

## South Africa's first human AIDS Vaccine trial

### What is the 040 vaccine trial?

HVTN 040 is a phase I trial to look at the safety and immune response of an experimental HIV vaccine. The term 'HVTN 040' is the name that the HIV Vaccine Trials Network (HVTN) uses to refer to this trial. The candidate vaccine is called AVX101, and it is an alphavirus replicon vaccine. Scientists designed this candidate vaccine to teach the human body how to fight off HIV infection. The hope is that a vaccine can eventually keep people from becoming infected with HIV.

This is a phase I study to assess the safety of this new HIV vaccine technology in people in the United States and South Africa. In addition, the study will measure the immune response generated by the vaccine. The vaccine candidate will be tested in healthy, HIV-uninfected volunteers.

### How does this candidate vaccine work?

This vaccine is made to work by entering a few special human cells that are involved in the immune response. The genetic material in the vaccine will reproduce once it is in these cells, causing these particular cells to produce the same HIV protein carried by the vaccine. In animal experiments, production of this protein elicits both a humoral immune response (production of antibodies against the HIV protein) and cell-mediated immune response (the ability to kill HIV-infected cells). Therefore, it is hoped that the humans who receive this vaccine will have the same result as the animals and be able to produce an immune response.

### Can this candidate vaccine cause HIV?

No, this candidate vaccine cannot cause HIV infection. The vaccine does not contain killed or weakened HIV. It contains only a copy of a small section of genetic material from HIV, known as the gag gene. Later versions of the test vaccine could include additional genes. The gag gene is only a small part of HIV. Therefore there is no possibility of the vaccine causing HIV infection. It does not include parts of HIV that would be needed to produce live HIV.

This vaccine is NOT made from live virus or from HIV-infected human cells, so there is NO possibility that it contains live or killed HIV virus. Therefore, it is NOT possible that someone can get HIV infection or AIDS by receiving this vaccine.

### Has this candidate vaccine been tested (in humans or animals)?

This vaccine has been tested in animals and in a few human volunteers. Animal studies have shown significant humoral (antibody) and cell-mediated (T cell) immune responses. Investigations using an early prototype of the vaccine in monkeys showed reduced viral load and improved clinical outcomes. The vaccine candidate has been tested in a small number of human volunteers in the USA and no safety concerns have been identified to date.

### Why is this approach being studied?

VEE has several characteristics that make it attractive as a vector for an HIV vaccine. First, it is easy to make the VEE vector carry HIV genes, while avoiding the potential for VEE itself to infect a trial volunteer. Particles made from VEE are able to target the immune system and to express the immunising genes they carry at very high levels (in large amounts). Research showing that this can create a highly effective vaccine in animals suggests that VEE can stimulate the desired immune response in humans.

### Who is running this trial?

The trial will be run by the HIV Vaccine Trials Network (HVTN), a global partnership dedicated to conducting international clinical HIV vaccine trials. The HVTN is funded by the National Institute of Allergy and Infectious Diseases (NIAID), of the US National Institutes of Health (NIH).

Collaborating organisations in the design of this vaccine product and the conduct of the clinical trial are AlphaVax, Inc., the US NIH and its HVTN, the University of North Carolina at Chapel Hill, the South African AIDS Vaccine Initiative (SAAVI) under the auspices of the South African Medical Research Council, the University of Cape Town, and the South African National Institute for Communicable Diseases.

The principal investigators are Dr Don Burke at Johns Hopkins in Baltimore and Dr Glenda Gray at the University of the Witwatersrand in South Africa. Additional participating trial sites are Columbia University, the University of Rochester, and Vanderbilt University in the United States and the HIV Vaccine Research Unit in Durban, South Africa.

### **What is the design of the trial?**

Forty-eight people will be enrolled in the trial, 24 in South Africa and 24 in the US. These people will randomly be divided into two groups of 12 people each. This is a double-blind, placebo-controlled trial – meaning that some of the participants will receive the test vaccine and some will receive a harmless substance which resembles the vaccine known as a placebo. Double-blind means neither the clinicians or the volunteers know which group they are assigned to in order to eliminate any bias. The two groups are then compared to see if the vaccine has made any difference.

Ten of these people will receive the candidate vaccine and two will receive the placebo. There will be two dosage amounts of vaccine candidate: the first group of 12 in each country will receive the lower dose, and the second group in each country will receive the higher dose. The trial will last approximately two years, with one year of participation expected from each volunteer. Participation will include nine clinic visits, three injection dates, and seven blood draws.

