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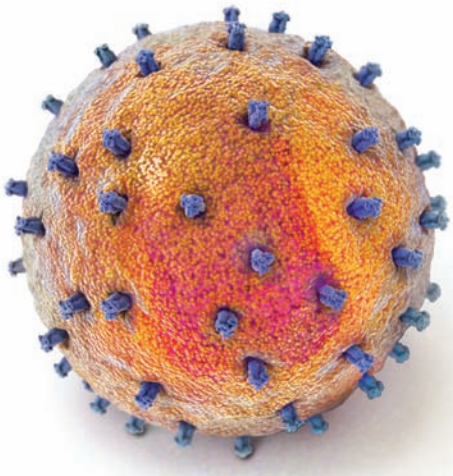

[SPOTLIGHT]

A Change of Tune

Following the first trial showing efficacy and continuing progress in other areas of research, a new chord of optimism was struck at AIDS Vaccine 2010 ***By Kristen Jill Kresge and Regina McEnery***

Although the prime-boost vaccine regimen tested in the controversial RV144 trial in Thailand provided only modest efficacy (31.2%) in preventing HIV infection, it was enough to make Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID) at the US National Institutes of Health (NIH), a convert.

"It is feasible to block acquisition of HIV infection. We know from the Thai trial that it can be done. Before, I was not so sure it was feasible," Fauci said at AIDS Vaccine 2010, held in Atlanta, Georgia, from Sep. 28 to Oct. 1. "The proof of concept here is huge. Our task now is to use the science to get us closer to a much more effective vaccine," he said. "I don't think there's any question we're going to get there."

During his signature overview talk at the annual conference, Fauci highlighted recent progress in the isolation of HIV-specific broadly neutralizing antibodies—proteins that bind to viruses and prevent them from infecting human cells—and the novel approaches researchers are now employing to try to visualize which parts of the virus' surface these proteins target. He also discussed plans to build on the results of RV144 and strategies for designing clinical trials.

Alan Bernstein, executive director of the Global HIV Vaccine Enterprise, which co-hosted AIDS Vaccine 2010 with Emory University's Center for AIDS Research, echoed Fauci's upbeat mood. "I believe we are seeing a real reason for optimism," said Bernstein.

RV144: The search continues

Without a doubt, the results of the RV144 trial helped galvanize AIDS vaccine research (see *VAX* October 2009 *Spotlight* article, *Vaccine Research Gains Momentum*). Now, researchers are mining the samples from the trial in the search for possible immune correlates of protection—the specific immune responses that were present in vaccinated individuals who did not become HIV infected—that could enable researchers to try to build upon what Nelson Michael, director of the US Military HIV Research Program (MHRP), called the "early but non-durable efficacy" of the prime-boost vaccine regimen tested in the RV144 trial. One year into the three-and-a-half-year trial the efficacy was as high as 60%.

Michael reported that MHRP and the 35 investigators at 20 different institutions who are collaborating on the analysis of RV144 samples are still evaluating a broad range of laboratory tests that may be used, come January 2011, to compare the immune responses of different subsets of RV144 volunteers. Even though these studies aren't yet underway, researchers at MHRP have already made some intriguing observations. In an exploratory analysis of 60 vaccinated volunteers from RV144 who remained HIV uninfected, researchers observed that these individuals had a high frequency of T-cell responses to two distinct areas on the surface of HIV that were not seen in 68 volunteers who became HIV infected during the trial, and which are very rarely seen in HIV-infected Thais (only one individual from a natural history study of HIV infection was found to have a T-cell response to the same region of HIV). Michael said researchers may be "on the pathway" to determining why the vaccine provided modest efficacy in preventing

ALSO IN THIS ISSUE

HIV infection, but he cautioned that the finding was far from conclusive.

In addition to studying the RV144 samples, researchers are also planning several follow-up studies to help elucidate the correlates of protection. There are also plans for two additional efficacy studies with either the same or similar candidates to those tested in RV144, which will start in 2013 or 2014.

The first efficacy trial is a Phase IIb trial in Thailand that Michael called a "top priority" because it has the potential to lead to licensure of the vaccine candidate in this region. This trial, which will be funded by the US Army, the Thai government, the NIH, and Sanofi Pasteur, will test the RV144 prime-boost regimen with an additional booster shot six months after the fourth vaccination (12 months after the first vaccination). This trial will enroll men who have sex with men (MSM) at high risk of HIV infection, a much different population than the low- to moderate-risk heterosexual men and women in RV144.

