

HIV/AIDS Vax

AN IAVI REPORT BULLETIN

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VAX is a monthly bulletin featuring shorter, non-technical versions of articles from the *IAVI Report*, the newsletter on AIDS vaccine research published by the International AIDS Vaccine Initiative. VAX is currently available in English, French, Spanish and Portuguese as a pdf (www.iavi.org/iavireport) or an e-mail bulletin. If you would like to receive VAX by e-mail, please send a request including language preference to: VAX@iavi.org

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RESEARCH & TRIALS

◆ South Africa Approves Its First HIV Vaccine Trials

In June 2003 the South African Medicines Control Council (MCC) approved South Africa's first HIV vaccine trial (called HVTN 040). This trial will test an experimental vaccine known as AVX101, developed by AlphaVax in the US. HVTN 040 will be conducted by US and South African scientists in the US HIV Vaccine Trials Network (HVTN).

In August the MCC approved a second trial. This trial will use a vaccine known as HIVA.MVA that was designed by scientists at the University of Nairobi (Kenya) and the University of Oxford (UK). The study will be conducted by an international team sponsored by the International AIDS Vaccine Initiative (IAVI).

The AVX101 and HIVA.MVA trials are separate, but they will be conducted at the same South African sites: one in Soweto and the other in Durban. HVTN 040 will enroll a total of 96 volunteers in South Africa and the US and will study three different doses of the vaccine to look for safety and immune responses. Testing will begin in the US and proceed in South Africa once safety is established.

The IAVI-sponsored trial of HIVA.MVA is planned to take place at sites in South Africa and Europe and will enroll a total of 111 volunteers—including approximately 50 South Africans. The vaccine used in this trial is also being studied in Kenya, Uganda and the UK.

Each trial will test a different delivery system, or vector, for carrying very small portions of HIV. None of these fragments can cause HIV. The two trials use vaccines based on different HIV subtypes, or clades (see *Primer*). HIVA.MVA is based on clade A which is common in east Africa. AVX101 is based on

clade C which is most common in South Africa.

Both trials are scheduled to start in late 2003. South Africa joins three other African countries—Uganda, Kenya and Botswana—which have started trials or approved them this year.

■ *To find out about the South African AIDS Vaccine Initiative:*
<http://www.saavi.org.za>

◆ Ongoing Trials in Africa

Right now there are six approved or ongoing HIV vaccine trials in Africa. All of the current trials are early safety studies (called Phase I or Phase I/II). Such trials usually enroll less than 100 volunteers and monitor them for any side effects or negative reactions. These studies will not provide information about whether the vaccine protects against HIV. Larger trials (Phase III) are needed—usually with thousands of volunteers—to find out whether a vaccine can protect against HIV. Phase III trials are carried out once vaccine safety has been established.

The list below shows approved and ongoing African vaccine trials:

■ BOTSWANA

VACCINE (CLADE): EP HIV-1090 DNA (B)

SITES: Botswana (2), US (1)

TRIAL SPONSORS; MANUFACTURER:

HVTN; Epimmune (US)

STATUS: Ongoing

■ KENYA

VACCINE (CLADE): HIVA.DNA and/or HIVA.MVA (A)

SITES: Kenya (1), UK (1)

TRIAL SPONSORS; MANUFACTURER:

IAVI, Kenyan AIDS Vaccine Initiative Medical Research Council (UK); Cobra/IDT

STATUS: Ongoing

VACCINE (CLADE): HIVA.MVA (A)

SITES: Kenya (1)

A PUBLICATION OF THE IAVI REPORT

[The Newsletter of the International AIDS Vaccine Initiative]

TRIAL SPONSORS; MANUFACTURER: IAVI, Kenyan AIDS Vaccine Initiative, Medical Research Council (UK); Cobra/IDT
STATUS: Ongoing