### **Who produced the vaccine candidate?**

The vaccine was developed and produced by a biotechnology company called AlphaVax, Inc., based in North Carolina, USA. The vaccine was developed together with South African scientists from the University of Cape Town.

### **Who is funding the trial?**

This trial is funded by the Division of AIDS (DAIDS), a part of the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH), which is within the US Department of Health and Human Services (DHHS). AlphaVax, Inc. made the product and is sponsoring the trial.

### **Who approved the trial, and what was the approval process?**

The study protocol, which outlines everything that will happen in the trial, went through extensive independent review by the Institutional Review Board, Institutional Ethics Committee and Bio-Safety Committee of each institution involved. The HVTN 040 trial has been reviewed by at least six such committees.

It has also been approved by the governmental authorities, the US Food and Drug Administration (FDA) and the South African Medicines Control Council (MCC).

The candidate vaccine is considered investigational, meaning that the FDA and the MCC will allow its use

only in research with a small number of participants (i.e. a phase I trial). The candidate vaccine has been made according to the guidelines established by the FDA and MCC, and has been reviewed by both agencies.

Finally, the Community Advisory Groups (at the various trial sites), which act as a link between the researchers and the community, while not part of the official approval process, give regular input into the trial design and proceedings.

### **When and where is this trial being run?**

This trial began in July 2003 in the United States and in November 2003 in South Africa. The US clinical trial sites are Columbia University in New York City, New York; the University of Rochester, Rochester, New York; Johns Hopkins University, Baltimore, Maryland; and Vanderbilt University, Nashville, Tennessee. The South African sites are the HIV Vaccine Research Unit at the Medical Research Council (MRC) in Durban and the HIV/AIDS Vaccine Division of the Perinatal HIV Research Unit, University of the Witwatersrand, based at Chris Hani Baragwanath Hospital in Soweto, South Africa.

### **Why is this vaccine candidate being tested in South Africa?**

This vaccine candidate has been developed based on HIV subtype C, which is the strain of HIV most prevalent in southern Africa (estimated to be responsible for over 90% of new infections in South Africa). HVTN 040 is based on subtype C with the intent of developing a vaccine that has a good chance of preventing future infections in South Africans. The gag gene which is inserted is based on gene sequences from viruses circulating in South Africa.

Scientists do not know yet if a vaccine might work better if it is matched to a local clade or virus type, so they are studying different variations to further understand the issue. At present there is insufficient evidence and further testing is needed. This vaccine candidate allows scientists to establish baseline safety information that could lead to additional studies to help in answering this important question.

### **What other candidate vaccines are being tested in South Africa?**

This is one of the first candidate vaccines to enter a phase I trial in South Africa. A second candidate, the HIVA.MVA, has also received regulatory approval to enter a phase I trial in South Africa shortly. This trial will be run by the International AIDS Vaccine Initiative. In addition, there are other South African developed candidate vaccines that are currently in the pre-clinical phase and could enter clinical trials during 2004. The aim would be to have a number of candidates in phase I trials simultaneously so that the most promising approaches can quickly be identified and can proceed to later trials.

### **What are the possible risks with this vaccine candidate?**

Any experimental vaccine carries possible risks, but based on the information they have, researchers do not expect that there will be serious safety issues. In addition to the HIV gag gene, the vaccine contains parts of a weakened (attenuated) strain of another virus called Venezuelan equine encephalitis (VEE) virus. The VEE is in the form of a replicon – it is not a normal virus structure. A different weakened (attenuated) strain of VEE has been used successfully in another vaccine product in humans for decades. Vaccine candidates using VEE have been tested extensively in experimental animals without causing any significant side-effects or infection. The candidate vaccine does not contain live HIV virus, and therefore there is no way for it to cause HIV infection.

The vaccine has already been administered to a small number of US volunteers as part of the HVTN 040 trial, so some very early safety data is available before it is given to South African volunteers. However, until the HVTN 040 trial, this candidate vaccine had never been tested in humans. While scientists believe that there are no serious safety risks, there is always the possibility that there could be problems that no

one expected. This is why this candidate vaccine, like any new drug or vaccine, needs to be tested for the first time in a few volunteers in a controlled clinical setting.

Many people, from scientists and doctors to community members, looked carefully at the information about the candidate vaccine to make sure that they thought it was safe enough to begin the trial. In addition to the protocol team, the HVTN has a central Safety Monitoring Board, which will watch carefully to make sure nothing goes wrong. If there are any problems, the trial will be interrupted for careful review. After additional review by persons not involved with the study, the trial can be resumed or permanently stopped, based on the review.