Another Phase IIb efficacy trial, which would also start in 2014, is being planned in southern Africa. This trial will involve high-risk heterosexual volunteers and is being funded by the Bill & Melinda Gates Foundation, the NIH, the HVTN, Sanofi Pasteur, and Novartis RSA, among others, according to Michael. He said the objective of this trial is to see if the efficacy seen in RV144 can be extended to other geographic regions where there is greater diversity of viral strains.

Other trials

Along with the post-RV144 studies moving through the pipeline, several other clinical trials are expected to start within the next few years, many of them to test viral vector-based vaccine candidates. These candidates use viruses to deliver fragments of HIV's genetic material into the body, with the aim of inducing the immune system to respond to HIV. Some of the viral vector-based candidates in development employ strains of a common cold virus known as adenovirus (Ad). The current crop of Ad vectors now advancing in clinical trials include an Ad35 candidate developed by IAVI and an Ad26 candidate developed by Dan Barouch, an associate professor of medicine at the Beth Israel Deaconess Medical Center (BIDMC) and Harvard Medical School. These vectors are now being evaluated alone and in combination in a Phase I trial (see *Global News*, this issue). There are also plans to test the Ad26 candidate in combination with another viral vector-based candidate that uses modified vaccinia Ankara (MVA), a weakened vaccinia virus, in a Phase I trial to start next year.

Researchers are also working to optimize what goes inside viral vectors—the HIV fragments known as antigens. One approach being explored is to computationally design antigens to deal with the overwhelming genetic diversity of HIV (see *VAX* March 2009 *Primer* on *Understanding How Inserts for Vaccine Candidates are Designed*). These antigens, called mosaics, have only been tested in animal models so far, but there are now plans for three clinical trials evaluating mosaic antigens in Phase I clinical trials in the next couple of years.

Antibody frenzy continues

Another area of recent progress in the HIV vaccine field is the discovery of several antibodies that can neutralize a remarkably high percentage of virus strains in laboratory tests (see *VAX* March 2010 *Primer* on *Understanding Advances in the Search for Antibodies Against HIV*). These broadly neutralizing antibodies (bNAbs) continued to create a buzz in Atlanta, where researchers reported on several new antibodies that were isolated from HIV-infected individuals and also on the incremental progress in understanding how these antibodies form and how they might be induced through vaccination.

Researchers from NIAID's Vaccine Research Center (VRC) reported on the isolation of two bNAbs that were identified from IAVI's cohort of chronically HIV-infected individuals. IAVI's Neutralizing Antibody Center at The Scripps Research Institute (TSRI) in California reported the isolation of 13 new monoclonal antibodies from four so-called elite neutralizers—individuals whose blood can neutralize a large number of HIV isolates—also from IAVI's cohort. Three of the antibodies identified by the NAC team target an area on the exterior of the virus that is not the target of the other bNAbs described so far. Additionally, researchers from the consortium known as the Center for HIV/AIDS Vaccine Immunology (CHAVI) reported on five other neutralizing antibodies isolated from their cohorts of both acutely and chronically HIV-infected individuals.

As researchers home in on the structures of the new crop of antibodies, they are developing a clearer picture of some of their unique attributes, including the degree to which some of them evolve and mature to become more potent neutralizers of HIV. Researchers in Atlanta described how they are using high-level genetic sequencing techniques to track the evolution of these antibodies in HIV-infected individuals, which may help researchers design more effective antibody-based AIDS vaccines.

More attention has also been directed toward understanding another type of antibody function; instead of neutralizing the virus by binding directly to it, the antibody binds to cells already infected with HIV, thus facilitating the killing of these cells by other immune cells (see *VAX* January 2010

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Primer on *Understanding Antibody Functions: Beyond Neutralization*). There are now several studies underway to try to understand this antibody mechanism better. Researchers in Atlanta presented both animal and clinical data suggesting that being able to trigger this kind of non-neutralizing antibody function could potentially improve vaccine efficacy.

There was also progress reported on new approaches to design vaccine antigens that could coax the immune system to produce such bNAbs. One method for designing these antigens involves stitching the precise part of HIV to which the bNAb binds into a computationally designed protein structure. This method, referred to as scaffolding, has shown promise in a recent animal study and was touted at the meeting by several researchers as a promising avenue of work. ■

GLOBAL NEWS

Trials Planned to Confirm Efficacy of Tenofovir Microbicide Gel

Following the encouraging results from the recent Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 trial that demonstrated that vaginal application of a microbicide gel containing 1% of the antiretroviral tenofovir, which is used in the treatment of HIV, reduced the HIV incidence in 889 South African women by 39%, researchers are planning two confirmatory trials that could potentially lead to licensure of the microbicide candidate (see *VAX* September 2010 *Spotlight* article, *Microbicides Finally Gel, Securing Spotlight in Vienna*).

