April 2006 • Vol.4 • No.4

VAX

AIDS VACCINE BULLETIN • WWW.IAVIREPORT.ORG

Spotlight

Clinical trials march on

AIDS vaccine researchers provide clinical updates and details on planned trials

The Keystone symposium on HIV Vaccines is a major meeting on the calendar of HIV researchers from various scientific disciplines. For one week each year it offers them a chance to share ideas, discuss, and often debate, their work. A practical and crucial part of this work is the progress made in conducting clinical trials with AIDS vaccine candidates to test their safety, immunogenicity, and possible efficacy. This year's Keystone meeting provided a comprehensive roundup of ongoing AIDS vaccine trials and related activities and showcased the work of several collaborating organizations that are expanding existing trials or unveiling plans for new ones.

Trial partnerships

Barney Graham of the Vaccine Research Center (VRC) at the US National Institutes of Health (NIH) kicked off this series of updates with a look at a series of ongoing trials with their lead vaccine candidates—a DNA plasmid vaccine and an adenovirus serotype 5 (Ad5)-based vaccine containing fragments of HIV's genetic material from multiple virus clades—administered sequentially in a "prime-boost" manner. These candidates entered Phase II testing late last year and are now in ongoing clinical trials in several countries in partnership with the HIV Vaccine Trials Network (HVTN), IAVI, and the Walter Reed Army Institute of Research (WRAIR; see *VAX* October 2005 *Global News*).

Both WRAIR and IAVI are testing these candidates in four east African countries. WRAIR and partners recently began recruitment at their sites in Kampala, Uganda and Kericho, Kenya, and enrollment will begin in May at another site in Tanzania, according to an update provided by Nelson Michael of WRAIR. His organization has been working in Tanzania on a three year study to measure HIV incidence there. The trial staff at both of the IAVI trial sites in Kigali, Rwanda and Nairobi, Kenya is now preparing to increase the total number of volunteers receiving these candidates (see *Global News*, this issue).

Another trial WRAIR is conducting in partnership with the VRC is in Kampala, Uganda and involves giving 31 volunteers, who have already received the VRC's DNA candidate in a previously completed trial, a booster vaccination with the Ad5 candidate. Results from a series of completed Phase I trials suggest that administering these candidates as a prime and boost is a more effective way of inducing strong immune responses.

These immune responses may face an even greater test soon in a preliminary efficacy trial involving thousands of volunteers. Preparations for a Phase IIb "test of concept" trial are now underway for the VRC's DNA/Ad5 candidate and Michael says WRAIR sites in Uganda, Kenya, and Tanzania are beginning preparations for this larger trial.

An important consideration for this and other larger trials will be the criteria used to determine if healthy, HIV-uninfected volunteers can participate. For the initial WRAIR trial with the VRC's DNA candidate alone (RV 156), 223 potential volunteers were screened to enroll just 31. Michael said many individuals were excluded from the trial because their results from general laboratory tests, including blood tests, differed significantly from the standard reference ranges used to determine trial eligibility. But these ranges were mostly developed based on North American or European populations, where the average background health of individuals differs significantly from that in developing countries where sanitation standards are not as high and there is increased exposure to pathogenic bacteria and viruses. Michael concluded that many eligible people were unnecessarily prevented from joining this trial. He therefore suggested that studies should be conducted to determine relevant reference ranges in the populations where vaccines will be tested to help alleviate this problem in future vaccine trials.

Michael also reported on the progress of other trials at the WRAIR. Enrollment is now complete in the only ongoing Phase III trial, taking place in Thailand, evaluating the efficacy of a prime-boost administration of two vaccine candidates: the ALVAC canarypox vaccine and the VaxGen gp120 vaccine, the latter having already been tested in a pre-

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vious efficacy trial. The final round of immunizations with this combination will occur in July and volunteers will be followed for an additional three years.

A hard look at MVA

Michael also reported on a series of clinical trials planned by WRAIR to test other prime-boost regimens. Many of these will involve using different DNA constructs developed by other groups as a prime, followed by a booster vaccination with a modified vaccinia Ankara (MVA) vaccine candidate that was developed by WRAIR and the NIH. These trials will take place at WRAIR sites in the US, Thailand, and Africa. The results from an already ongoing Phase I trial with WRAIR's MVA vaccine candidate will be presented later this year at the 2006 AIDS vaccine meeting in Amsterdam.