### **What is VEE?**

In addition to a synthetic piece of the HIV virus called the gag gene, this vaccine candidate contains parts of a weakened (attenuated) strain of another virus known as VEE (Venezuelan equine encephalitis) virus. The gag gene is the part of the candidate vaccine that should make the immune response specifically tailored to fight HIV.

The natural VEE virus typically infects horses, although occasional human infections occur. VEE infections in humans are rare. In these cases the VEE virus usually produces flu-like symptoms. For this vaccine, VEE has been designed so that it cannot reproduce itself. Infection cannot occur with a replicon because all the structural genes are removed. When a virus cannot reproduce it no longer can cause an infection, and therefore this vaccine candidate is not expected to cause VEE infections. As a further safety measure, the type of VEE virus used has been changed so that it is weakened, lessening its ability to cause harm. It is not expected that serious illness will result from the use of the VEE vector, but there is a very, very small chance that this could happen. Procedures are in place to monitor volunteers just in case an illness related to VEE does develop.

The altered VEE virus is the carrier or vector for a particular piece of HIV (the gag gene of HIV) that is put into the RNA of the VEE virus using standard scientific methods. The gag gene is synthetically made, is only a small part of the HIV virus, and cannot cause HIV infection. The VEE virus vector carries the gag gene into the cells, where it will cause the cells to make gag proteins. These proteins might be part of what would one day help the body fight off real HIV.

### **How will trial volunteers be protected during this trial?**

Before deciding to enter the trial, potential volunteers are provided with the following: information about HIV and AIDS; the reasons for the trial; possible risks and benefits of participation; and, a description of the trial procedures. They are also informed that any new, experimental vaccine may have unknown risks. These may include side-effects due to injection of the vaccine, and issues of stigmatisation associated with taking part in HIV studies. Volunteers will be reminded frequently that being part of this trial does not mean that they are less likely to become infected with HIV. Volunteers are provided with risk-reduction counselling at each visit, explaining current proven ways to avoid HIV infection (including, for instance, abstinence and correct and consistent condom use).

Volunteers who are eligible and willing to participate after the study has been fully explained to them will be asked to give informed consent before they enroll in the study and on an ongoing basis throughout the study. Volunteers will be given plenty of time to consider whether or not they want to participate. Volunteers do not have to join the study and can leave the study at any time.

The role of the volunteer in HIV vaccine clinical trials is essential. Those involved in the design of the trial have considerable respect for trial volunteers, and are dedicated to the continued support of these volunteers.

## HIV & AIDS – The Facts

### What is HIV?

- HIV stands for Human Immunodeficiency Virus.
- It is classed as a retrovirus. This means that the virus uses the body's own cells to reproduce itself.
- While several theories exist, the origin of this virus is still unclear.

### How does the virus affect the body?

- The immune system of a healthy individual is able to fight infections from invading bacteria, viruses and diseases to which the body is exposed.
- HIV attacks the immune system thereby weakening it and making it vulnerable to infections.

### How does the virus work?

- The immune system consists of cells called T-helper cells that contain a protein called CD4.
- The virus enters the blood and gains access to the T-helper cells by attaching itself to the CD4. Once inside, the viral genetic material called RNA (ribonucleic acid) changes into viral DNA (deoxyribonucleic acid) by an enzyme called reverse transcriptase. The viral DNA becomes part of the human DNA, which, instead of producing more cells of its own type, starts producing HIV viruses.
- An enzyme called protease organizes the viral chemicals and a new virus is formed. This virus then exits the cell, killing it in the process, and floats freely in the bloodstream ready to infect another cell.
- The body responds to this invasion by creating more T-helper cells, thereby creating more cells for the virus to infect.
- The process takes time. Eventually, the immune system is too weak to fight infections that the body is exposed to.
- The normal range for CD4+T cells in a healthy person is 800-1200 cells per cubic milliliter of blood. When an HIV infected person's CD4+ T cell count falls below 200, he or she becomes increasingly vulnerable to [opportunistic infections](#).

### How is the virus transmitted?

- HIV is commonly spread through body fluids such as blood, semen, vaginal fluid, breast milk and other fluids containing blood.
- The virus is transmitted through the following ways: by having unprotected sex with an infected person. The virus can be transmitted through infected blood, by sharing needles with an infected person and also through blood transfusions (where the blood has not been screened for the virus). Pregnant women can also pass the virus to their babies during pregnancy or delivery as

well as through breast-feeding.

