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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

AIDS Vaccine Trials Go Viral

Investigators tap social networking to pique interest and boost enrollment in vaccine trials *By Regina McEnerly*

ALONG WITH TRADITIONAL OUTLETS like billboards, newspaper and radio advertisements, printed handouts, and social events, many clinical research centers are now also tapping into social media with relish to try to generate interest among potential volunteers for AIDS vaccine clinical trials.

Since its launch last summer, approximately 250 of the planned 1,350 volunteers have been enrolled in HVTN 505, a Phase II trial that is being conducted by the HIV Vaccine Trials Network (HVTN) at 15 sites in 12 US cities. With the pace of enrollment slower than investigators would like, several of the sites have turned to social media and online classifieds to try and draw volunteers to the study.

Using the Internet to draw attention to AIDS vaccine trials is not new, of course. HVTN established a separate website for the STEP trial, a Phase IIb AIDS vaccine trial that was launched in 2004, and its companion study, known as Phambili, which was launched in South Africa in 2007. But now, trial sites are also utilizing social media, such as Facebook.

Although it does not recruit volunteers for the individual trial sites, HVTN's headquarters has been posting information about HVTN 505 on its Facebook page and posting advertisements on the Facebook pages of individuals whose demographics

seem to fit the requirements for enrollment. Trial sites are also using social media to reach potential volunteers in their regions. A trial site in San Francisco recently posted a video (available at www.SFisReady.org) of nine volunteers who had participated in previous vaccine trials talking about what it was like to participate and addressing some of the misconceptions regarding AIDS vaccine candidates.

Jennifer Sarche, director of community programs for the HIV Research Section of the San Francisco Department of Public Health, says viewers can easily share the video with friends on Facebook or MySpace.

Sarche views the use of social media strategies as part of a larger goal of community education. "We believe the Internet is a place for people to learn more about vaccines at their own pace," she says. "Then, if a person has seen that their friend is one of our sites' fans, and has watched our videos, and read more about it, they'll be a person who is more likely to stop and talk when they see one of our recruiters on the street. Half of our enrolled participants have come from that active street outreach."

A little help from your friends

For HVTN 505, investigators are seeking to enroll HIV-uninfected men who have sex with men (MSM) or transgendered

women who have sex with men. The trial is testing the safety and efficacy of a combination of two AIDS vaccine candidates that are administered sequentially in a prime-boost regimen. Volunteers first receive three vaccinations with a DNA-based candidate that contains non-infectious HIV fragments or immunogens, followed by a second vaccine candidate that employs an inactivated strain of the common cold virus, known as adenovirus serotype 5 (Ad5), to ferry HIV immunogens into the body to provoke an immune response against HIV. Neither vaccine candidate can cause HIV infection.

Participation in HVTN 505 is also limited to volunteers who do not have pre-existing immunity to the naturally circulating Ad5 virus because the results of the STEP trial, which involved a different

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Ad5-based candidate, suggested that male volunteers who received the vaccine had a higher risk of acquiring HIV if they were uncircumcised and had pre-existing antibodies against the Ad5 vector, as compared to placebo recipients with the same characteristics.

In fact, the STEP trial results may be part of the reason enrollment in HVTN 505 has been slow. Cheryl Stumbo, a communications specialist at HVTN's headquarters in Seattle, says that some trial sites are still confronting a skeptical public that is unsure whether the vaccine candidate could actually work given that the Ad5 candidate tested in the STEP trial was not effective.

Stumbo says other factors are also to blame for the sluggish pace of enrollment in HVTN 505, including the economic recession, which she said has "put some people in bad moods," and may be delaying them

from doing something altruistic, like joining a vaccine trial.

It's not clear how much of an impact the use of social media will ultimately have on enrollment for HVTN 505. Peggy Johnston, director of the Vaccine Research Program in the National Institute of Allergy and Infectious Diseases' Division of AIDS, which developed the two vaccine candidates being tested in the HVTN 505 trial, says while no "immutable deadline" has been set, the goal is to complete the trial within four and a half years after enrollment of the first volunteer. Johnston says the shelf life of the vaccine is not usually a factor in determining trial futility.