Researchers now hope to be able to replicate the results of CAPRISA 004 in a confirmatory trial involving 3,000 women enrolled at six clinical research centers in South Africa. The trial known as FACTS 001 will evaluate the same dosing regimen tested in the CAPRISA 004 trial, pending approval by South African regulatory authorities. Women in CAPRISA 004 received regular HIV prevention counseling and were instructed to apply the gel up to 12 hours before sex and as soon as possible following sex, but within 12 hours, a regimen referred to as BAT24. Eligibility criteria for enrollment in the FACTS 001 trial will be expanded to include girls ages 16 and 17 because they are considered to be at high risk of HIV infection through heterosexual sex. Salim Abdool Karim, director of CAPRISA, says he hopes to begin the confirmatory trial in early 2011, with results expected in 2013.

A second confirmatory trial is also being planned to determine whether a single dose of the microbicide gel around the time of intercourse is sufficient to protect against HIV. A trial referred to as MDP 302 will compare the efficacy of the CAPRISA 004 BAT24 dosing regimen with one dose of tenofovir gel right before sexual intercourse or, failing that, as soon as possible after intercourse. Plans are to enroll 3,750 women from up to five African countries, including Uganda, Tanzania, and Mozambique.

The South African Department of Science and Technology and the US Agency for International Development (USAID), which together funded CAPRISA 004, will provide most of the funding for FACTS 001. The MDP 302 trial will be partly funded by the Medical Research Council in the UK, with other funding sources to be determined.

Other follow-up studies will determine the best way to deliver the microbicide and how tenofovir gel use impacts the safety and effectiveness of oral tenofovir for HIV treatment. —*Regina McEnery*

Phase I Trial of Adenovirus-based Prime-boost Regimen Begins in Boston

A Phase I trial designed to test the safety of two vaccine candidates and their ability to induce immune responses to HIV recently began at Brigham and Women's Hospital in Boston. Vaccinations of volunteers in the trial, known as IAVI B003/IPCAVD-004, began in October, following approval by the US Food and Drug Administration and Harvard's institutional review board. Pending regulatory approval, investigators will also enroll additional volunteers for the trial in Africa. The overall goal is to enroll approximately 212 HIV-uninfected individuals at low risk of HIV infection at as many as six clinical research centers.

The two vaccine candidates use different types of adenovirus (Ad26 and Ad35), a common cold virus, as a vector to deliver non-infectious HIV genes into the body with the goal of inducing an immune response against HIV. The two candidates will be tested either in combination or alone. One candidate, referred to as Ad26.ENVA.01, was developed by Dan Barouch, an associate professor of medicine at the Beth Israel Deaconess Medical Center (BIDMC) and Harvard Medical School, and manufactured by the Dutch biopharmaceutical company Crucell. The other, referred to as Ad35-ENV, was developed by IAVI and manufactured by the French biopharmaceutical company Transgene.

Data from ongoing clinical trials that were presented at the recent AIDS Vaccine 2010 conference in Atlanta suggest that both Ad26 and Ad35 candidate vaccines are safe and immunogenic.

The trial is a joint effort by IAVI, BIDMC, the Ragon Institute, Harvard University, Massachusetts Institute of Technology, the National Institute of Allergy and Infectious Diseases' (NIAID) Division of AIDS (DAIDS), the HIV Vaccine Trials Network (HVTN), and Crucell. It is funded by the HVTN, DAIDS, the Ragon Institute, and IAVI. —*Andreas von Bubnoff*

[PRIMER]

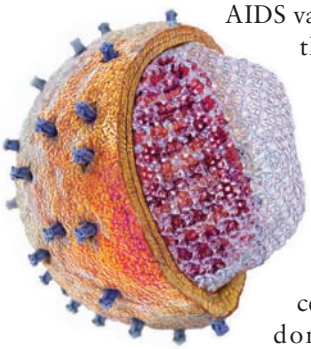
Understanding Adaptive Clinical Trial Designs

Researchers are looking at new methodologies to make late-stage efficacy trials more flexible and faster *By Regina McEnery*

Before AIDS vaccine candidates can be approved and licensed for use, their safety and efficacy must be demonstrated in a series of animal and human studies. The process begins with animal studies and then small Phase I clinical trials that are primarily conducted to assess the safety of the vaccine candidate in humans.

