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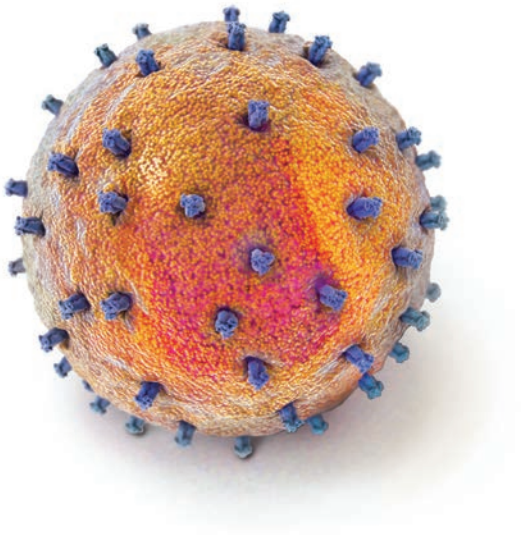

[SPOTLIGHT]

A Hot Cup of CROI

The Seattle conference provided updates on PrEP, the search for a cure, and the structure of HIV's Envelope protein *By Regina McEnery*

The 19th conference on Retroviruses and Opportunistic Infections (CROI), which drew 4,200 participants March 5-8 to the foggy city of coffee houses and technology start-ups, showcased a number of recent developments in some of the hottest areas of HIV research. Attendees were briefed on progress in the lately invigorated field of HIV cure research and studies assessing the influence of hormonal contraception on HIV acquisition and progression. And in two riveting talks, including one that kicked off the conference, attendees got an update on the discovery and analysis of broadly neutralizing antibodies against HIV, which many researchers believe will have to be elicited by an AIDS vaccine to prevent infection by a broad range of circulating HIV variants.

But, more than anything else, it was the use of antiretroviral (ARV) therapy in preventing HIV transmission that dominated the conference. In an apparent nod to that fact, the organizers of CROI chose the South African research couple Quarraisha and Salim Abdool Karim to deliver the 6th N'Galy-Mann Lecture on opening night.

The Karims led CAPRISA 004, a clinical trial in South Africa that in 2010 provided the first proof that a vaginal microbicide can prevent HIV transmission (see *VAX* Sep. 2010 *Spotlight* article, *Microbicides Finally Gel, Securing Spotlight in Vienna*). The Karims have spent more than two decades studying the evolving epidemic in sub-Saharan Africa, which accounts for two-thirds of all people living with HIV in the world, with a particular focus on high-risk heterosexual women. The 39% efficacy obtained in the CAPRISA 004 trial was, though modest, a significant triumph for their team. That breakthrough has been followed by encouraging, if mixed, results from studies of daily oral pre-exposure prophylaxis (PrEP)—the administration of ARVs to prevent HIV acquisition—as well as vaginal microbicides containing ARVs. The prophylactic value of ARVs was further bolstered in 2010 by the results of the HPTN 052 study, which found that earlier treatment of HIV-infected individuals in relationships with HIV-uninfected people reduced HIV transmission to their partners by a stunning 96% (see *VAX* July 2011 *Spotlight* article, *An Antiretroviral Renaissance*).

Salim Abdool Karim noted that follow-up studies examining why efficacy in the CAPRISA 004 trial wasn't higher have been illuminating. "What we have learned," he said, "is that adherence is critical, that you have to have high enough levels of the drug to achieve protection, and that genital inflammation increases the risk of HIV acquisition."

These lessons might be applicable to oral PrEP regimens as well. Findings from an array of studies presented at CROI suggest that adherence is an important determinant of PrEP efficacy. They also suggest that biological factors interfere with PrEP efficacy, even when volunteers take their drugs consistently. Such factors are likely to be a major focus of future studies, as researchers try to develop a more comprehensive picture of when, where and how PrEP might best be used.

That picture is likely to be complicated. "The reality doesn't necessarily match the vision," said Jared Baeten, a University of Washington associate professor of global health, in a talk that addressed conflicting results of some of the recent PrEP studies. "We have four completed PrEP trials that demonstrate efficacy, but we have two trials in women with high incidence where the entire study or individual arms have demonstrated futility," said Baeten, who was

ALSO IN THIS ISSUE

also a co-investigator in the Partners PrEP Study, which found high PrEP efficacy in serodiscordant couples.

PrEP's twisted tale

One trial that failed to demonstrate efficacy was FEM-PrEP, which enrolled nearly 2,000 high-risk heterosexual women from Kenya, South Africa, and Tanzania and was discontinued in March 2011. A data safety monitoring board determined that the trial was unlikely to establish whether or not daily oral administration of Truvada—a combination of the ARVs tenofovir (TDF) and emtricitabine (FTC)—is effective in reducing HIV acquisition (see April 18, 2011, *IAVI Report* blog, *Oral PrEP Trial in Women Stopped Early*).