## What is AIDS?

- AIDS stands for Acquired Immune Deficiency Syndrome. A syndrome is a collection of symptoms and illnesses.
- When a person is infected with the virus, he is said to be HIV positive.
- This means that the person is carrying the HI virus and the process of immune system deterioration has begun.
- HIV/AIDS usually has a long incubation period. This means that a person may be infected for many years without showing any symptoms.
- HIV infection can, theoretically, be divided into 4 stages or phases:

### 1. **The primary HIV infection phase (or acute [sero-conversion](#) illness)**

This phase is characterized by infection of the virus or [sero-conversion](#). [Sero-conversion](#) usually occurs 4-8 weeks after infection with the HI virus. Some people experience flu-like symptoms such as sore throat, headache, mild fever, fatigue, muscle and joint pains, swelling of the lymph nodes, rash, and (occasionally) oral ulcers. These symptoms usually last for between one and two weeks.

### 2. **The asymptomatic latent phase**

In this phase, the person does not experience any symptoms, but the virus remains active. Infected people are usually not aware that they have the virus and may unwittingly infect others.

### 3. **The symptomatic stage**

In this phase, the person begins to experience symptoms. At first they appear to be mild e.g. Mild to moderate swelling of the lymph nodes in the neck, armpits and groin; Occasional fevers; Skin rashes and nail infections; Weight loss up to 10% of the person's usual body weight; General feelings of tiredness and not feeling well.

Later, major symptoms appear as the immune system deteriorates. At this stage the CD4 count is very low while the [viral load](#) is high. [Opportunistic infections](#) appear e.g. Oral and vaginal thrush infections which are very persistent and recurrent (Candida); Recurrent herpes infections such as cold sores (herpes simplex); Recurrent herpes zoster (or shingles); Night sweats; Persistent diarrhoea for more than a month; Weight loss (more than 10 percent of the usual body weight)

### 4. **AIDS-defining conditions**

It usually takes about 18 months for the symptomatic stage to develop into full-blown AIDS. At this stage the immune system is too weak to fight disease and [opportunistic infections](#). Symptoms become more acute and the person becomes infected by rare and

unusual organisms that do not usually respond to antibiotics.

A person in the final stage of AIDS typically has a very short time to live. They may be plagued by the following problems: Respiratory infections, persistent cough, chest pain and fever; Pneumonia, especially pneumocystis carinii pneumonia (PCP); Severe herpes zoster (shingles); Karposi's sarcoma; Lymphoma or cancer of the lymph nodes;

Tuberculosis is a very serious opportunistic infection which affects people with AIDS.

According to a UNAIDS Report (2000, c), up to 50 percent of HIV-infected individuals in Africa have active tuberculosis; Other sexually transmitted diseases.

### How is HIV/AIDS treated?

- Although there is no cure for HIV/AIDS, the disease can be managed by living a healthy lifestyle and using anti-HIV drugs. An HIV positive person may live with the disease for a long time.
- The primary method of treating HIV/AIDS is the use of drugs called anti-retrovirals (ARV's). These are potent drugs that slow down the growth of the HI virus in the body by inhibiting the two enzymes responsible for replication i.e. reverse transcriptase and protease.
- Experts recommend taking a cocktail of three or more ant-retroviral drugs known as Combination Therapy or Highly Active Anti-retroviral Therapy (HAART). Using Monotherapy (one drug only) may have short-term effects, but the virus quickly becomes resistant to it.

### How does ant-retroviral therapy work?

- As mentioned earlier, the HI virus enters the T-helper cell by attaching itself to the CD4 protein. Once inside, the reverse transcriptase enzyme changes the viral RNA into viral DNA that joins the human DNA. The cells now produce viral RNA that assembles and buds out of the host cell to form a new virus.
- Anti-retroviral drugs are classed in to 3 main groups:
  - Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI's). These drugs target the HIV protein reverse transcriptase preventing the translation of viral RNA into viral DNA (e.g. AZT, ddi, ddC & 3TC).
  - Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI's) also target the reverse transcriptase but in a slightly different way (e.g. Nevirapine, delavirdine and efavirenz).
  - Protease Inhibitors (PI's) targets the HIV protein Protease and blocks it so that a new virus cannot assemble in the host cell and be released.
- By slowing down the reproduction of HIV, these drugs help give the body a chance to build up it's CD4 count and thereby boosting the immune system.
- Because the HI virus replicates so rapidly, sometimes 'mistakes' are made in the process. These are called mutations. This means that the original virus may not be the same as the reproduced one.
- Because the anti-retroviral drugs target certain strains of HIV, other strains like the mutated ones, will not be affected by these drugs and they become drug resistant. They are also able to produce more strains that are unaffected by drugs

- It is therefore vital that the drugs be taken exactly as prescribed.
- Preventative measures can be taken to ensure that one is not infected with HIV e.g. safer sex i.e. using a condom during sexual intercourse, abstinence and being faithful to one partner.
- Research is currently being conducted by, among others, the South African AIDS Vaccine Initiative (SAAVI) into the developing of a vaccine for general use.

