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Spotlight

The red carpet rolls out at CROI

Exciting new treatments and prevention strategies highlight annual meeting

This year's 14th annual Conference on Retroviruses and Opportunistic Infections (CROI) took place February 25-28 in Los Angeles. On that same night, just across town, another event attracted a great deal of attention. It was the 79th Annual Academy Awards, or Oscars, ceremony where both American and international film stars gathered to celebrate the best movies, actors, and actresses of the year.

Although CROI is definitely a less glitzy and glamorous affair, it is still a highlight on the conference calendar of researchers working in the HIV/AIDS field, providing them with an opportunity to showcase the latest advancements in prevention and treatment. This year's meeting drew nearly 4000 HIV researchers and clinicians from around the world and brought exciting news on both fronts. Presentations centered on two new antiretrovirals (ARVs) that act in entirely novel ways to control HIV infection as well as several HIV prevention strategies.

"This has been quite a remarkable year in the study of HIV interventions," said Judy Wasserheit of the University of Washington in Seattle.

Best in show

The field of HIV treatment was reenergized at CROI by news of the first drugs in two novel classes of ARVs. The first is a small molecule drug, known as maraviroc, which acts on human immune cells, rather than the virus itself. It effectively blocks a protein called CCR5 on the surface of $CD4^+$ T cells that HIV uses to enter and infect these immune cells. When this drug is administered to HIV-infected individuals it helps limit HIV's ability to replicate. The US Food and Drug Administration is now considering granting a license for the sale and use of maraviroc.

Another novel ARV is also a step closer to becoming a reality. Many ARVs work by acting on the virus and disabling different enzymes it uses to replicate. For more than a decade researchers have been trying to interfere with HIV's integrase enzyme in particular, to prevent the virus from inserting its genetic material into the cell's DNA—a necessary step in the infection of cells. Identifying drugs that are safe and could effectively inhibit HIV's integrase enzyme has proven an arduous task. But now, based on Phase III trial results presented by US pharmaceutical company Merck, a new integrase-inhibitor called raltegravir appears to be highly effective at lowering viral replication, as measured by a significant drop in the copies of virus in the blood of HIV-infected individuals.

News of these novel ARVs caused quite a stir at CROI and many insisted that there hasn't been this much enthusiasm about HIV treatment since researchers first discovered that administering drugs in combination, a concept known as highly-active antiretroviral therapy (HAART), was an effective strategy for controlling HIV infection.

And the nominees for HIV prevention are… Circumcision

Some of this excitement also spilled over into the HIV prevention sessions. Ronald Gray of Johns Hopkins University in Baltimore presented results from the US National Institutes of Health-sponsored trial in Rakai, Uganda that enrolled 5000 men who were randomized to be circumcised either immediately or after two years. This trial was stopped prematurely by the data safety monitoring board, an independent group that monitors the progress of ongoing trials, in December 2006 because of indications that the intervention could lower the risk of HIV acquisition in men by more than 50%. These results support those from another randomized controlled clinical trial of male circumcision in South Africa (see *VAX* August 2005 *Spotlight* article, *A comprehensive response*).

At the time the trial was stopped, 44% of the men had completed the full two year follow-up. Only 22 of the circumcised men acquired HIV during this time, compared to 45 men in the control group—a cumulative HIV incidence rate of 0.7% in circumcised men compared to 1.3% in uncircumcised men over the two-year study.

All circumcised men were counseled to avoid sexual contact for the first 30 days following surgery while the wound was still healing and 89% said they followed these instructions. Despite this reported curtailing of sexual activity, researchers observed that HIV incidence actually decreased more among circumcised men during the second year of the trial. Gray hypothesized that

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this may be due to the time it takes for the wound to completely heal, but researchers are unsure how long this process actually takes. There is some concern, based on data shared with the World Health Organization (WHO) after CROI's completion, that if men do engage in sexual activity before the circumcision wound heals, they may be more likely to transmit HIV to their female partner(s).

Investigators in the Rakai study also collected data from the trial volunteers on sexual risk behaviors, including number of sexual partners and condom use. This data indicated that behavioral disinhibition—where volunteers in a trial alter their behavior because of the perception that they are protected against HIV infection—was not a dominant influence in this trial.

Surprisingly, investigators also found that circumcised men who reported multiple sexual partners had even lower HIV incidence rates than monogamous circumcised men. Circumcised men who reported having symptoms of genital-ulcer diseases—including herpes, syphilis, or chancroid—were also significantly less likely to contract HIV. Overall, circumcision reduced the rate of these symptomatic genital-ulcer diseases by 47%. Although circumcision is protective irrespective of co-infection with these sexually-transmitted infections (STIs) or number of sexual partners, this data indicates it could have the most profound impact in men who are at the highest risk of HIV infection.

…HSV suppression

The role that other STIs play in HIV transmission has long been speculated—especially for herpes simplex virus-2 (HSV-2), the cause of genital herpes. There are currently several ongoing studies to test whether treating HSV-2 infection with the drugs acyclovir or valacyclovir can reduce transmission of HIV by either reducing its quantity in the genital tract or by limiting the ulcerations that are common symptoms of HSV-2 infection (see *VAX* November 2005 *Spotlight* article, *HIV prevention in a pill?*).