Lut Van Damme, the trial's principal investigator, presented follow-up studies that suggest inadequate adherence to the prescribed drug regimen may have undermined the trial, which tallied 33 infections in its Truvada arm and 35 in its placebo arm. Analyses of blood plasma collected during the trial from the 33 women in the Truvada arm who acquired HIV and about 99 matched uninfected controls found detectable levels of TDF in fewer than half of the samples. Notably, this contrasted with the 86% adherence rate suggested by weekly pill counts—the number of pills dispensed per week minus those returned—and with the claims of 95% of the volunteers who said they had taken the drug faithfully. Van Damme noted that these data raise questions about the value of pill counts in measuring adherence, and about what became of the pills that were neither taken nor returned.

Another study that underscored the importance of adherence was the Partners PrEP trial of 4,758 heterosexual serodiscordant couples in Kenya and Uganda. Results from that trial revealed in 2011 that a daily dose of TDF reduced the risk of HIV infection by 62%, and a similar regimen of Truvada cut that risk by as much as 73%. Recent findings presented by Deborah Donnell, principal investigator of the HIV Prevention Trials Network and a statistician in the Partners PrEP Study, indicate that individuals who remained HIV uninfected in the TDF and Truvada arms of the study had detectable levels of the drug on 83% and 81% of their study visits, respectively. Drug levels were much lower in the 29 participants in both arms of the trial who acquired HIV. Only about a third of them had detectable levels of TDF when investigators first identified HIV antibodies in their blood plasma. "Even in visits prior to seroconversion, these people were not taking their drug as often as those who did not seroconvert," Donnell said.

Yet adherence does not always predict PrEP efficacy either. In her sub-analysis, Donnell noted that nine of the HIV-infected participants who had been assigned to either the TDF or Truvada arms did have detectable levels of TDF. Eight of them had drug levels that were consistently high or detectable throughout the follow-up—an indication the drug was being taken faithfully. "Of course, we don't know what the level of the drug was at the time they got HIV infected," said Donnell.

The Envelope, please

ARV-based prevention strategies may have taken up most of the airtime at CROI, but one of the most riveting presentations at the conference dealt with basic science—namely the race to characterize the structure and vulnerabilities of HIV's Envelope protein. This molecular complex, comprising three pairs of two distinct proteins, juts out like a spike from HIV's surface and plays a central role in its infection of target cells. Due to the dynamism, complexity, and general instability of this spike, researchers have not yet been able to determine its precise functional structure.

In his keynote speech kicking off the conference, Dennis Burton, a professor of immunology and biology at The Scripps Research Institute in California and the director of IAVI's Neutralizing Antibody Center at Scripps, covered advances in the identification and analysis of antibodies that can neutralize a broad spectrum of HIV variants. In the absence of a precise molecular structure for the spike, these antibodies provide an approach to identifying discrete regions of vulnerability on the protein that might be exploited for vaccine design. Researchers today, Burton noted, have in hand at least two dozen such antibodies, most of which have been discovered in just the last two years. By capturing in atomic detail how each binds to HIV's Envelope protein, Burton and other researchers hope to be able to reverse-engineer candidate immunogens—the active ingredients of vaccines—that might elicit similar antibodies (see *VAX* March 2011 *Primer* on *Understanding HIV's Envelope Protein*).

Meanwhile, researchers continue to pursue the elusive prize of the Envelope's structure. Joseph Sodroski, associate director of the Harvard Medical School's Center for AIDS Research, described in a later talk how his team is applying a cutting-edge imaging tool—known as cryo-electron microscopy—to bring the Envelope trimer into multi-dimensional focus. Their findings could eventually help scientists design better AIDS vaccine candidates.

Chasing the cure

A number of CROI sessions also focused on the surging field of HIV cure research, which one scientist compared to the state of antiretroviral research 15 years ago, when highly active antiretroviral therapy was about to revolutionize AIDS care. Scientists believe one possible way to cure HIV would be to locate and drain reservoirs of latent HIV-carrying cells. Such reservoirs persist even in people whose circulating HIV has been effectively

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suppressed by ARVs. Perhaps the most talked about study in this arena was presented by David Margolis, director of the School of Medicine at the University of North Carolina, who led one of the first major cure-related clinical trials. Margolis and his colleagues used a cancer drug called vorinostat to roust latent cells, forcing the human immunodeficiency viruses piggybacking in their chromosomes to reveal themselves. Margolis reported that when he and his colleagues gave six HIV-infected participants on ARVs who had undetectable viral loads just a single dose of the drug, they detected in the patients a sudden increase of HIV RNA in pools of $CD4^+$ T cells—which are among the cell types that primarily harbor latent HIV. Though forcing reservoir cells to reveal themselves is an important first step, it remains unclear how they would subsequently be cleared.