#### **Are there side effects to the drugs?**

- As with any drug, anti-retroviral drugs do cause certain side effects.
- Different people experience different effects and the degree to which it is tolerated or accepted varies from person to person.
- Possible side effects include: headaches; fever; fatigue; diarrhoea; vomiting; nausea; loss of appetite; abdominal pain; skin rashes; lactic acidosis; pancreatitis; anemia (decrease in red blood cells); hepatitis (inflammation of the liver).
- In general it is always best to be well informed and to consult a doctor when taking these drugs.

#### **How do I get tested for HIV?**

- The HIV antibody test is available free of charge at certain clinics and GP's.
- After infection, it may take up to three months for the HIV antibodies to be produced. So, if a person is concerned that they may be infected, they may only know after the three-month "window period".
- A person should receive pre and post test counseling testing procedure and the possible results are explained
- The most commonly used test is called the ELISA (enzyme-linked immunosorbent assay) test. This tests for the presence of antibodies (the immune system's response) to the HI virus.
- PCR (Polymerase Chain Reaction) tests for the presence of the virus itself, and can therefore be used from 2 weeks after infection. This test is available at the cost of approximately R350.00.
- Rapid Tests. Rapid HIV tests look for antibodies to the virus, but do not require specialized laboratory equipment. This makes it both cheaper and quicker than the ELISA.

#### **What is MTCT (Mother-to-child transmission)?**

- A pregnant mother can pass the HI virus to her unborn child. This is known as mother-to-child transmission (MTCT) or vertical transmission.
- Mother-to-child transmission is one of the major causes of HIV infection in children.
- The virus is transmitted in three ways: via the placenta during pregnancy; through blood

contamination during childbirth or through breastfeeding.

- The virus cannot be transferred directly from an infected father to the baby. The mother first has to be infected for it to transfer to the baby.

#### **Should HIV positive mothers breastfeed?**

- There is an ongoing debate about whether HIV positive mothers should breastfeed their babies.
- In Africa there are very complex factors to take into consideration, such as:
  - Mothers may not have access to clean and safe water supplies
  - Formula milk may not be accessible and is often too expensive
  - Mothers may not know how to safely prepare the formula
  - Mothers are often stigmatized for bottle-feeding
- In these cases, the World Health Organisation (WHO) recommends breastfeeding to prevent the baby dying from malnutrition or diarrhoea.

#### **Can MTCT be treated?**

- Anti-retroviral drugs such as AZT and Nevirapine can substantially reduce the chances of MTCT but is not a cure for the mother.
- The South African government has started two pilot sites per province and has been compelled by the High Court to implement a comprehensive programme for the prevention and treatment of MTCT.

#### **What about AIDS in South Africa?**

- The first recorded case of HIV in South Africa was in 1982. South Africa is currently one of the most severely affected countries in the world.
- It is therefore essential to effectively monitor the growth of this epidemic.
- The [national HIV prevalence](#) was first calculated in the 1990's using the Antenatal Survey. This is a mechanism developed by the Department of Health to monitor and research the growth of the epidemic. It involves a series of annual HIV surveys amongst women attending antenatal clinics in the public health sector. The survey uses pregnant women to gain estimates of HIV prevalence.
- According to the 2001 Antenatal Survey, it was estimated that 4.74 million people had been infected in South Africa.

- This type of survey does, however, have some limitations. For example, estimating national prevalence in the general population is difficult since the survey is limited to pregnant women.
- It is also difficult to draw conclusions about parts of the population that is not sexually active or those who have adopted prevention practices such as condom use.
- This presented a need for surveillance tool that presented a deeper understanding of the epidemic and which included behavioural patterns.
- In December 2002, the first independent and nationally representative study of HIV/AIDS was released.
- The study, commissioned by the Nelson Mandela Foundation and the Nelson Mandela Children's Fund and conducted by the Human Sciences Research Council (HSRC) in collaboration with the Medical Research Council (MRC) and the Centre for AIDS Development, Research and Evaluation sampled 9 963 people countrywide and included anonymous saliva-based HIV test from 8 840 participants.
- The study presented a national prevalence of 11.4% This means that 4.5 million people have been infected.

