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

NOVEMBER 2003
Vol.1 ■ Num.4

In this issue

RESEARCH & TRIALS

◆ Two AIDS Vaccine Trials Start in South Africa

In November a Catholic priest from Pretoria and a 32-year old mother of two from Soweto were the first volunteers immunized in South Africa's first AIDS vaccine trials. One trial is co-sponsored by the International AIDS Vaccine Initiative, the other by the US HIV Vaccine Trials Network. Both trials are coordinated by the South African AIDS Vaccine Initiative (SAAVI). South Africa is the first African country to launch two AIDS vaccine trials of different candidates in the same month—a step that signals the country's strong commitment to AIDS vaccine research.

The IAVI co-sponsored trial will test a candidate called HIVA.MVA in South Africa and Switzerland. The HVTN co-sponsored trial will test a candidate called AVX101 in South Africa and the United States. For more details on the vaccine candidates tested in these trials see the September 2003 issue of *VAX* at www.iavi.org/iavireport.

■ *For press releases about these trials visit the SAAVI website:* www.saavi.org.za

◆ VaxGen Releases Results of Thai Phase III Trial

On 12 November the VaxGen company announced the results of the second Phase III trial of its vaccine candidate AIDSVAX, which was designed to protect HIV-negative people from HIV infection and disease. The company said that the vaccine offered no protection in a study of 2546 intravenous drug users (IDUs) in Thailand. A **Phase III trial** of a very similar version of AIDSVAX took place in 5417 homosexual men and high risk women from North America and Europe. Results from this trial were released earlier this year and also showed that the vaccine gave no overall protection.

Although the scientific results were negative there were positive lessons from the Thai trial. The vaccine was safe and did not cause any serious side effects. Importantly, volunteers did not report increased rates of high-risk behavior. One concern for AIDS vaccine trials is that volunteers might assume that they have received an effective vaccine and so increase high-risk behavior—even though during the trial they receive ongoing counseling that there is no way of knowing whether they have been given an effective vaccine and that they should not assume that they are protected from HIV infection. The Thai trial also showed that IDUs can be reliable participants in lengthy vaccine trials; more than 90 percent of the original participants completed the 3-year trial.

The November announcement of the Thai trial data did not mention VaxGen's earlier claims of race- and gender-based effects. In February when the company announced the data from its first Phase III trial it claimed that there were signs of different levels of protection in non-white populations (African-Americans, Hispanics, Asians and others) as compared to whites, and in women as compared to men. Since then, additional data analysis has not produced any evidence to support these claims.

Phase III vaccine trial: *A large study that is designed to determine the ability of a vaccine to protect against HIV infection or disease. Phase III trials usually include hundreds or thousands of volunteers and can also gather additional information about safety needed to evaluate the overall benefits and risks of the vaccine.*

◆ Prime-Boost Trial Begins in Thailand

Thailand began immunizations for its second Phase III AIDS vaccine trial on 20 October. This study will test a combination of two vaccines called ALVAC and AIDSVAX in about 16,000 HIV-negative people who will be followed for approximately three and a half years. Trial co-sponsors include US Military HIV Research Program and Mahidol University in Thailand. The trial will take place in 8 districts in Thailand.

ALVAC vCP1521 is a candidate that combines small fragments of HIV genetic material with a virus called canarypox that normally infects birds. Previous trials have shown that canarypox-based vaccines are safe for use in humans. The AIDSVAX candidate has been tested alone in two large-scale trials (see above) but has not shown any protection. Sponsors say that the current trial is still going ahead because it is possible that the vaccines will provide some protection when used in combination.

