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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

## Researchers Rally Around PrEP

Building on two efficacy trials showing antiretrovirals can prevent HIV infection, discussions about this prevention strategy dominated the annual retrovirus conference *By Regina McEnergy*

THE 18<sup>TH</sup> CONFERENCE ON RETROVIRUSES and Opportunistic Infections (CROI), which took place from February 27 to March 2 in Boston, turned into a PrEP rally.

Three of the six plenary talks dealt with aspects of pre-exposure prophylaxis (PrEP)—the administration of antiretrovirals (ARVs) either orally or topically prior to HIV exposure to protect against infection—and researchers discussed and debated new evidence from both clinical and preclinical PrEP studies, as well as the challenges involved in implementation of this strategy.

The momentum behind PrEP was already evident at last summer's XVIII International AIDS Conference in Vienna, where researchers reported results of the CAPRISA 004 trial of 889 high-risk South African women that showed a vaginal microbicide gel candidate containing 1% of the antiretroviral tenofovir (TDF) was able to reduce HIV incidence by 39% (see *VAX* Sep. 2010 *Spotlight* article, *Microbicides Finally Gel, Securing Spotlight in Vienna*). This was followed in November by results of the large, international iPrEx trial of nearly 2,500 men and transgendered women who have sex with men, which found that daily administration of TDF combined with the ARV emtricitabine (FTC) was 44% effective in preventing HIV infection (see *VAX* Jan. 2011 *Spot-*

*light* article, *Prepping for the Future*).

At CROI, iPrEx Principal Investigator Robert Grant, an associate professor of medicine at the University of California in San Francisco, presented an additional six months of follow-up data from the iPrEx trial that showed the daily TDF/FTC regimen resulted in a slightly lower, but still statistically significant efficacy of 42%. "I don't think this efficacy is modest at all," said Grant. The new HIV infections that occurred during the additional six months of monitoring were among volunteers who didn't take the drugs consistently. "It was protective when used and not protective when not used," Grant said. "Our data show that 50% [of volunteers] took the pill almost every day. That's remarkable."

But the focus now is on the other half of the trial volunteers who did not consistently take the daily PrEP regimen. Adherence was one of the main topics of discussion at a community forum on ARV-based prevention held on March 1, co-sponsored by the Boston-based Fenway Health and the New York-based prevention research advocacy organization AVAC. Grant challenged the notion that adherence will always be higher in a clinical trial and said that he suspects adherence to PrEP will likely be higher when volunteers are told they are receiving the PrEP drugs and not placebo, and that these drugs have now been

shown to be effective in protecting against HIV only when taken reliably. "Adherence is a solvable problem," said Grant.

To better understand what factors influence adherence, Grant said the iPrEx study group will conduct an unblinded, open-label study in which all of the HIV-uninfected participants from the iPrEx study will be eligible to participate. The intent of the open-label study is to measure the efficacy of PrEP and the adherence to the daily regimen when participants know they are taking a drug that can protect them against HIV infection. The study will also continue to assess the long-term safety of TDF/FTC in healthy individuals.

Researchers also reported more safety data on oral PrEP from a sub-analysis of the iPrEx trial and an unrelated safety study of 400 HIV-

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uninfected men who have sex with men (MSM) in the US. Both of these studies showed a small but statistically significant drop in bone mineral density—a marker for bone fractures—among HIV-uninfected men who received ARVs for prevention as compared to those who did not. Initiation of TDF has been associated with decreases in bone mineral density in HIV-infected individuals, but its impact in uninfected individuals was not known. Neither study saw an increased rate in bone fractures among volunteers receiving PrEP regimens, but more long-term data is necessary to fully assess this side effect, researchers said.

“We celebrate the fact we now have proof-of-concept through the iPrEx and CAPRISA 004 studies, but ongoing trials are still critical to providing additional data on safety, efficacy, adherence, and resistance,” said Connie Celum, director of the International Clinical Research Center at the University of Washington, during her plenary

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talk. Additional analyses of the iPrEx trial presented at CROI showed that there was no detectable drug-resistant virus in any of the trial volunteers who were uninfected at the start of the trial and became HIV infected despite receiving the PrEP drugs.