### What is Government's response to AIDS?

- The South African Government and civil society have been at odds about the provision of anti-retroviral drugs to the public, in particular, to mothers infected with HIV to prevent transmission to their unborn children.
- This tension has been worsened by the debate about the causal link between HIV and AIDS and our President's involvement with known dissidents in the scientific community.
- However, in a statement released in April 2002, Government stated its commitment to intensifying its campaign to prevent HIV infection. It was also stated that this campaign rests on the premise that HIV causes AIDS.
- Government's response included the development of the HIV/AIDS and STI Strategic plan for South Africa, 2000-2005.
- This is a broad national strategic plan that includes the following priority areas:
  - **Prevention**
    - Promoting public awareness and a safe and healthy lifestyle
    - The effective management of sexually transmitted diseases (STI's)
    - Reducing mother to child transmission
    - Providing adequate access to voluntary testing and counseling

- Providing post exposure services
  - **Treatment, care and support**
    - To provide adequate treatment, care and support in health facilities and communities
    - Work to lower the cost of anti-retroviral drugs and make it accessible
    - Improving the programme of home-based care
  - **Research, monitoring and surveillance**
    - Development of a vaccine
    - Conduct regular surveillance of the epidemic
  - **Human and legal rights**
    - Developing an adequate legal framework that ensures an appropriate social environment
- The problem of making antiretroviral drugs accessible to the public is further complicated by the patent protection.
  - The World Trade Organisation's agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) obliges all WTO member states to provide 20 years of patent protection for medicines.
  - This means that the production of [generic drugs](#) is prohibited during this period.
  - This agreement may only be overridden in a case of national emergency or in circumstances of extreme emergency.
  - TRIPS allows for the issuing of compulsory and voluntary licensing.
  - Voluntary licensing means that the government grants a production licence to a third company to produce the generic drug with the consent of the patent holder. The patent holder usually receives a token royalty.
  - With compulsory licensing, the production licence is granted without the consent of the patent holder.
  - The South African Patents Act provides for compulsory licensing in the event that the patent holder can be shown to abuse the patent.
  - In February 1998, a court action was instituted against the South African government by the Pharmaceutical Manufacturers Association (PMA) to defend the industry's patent rights.

- The action was aimed specifically at Section 15c of the Medicines and Related Substances Control Amendment Act, which allows government to purchase drugs from other countries where prices are lower, therefore allowing for parallel trading of those drugs with the local equivalent as well as compulsory licensing.
- The case was withdrawn in April 2001 due to international political and public pressure.
- In 2001 (month?) the Treatment Action Campaign (TAC) launched a legal appeal against government to provide the antiretroviral drug Nevirapine to pregnant HIV positive mothers to prevent mother to child transmission.
- In December 2001, the Pretoria High Court ruled in favour of the TAC and ordered the state to make Nevirapine available to women at public facilities that are not part of the existing pilot sites.
- The government lodged an appeal with the Constitutional Court stating that the judiciary could not issue orders concerning matters of government policy.
- The appeal was granted by the Pretoria High Court and in April 2002, the Constitutional Court issued an interim order that obliged government to provide Nevirapine in public facilities that had the capacity to administer it.
- This was followed by a rule in favour of the TAC.
- In a Cabinet Statement released in April 2002, government announced that it was intensifying the campaign against HIV/AIDS and its prevention.

### What is Post-Exposure Prophylaxis?

- Prophylaxis refers to disease prevention. Post-exposure prophylaxis (PEP) means taking anti-retroviral drugs directly after you have been exposed to stop the exposure leading to infection.
- PEP may be given in cases of needle stick injuries. This refers to health workers who accidentally prick themselves with needles containing contaminated blood.
- PEP may also be administered in the case of sexual assault.
- Currently the national protocol for administering prophylactic ARV's have been modeled on those administered for needle stick injuries. It is offered after survivors have been given comprehensive counseling as part of the existing service to rape survivors.

For more information on this topic, [search](#) this website for articles.

### Definitions

**Sero-conversion** refers to the moment the person's HIV status changes from negative to positive.

**Viral load** refers to the amount of free virus particles detected per milliliter of blood

**Opportunistic infections** refers to infections that leads to disease in people with a weakened immune

system

**National HIV** prevalence refers to the number of current cases per population at risk

**Generic drugs** are cheaper versions of the same drug.

## Basic Qs & As on AIDS Vaccine

### International AIDS Vaccine Initiative (IAVI)

<http://www.iavi.org/>

#### What is a vaccine?

A vaccine is a substance that teaches the body to recognise and defend itself against bacteria and viruses that cause disease. A vaccine causes a response from the immune system (the body's defence system), preparing it to fight--and also remembering how to fight--if exposed to the virus at a later time. A successful vaccine can cause the body to stop or disable an invading virus. A vaccine is not a cure, but prevents infection or slows down disease progression.