"Unless trial length is predicted to be so long that the total cost becomes fiscally indefensible, or if results from other trials become available and make HVTN 505 irrelevant, NIAID remains committed to the completion of HVTN 505," says Johnston.

Targeted recruitment

Other efforts at using social media to boost enrollment involve online classifieds and blogs. After obtaining approval from the trial's Institutional Review Board, the Fenway Institute (formerly Fenway Community Health) in Boston posted a listing on two separate craigslist pages seeking volunteers for HVTN 505. In addition, a Fenway recruiter combs craigslist's personal ads looking for people who appear to fit the eligibility requirements for the trial and then

contacts the individuals to ask if they would consider participating in the study. Coco Alinsug, Fenway Institute's recruitment coordinator, says the site has screened about 90 MSM for the HVTN 505 trial, and enrolled about 17 of them, most of whom were found through their online efforts.

Some individuals, moved by a desire to support AIDS vaccine research, have taken social media into their own hands by creating personal blogs that encourage others to volunteer for a clinical trial. Three months ago, Memphis resident Andrew Prislovsky began blogging on his website, the Accidental Activist, about his experiences as a volunteer in a vaccine trial known as HVTN 080. The Phase I trial, launched in November 2009, involves 48 volunteers and is designed to assess the safety of and immune responses induced by a DNA-based vaccine candidate.

Prislovsky says his sister's difficult, but ultimately successful, battle with breast cancer moved him to join a trial, but it was World AIDS Day that propelled him to get involved specifically with HIV/AIDS. After he enrolled in HVTN 080, Prislovsky learned from the director of the Nashville trial site about its struggles to find volunteers for some of its AIDS vaccine studies. That's when he decided to blog about his experiences. "My whole point is that the average person can do something," says Prislovsky. "I'm just a cog in the wheel, but 30 years from now it might make a difference. ■

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GLOBAL NEWS *By Regina McEney*

Combating Global Poverty Through Vaccine Development and Distribution

IN SOME WAYS, VACCINE development has never looked more promising. A report released last year by the World Health Organization (WHO), the World Bank, and the United Nations Children's Fund (UNICEF), declared that the last 10 years were the most productive ever in the history of vaccine development. Then, in January, at the World Economic Forum's annual meeting in Davos, Switzerland, the Bill & Melinda Gates Foundation announced they were committing

US\$10 billion over 10 years to fund the research and development of new vaccines, and distribution of existing vaccines to people in the world's poorest countries.

US President Barack Obama and his administration have also placed renewed emphasis on vaccine development. In a memo circulated in May, the Obama administration mentioned "seeking and then scaling up potential game-changers, such as vaccines," as a

way to solve longstanding challenges such as poverty.

While global health organizations and many public health researchers say vaccines are one of the most cost-effective ways of saving children's lives and reducing poverty, the WHO estimates that only about 18% of the \$6 billion annual global vaccine market is spent in developing countries, a point underscored at the 13th Annual Conference on Vaccine Research, which took place in Bethesda, Maryland from April 26-28.

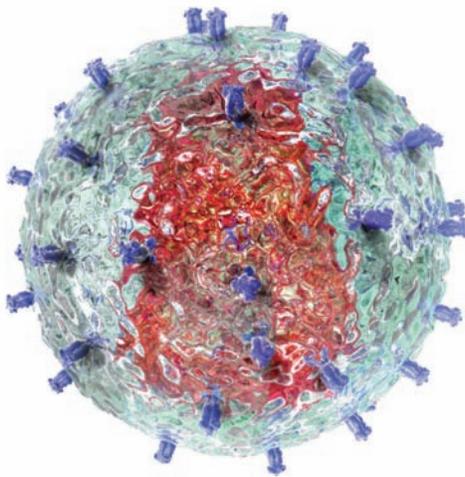
The 400 researchers and public health workers who gathered at the meeting, which was organized by the National Foundation for Infectious Diseases, emphasized how difficult vaccine discovery and distribution can be. Vaccines typically take many years and a hefty investment of between \$200 million and \$500 million to develop, noted Don Francis, founder of the nonprofit organization Global Solutions for Infectious Diseases, during his keynote speech. And even when vaccines do get licensed, it can take decades until the disease is eradicated because of the logistical difficulties and expenses involved in distributing vaccines on a global scale. Although the first polio vaccine was licensed in 1955, it took 36 years for the virus to be eradicated in North America, and 50 years for it to be eradicated in all but four countries where it is still endemic, Francis noted.