The US Centers for Disease Control and Prevention (CDC) expects to release guidelines soon on the use of PrEP among MSM, and Gilead (manufacturer of Truvada, a combination of TDF/FTC) says it intends to file a supplemental investigational new drug application with the US Food and Drug Administration for the use of Truvada for prevention. At the same time, PrEP efficacy trials are now being conducted in other populations, including injection drug users, serodiscordant couples, and heterosexual women at high risk of HIV infection.

While adherence may be a major challenge, the cost of PrEP also looms large, particularly in low- and middle-income countries where only about a third of the 15 million HIV-infected people who qualify for treatment are receiving it. Researchers are now using mathematical models to assess in which high-risk groups or settings PrEP might be most cost effective.

Researchers also presented data at CROI showing some women prefer using an ARV-based microbicide gel to taking oral PrEP. At the conclusion of a Phase II study comparing oral administration of TDF with topical application of a TDF microbicide gel in 144 HIV-uninfected sexually active women from Africa and the US, researchers from Johns Hopkins University found that while 100% of African women reported they would use either the pill or gel form of PrEP if it was found to be effective, the African women reported greater sexual satisfaction when using the gel. In contrast, 72% of US women said they preferred the pill. This study showed that the concentration of TDF in vaginal tissue was much higher following topical application. Still, it is unknown what concentration of drug is associated with protective efficacy, so it is unclear whether higher concentrations are necessary.

While most of the clinical trials of PrEP that are underway are testing either TDF or Truvada, other ARVs are also being explored pre-clinically for their ability to prevent HIV infection. New data presented at CROI by the CDC suggests another ARV may have a role in preventing HIV infection if administered vaginally soon after virus exposure, a strat-

egy known as post-exposure prophylaxis, or PEP. Results of a non-human primate study showed for the first time that administration of a vaginal gel containing raltegravir—an ARV known as an integrase inhibitor because it blocks HIV’s enzyme that integrates the virus’ DNA into the genome of human cells—prevented HIV infection in five of six pig-tailed macaques when applied topically three hours after the animals were exposed to SHIV (a combination of HIV and simian immunodeficiency virus, the monkey equivalent of HIV). The monkeys that received the gel remained uninfected after being exposed 20 times to the SHIV strain used in this study, while four animals that received a placebo gel became infected after an average of 10 SHIV exposures.

Because the raltegravir gel was able to protect the monkeys when applied right after SHIV exposure, researchers believe it may also be able to block infection in adults when used shortly before or after exposure to HIV.

Researchers also reported findings from a Phase I study of a microbicide gel containing 1% of TDF, the same formulation used as a vaginal microbicide in the CAPRISA 004 trial, when applied rectally in men and women. The study involved 18 HIV-uninfected men and women at two sites in the US. Trial participants in the rectal microbicide study were first given a single dose of oral TDF. Two weeks later, they were randomized to receive either a rectal dose of 1% tenofovir gel or a placebo gel. Two weeks after that they were asked to use either the tenofovir gel or the placebo gel once a day for seven days.

UCLA Professor of Medicine Peter Anton, who led the study, said three of the 18 participants experienced eight grade three adverse events that were considered to be severe after using the rectal microbicide, primarily diarrhea, cramps, and gastrointestinal discomfort.

Researchers collected more than 2,000 colon and rectal tissue samples from study participants and exposed the samples to HIV in a laboratory. Researchers found that the samples from participants who received the TDF gel showed significant inhibition of HIV, suggesting this approach may be useful in blocking rectal transmission. Other studies will be necessary to show whether a rectal microbicide can actually block HIV infection. ■

## IAVI Founder and CEO to Resign this June to Head GAVI Alliance



IN JUNE, SETH BERKLEY will relinquish his role as president and chief executive of IAVI after spending 15 years at the helm of the organization he founded in 1996. Berkley will become chief executive officer of the GAVI Alliance, a Geneva-based global health partnership launched in 2000 to increase access to immunizations, a subject that is near and dear to him.

This decision, which Berkley calls “the most difficult of my life,” comes at a time when the AIDS vaccine field has been buoyed by the first evidence of vaccine efficacy in humans (coming from the RV144 trial in Thailand) and a spate of discoveries of new antibodies that scientists see as a clue for vaccine development. “It is the most exciting time we’ve ever had in the AIDS vaccine field,” Berkley says. Still, he felt it was overall the right time to make this change. “I know IAVI and the field will succeed.”