#### What is the history of vaccines?

The first modern vaccine was developed in 1796 by Edward Jenner to prevent smallpox. Through vaccination, smallpox, which at the time killed about a million people per year in Europe, has been eradicated. Now, there are also vaccines to prevent many other diseases, including rabies, tetanus, measles, mumps and polio. These vaccines save millions of lives.

#### Why an AIDS vaccine?

The 2002 report by the United Nations Programme on HIV/AIDS (UNAIDS), estimated that about 42 million people are living with HIV/AIDS worldwide, including 4,7 million South Africans (one in every nine). According to the Medical Research Council's (MRC) 2001 report, The Impact of HIV/AIDS on adult mortality, AIDS accounted for about 25 percent of all deaths in 2000 and was the leading cause of death in South Africa. Development of a vaccine is the only long-term hope to control the HIV epidemic. However, it must be part of an overall strategy that includes prevention, treatment, care and support.

#### How would an AIDS vaccine work?

An effective AIDS vaccine would teach the body to recognise the human immunodeficiency virus (HIV) that causes AIDS, and would boost the immune system in slowing and neutralizing the virus if it enters the body. The information on how to defeat the virus would then become part of the immune system's memory so that it would remember how to fight back if it encountered the virus again. An AIDS vaccine cannot cause a person to become infected with HIV.

#### Can an AIDS vaccine cause AIDS?

No, a vaccine cannot cause HIV infection or AIDS. AIDS vaccines do not contain any live virus that could spread and cause infection. AIDS vaccines generally contain only harmless particles or copies of particles of the virus, which cannot cause infection. A vaccine is a bit like a motor car with the engine removed – it is still recognisable as a car but it can't drive.

#### Is there a preventative AIDS vaccine available?

Currently, there is no effective AIDS vaccine available. However, there are several possible vaccines that may work and will be tested in clinical trials. Testing a vaccine takes a long time to ensure that it is safe and effective. It normally takes 10 to 20 years to bring a vaccine to the market.

## **How do you test an AIDS vaccine?**

Both vaccines and drugs are tested in stages taking a number of years. Initial laboratory work is followed by animal studies to establish overall safety and then human clinical trials. During the human trials the candidate AIDS vaccine is tested in volunteers to evaluate safety and establish effectiveness. There are three phases in these trials.

Phase I involves about a relatively small number of healthy, HIV-negative, adult volunteers at low risk of HIV infection and tests for safety. Phase II involves about 200 - 500 of healthy HIV-negative adult volunteers, some of whom are at higher risk of HIV infection and tests for safety, an immune system response, as well as early information on the required dose and route of administration. A Phase III trial involves several thousand adult volunteers at high risk of HIV infection to assess if the vaccine prevents infection with HIV.

All these phases usually make use of placebo groups – in other words, some of the participants receive a harmless substance that resembles the test vaccine. The 'placebo' group is then compared with the group that received the actual test vaccine. Use of placebo groups in Phase I and Phase II has nothing to do with protection. All volunteers receive extensive risk-reduction counselling throughout the trial and access to other prevention methods such as condoms.

## **Who participates?**

Only adult volunteers who meet the criteria outlined above and understand the study and agree to give informed consent can participate.

## **How are people's rights safeguarded?**

People's rights are safeguarded by:

- International guidelines for ethical vaccine and pharmaceutical trials;
- A sound constitutional and legal framework within South Africa;
- An independent system of ethical review based on ethical principles and guidelines for each trial site;
- Well-informed and mobilised communities that actively participate in the research;
- Ensuring 'informed consent'. This is the agreement free of coercion or undue influence, by volunteers to participate, based on a complete understanding of all the relevant information;
- Taking active steps to minimise potential harm to participants and to maximise the expected benefits of research;
- Ensuring that trial participants and research communities are chosen fairly;
- Employing competent and highly trained research staff; and,
- Protecting confidentiality.

## **What about vaccines in South Africa?**

There are a number of potential candidate vaccines in development in South Africa. As of 25 August this year, two vaccines have been approved for human trials. The IAVI MVA.HIVA trial is the second to be approved. The first was the AlphaVax AVX101 candidate vaccine, approved in June this year. Co-ordination of the development and testing of these candidate vaccines is the responsibility of the South African AIDS Vaccine Initiative (SAAVI). The Medicines Control Council

(MCC) must approve all vaccine trials and institutional ethics review boards.