Two studies presented at CROI looked specifically at the quantity of HIV in the genital tract of women given acyclovir to treat their HSV-2 co-infection. The first study of 67 women in Chang Rai, Thailand, conducted by the US Centers for Disease Control and Prevention (CDC), found that women taking acyclovir had a modest reduction in the levels of HIV in the genital tract. Eileen Dunne of the CDC suggested this could predict acyclovir's protective effect in preventing HIV transmission in women co-infected with both viruses, particularly in women experiencing the symptomatic ulcerations of HSV-2 infection that make HIV transmission more likely.

But the second study, a Phase IIb trial involving 299 HIV/HSV-2 co-infected women, presented by Sinead Delany of the Reproductive Health and HIV Research Unit in Johannesburg, South Africa, found there was no difference in the levels of HIV in the genital tract of women given acyclovir over a four-month period. Delany said further study is required to determine whether acyclovir therapy can actually lower HIV transmission rates because even if the treatment does not reduce the levels of HIV in the genital tract, preventing HSV-2 ulcerations might still reduce HIV transmission. Results from ongoing trials that are designed to answer this question won't be available until 2008.

…PMTCT

If interventions like HSV suppression or pre-exposure prophylaxis (see *Treatment as prevention*, *IAVI Report* **10**, 3, 2006) are found to work, the big challenge will be delivering them. That's where the provision of ARVs for the prevention of mother-to-child transmission of HIV (PMTCT) can provide a sobering lesson (see *VAX* February 2005 *Spotlight* article, *Preventing mother-to-child transmission*). The first trial showing that simply providing ARVs to pregnant women during delivery could protect their infants from contracting HIV was completed 13 years ago, but currently only 9% of pregnant women globally have access to programs providing these ARVs. The number of pediatric AIDS cases in the US reached an all-time low of 58 in 2005, but "each of these cases represents a failure of prevention," said Harold Jaffe from Oxford University in the UK. "We do need better prevention tools," he said, "but until we have them we have to do better with what we've got."

Researchers are now facing a similar challenge as they begin to consider recommending and implementing safe male circumcision programs. WHO officials are currently compiling guidelines on how circumcision should be utilized as an HIV prevention tool. Their primary concern now is safety, not acceptability. Surveys done during the Rakai study showed that 60% of men said they were willing to be circumcised and some of the volunteers randomized to receive circumcision after two years actually tried to re-enter the trial under false names in the hope of getting circumcised sooner, said Gray. The biggest concern with broad implementation of circumcision is that the procedure must be performed in a sterile setting to avoid the risk of infection. During the Rakai trial, almost 4% of the surgeries led to a modest or severe adverse event, although Gray believes this to be an overestimate. At a meeting in March the WHO discussed surveillance plans for monitoring safety outcomes once circumcision becomes more widespread outside the controlled setting of clinical trials.

…Vaccines

Meanwhile some of the leading vaccine candidates are now, or will soon be, in preliminary efficacy trials. A summary of these candidates was provided by Merlin Robb of US Military HIV Research Program (USMHRP). The two most advanced candidates include Merck's adenovirus serotype 5 (Ad5) vaccine candidate, which is already in two Phase IIb test-of-concept trials in the Americas, Caribbean, and Australia, as well as in South Africa (see *VAX* February 2007 *Global News*), and the DNA and Ad 5 candidates developed at the VRC. These candidates are expected to enter a Phase IIb test-of-concept trial, known as PAVE 100, in partnership with IAVI, USMHRP, and the HIV Vaccine Trials Network (HVTN) before the end of the year. Talk of these trials was greeted with optimism. "We really are entering a new era of vaccine development," said Scott Hammer of Columbia University in New York City. "We have vaccines now that are immunogenic, at least in early phases of development."

Protocols are also in development for other new vaccine trials that will test Merck's Ad5 vaccine candidate and the VRC's DNA/Ad5 candidates in different

populations. The VRC is considering testing their candidates in a cohort of adolescent volunteers, as part of the PAVE 100 trial. Merck is also preparing a study protocol to evaluate their candidate in a trial involving infants born to HIV-infected mothers to see if the vaccine could protect babies from HIV infection through breastfeeding. This is particularly important in light of new research presented at CROI that showed that replacing breastfeeding with infant formula (a breast milk replacement) in developing countries, where women have limited access to clean water, can be equally problematic. For several years researchers have promoted use of infant formula as a safer alternative to breastfeeding for infants of HIV-infected women; however, a study in Botswana found that infant formula increased a baby's chance of dying from diarrheal disease by 50 times.

Early weaning, where women stop breastfeeding after only four months, is an alternative strategy to control the transmission of HIV through breastfeeding. But a study measuring the efficacy of this approach in Zambia found that it had absolutely no effect on the number of HIV infections or mortalities in children by the time they reached age two. A trial with Sanofi Pasteur's canarypox vaccine candidate, vCP1521, is already being tested in infants born to HIV-infected mothers in Uganda.