Despite these obstacles, vaccine researchers are increasingly focusing on the link between poverty and disease, and the conference opened with an array of talks about the vital role human and animal vaccines can play in reducing poverty and in strengthening economic and political security, particularly in developing countries.

One area of focus is scaling up distribution of the recently licensed vaccines against rotavirus, which causes diarrheal disease, and pneumococcal bacteria, which cause pneumonia, in developing countries, where the death rate from these infections is highest. There is also more attention being given to an array of 13 so-called neglected tropical diseases (NTDs) that cause about 530,000 deaths annually and afflict about one billion of

the world's poorest people.

A number of scientists at the recent vaccine conference are hoping the emphasis on vaccines as a way to combat poverty will translate into increased funding for vaccine research and development. Though NTDs receive much less treatment and prevention funding than HIV/AIDS, tuberculosis, and malaria, they have devastating consequences on maternal and child health, and may increase susceptibility to HIV/AIDS and malaria or worsen disease progression in those already infected.



“NTDs impair intellectual and physical development in children, cause adverse pregnancy outcomes, and reduce worker productivity,” said Peter Hotez, chair of microbiology, immunology, and tropical medicine at George Washington University Medical Center in Washington, DC.

A number of vaccine candidates against NTDs, so-called anti-poverty vaccines, are in the clinical pipeline. Hotez, who also heads up The Sabin Vaccine Institute, said they are hoping to soon begin a Phase IIb test-of-concept trial in Brazil of a vaccine candidate against hookworm, a parasitic worm that lives in the small intestine and infects about 576 million people, mostly in developing countries. Hookworm infection typically occurs when the larvae from hookworm eggs penetrate a person's skin. The larvae eventually latch onto the intestinal wall, where they mature into adult hookworms and produce more eggs. Hookworm infec-

tion can cause, most seriously, anemia and iron deficiency due to severe blood loss. Prolonged, untreated hookworm infections can also result in mental retardation.

The Sabin Institute is also hoping to begin clinical trials of a vaccine candidate against schistosomiasis, another parasitic disease which infects approximately 207 million people worldwide, most of them in Africa. Both the Sabin Institute and the Institut Pasteur in France are developing vaccines against two different parasites that trigger schistosomiasis. The vaccines would be used along with drug treatment to reduce or delay disease progression.

Schistosomiasis is referred to as snail fever because the parasitic worms that spread the disease live in snails. People become infected when they come in contact with fresh water contaminated by the parasites that the snails excrete. The worms grow inside a person's blood vessels and produce eggs, which then travel to the intestines or bladder. Like hookworm, repeated bouts of schistosomiasis can cause anemia and malnutrition. In rare instances, the eggs can be found in the brain or spinal cord, causing brain damage and paralysis.

More effort is also being given to control of foot-and-mouth disease, a highly contagious disease of cattle, buffalo, sheep, and pigs. The disease rarely affects humans, but the speed in which it spreads through livestock can seriously reduce milk and meat production, and the trade bans that result after outbreaks seriously affect the economies of food-exporting nations.

Researchers are excited about a novel livestock vaccine for foot-and-mouth disease developed by researcher Martin Grubman at the Plum Island Animal Research Center in New York in collaboration with the US Department of Homeland Security and GenVec, a biopharmaceutical company in Maryland. Luis Rodriguez, research leader at the Plum Island Animal Research Center, said studies of the vaccine candidate showed it was able to prevent clinical disease in cattle when they were challenged with the virus that causes foot-and-mouth disease. ■

Understanding if Broadly Neutralizing Antibodies are the Answer

Researchers are pursuing multiple paths to determine if antibodies can block HIV infection

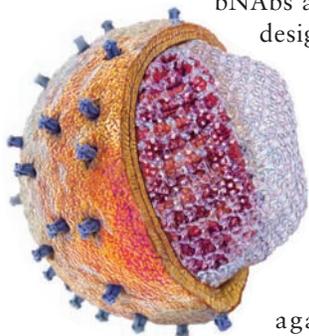
By Regina McEnergy

ANTIBODIES ARE Y-SHAPED PROTEINS that work primarily by latching onto viruses and preventing them from infecting target cells. Antibodies are induced by most, if not all, existing vaccines and are thought to play a crucial role in the protection these vaccines afford.

