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Spotlight

AIDS vaccine researchers find promise

Recent data from clinical trials and shared lessons on recruitment and retention of volunteers highlight annual AIDS vaccines meeting.

At the closing session of the AIDS Vaccine 2005 meeting in Montreal researchers summarized the state of the field and outlined the possibilities and problems that scientists, ethicists, and policy makers will face in the coming year. Many obstacles remain to the development of an effective AIDS vaccine, but during this year's annual conference the researchers who gathered received a promising report on the field. After four days of presentations that highlighted the advancements regarding clinical trials, the development of novel vaccine vectors, and the strategies for recruiting and educating trial volunteers, the speakers summarizing the meeting struck an optimistic tone.

One of these speakers, Lawrence Corey of the HIV Vaccine Trials Network (HVTN), predicted that the next year would bring substantial data on vaccines that induce cell-mediated immunity, the major focus of many of the current candidates in clinical trials. He also emphasized the importance of researchers working with and gaining the support of affected communities, as their involvement will continue to be critical. And as the annual meeting heads for European soil—in 2006 it will take place in Amsterdam—the research community began discussions about some of the remaining ethical dilemmas surrounding the design of clinical trials, including the need to evaluate AIDS vaccines in adolescent volunteers.

Clinical results

The Vaccine Research Center (VRC) at the US National Institutes of Health has tested a series of DNA vaccines developed in partnership with the biotechnology company Vical in Phase I clinical trials. Volunteers in one of these trials, VRC 004, received a DNA-based vaccine containing copies of four HIV genes from multiple subtypes, including those that are most prevalent in Africa and parts of Asia. These volunteers were later enrolled into trial VRC 009 where they received a second inoculation, known as a boost, with a different candidate that used an adenovirus as a vector to deliver HIV fragments to the immune system. The adenovirus vaccine was developed in partnership with the company GenVec. The natural form of this adenovirus vector can cause respiratory infections, including the common cold, but neither the DNA nor the adenovirus candidate used in this trial can cause HIV infection.

Barney Graham of the VRC presented the impressive results of VRC 009 in Montreal. Researchers observed that after receiving both vaccine components volunteers had a 10-20 times stronger antibody response than was induced by the DNA candidate alone. Graham also reported that cellular immune responses ($CD8^+$ T cells) after boosting were comparable to those seen in people who are HIV infected but do not progress to AIDS within the average time-span, a group known as long term nonprogressors.

Because the VRC 009 trial enrolled volunteers from a previous trial there was a longer than normal period between the prime and boost inoculations. Graham speculated that this 2-year gap could be partially responsible for the strong results. "The long boosting interval probably does play a role in the improved immune response," Graham said at the meeting. He did acknowledge that this represents an impractical vaccination schedule, but said that these results argued for further testing of this approach with a more typical vaccination schedule.

This additional testing is now in progress and the VRC and HVTN just recently started enrolling 480 volunteers for a Phase II trial of this DNA/Ad5 combination vaccine to assess both its safety and immunogenicity (see *VRC starts Phase II vaccine trial*, this issue).

Promising news was also reported from another adenovirus-based vaccine developed by Merck. The company recently decided to increase enrollment in its Phase IIb 'test of concept' trial with the MRKAd5 candidate and the rationale for this decision was presented at the conference by Robin Isaacs of Merck (see *Merck and HVTN*

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expand Phase IIb trial, this issue). He also reported that approximately 1,200 volunteers have received the Ad5 candidate so far in all clinical trials and that the only side-effects observed are injection site reactions and fever after initial dosing. Results of this Phase IIb study are not expected until 2008. In the meantime Merck continues to look at other strains or serotypes of adenovirus, including Ad6, in order to broaden the immunogenicity of the vaccine and find what he refers to as the "ultimate" adenovirus-based vector.

As promise of the adenovirus-based vaccines continues to grow, others continue the search for novel viral vectors. The pharmaceutical company Wyeth has been working on vesicular stomatitis virus (VSV) as a potential vector for several years. This virus has proven a potent delivery system for other diseases in laboratory and animal experiments.

At the conference Stephen Udem, vice president of viral vaccine research at Wyeth, presented much of the company's work on preparing these vectors for Phase I clinical trials. This work involved improving the safety of the vector while retaining its immunogenicity. Udem says the approach is "well regarded" by the US Food and Drug Administration and he predicts the VSV-based AIDS vaccine candidate could be in clinical trials within a year. The agency is currently in the process of reviewing the company's application to begin Phase I trials. "It's a remarkably effective agent," he says, and although he is continually surprised by the ability of HIV to escape the immune system, he is equally impressed by VSV as a vector.

Learning from experience

Another important focus of the AIDS vaccine meeting was the need to continue optimizing the design of vaccine trials, including ways to include more women volunteers. Several presentations in Montreal highlighted the experiences of researchers at trial sites, bringing to light some of the progress and problems in enrolling volunteers for ongoing trials or cohort studies.

Stephen Mawa of Makerere University and the Walter Reed Project in Kampala, Uganda presented on the experience of recruiting for a Phase I trial in 2004 with the VRC's DNA candidate (VRC 009). The trial site staff conducted more than 20 informative seminars for both community leaders and the general public—each attended by as many as 100 people—as well as using newspaper and radio advertisements to recruit potential volunteers. In total the site directly interacted with more than 4,000 people and although several hundred women were screened, only a few were enrolled.

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Despite these extensive outreach efforts the majority of volunteers reported hearing about the study from friends. Mawa emphasized the need to engage in continuous AIDS vaccine advocacy and education since "word of mouth" will likely be an important recruitment tool in the future.