■ SOUTH AFRICA

VACCINE (CLADE): AVX101 (C)
SITES: South Africa (2), US (4)
TRIAL SPONSORS; MANUFACTURER: HVTN; AlphaVax
STATUS: Approved

VACCINE (CLADE): HIVA.MVA (A)
SITES: South Africa (2), Europe
TRIAL SPONSORS; MANUFACTURER: IAVI; Cobra/IDT
STATUS: Approved

■ UGANDA

VACCINE (CLADE): HIVA.DNA and/or HIVA.MVA (A)
SITES: Uganda (1)
TRIAL SPONSORS; MANUFACTURER: IAVI, Uganda Virus Research Institute; Cobra/IDT
STATUS: Ongoing

■ **To download a poster of current ongoing HIV vaccine trials:**
<http://www.iavi.org/iavireport>

GLOBAL NEWS

◆ African AIDS Vaccine Programme Meets in Ethiopia

On 13-16 June 2003 nearly 200 scientists, trial investigators, national authorities and community representatives from Africa and other parts of the world gathered for the second meeting of the African AIDS Vaccine Programme (AAVP). The theme of the meeting was: "Strategies for the Development of HIV Vaccine Trial Sites in Africa: Challenges and Opportunities."

"AAVP represents a unique opportunity for African researchers to lead the continent in scientific advances. This meeting brings together many of the key players in AIDS vaccine research in Africa and around the world to share experiences and build a platform of accelerated action," said Pontiano

Kaleebu, vice-chairman of AAVP and a principal investigator of the IAVI-UVRI trial at the Uganda Virus Research Institute.

Many people at the meeting were talking about the new wave of vaccine trials in Africa (see *Research & Trials*). Crucial issues such as the medical care that should be given to trial volunteers and their communities, and the enrollment of women and adolescents were also discussed in detail.

There were also updates on AAVP activities. Since its founding in 2000, AAVP has helped to organize African laboratory trainings in techniques used in AIDS vaccine research; organized an active community task force; and developed a consensus document on clade (see *Spotlight*). In 2002, AAVP also assessed African ethics committees—panels that review proposed trials to ensure that they meet local and international ethical standards. Looking ahead, AAVP plans to develop guidelines for countries that want to develop a national plan to support AIDS vaccine development.

■ **To learn more about AAVP and download the AAVP newsletter:**
http://www.who.int/vaccine_research/diseases/hiv/aavp/en

SPOTLIGHT

◆ Do Clades Matter for HIV Vaccines?

HIV is the most genetically diverse virus known (see *Primer*). HIV is presently divided into nine distinct subtypes, or clades. Clades can be thought of as branches on a family tree. HIV is also one of the most rapidly changing viruses known today. High rates of **mutation** and **recombination** are constantly giving rise to new viral versions or 'strains.'

The broad diversity of HIV leads to one of the biggest scientific unknowns facing AIDS vaccine developers: Is a single "universal" vaccine against all versions of HIV possible? Or will it be necessary to

make many different vaccines, each tailored to the most common versions of HIV in a given region? Even worse, could it mean that a new vaccine might be needed every year, as with flu vaccines?

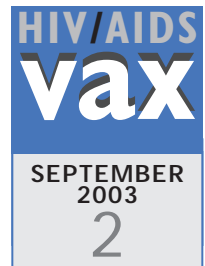
The answers to these questions will influence how quickly a successful AIDS vaccine can be found and distributed around the world. It will be a huge undertaking to manufacture and distribute a single approved vaccine. Doing it with many different vaccines, or again every year, could be a nightmare.

The issue of HIV diversity has also come up in planning vaccine trials. Clades are roughly grouped by geographic region. Trial sponsors, scientists and politicians have all asked whether it makes sense to conduct trials of vaccine candidates that do not match the host country's main clade.