In the meantime, this same candidate is also being evaluated in another series of clinical trials at the Karolinska Institute in Stockholm, Sweden. These Phase I trials are designed to compare the safety and immunogenicity of either intramuscular or intradermal injections of a DNA plasmid vaccine candidate developed at the Swedish Institute for Infectious Disease Control, followed by a boost with WRAIR's MVA vaccine candidate. The 40 participants receive either three DNA immunizations followed by a single MVA boost, or an inert substance known as placebo.

The final volunteer in this trial will complete the vaccination schedule in May and Eric Sandström, a researcher at the Karolinska Institute, says results on these candidates will also be presented in Amsterdam. "We look forward to a very pleasant presentation," he says, modestly hinting at the results. Previous clinical trials with MVA-based vaccine candidates have produced disappointing results but Sandström suggests this combination may be different. "Both immunizations have been safe and well tolerated and, compared to published results on this approach, we are encouraged by the data."

Sandström and his colleagues in Tanzania, Sweden, Germany, South Africa, and the US are also starting a trial with the same vaccines in 60 volunteers in Dar es Salaam, Tanzania, once final approval from the local authorities is received.

IIb take II

Detailed plans for another new trial were also presented at Keystone by John Hural of the HVTN. The US-based company Merck and the HVTN are now completing site preparations for an additional Phase II "test of concept" trial with Merck's Ad5 vaccine candidate. This candidate is already being tested in a Phase IIb trial, known as the STEP study, in North and South America, the Caribbean, and Australia. But the South African trial marks the first time this candidate will be evaluated in a population where the predominantly circulating clade of HIV is different from that in the vaccine. The HIV antigens in the vaccine are from clade B, while the epidemic in South Africa is mainly clade C. Although there is still uncertainty about how important this clade matching is, Merck wants to find out early on if this vaccine will be effective against different HIV clades.

This South African trial will enroll 3000 volunteers at 5 HVTN sites, 40% of whom are required to have low levels of pre-existing Ad5 immunity, which occurs after someone is exposed to this naturally-circulating virus that causes cold-like symptoms (see *VAX* February 2005 *Primer* on *Understanding Pre-Existing Immunity*). Due to the high prevalence of pre-existing immunity to this serotype of adenovirus in South Africa, initial expectations are that 6000 people will need to be screened across the sites in order to enroll just 1200 volunteers that meet this criterion. Hural acknowledges that this will be a huge task but emphasizes that all of the South African HVTN sites are now undergoing expansion in order to handle this number of volunteers. And by the time it begins, Hural says each site will also be capable of processing volunteer specimens and preparing them for shipment.

Recruitment efforts for the South African trial, HVTN 503, will also focus more on women. In the STEP study only 800-900 of the 3000 total participants are women, but in this second Phase II trial, HVTN plans to enroll equal numbers of male and female volunteers. This is reflective of the high number of infections among women in South Africa. A study of almost 12,000 15-24 year olds living in South Africa in 2003 reported that HIV prevalence in women was 15.5%, compared to only 4.8% in men of the same age group (*AIDS* **19**, 1525, 2005). And this may not be the only country where women are disproportionately infected with HIV. "I don't think there's a case from Africa where you don't see this gut-wrenching stratification by gender," says Michael.

This study is expected to start once Merck's assay, which will be used to determine baseline eligibility for the trial, is successfully transferred to the South African sites. Merck expects that enrollment will begin before the end of the year.

Global News

Trial sites in Kenya and Rwanda expand recruitment

The projected number of individuals participating in a Phase I AIDS vaccine trial in Kenya and Rwanda, conducted by IAVI in partnership with the VRC, will be increased after approval was granted recently from the local institutional review boards in the countries. Project San Francisco began enrolling volunteers at the site in Kigali, Rwanda late last year—marking the start of the first AIDS vaccine trial in the country—and the Kenya AIDS Vaccine Initiative (KAVI) at the University of Nairobi began recruitment in January. Total enrollment for both sites was initially set at 64 volunteers but will now be increased to 104.

This trial is one of three closely coordinated trials testing the safety and immunogenicity of a "prime-boost" vaccination regimen with the VRC's DNA plasmid and adenovirus serotype 5 (Ad5) vaccine candidates (see *Spotlight*, this issue).