■ *To learn more about the US Military HIV Research Program:* www.hivresearch.org
■ *To learn more about the Thai trial:* www.primeboostphase3-thailand.org/index_eng.html

GLOBAL NEWS

◆ German Research Institute Holds AIDS Vaccine Conference

On 21-22 October the Robert Koch Institut (RKI) in Berlin hosted a scientific symposium on AIDS vaccine development and innovative therapy concepts. Conference sessions included panels on current AIDS vaccine strategies and AIDS vaccine development from laboratory studies to trials in humans. In the opening sessions, RKI president Reinhard Kurth called for increased funding for AIDS research in Germany and called the epidemic "the biggest medical catastrophe in our time." Germany now spends 7 million euros annually on AIDS vaccine research. German regulatory authorities are currently reviewing a proposal for an IAVI co-sponsored trial of a vaccine called recombinant adeno-associated virus (rAAV), which combines a safe form of a virus called parvovirus with fragments of HIV genes.

SPOTLIGHT

◆ Health Care for Vaccine Trial Volunteers

AIDS vaccines cannot cause HIV infection and all AIDS vaccine trial volunteers are HIV negative at the start of the trial. These volunteers receive condoms and HIV prevention counseling throughout the trial. However, some volunteers will still be exposed to HIV, for example through sex with a spouse or casual partner who is HIV positive. This means that in almost every large-scale AIDS vaccine trial some volunteers will become infected with HIV through high-risk behavior.

Since the majority of large-scale AIDS vaccine trials are planned for the developing world, many volunteers who become infected with HIV are likely to live in places where ordinary health care is quite basic, and where HIV positive people usually cannot obtain antiretroviral drugs (ARVs), the powerful medications that can help control HIV infection. While vaccine trial sponsors feel that everyone with HIV should receive ARVs when needed, they are generally unable to provide them to entire communities since such broad health care can exceed the budget of a single AIDS vaccine trial. This leads to a dilemma about whether trial sponsors should pay for ARVs for trial volunteers who become infected with HIV through high-risk behavior, even if they cannot provide ARVs for other community members with HIV.

All AIDS vaccine trials provide a package of health care services to volunteers. This includes voluntary counseling and testing for HIV, prevention counseling, condoms, and treatments for common illnesses such as sexually transmitted diseases (other than HIV) and malaria. In the past ARVs have not been included in this package. One reason for this is that AIDS vaccine trial volunteers are healthy and HIV negative, so trial health services focus on prevention through counseling, condom distribution and other strategies. Volunteers are also counseled that there is no way of knowing whether the experimental vaccine will provide any protection against HIV. All volunteers are also told that some of them will receive the vaccine and some will receive a placebo (inactive substance), and that neither the volunteers nor the trial staff will know which substance has been given to the volunteers. In spite of such counseling and services a small percentage of volunteers who are HIV negative at the beginning of the trial will become HIV infected through high-risk behavior during the trial.

Until recently, sponsors have chosen not to provide ARVs as part of vaccine trial health care, largely because of the cost of the medications and the inequalities that would be created in a community where some people (trial volunteers) had access to ARVs and others did not. In some cases people might decide to volunteer for the trial to receive ARVs that they could not obtain any other way. This may be less likely with an AIDS vaccine trial since volunteers find out that they are HIV negative (and so do not need ARVs) during the initial screening visits for the trial. These considerations are weighed by regulatory committees during the trial review process (see ***Primer***). These committees ensure that the package of care and benefits are fair but do not have an inappropriate or 'undue' influence on a volunteer's decision to participate.

Today standards for HIV care in developing countries are starting to change. Since 2000 the cost of ARVs has fallen sharply and many countries are developing national plans for introducing these medications. The four African countries with ongoing vaccine trials—Botswana, Kenya,

Uganda and South Africa—all have national plans to expand access to ARVs through government programs.

These changes have led AIDS vaccine trial sponsors to re-examine whether or not ARVs should be part of trial-sponsored health care for volunteers. In 2003 several major sponsors decided to add ARVs to the care provided for persons who become infected with HIV through high-risk behavior while participating in AIDS vaccine trials.