Hormonal worries

A number of recent studies have suggested that the use of hormonal contraception may increase a woman's risk of HIV acquisition and of transmitting the virus to men (see *VAX* Nov. 2011 *Primer* on *Understanding the Effects of Hormonal Contraception on HIV Transmission*). Results from two new studies reported at CROI added a little texture to this evolving story. One of them, the Methods for Improving Reproductive Health in Africa (MIRA) study, was a Phase III trial evaluating the use of diaphragms and lubricants in 4,913 sexually active women ages 18-49. Researchers conducted a subanalysis of women who also reported using oral or injectable forms of contraception—such as Depo-Provera—and compared them to women who did not use these agents.

Sandra McCoy, an assistant adjunct professor of epidemiology at the University of California-Berkeley, who presented the findings, reported that women who used injectable hormones were 1.4 times more likely to acquire HIV when condoms were used infrequently or not at all, compared to women who were not using such contraception. But there was no elevated risk of HIV among women who used oral contraception.

The second study, from the University of Washington, compared rates of HIV disease progression among 2,236 HIV-infected African women using hormonal contraception with those who were not. The study revealed that hormonal contraception did not accelerate disease progression and was further associated with a reduced risk of developing HIV-related disease.

The findings come on the heels of a Feb. 20 statement by the World Health Organization (WHO) that prior studies linking hormonal contraception to elevated risk of HIV acquisition are "insufficiently conclusive" to justify changing current guidelines. The statement did add, however, that because of the possibility that hormonal contraception might increase HIV risk, women who use injectable contraceptives containing progesterone should always use male or female condoms and other HIV preventive measures.

During her keynote talk at CROI, Quarraisha Abdool Karim criticized the WHO statement for its vagueness. "I think it is a very weak statement," she said in response to a question. "It overemphasizes the role of Depo-Provera in terms of fertility control. And in a country like South Africa, with its huge HIV burden and extensive use of Depo-Provera, I was expecting something more definitive to come through from that consultation." ■

GLOBAL NEWS *By Regina McEnery*

Two Documentaries Capture Historic Moments in the US AIDS Epidemic

Earvin "Magic" Johnson, the Los Angeles Lakers basketball star whose megawatt smile was about as famous as the dazzling moves that inspired his nickname, shocked the sports world on Nov. 7, 1991, when he announced that he had contracted HIV and would retire that day from the Lakers.

In a 90-minute documentary, entitled "The Announcement," narrated by Johnson and produced by ESPN Films for the network's entertainment television channels, the basketball legend recounts the tense private moments leading up to his explosive disclosure, describing, among other things, his anguish at the thought that he may have infected his wife, Cookie, and their unborn child. It turned out he had not. Still, Cookie was opposed to his making a public announcement. This was not surprising. The nation, and certainly the world of professional sports, hadn't quite come to terms with the HIV epidemic.

But the diagnosis was not a death sentence, as many at the time assumed it would be. Thanks to a new class of HIV drugs called protease inhibitors and the development of highly active antiretroviral therapy (HAART), Johnson has lived a relatively healthy life with the virus for more than 20 years. He has in that time become an inspiring advocate for the treatment and prevention of HIV infection, working to remove the stigma associated with HIV, which today infects more than 33 million people worldwide. The documentary is as much about how Johnson has lived with his diagnosis as it is about the impact of his announcement, which shocked his friends and fans and left many in tears. The film first aired on March 11 and is scheduled to be shown through April 14.

A second documentary, "How to Survive a Plague," by journalist and first-time director Donald France, examines how the activist group, AIDS Coalition to Unleash Power (ACT UP)—and the Treatment Action Group, an offshoot of ACT UP—drew attention to the HIV epidemic. Scores of gay activists, terrified by the specter of AIDS in the 1980s and 1990s, fought to save the sick and dying using a range of aggressive tactics that included not only protests at Capitol Hill but such antics as infiltrating the set of a nightly news broadcast and marching outside the home of Anthony Fauci, the director of the US Institute for Allergy and Infectious Diseases, which was funding many of the AIDS drug trials.

Fifteen years after the first cases of AIDS were detected, HAART was rescuing AIDS patients from the brink of death and transforming the US epidemic. ACT UP is credited with putting AIDS on the national health agenda and so speeding these developments. Two special screenings of the documentary were held in New York City in March—on the 25th anniversary of the very first ACT UP demonstration. It is due to open in theatres this fall. ■

[PRIMER]

Understanding the Complexities of Adenoviral Vector Vaccines

What are the potential advantages and disadvantages of using vectors derived from the adenovirus—which causes the common cold—as vehicles for AIDS vaccine candidates? ***By Regina McEnery***

Every vaccine prevents infection by teaching the body to detect and destroy the particular viral, bacterial, or parasitic pathogen it is devised to target. Many do so by presenting the immune system with weakened or killed versions of the targeted pathogen, thus instilling a lasting immune memory of the responses required to disable it. But such approaches are not favored in AIDS vaccine development: An incompletely killed batch of HIV could cause an incurable and potentially lethal infection. And, given HIV's extraordinary mutability, there's a substantial risk of similar consequences if a weakened virus were to spontaneously revert into a highly virulent form.