Other developments in Kenya include the opening of two new community clinics in Kilifi by the Kenya Medical Research Institute (KEMRI), with support from IAVI. One of these clinics, the Comprehensive Care and Research Clinic, will offer HIV testing and counseling services that can help facilitate

future AIDS vaccine trials in the country, as well as house a clinical trials laboratory. Part of this building has also been reserved for provision of HIV treatment and care through the District Hospital, including a program for the prevention of mother-to-child transmission that tests over 4000 pregnant women each year.

The other newly-established clinic will focus mainly on couples voluntary counseling and testing that can help identify individuals in serodiscordant relationships, where one partner is HIV infected and the other is not. This type of counseling will help identify HIV-uninfected individuals who are therefore at high risk for HIV infection within their marriage or partnership and can possibly be volunteers for future AIDS vaccine trials (see *VAX* October 2005 *Primer* on *Understanding Couples Voluntary Counseling and Testing*). Couples counseling is an established practice at sites in Rwanda and Zambia, but this clinic is one of only a few to utilize this approach in Kenya.

KEMRI also opened a new drop-in center and clinic in Mtwapa for HIV-uninfected individuals who are at high risk for HIV infection. Over 300 uninfected volunteers have already been enrolled in a study to help promote an understanding of HIV infection and identify ways they can lower their risk. Collaborators from the University of Washington will treat volunteers for sexually-transmitted diseases, including offering antiretroviral (ARV) treatment to those who become infected with HIV from exposure in their community during the course of the study.

African Union launches HIV prevention campaign

The African Union in partnership with the Joint United Nations Programme on HIV/AIDS (UNAIDS) initiated a unified call from leaders of many African nations to increase and improve HIV prevention services on the continent. On April 11 government leaders from several countries kicked off this initiative. Among these was Meles Zenawi, the Primer Minister of Ethiopia, who emphasized how the scale up of prevention services can have profound effects in dealing with the epidemic.

Elements of this comprehensive prevention plan include addressing the root causes of HIV transmission, improving the availability of and access to HIV testing and counseling services to increase knowledge about the virus and help prevent transmission, and developing strategies specifically targeting women and youth with important messages on HIV prevention. At the launch, First Lady Jeannette Kagame of Rwanda spoke about the disproportionate number of women in Africa who are HIV infected. Other components of the effort include the need to strengthen and expand existing healthcare systems and programs to prevent mother-to-child transmission of HIV.

Of the 5 million new HIV infections in 2003, 3.2 million occurred in sub-Saharan Africa, according the latest UNAIDS statistics. And although access to HIV treatment and care has increased in recent years, the huge number of new infections can cause a significant burden on existing programs.

The World Health Organization (WHO) and UNAIDS predict that implementation of broad prevention programs such as these could help avert 63% of new HIV infections that are expected to occur in the next 6 years. This initiative was launched in advance of a Special Summit on HIV/AIDS, tuberculosis, and malaria that will convene next month in Abuja, Nigeria involving African Union heads of state.

Study of early HIV infection begins enrollment

Active recruitment and enrollment of volunteers has now started at research sites in Lusaka, Zambia; Masaka, Uganda; Kigali, Rwanda; and Kangemi, Kenya for a multi-centre, epidemiological study of newly HIV-infected individuals being conducted by IAVI. Volunteers who were recently infected with HIV through incidental exposure were identified through participation in incidence studies where they were counseled on risk-reduction practices and tested for HIV at least four times a year.

This new study will track these HIV-infected individuals for up to five years to follow the natural course of HIV infection in these cohorts. All volunteers will receive counseling and care and will be referred to a program offering antiretroviral (ARV) treatment when needed. Investigators will analyze samples of the newly-transmitted virus and evaluate early disease progression. Data from this study could help AIDS vaccine researchers in the design of new preventive vaccine candidates (see *Primer*, this issue).

The IAVI research study will also begin recruiting recently HIV-infected volunteers at other sites in Entebbe, Uganda; Cape Town, South Africa; and Kilifi, Kenya. Other groups, including the recently established Center for HIV/AIDS Vaccine Immunology (CHAVI), are studying individuals during the earliest stages of acute HIV infection. Links between these efforts and the IAVI-led research studies have already been established.

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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.iavireport.org) or an e-mail bulletin.

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.

How can studying what happens immediately following HIV infection help researchers design an AIDS vaccine?