Right now, there is no clear answer to the question: Do clades matter for HIV vaccines? One reason for this uncertainty is that the clade system (which is based on genetic sequences of the virus) is only one possible way of sorting viruses. Another option is to sort HIV versions by the immune responses that they cause. This approach is called organizing viruses by 'immunotype.' (Different versions of HIV cause different immune responses in people. These responses can temporarily control the virus which is why most people with HIV do not get sick right away.)

This approach could be important since immune responses are what really matter for vaccines. Vaccine educators in the fishing district of Rakai, Uganda use this explanation: A range of nets is used to catch different species of fish, according to their size. Grouping fish (viruses) by their color (clade) does not always give information about the best net (vaccine) to catch them.

There are other obstacles to answering the diversity question.



New approaches for **sequencing** the genes of HIV have helped uncover aspects of viral diversity beyond the broad categories of clade. For example, there are parts of the world where the most common virus is a recombinant strain—a genetic patchwork of two different clades. Ongoing studies in Tanzania are looking closely at viruses isolated from highly-exposed women bar workers. Researchers Francine McCutchan (Henry M. Jackson Foundation, US) and Michael Hoelscher (University of Munich, Germany) are finding that many women carry new recombinant viruses. Some of these women seem to have been infected with more than one clade.

So how can the world find out whether or not clade—or other forms of viral diversity—matters for vaccines? In practice, it will mean studying the same vaccine in clade-matched and -unmatched settings, to see if there are differences in protection. This is the only way to definitively resolve the issue.

But there are also clues to gather along the way. For instance, scientists are testing the ability of vaccine-generated immune responses to “recognize” fragments of viruses from other clades. To do this scientists collect blood samples containing immune responses from trial volunteers who have been given an experimental HIV vaccine based on a particular clade. Then in a lab these immune responses are exposed to pieces of viruses from other clades and the immune activity is measured. (Similar experiments have been done using samples from HIV-infected individuals.)

Using these techniques, scientists are finding some reasons for hope: vaccine-induced responses frequently recognize at least some versions of HIV from other clades—although the activity is different to that seen against the matched clade. So far this has been seen with one

arm of the immune system (cellular immune responses) but not with the other (antibodies).

These data are encouraging to some. But many questions remain: Will cross-clade responses observed in labs translate into cross-clade protection in the real world? Are there other ways to group viruses that should be investigated? What is the best way to choose viral fragments, or ‘immunogens,’ for vaccines that will provide broad protection against diverse versions of HIV?

Perhaps most importantly, will countries and regions be open to testing vaccines which are not based on the local clade (un-matched) as well as ones that are based on the local clade (matched)? Here things look positive. Africa has several clinical trials underway, including some unmatched ones. These trials could help move the world closer to an answer to the clade question in the next few years. The African AIDS Vaccine Programme (see *Global News*) recently released a document recommending a combination of matched and un-matched trials in Africa. “I see a major shift,” says Jose Esparza, coordinator of the WHO-UNAIDS HIV Vaccine Initiative. “There is widespread recognition across Africa that the question of diversity needs to be rigorously tested through well-designed clinical trials in matched and unmatched settings.”

Mutation: A change in genetic material. This may occur at a single point (an individual nucleotide) or it may involve a partial loss or gain of stretches of genetic material.

Recombination: A process by which pieces of genetic material from two different sources are joined (spliced) together

Sequencing: The process of “reading” genetic material, which is composed of building blocks called nucleotides. Sequencing reveals the order of nucleotides in a given chain and shows the genetic “fingerprint” of the virus.

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

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

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

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

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

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

HIV diversity is still increasing due to several processes. One process is called mutation. HIV reproduces (or replicates) in an

infected person by making more copies of its genome. When it copies itself it frequently makes errors, called mutations. Mutations are the main reason why each person's viral population is slightly different, even from the HIV that he or she was originally infected with.

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

A problem for vaccines?

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

or disease if the person is later exposed to the complete virus [HIV].

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

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

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

PRIMER UNDERSTANDING viral DIVERSITY