The most promising candidates are eventually tested in larger clinical trials that are designed to determine the efficacy of the vaccine candidate. These trials are typically Phase IIb test-of-concept trials or even larger Phase III efficacy trials (see *VAX* September 2005 *Primer* on *Understanding Test-of-Concept Trials*). Only a handful of efficacy trials have been conducted for HIV vaccine candidates so far, and until recently, none of them yielded positive results. This changed in 2009 when the results from the RV144 trial in Thailand, involving 16,000 volunteers, provided the first evidence of protection against HIV infection through vaccination.

Following these results, many AIDS vaccine researchers and advocates are calling for more clinical trials and more efficient ways of conducting them. The Global HIV Vaccine Enterprise, a research alliance formed in 2003 to accelerate development of an AIDS vaccine, called for the exploration of new approaches to conducting clinical trials in its 2010 Scientific Strategic Plan, launched this September. And at the recently held AIDS Vaccine 2010 conference in Atlanta, there was extensive discussion about alternate clinical trial designs. One approach being promoted by the HIV Vaccine Trials Network, a leading sponsor of AIDS vaccine trials around the world, is a so-called adaptive clinical trial design that can test multiple candidates simultaneously, comparing them to the same placebo group in a randomized, blinded, Phase IIb trial to see if they are able to prevent HIV infection (see *VAX* October-November 2007 *Primer* on *Understanding Randomized, Controlled Clinical Trials*). Adaptive trials allow investigators to modify the trial while it's underway, giving them more flexibility to drop candidates that don't seem to be working. This type of trial design would not allow for a direct comparison of different vaccine candidates, but it would allow investigators to rank the different candidates based on how well they work.



More nimble trials

So how would the methodology used in adaptive trials differ from that used in earlier AIDS vaccine efficacy trials? In the late-stage vaccine trials conducted thus far, such as RV144 or the STEP trial, a Phase IIb trial of Merck's HIV vaccine candidate MRKAd5, the efficacy of each vaccine regimen was evaluated by comparing its effectiveness among vaccinated volunteers to that of placebo recipients. The trials were blinded—meaning volunteers were not aware during the trial whether they had received the vaccine or the placebo—but Data Safety Monitoring Boards (DSMB) collected and analyzed safety and efficacy data at pre-specified time points during the course of the trials and could then determine whether the trials should continue or be stopped either for safety reasons or for futility if there was no evidence the vaccine candidate was working. An interim analysis conducted during the STEP trial is what led the trial's DSMB to recommend stopping immunizations because the data suggested the vaccine candidate was not effective.

Adaptive trials allow investigators to modify the trial while it's underway, giving them more flexibility to drop candidates that don't seem to be working.

But aside from halting a study for safety or futility reasons, AIDS vaccine researchers have had limited ability to respond immediately to any of the interim data. This means that every trial has gone to completion, or near completion in the case of the STEP trial. However, with adaptive clinical trials, more frequent interim analyses could allow investigators to identify promising candidates more quickly and weed out those with no apparent benefit.

If the interim data indicates that a vaccine candidate is clearly not meeting predetermined efficacy levels, researchers have the flexibility to shrink or drop that arm of the study while continuing the others. For instance, in a trial population with a 4% annual HIV incidence rate and 2,000 volunteers per group, it would be possible to reach a decision point on whether a vaccine candidate is working in approximately 20 months, as long as volunteers are rapidly enrolled in the trial. If this type of adaptive trial design was employed in past efficacy trials, RV144 could have been stopped two-and-a-half years earlier and the STEP trial could have been stopped nine months earlier, according to researchers.

One important caveat of adaptive clinical trials is that they are not suitable for licensure. That means that the results from an adaptive clinical trial could not be submitted to a regulatory body to serve as the basis of getting the vaccine licensed for use. The more frequent interim data analyses that are conducted in adaptive trials, and the flexibility that researchers will have to respond to the data, reduce the overall power of the study, making it more difficult to interpret the results. For that reason, adaptive trials are meant to serve more as a research tool that allows investigators to rapidly prioritize candidates for further study. Those that show promise could then be tested in much larger, more stringently designed clinical trials that could serve as the basis for licensure. ■