When IAVI was created, the landscape of AIDS vaccine research was much different than today. “The reason IAVI was started was because there was very little interest in AIDS vaccines from either public or private sectors. We had a fundamental belief that science could solve the problem,” he says. In 1993, less than US\$160 million was being spent globally on AIDS vaccine research and development. In 2009, the global investment reached \$868 million. Both IAVI and Berkley, whose passion is unwavering, deserve some of the credit for that difference.

For the past 17 years, Berkley has campaigned tirelessly to keep AIDS vaccine research on the agenda. And IAVI, which has more than 200 employees and an annual budget of approxi-

mately \$87 million, has helped to advance the research and development process through its own network of laboratories, consortia, and collaborations.

Berkley’s roots in AIDS extend back to the late 1980s. Working as an epidemiologist at the Ministry of Health in Uganda, Berkley helped characterize the extent of the epidemic in that country and set up its National AIDS Control programs.

Margaret McCluskey, a senior adviser at the US Agency for International Development, called Berkley a “visionary and courageous” leader. “Seth had the insight to really partner with in-country scientists and stakeholders,” she says, “and the vision to say we have to take up the mantle to agitate and inform policy makers over the long term.”

McCluskey also credits Berkley and IAVI with trying to fill the gaps left by the work of government research agencies and the pharmaceutical industry. “He realizes the benefits of vaccines in global public health,” says McCluskey, adding that his work at GAVI will “only make it easier to roll out new vaccines, including an eventual HIV vaccine.” The GAVI Alliance has funded immunizations for more than 288 million children, saving an estimated five million lives, according to the World Health Organization. “The challenge is to get that story out and get funds for it,” says Berkley. “The other two aspects are to try to drive down the price of vaccines and also to get governments to put more of a priority on immunization.” At least initially, this will probably involve Berkley racking up even more travel miles after he relocates to Geneva with his wife and two children, ages four and six, in August. —*Kristen Jill Kresge*

## Phase I Trial of Novel Prime-boost Regimen Starts in Africa

A PHASE I CLINICAL TRIAL known as B002, which started in February, will test the safety and immune responses induced by two HIV vaccine candidates administered either sequentially, in a prime-boost regimen, or simultaneously. One of the candidates is based on a non-infectious adenovirus serotype 35 (Ad35) vector that is used as a vehicle to deliver non-infectious fragments of HIV to the immune system. The other candidate consists of a protein administered along with an adjuvant that is intended to boost the immune responses.

Vaccinations already began at a clinical research center run by the Kenya AIDS Vaccine initiative (KAVI) in Nairobi. IAVI, the trial’s sponsor and the developer of the Ad35 candidate, has also applied for regulatory approval to conduct additional arms of the B002 trial in Lusaka, Zambia, and in Entebbe and Masaka, Uganda, and plans to enroll approximately 140 HIV-uninfected volunteers between the ages of 18 and 40. The trial is being conducted in partnership with GlaxoSmithKline (GSK;

the pharmaceutical company that developed and manufactured the protein vaccine candidate), KAVI, and other partners in Africa, pending approvals.

Researchers will measure immune responses in blood samples from volunteers, as well as in genital and oral mucosal fluids collected from volunteers who agree to provide such samples. The mucosal work will be done at the clinical research center in Nairobi, says Patricia Fast, chief medical officer at IAVI.

Previous Phase I trials have shown that separately, both the Ad35 and protein candidates have acceptable safety profiles and induce immune responses against HIV. The B002 trial is the first time these two vaccine candidates will be tested in combination. “There is a lot of interest in combining vectors and proteins following on the success of RV144,” says Fast, referring to the trial conducted in Thailand that showed that a different viral vector-based/protein prime-boost regimen provided a modest 31% protection against HIV infection. —*Andreas von Bubnoff*



# Understanding HIV's Envelope Protein

What are the challenges to understanding this protein's structure and how would revealing its structure impact the design of possible HIV vaccine candidates? *By Regina McEnerly*

OVER THE PAST TWO YEARS, researchers have isolated nearly two dozen new antibodies against HIV from the blood of infected individuals (see *VAX* Oct. 2009 *Spotlight* article, *Vaccine Research Gains Momentum*). When tested in the laboratory, these antibodies are capable of inactivating or neutralizing many of the HIV strains currently in circulation and are therefore referred to as broadly neutralizing antibodies (bNAbs). Many of these bNAbs can also neutralize HIV at relatively low concentrations, suggesting they are quite potent.