### **Why an HIV/AIDS vaccine for South Africa?**

A vaccine that can prevent HIV/AIDS in South Africa is vital for reducing the country's incidence of HIV. Although it is important to develop vaccines based on the subtype C virus, the most common HIV subtype in South Africa, vaccines based on other subtypes could also be tested as they may offer protection and could help resolve the outstanding scientific issue regarding the significance of the HIV virus subtype, or "clade" in vaccine development.

### **Where will the vaccine trials be held?**

Two sites are ready to begin clinical trials - the AIDS Vaccine Division of the Perinatal HIV Research Unit (PHRU) of the University of the Witwatersrand at the Chris Hani Baragwanath Hospital in Johannesburg, and the SAAVI HIV Vaccine Research Unit at the MRC in Durban. Additional trial sites in other regions are in the early stages of development.

### **Why are these trials being done in South Africa?**

With South Africa's high rates of infection it is important to develop a vaccine that will work for the strains of the HIV virus circulating in the country. It is only possible to evaluate whether any candidate vaccines work in South Africa by testing them in South Africa.

### **What about vaccines in other countries?**

The International AIDS Vaccine Initiative (IAVI), the US National Institutes of Health (NIH), the European Union (EU), the Centres for Disease Control and Prevention (CDC) in the US, and others, all support the development of AIDS vaccines. Clinical trials are under way in countries including the US, Thailand, Britain, Kenya, Uganda, India, Botswana, Haiti, Brazil and Peru. Several pharmaceutical companies are also involved in vaccine development. International efforts are focusing on vaccines that will be inexpensive to make and easy to access by both rich and poor countries. International collaboration will ensure that breakthroughs are shared to speed up the development of an effective AIDS vaccine.

### **Why is it necessary to do many trials?**

As yet it isn't known which approach will provide an immune system response that is sufficient to protect against the virus – so many different approaches may need to be tested. The testing process takes a long time (at least 7 to 10 years for each candidate vaccine) so it makes sense to run trials of different vaccines at the same time to develop a successful vaccine as quickly as possible.

### **Why does it take so long to get to Phase III trials?**

Each phase involves monitoring the volunteers over a lengthy period. Until this has been completed, and the candidate vaccine has been shown to perform satisfactorily, a candidate cannot move on to the next trial phase.

### **In Phase III trials, will volunteers be injected with HIV to test the efficacy of the vaccine?**

Definitely not. At no stage are volunteers injected with anything other than synthetic copies of portions of genes, which cannot cause HIV or AIDS.

### **What is the quality of the research teams and the laboratory that will be analysing samples taken during these trials?**

The principal investigators (PIs) in charge of the Johannesburg and Durban validate trials units are highly respected, locally and internationally, for their work in this field. The South African Immunology Laboratory at the National Institute for Communicable Diseases in Johannesburg is a world-class and internationally validated facility, which is regularly audited by local and international organisations, to ensure it maintains this standard.

**Why must volunteers be HIV negative?**

A preventive vaccine is intended for people who are uninfected with HIV. Therefore the trials must be conducted among uninfected people.

**Why the focus on prevention and not a cure for HIV?**

Ultimately, a vaccine to prevent HIV infection represents the best hope for stopping AIDS. We are concentrating on vaccine research; other researchers will be seeking a cure. If we could stop new infections there would be fewer people needing treatment.

**Are the trials focusing only on black people?**

No, volunteers should reflect representative samples of the South African population. However, these are not exclusively South African trials-- they are part of a global effort to develop a vaccine against HIV/AIDS.

**Will there be enough volunteers for simultaneous trials?**

Each Phase 1 trial will enrol roughly 50 to 100 volunteers. More than enough candidate volunteers are ready. Both sites continue to interview and screen volunteers. If one site does not have sufficient volunteers, the number can be made up at the other site.

**How many volunteers can be expected to drop out of the trials?**

The interviews and counselling before the trials start are designed in part to ensure that volunteers will stay the course. While it is not unusual for a very small number not to drop out, in some trials there are no dropouts at all.

**How many volunteers are expected to contract HIV during these trials?**

Ideally, none. For the phase I trials, volunteers are healthy HIV-negative adults.

**If any do contract HIV during the trials, will they be provided with anti-retrovirals?**

Yes. The government of South Africa has recently established that participants in HIV vaccine trials who become HIV-infected during the period of the trial will be provided with anti-retrovirals. IAVI's own guidelines support provision of anti-retrovirals as one component of comprehensive care. The detailed policy is not yet available from the government, but from what we understand, it is similar to IAVI's own guidelines.