease in infants

By Kristen Jill Kresge

Almost all infants, everywhere in the world, have been infected with rotavirus by age five. This common pathogen can cause a range of symptoms, from mild gastrointestinal discomfort to the diarrheal disease known as acute gastroenteritis that can lead to serious dehydration. And although even the most severe cases of the disease can usually be treated easily with replenishment of fluids or electrolytes, rotavirus kills 600,000 children each year, the vast majority in developing countries where access to healthcare services is limited. This single virus accounts for about 5% of all childhood deaths worldwide.

Yet as organizations such as the Program for Appropriate Technology in Health (PATH), a Seattle-based non-profit organization, meet with policymakers in developing countries to discuss rotavirus, they find many have never even heard of it. These meetings are the first step in preparing governments for the introduction of two new vaccines that may help prevent the tragic consequences of this viral infection.

Despite setbacks with an earlier rotavirus vaccine, which was abruptly revoked over safety concerns, continued efforts by vaccine manufacturers GlaxoSmithKline (GSK) and Merck culminated earlier this year in landmark clinical trials showing that both company's rotavirus vaccines were highly effective in preventing severe gastroenteritis in infants, and were not associated with similar safety issues.

"Given the challenges and the enormous resource requirements, it is just amazing that we actually have two new products," says Umesh Parashar, a medical epidemiologist at the US Centers for Disease Control and Prevention (CDC). His enthusiasm for these vaccines is tempered by only one thing. Neither have been tested

in efficacy trials in Africa or Asia, so it's unclear if they will be as effective at preventing severe disease in these populations as the already completed Phase III trials indicated in infants from the US, Europe, and Latin America. "That's the biggest scientific question that remains," says Parashar.

Evidence suggests that immune responses induced by orally administered vaccines are reduced in these populations. Trials in developing countries demonstrated the need for additional doses of oral polio vaccine to stimulate equivalent immunity, and both cholera vaccine and earlier versions of rotavirus vaccine performed less favorably in these settings. So it is essential that the new rotavirus vaccines are tested there before rotavirus vaccination programs can be implemented around the world.

GSK has already started two trials in Malawi and South Africa and Merck plans to initiate trials by the end of the year at yet to be identified sites in Africa and Asia, all of which are being conducted in cooperation with PATH. Although data from these studies isn't expected until 2009, organizations like the Global Alliance for Vaccines and Immunizations (GAVI), PATH, the World Health Organization (WHO), and the CDC are already actively engaged in accelerating the testing and introduction of rotavirus vaccines in countries where the most deaths from severe gastroenteritis occur.

The culprit

Many serotypes of rotavirus are currently in circulation around the globe, but luckily for vaccine developers more than 80% of rotavirus-related disease is caused by just four of these serotypes. Rotavirus is transmitted orally and once inside the body, it can trigger the diarrhea and vomiting that together account for the often

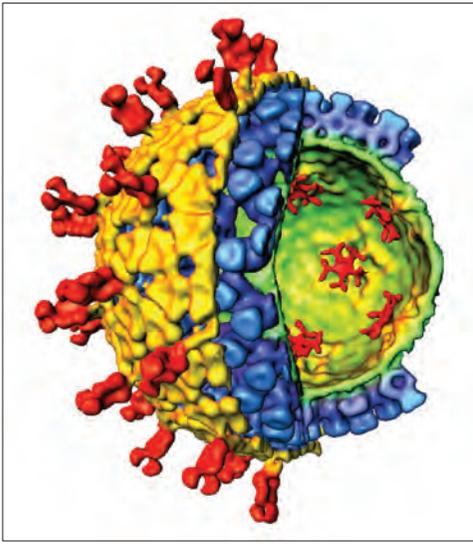


Figure 4. Reconstructed image of the rotavirus particle. *The major immune response in rotavirus infection is against the VP7 (yellow) and VP4 (red) proteins on the outer surface of rotavirus. Researchers are using the human rotavirus version of these proteins in a bovine or simian rotavirus background to construct the new vaccines, Rotateq and Rotarix.*

rapid and severe dehydration. In developing countries, where prompt access to healthcare services is limited, approximately 1 in 200 children who are infected with rotavirus will die.