Now, scientists are using these antibodies to design vaccine candidates that would ideally be able to induce similar antibodies in people before they are exposed to HIV, thereby protecting them against infection (see *VAX* May 2010 *Primer* on *Understanding if Broadly Neutralizing Antibodies are the Answer*). However, there are several significant challenges to designing a vaccine capable of eliciting such bNAbs.

## Immunogen Design

Researchers start by understanding how these antibodies successfully bind to and neutralize HIV. All of the bNAbs bind to HIV's Envelope protein, or Env for short, which is the protein that juts out from the surface of the virus in spike-like protrusions (see image, right). By studying how they bind to HIV, researchers hope to identify the non-infectious pieces of the virus they could put into a vaccine candidate to provoke the body's immune system to make similar antibodies. The pieces of the virus used in a vaccine to invoke an immune response are referred to as immunogens. Because the antibodies bind to the HIV Envelope spikes that dot the surface of the virus, the immunogens will likely be parts of this protein.

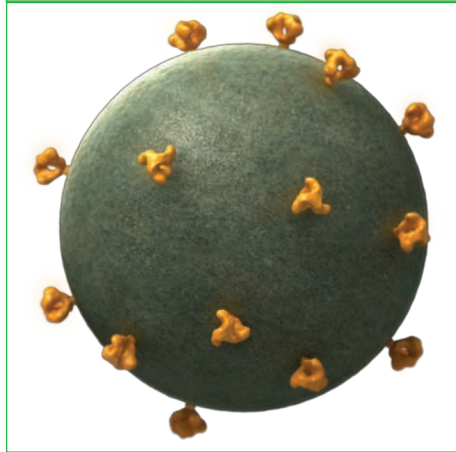
However, the process of selecting the pieces of HIV Envelope to put into a vaccine candidate is made more difficult by the fact that this protein is rather unstable. The HIV Envelope, also known as gp160, is actually composed of two different proteins that are

weakly bound together. One of these proteins, known as gp120, is what forms the spike, and the other protein, known as gp41, is what makes up the base of the spike. Making matters even more complicated, each of the HIV Envelope spikes is actually composed of three identical gp120/gp41 proteins that are linked together. This three-pronged protein structure is referred to as the trimer.

## HIV Envelope Spikes

Three-dimensional image of HIV showing HIV Envelope spikes on the surface of the virus. These spikes make contact with human cells that the virus infects. The images of these spikes, which are actually three-armed structures known as trimers, were created using a technique called electron tomography that has also provided insights into how their shape changes after HIV makes contact with a human target cell.

*Image courtesy of Sriram Subramaniam and Donald Bliss at the US National Institutes of Health.*



The HIV Envelope trimer is what binds to human cells, allowing the virus to infect them. To infect human cells, the trimer spikes must be able to undergo complex changes in their conformation, and therefore they are very flexible. As a result, this trimeric protein is unstable, making it more difficult for researchers to

fully understand the structure of HIV Envelope and see how some bNAbs bind to it. Researchers have been stymied by the instability and flexibility of the HIV Envelope trimer for many years. Their inability to stabilize the trimer has in turn hampered the development of AIDS vaccine candidates.

## X-ray crystallography

To study the structure of proteins, researchers typically use a method known as X-ray crystallography. This method involves sending a beam of X-rays through a solid, crystalline structure of the protein. This allows researchers to determine the precise arrangement of the different atoms that make up the protein, and then to determine how these atoms interact with other proteins, such as antibodies. X-ray crystallography has been used to reveal the structure of several of the key enzymes HIV uses to infect cells and reproduce.

To use X-ray crystallography to study the HIV Envelope trimer, researchers first have to be able to develop a stable crystalline structure of the trimer bound to one of the bNAbs. This has been incredibly difficult because the trimer is so unstable and flops around in space. Researchers have tried several different methods to stabilize the trimer, including adding pieces of synthetic protein into the structure to prop it up and prevent it from shifting around, but, so far, none of these attempts have stabilized the trimer enough that a pure crystal of it bound to an antibody could be obtained.

Researchers have, however, successfully crystallized a single HIV gp120/gp41 protein, which is referred to as a monomer. Some of the bNAbs that have been identified will bind to the HIV monomer, while others only bind to the trimeric HIV Envelope structure. This, plus the fact that the trimeric form of HIV Envelope is what naturally exists, makes the quest to get a crystal structure of the trimer an important goal. ■