While it is still unclear precisely what types of immune responses will need to be triggered by a vaccine to protect against HIV infection, many scientists believe that an AIDS vaccine will need to induce antibodies (see *VAX* February 2007 *Primer on Understanding Neutralizing Antibodies*). And because HIV is an incredibly diverse virus, with multiple clades or serotypes in circulation around the world, researchers are focusing on developing vaccine candidates that can induce antibodies that are capable of blocking or neutralizing many circulating HIV strains, so-called broadly neutralizing antibodies (bNAbs).

Such bNAbs against HIV exist. The immune systems of individuals who are naturally infected with HIV generate antibodies against the virus, some of which are broadly neutralizing. By screening blood samples from HIV-infected individuals, researchers have been able to isolate several bNAbs. Just recently, eight new bNAbs were discovered, some of which are more potent than those previously identified (see *VAX* March 2010 *Primer on Understanding Advances in the Search for Antibodies Against HIV*).

Researchers are now studying these bNAbs and using them to design vaccine candidates that would ideally be able to induce these antibodies in people before they are exposed to HIV, thereby protecting them against infection.



However, this is a difficult task and it may take some time before vaccine candidates based on these bNAbs are ready for clinical testing. Until then, researchers are also conducting other studies in animals and humans to try to determine whether these bNAbs will be capable of blocking HIV infection.

Protection in animals

There is evidence from studies in animals to suggest that if scientists could learn how to induce bNAbs against HIV through a vaccine, they might be able to block infection. To evaluate this, researchers conduct what are referred to as passive immunization studies. In these studies, researchers inject bNAbs directly into animals and then purposely expose them to either HIV, or a hybrid virus known as SHIV that is a combination of HIV and simian immunodeficiency virus, the monkey form of HIV.

In studies with one of the bNAbs known as b12, scientists found that this antibody was able to block HIV infection in mice that were genetically altered to have human immune cells. In some studies, non-human primates passively immunized with b12 were completely protected against infection when they were purposely exposed to SHIV. While in other studies, infection of b12-immunized monkeys was delayed compared to those that were not immunized with b12.

Researchers are now planning to do similar studies in non-human primates with some of the newly discovered, more potent bNAbs to see how well they can protect against infection in animal models.

Evidence for protection in humans

Although these passive immunization studies in mice and non-human primates provide some evidence that bNAbs can block HIV infection from occurring, there is little evidence that this is also true in humans.

For many years, researchers have been

studying individuals who although repeatedly exposed to HIV, seem to be able to ward off infection. Although it has been suggested that antibodies may be what protects these individuals from infection, in these cases, it is difficult to draw firm conclusions.

Another way researchers are attempting to learn if bNAbs can protect against HIV is by studying the passive transfer of maternal antibodies. Pregnant women pass antibodies to their fetuses through the placenta. If the mother is HIV infected, she may also pass HIV-specific antibodies to her fetus.

In a study of 100 infants born to HIV-infected mothers, researchers found that although the mothers had indeed transferred HIV-specific neutralizing antibodies to the infants, there was no evidence that these antibodies actually protected the infants against HIV infection during the breast-feeding period. While this suggests that these antibodies were not effective at blocking HIV, it does not mean that some of the newer, more potent bNAbs would not be effective.

To determine this, researchers are considering conducting a clinical trial of passive immunization in HIV-uninfected people. This type of study would show whether directly administering one or more of the more potent, recently discovered bNAbs into HIV-uninfected individuals through injection would protect them against HIV if they were naturally exposed to the virus.

Scientists are also hoping to conduct a clinical trial soon to evaluate another antibody strategy, known as gene transfer, to see if it can protect against HIV infection (see *VAX* November 2008 *Primer on Understanding Approaches to Inducing Neutralizing Antibodies*). Rather than directly injecting bNAbs, the gene transfer approach involves introducing the genes that could make the bNAbs into HIV-uninfected people. ■