The personal toll associated with such a pervasive virus spurred researchers into developing vaccines that would completely prevent infection. However they soon changed course when studies of natural infection showed that children who are repeatedly infected with the virus develop some level of natural immunity that, although not able to prevent subsequent re-infection, can reduce the risk of developing severe disease. After a second infection it becomes unlikely that an infant will ever experience severe gastroenteritis. “Efforts were then focused on developing a vaccine to mimic this effect,” says Parashar.

Several vaccine candidates were developed based on different animal strains of rotavirus. One developed by Wyeth called Rotashield was based on a monkey virus engineered to express proteins from the human rotavirus strain (Figure 4). After clinical trials showed this vaccine to be

effective it received approval and licensure from the US Food and Drug Administration (FDA). But just nine months later physicians in the US were advised by the CDC to immediately suspend use of the vaccine after a small number of unexpected cases of intussusception occurred in infants who received Rotashield. Intussusception is a serious bowel obstruction that happens when part of the small intestine folds over itself like a collapsing telescope. If left untreated it can sometimes be fatal.

Further analysis showed that most cases of intussusception occurred within two weeks of infants receiving their first vaccination, suggesting Rotashield was the cause. A study by the CDC calculated that the intussusception risk for vaccinated infants was between 1 in 4500 and 1 in 9500. “That level of risk was not considered acceptable in the US,” says Parashar, where only 20 deaths each year are attributable to rotavirus infection. Wyeth soon withdrew Rotashield from the market and stopped manufacturing the vaccine.

This ignited debate among scientists and bioethicists over whether or not the vaccine could still provide benefit in developing countries where the death toll is much higher. In an article bioethicist Charles Weijer of Dalhousie University, Canada said it was “imperialistic to transfer this standard of care to a country in which 1 in 200 children die of rotavirus infection.”

Weijer calculated that even in a worst-case scenario, the intussusception associated with Rotashield would have caused 2000-3000 deaths per year, which is far fewer than the 600,000 deaths caused by rotavirus-induced severe gastroenteritis.

“One of the challenges with this vaccine was that it hadn’t already been tested in Africa and Asia,” says Parashar. Not knowing if the vaccine was even effective in these developing-country settings made it difficult for policymakers to overlook the possible adverse effects. But if Rotashield had been tested simultaneously in developing countries there may have been greater enthusiasm for the vaccine preventing rotavirus-related death, and possibly even a movement to seek independent licensure.

Small risk, huge trials

Soon after Rotashield's withdrawal Merck was preparing to take their lead rotavirus vaccine candidate into large-scale efficacy trials. Suddenly the trial plans changed dramatically. To rule out the possibility of intussusception the Phase III trials would need to include 60,000-100,000 infants. Both financially and organizationally this was no small matter. However the company chose to move forward and began a placebo-controlled trial with their rotavirus vaccine, Rotateq, in more than 69,000 infants in 11 industrialized countries. GSK was faced with a similar situation with their vaccine, known as Rotarix, and they too pushed ahead with a trial involving 63,000 children in Finland and 11 countries in Latin America.

These trials are the largest industry-sponsored vaccine trials ever conducted and both showed that the vaccines were highly effective. Rotateq prevented 74% of any rotavirus-related gastroenteritis and 98% of severe cases. The vaccine also reduced the number of hospital visits for gastroenteritis by 86%. Immunization with Rotarix prevented 85% of severe gastroenteritis cases and associated hospitalizations and was 100% effective at reducing the most severe cases of the disease. Just as importantly, neither live-attenuated vaccine was associated with an increased risk of intussusception. "It was likely a Rotashield-specific issue," says Mark Feinberg of Merck.

A few months after the final data was released, Merck received approval to license and market Rotateq in the US and GSK received licensure for Rotarix from the European Commission. Rotarix is also licensed in Mexico, Brazil, Philippines, and Singapore.