To circumvent these risks, scientists employ a range of genetic engineering tools to devise HIV vaccine candidates that contain fragments of HIV designed to elicit protective antibody or cellular immune responses but could never cause HIV infection. One such strategy relies on engineered viruses. These viruses, known as vectors, are weakened by researchers, so they are unlikely to cause disease. They are also manipulated so that, in addition to most of their own genes, they carry genes encoding fragments of HIV—the active ingredients of vaccines, known as immunogens—that might elicit protective immune responses against the virus (see *VAX* Sep. 2004 *Primer* on *Understanding Viral Vectors* and *VAX* Dec. 2007 *Primer* on *Understanding Replicating Viral Vectors*).

The Ad5 setback

One viral vector vaccine candidate that seemed particularly promising five years ago was derived from adenovirus serotype 5 (Ad5)—one of the many variants of the virus that causes the common cold. Unfortunately, the candidate, which was developed by Merck and known as MRKAd5, did not work in a large international efficacy trial named STEP (see *VAX* Oct.-Nov. 2007 *Spotlight* article, *A Step Back?*). That study also uncovered an unexpected and alarming phenomenon in a subgroup of volunteers: uncircumcised men who have sex with men (MSM) who had been naturally exposed to Ad5 prior to joining the trial and had generated antibodies to the virus in response. (Antibodies are large, exquisitely precise immune system proteins that latch onto viruses and other pathogens to neutralize them or tag them for destruction.) In this population, researchers found that volunteers who had been vaccinated with the MRKAd5 candidate had higher rates of HIV infection than those who had received the placebo. Five years after the STEP trial was stopped, scientists are still trying to determine why this was the case and have been reluctant to develop new candidates that employ Ad5 as a vector.

Researchers have found that pre-existing Ad5 antibody immunity from natural exposure to Ad5 appears to dampen cellular immune responses to the HIV proteins encoded by the vector.

For this reason, researchers are exploring the possibility of using other adenoviruses, such as Ad26 and Ad35, as vectors for HIV vaccines. They reason that people are less likely to have pre-existing immunity to these vectors because fewer people are exposed to the naturally circulating viruses on which they are based. These alternative adenoviral vectors also elicit immune responses distinct from those induced by Ad5.

Although adenoviruses aren't the only vectors available for making AIDS vaccine candidates, researchers continue to study them because these viral vectors are known to induce strong immune responses. One recent study in nonhuman primates compared the effectiveness of different vaccines containing adenoviral vectors delivered in a heterologous prime-boost regimen—in which two different vaccines are delivered sequentially, weeks or months apart. Candidates built from alternative adenoviral vectors were more effective than those based on other vectors or DNA in protecting rhesus macaques from repeated exposure to relatively virulent strains of simian immunodeficiency virus (SIV)—the monkey equivalent of HIV. These prime-boost combinations were also associated with greater control of viral load by macaques that became infected with SIV.

Prime-boost regimens of alternative adenoviral vectors have also been found to be safe and immunogenic in early stage HIV vaccine trials. Several such trials are currently evaluating prime-boost regimens that include Ad26- or Ad35-based candidates (see *VAX* Jan. 2012 *Global News* and *VAX* Nov. 2010 *Global News*).

Lingering questions

It is still not entirely clear if these alternative adenoviral vectors will be free of the issues related to pre-existing immunity that compromised the Ad5 vector. For example, researchers recently found that many STEP trial participants don't just have Ad5-specific antibodies, but also cellular immune responses to Ad5, and that even participants without Ad5-specific antibodies had such cellular responses.

They also found that, in participants of another trial that evaluated the MRKAd5 vaccine used in STEP, pre-existing Ad5-specific cellular responses recognize regions of the Ad5 virus that are shared by other adenovirus strains. That includes less common strains, in which—in theory—the risk of pre-existing immunity is not as great. Further, such cellular immune responses were associated with a dampened cellular immune response to the HIV immunogens encoded by the vector—a response essential to the efficacy of such vaccines.

This has raised questions about whether the same dampening effect will be found in vaccine candidates that use alternative adenoviral vectors, and whether that might diminish their efficacy. Some scientists suspect the effect may be negligible because the immune responses induced by prime-boost regimens of adenoviral vectors are so vigorous. So, at least for now, researchers plan to continue evaluating adenoviral vector-based HIV vaccine candidates in clinical trials. ■