Sanjay Mehendale of the National AIDS Research Institute in Pune, India, where the country's first AIDS vaccine trial began earlier this year, presented more encouraging news on recruiting women for this Phase I vaccine trial. Preparations included sensitizing the trial staff about the need to recruit women, conducting meetings with local women's groups, as well as training the staff on gender-related issues that could affect participation. The IAVI-sponsored Phase I study enrolled 11 male and 9 female volunteers to receive either the low- or medium-level doses of the adeno-associated virus based vaccine called tgAAC09.

But getting this many female volunteers was not easy. To enroll just 9 women the site staff had to screen five times that number, illustrating that significant screening resources may be necessary if investigators are to recruit a balanced number of women in larger Phase II or III clinical trials in this country.

In preparation for such trials Projet San Francisco (PSF), a research group founded in Rwanda in 1986 by Susan Allen of Emory University, has been working extensively with African couples, including discordant couples where one partner is HIV infected and the other is uninfected. The PSF sites have been successful at bringing women into clinics for HIV counseling and testing and possible enrollment in a vaccine trial (see *Primer*, this issue) and now represent the world's largest cohorts of HIV serodiscordant couples.

More than 20,000 couples have been screened at one of PSF's sites in Kigali, Rwanda over the past 3 years, 950 of whom have been identified as serodiscordant, according to a presentation by Erin Shutes who works at this site. The retention rates for these couples cohorts are around 90% through one year, offering a unique opportunity for investigators to reach potential female volunteers for vaccine trials. The researchers in Kigali are now preparing for a Phase I vaccine trial that will commence later this year pending final regulatory approval (see *VRC starts Phase II vaccine trial*, this issue).

Beyond the strategies for recruiting female volunteers, researchers within the AIDS vaccine community are also starting to consider evaluating promising candidates in adolescent volunteers. The inclusion of adolescents in AIDS vaccine trials brings up several ethical questions including informed consent, and will be an important issue for debate and discussion in the coming years. The Montreal meeting pro-

vided merely the background for what will be a thorny issue in AIDS vaccine research, but as Glenda Gray of the University of Witswatersand reminded researchers, "HIV prevalence among adolescents in South Africa is horrific and excluding them from efficacy trials is a big mistake."

Global News

Merck and HVTN expand Phase IIb trial

Enrollment in Merck's ongoing Phase IIb AIDS vaccine trial with the MRKAd5 vaccine candidate has been expanded to include double the number of volunteers researchers originally planned at sites in North America, South America and the Caribbean. The test of concept trial (see September *Primer* on *Understanding Test of Concept Trials*) started in January of this year and is a collaboration between Merck, the HIV Vaccine Trials Network (HVTN), and the National Institute of Allergy and Infectious Diseases. Final results are not due until 2008 on the vaccine candidate that uses a viral vector to carry three copies of HIV genes to the immune system.

MRKAd5 has previously generated strong cellular immune responses in humans. But because it uses Ad5, a naturally circulating strain or serotype of the virus that can cause the common cold, researchers thought it might be ineffective in those who have already developed adenovirus-directed immunity (see February *Primer* on *Understanding Pre-existing Immunity*). However, the results of studies now completed show that MRKAd5 is able to generate immune responses even in volunteers with high levels of pre-existing immunity to Ad5, leading the company to expand the trial to include 1,500 additional volunteers that have high levels of Ad5 antibodies at the start of the trial.

"We have found that the vaccine candidate consistently produces a detectable immune response in 60-70% of people," says Robin Isaacs, executive director of vaccine research at Merck. "If we continue to find that people with high Ad5 antibody levels have a good response to the vaccine then it may make the candidate vaccine useful for a larger number of people."

VRC starts Phase II vaccine trial

The Vaccine Research Center (VRC) and HVTN have also started a Phase II clinical trial with a two-part vaccine including a DNA-based vaccine candidate followed by a boost with an adenovirus serotype 5 vector. This vaccine candidate differs from the ongoing Phase IIb Merck trial (see above) because it uses a different version of the Ad5-based vaccine candidate and also first uses a DNA vaccination to prime the immune system. The VRC has observed an improved response when the DNA vaccine candidate and Ad5 are administered in a prime/boost manner (see *Spotlight*, this issue).

This study, HVTN 204, seeks to enroll 480 volunteers at sites in North and South America, Africa, and the Caribbean in order to determine the safety and level of immune responses generated by the candidate as compared to an inactive substance known as placebo. Volunteers that are randomly selected to receive the DNA/Ad5 candidate will receive 3 injections of the DNA and a single Ad5 boost over a period of 6 months. Half of the trial participants will be enrolled at HVTN sites in the Americas as well as in Haiti and Jamaica, while the other half will be at sites in South Africa and Botswana.

This vaccine is the first developed at the VRC to move into the second stage of clinical testing. The US-based company Vical is manufacturing the DNA portion of the vaccine and the adenovirus vector was developed by the VRC in collaboration with GenVec. The DNA/Ad5 candidate includes HIV genes from subtype A and C, which are the most prevalent forms of the virus in Africa and parts of Asia. Volunteers can not become HIV infected from this vaccine candidate.

This same candidate will be evaluated further in a series of Phase I and II clinical trials in Africa in cooperation with IAVI and the US Military HIV Research Program, pending regulatory approvals in these countries.

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Editor
Simon Noble, PhD

Senior Science Writer
Philip Cohen, PhD

Science Writer
Kristen Jill Kresge

All articles written by Kristen Jill Kresge.

VAX is a project managed by Kristen Jill Kresge.

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International AIDS Vaccine Initiative

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IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 23 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it.

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

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 April *Primer* on *Understanding Research Voluntary Counseling and Testing*). 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 June *Primer* on *Understanding Informed Consent*), 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 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 partner'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 (see *Spotlight*, this issue). 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 1,500 women that were seen at the Kigali center, 1,000 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.