These vaccines were developed without a good animal model and, even after large studies proved their efficacy, researchers have yet to identify exactly what immune response is responsible for protection. This gives hope to AIDS vaccine researchers who are working under similar constraints. Paul Offit of the Children's Hospital of Philadelphia in the US and one of the co-discoverers of Rotateq says that in comparison "rotavirus vaccines were much easier to make," yet it still took a quarter of a century of research and development.

Rolling out vaccines

Before the WHO will recommend rotavirus vaccination for infants in developing countries, where infants are at the greatest risk of developing life-threatening gastroenteritis, the vaccines must be tested in these populations. Despite the experiences of Wyeth with Rotashield, neither manufacturer chose to run efficacy trials with their second-generation vaccines in both developed and developing countries simultaneously. According to Feinberg, Merck decided their large efficacy trial would only be conducted in countries where they were confident all possible cases of intussusception could be detected and treated quickly. "Now that we know the vaccine is highly efficacious and well tolerated we want to move forward as quickly as possible in resource-poor countries," he says.

This is happening with the help of PATH, whose goal is to reduce the delay between initial licensure of vaccines and availability in developing countries. The first step is talking with policymakers in the 72 poorest countries and educating them about the disease and the vaccines. "If we go to countries right now and say we want to talk about rotavirus, they say 'What's that?'" says John Wecker of PATH. These countries know they have a diarrheal disease but are unaware that rotavirus is the cause. "We want to provide a solid evidence base for developing-country governments, and we have a long way to go," he adds.

In the future PATH will also have to explain the characteristics that differentiate Rotateq from Rotarix, mainly serotype coverage and dosing schedule, so that representatives from developing countries can choose which vaccine to include in their immunization programs.

But in the end their decisions may be mainly driven by price. PATH is now holding consultations with the manufacturers on pricing. In the US, Merck's vaccine costs \$180 for the three-dose course, making it one of the highest-priced childhood immunizations. Wecker is confident that financial subsidies provided by GAVI will help reduce the cost burden in developing countries.

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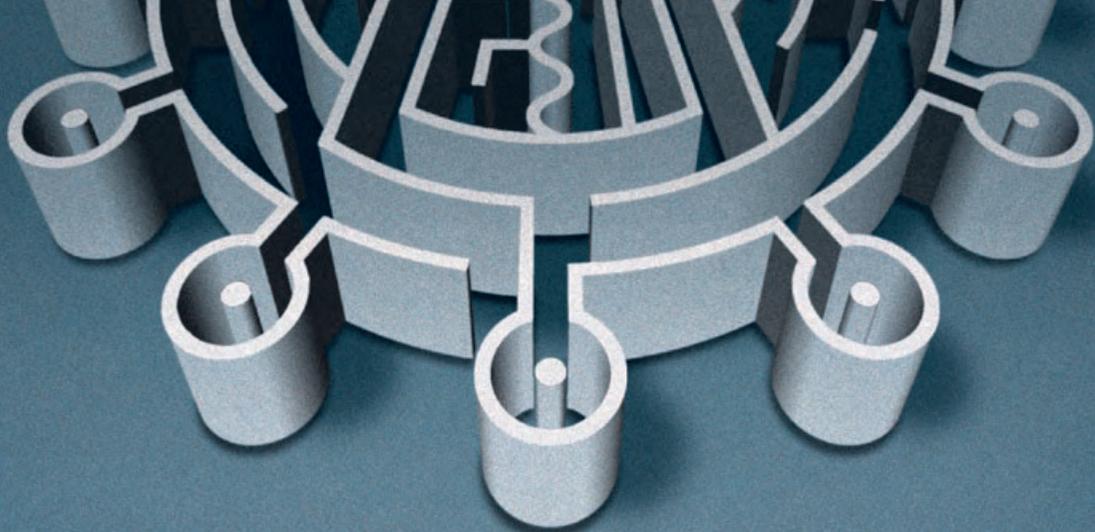
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