The sponsors who have made this decision include the International AIDS Vaccine Initiative (IAVI), the HIV Vaccine Trials Network (HVTN), the South African AIDS Vaccine Initiative (SAAVI) and the US Military HIV Research Program. Each sponsor has developed a slightly different policy. IAVI, the HVTN, and SAAVI have all committed to ensuring payment for ARVs for a specified time period (generally 5 to 10 years) starting from whenever the volunteer starts treatment (this decision is based on medical measurements of disease, including CD4 cell count and viral load testing, and on the volunteer's desire to take the medications). The US Military HIV Research Program hopes to raise funds so that it can treat vaccine trial volunteers and surrounding community members for life.

Leaders of these organizations say that they have decided to provide ARVs partly because these drugs are becoming more widely available in resource-poor settings. This makes it less likely that trial-sponsored ARVs will have an undue influence on individuals' decisions about whether or not to volunteer for the trial.

Sponsors also point out that today's vaccine candidates may not provide complete protection against HIV. Instead, it is possible that vaccinated volunteers who become infected with HIV through high-risk behavior will have less severe disease and live longer than volunteers who receive the placebo and become HIV-infected via high-risk behavior.

AIDS vaccine researchers plan to look for this type of vaccine effect by studying volunteers who receive either the vaccine or the placebo and go on to become HIV infected through high-risk behavior during trials. These volunteers will be followed closely to see if the experimental vaccine protects against AIDS-related illness and disease. Trials will also observe when these volunteers need to start taking ARVs based on current medical guidelines, and whether volunteers who receive the vaccine are able to delay starting treatment compared to those who receive the placebo. Sponsors feel that these volunteers are making significant contributions to research and that it is important to ensure that they receive ARVs when needed.

Now that many trial sponsors have made commitments to provide ARVs they must figure out how to put these policies into action. One challenge is that volunteers may not become eligible for treatment until several years after the trial is over. People with HIV can remain healthy without ARVs for several years following infection. By the time some volunteers are ready to begin treatment the trial will most likely be over and the trial sponsor may not have continued to work in the country.

As a solution to this, IAVI, SAAVI and the HVTN have all agreed to ensure that funds will be available to pay for volunteers' treatment in the future. These funds will be available when a volunteer needs to begin treatment and could be used to pay for care through local or national programs. There are different models for how the funds will be managed. In South Africa, for example, the funds will be given to a health insurance company that will pay the volunteers' chosen doctors.

Another challenge is deciding how long sponsors should pay for ARVs. So far only one sponsor, the US Military HIV Research Program, plans to pay for treatment for life and this program has yet to raise the funds needed to meet this goal. Other sponsors have agreed to pay for ARVs for five to ten years. The hope is that by the time the sponsor-funded treatment is finished the host country will have an expanded national ARV program, so that volunteers can continue treatment at little or no cost.

There are also concerns about the care that will be offered to people who are screened during the enrollment process for the trial but are found to be HIV positive. Since these people cannot enroll in the trials (AIDS vaccine trial volunteers must be HIV negative) they are not eligible for care from the sponsor under most current policies. In most trials these people will be referred to existing health care services including clinics and support groups. Many sponsors are working with these local groups to help strengthen their ability to provide needed services.

In the coming months and years the new policies will be discussed and tested in different countries. Sponsors say that the exact details of the policies will be developed in consultation with local groups, and will depend on local and national plans for expanding ARV access.

EDITORS **Emily Bass, Simon Noble**

PRODUCTION **Michael Hariton**

DESIGNER **DESIGNdeFrancesco.com**

All articles in this issue of *VAX* are by Emily Bass.

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International AIDS Vaccine Initiative

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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.

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

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OFFICIAL APPROVAL

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

Who is involved in the official approval process?

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

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

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

What trial materials are reviewed?

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

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

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

When can a trial begin?

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

PRIMER
UNDERSTANDING
trial
APPROVAL

What happens once a trial has started?

After an AIDS vaccine trial begins, ERCs, IRBs and other groups receive regular updates that allow them to determine whether the trial is safe and ethical and that trial sponsors are fulfilling their obligations to participants. These committees also have the power to stop the trial if there are any concerns for safety or if the trial is not being conducted ethically.

BUILDING COMMUNITY SUPPORT

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

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

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

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