There are many reasons why HIV is such a difficult virus to combat. One is that HIV directly attacks the human immune system, the body's defense against pathogens like viruses and bacteria. The primary target of HIV is the $CD4^+$ T cells, an important immune cell that directs the body's response to an infection. During HIV infection huge numbers of these cells are infected and killed each day, but new ones take their place.

Doctors or nurses can monitor the progression of HIV disease by $CD4^+$ T-cell counts, which are a measure of the number of $CD4^+$ T cells circulating in the blood. For many years after initial infection the quantity of these important immune cells can stay the same or drop only slightly, but in most people the virus will eventually take over and the total number of $CD4^+$ T cells will start to dwindle.

A typical definition of AIDS is when the total number of $CD4^+$ T cells in an HIV-infected person dips below 200 in a milliliter of blood (in people with healthy immune systems there are between 600-1200 $CD4^+$ T cells in this same amount of blood) or when a person develops one of several AIDS-associated illnesses. Once the $CD4^+$ T-cell count is dangerously low, the immune system is incapable of defending the body from attack by other pathogens and a person also becomes susceptible to many opportunistic infections, which can be deadly.

Measuring the number of $CD4^+$ T cells in the blood is a convenient way for researchers to estimate the damage HIV is doing to the immune system, since blood samples are easily obtained. But the majority of the body's $CD4^+$ T cells aren't in the blood. Rather they are found in the mucosal tissues, such as those lining the respiratory, gastrointestinal, and genital tracts. Looking only at the blood may paint an inaccurate picture of what is really happening during HIV infection, so researchers have recently focused on studying the immune responses occurring specifically at these mucosal sites.

Looking at the gut

When researchers looked at mucosal tissues they found something very interesting. In both animal models and humans, researchers observed a massive killing of $CD4^+$ T cells at mucosal surfaces in the intestine, or gut, very early in the course of HIV infection.

For many years scientists were more concerned with the dynamics of the human immune system much later in HIV infection when it begins to fail. But research now suggests that a critical destruction of immune cells occurs long before a person exhibits symptoms or develops AIDS, and often even before an individual knows they are infected with HIV (see *VAX* November 2005 *Primer* on *Understanding HIV Testing*).

The bulk of $CD4^+$ T-cell death in these tissues actually occurs within a few weeks after a person contracts the virus, during a period referred to as acute infection. Although the number of $CD4^+$ T cells in the blood also decreases during this initial stage of HIV infection, researchers found that the greatest depletion is seen in the mucosal tissues of the gut.

Researchers have also found that the immune system has trouble repairing damage in these mucosal tissues. $CD4^+$ T-cell counts often rebound quickly in the blood once an individual starts taking antiretrovirals (ARVs), but the $CD4^+$ T cells in the gut are restored much more slowly than in blood, even in HIV-infected individuals who have been receiving treatment with ARVs for several years.

This may mean that the loss of $CD4^+$ T cells at the mucosal surfaces is a better predictor of disease progression than monitoring their quantity in the blood.

But it would be difficult to monitor HIV-infected individuals by repeatedly measuring $CD4^+$ T-cell counts at mucosal sites. Testing these tissues requires a procedure known as a biopsy, which is a more invasive process than collecting a blood sample. Researchers are now looking for ways to analyze subtle differences between $CD4^+$ T cells in the blood in order to more easily determine and predict what is happening in the gut.

Implications for vaccines

This research has many implications for AIDS vaccine design and research. If the critical battle between HIV and the immune system takes place in the earliest stages of HIV infection, as this research suggests, it is important to closely study the virus that is transmitted and to characterize the nature of the immune responses in the first weeks and months of infection.

Many organizations involved in developing AIDS vaccine candidates are therefore interested in studying recently HIV-infected individuals. IAVI is one group conducting this type of epidemiological study with recently HIV-infected volunteers at several centers in Africa (see *Global News*, this issue).

Other research organizations are working with collaborators to identify and follow newly-infected individuals at sites in many countries around the world. Information collected from these studies may offer clues to help better define the target for a preventive vaccine.

Another important implication from this research is the need for AIDS vaccine candidates that induce strong immune responses at mucosal tissues, especially those lining the intestine. Several researchers think this will be necessary for a preventive vaccine to be effective and many methods are now being explored to enhance the mucosal immunity induced by existing AIDS vaccine candidates (see *VAX* December 2005 *Primer* on *Understanding Mucosal Immunity*).