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).
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.

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-
VAX is a project managed by Kristen Jill Kresge.

VAX is a monthly bulletin from IAVI Report, the newsletter on AIDS vaccine research published by the International AIDS Vaccine Initiative (IAVI). It is currently available in English, French, German, Spanish and Portuguese as a downloadable pdf file (www.iavinreport.org) 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

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.

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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.