Global News

Therapeutic vaccine trial shows no benefit

At the 14th annual Conference on Retroviruses and Opportunistic Infections, Brigitte Autran of the Hospital Pitié-Salpétrière in Paris presented results showing that therapeutic vaccination with the recombinant canarypox vaccine candidate vCP1452, developed by Sanofi Pasteur, offered no benefit to individuals interrupting their current antiretroviral (ARV) treatment (CROI; www.retroconference.org/2007). Volunteers in this trial received either three or four injections (three primes and one boost) of the vaccine candidate or placebo and were given the option to suspend ARV therapy after receiving the first dose of vaccine. Researchers then monitored these individuals closely and placed them back on therapy if their $CD4^+$ T cells declined below 250 cells per ml of blood—a sign that the immune system is starting to fail.

In previous studies the vaccine candidate showed significant immunogenicity in HIV-infected volunteers and provided modest benefit, according to Autran. But at CROI she reported that in this latest study all volunteers who received the vaccine candidate actually had to resume HAART sooner than those who received placebo. Half of the 20 volunteers who received three immunizations and 14 of 19 who received four injections of vCP1452 had to resume therapy. Meanwhile, only 3 of the 15 volunteers who received placebo had a decline in $CD4^+$ T-cell count that warranted resuming ARV treatment.

Autran called these results "very disappointing" but said that she didn't think this trial should stop further study of this therapeutic vaccination approach. This Sanofi-Pasteur vaccine candidate, vCP1452, is also currently being tested in a preventive AIDS vaccine clinical trial alone or in combination with another vaccine, known as LIPO-5, at HIV Vaccine Trials Network (HVTN) sites in the US. For more information about this or other preventive AIDS vaccine trials, visit the *IAVI Report* clinical trials database (www.iavireport.org/trialsdb).

Canada launches new HIV vaccine development program

The Canadian government, with additional funding from the Bill & Melinda Gates Foundation, is establishing a research institute dedicated to the development of an effective AIDS vaccine. In February Prime Minister Stephen Harper announced his government's pledge of just over US$95 million to fund the new program, which is called the Canadian HIV Vaccine Initiative, and the Gates Foundation also announced it is committing up to $24 million to the project. The Foundation's contribution is another component of the Global HIV Vaccine Enterprise, which was established in 2003 as a way to further accelerate AIDS vaccine research and development.

The primary goals of the Canadian HIV Vaccine Initiative are to support Canadian scientists who are working on the scientific challenges to developing promising AIDS vaccine candidates, construct a new facility capable of manufacturing vaccine candidates for testing in clinical trials, and foster collaboration between researchers, both in Canada and internationally. Canada was one of the first countries to create a national AIDS vaccine plan and the government recently awarded IAVI CAD$20 million to continue its work on the development of a safe and effective AIDS vaccine.

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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 24 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. For more information, go to www.iavi.org.

What evidence exists for immune control of HIV/SIV?

Developing a safe and effective AIDS vaccine is both an urgent public health issue and a huge scientific challenge. The genetic variation of HIV, which is due to the virus's very rapid mutation rate, far exceeds that of many other viruses. To illustrate, the *global* variation of influenza virus each year is less than the variation of HIV in a single infected individual. This genetic variation means that HIV can escape the immune responses mounted against it by the human immune system during the course of natural infection.

Many successful vaccines have used a killed or weakened version of the virus to induce strong pathogen-specific immune responses. But these classical approaches are not being considered for HIV because of safety concerns. Researchers worry that a killed or weakened virus could mutate once inside the body and regain its ability to cause disease (pathogenicity). Despite these obstacles, many researchers still think it is possible to develop a vaccine that will protect against HIV/AIDS.

There is evidence from several different categories of individuals, including exposed seronegatives and long-term nonprogressors, which suggests the human immune system is capable of controlling or even preventing HIV infection, as well as evidence from non-human primate studies to support the notion that vaccine-induced protection is possible. Analyzing the immune responses to HIV or SIV in certain individuals and non-human primates will provide valuable information to researchers who are designing AIDS vaccine candidates.

Exposed seronegatives

One group of individuals that seems to be protected from HIV infection is known as exposed (or highly-exposed) seronegatives (ESNs). These individuals remain free of HIV infection despite frequent exposure to the virus through sexual contact with HIV-infected partner(s). The most well-studied cohort of ESNs is a group of commercial sex workers in Nairobi, Kenya, but several other cohorts are also currently being followed by researchers, including serodiscordant couples where one partner is HIV infected and the other remains uninfected. Researchers are analyzing the immune responses—both cellular and antibody—to HIV in these individuals, as well as any genetic characteristics that they have in common, to try to find out what enables their immune systems to fend off HIV infection. Information collected from ESNs may provide important clues for the design of a preventive AIDS vaccine.

Natural control

HIV begins replicating very rapidly immediately after an individual is infected and the viral load—the amount of virus in the blood—skyrockets. But after the first few weeks and months of infection, the immune system responds to the virus through the adaptive immune system (see *VAX* February and March 2004 *Primers* on *Understanding the Immune System*, *Parts I* and *II*) and makes both cellular and antibody responses specific to HIV. In almost all individuals the immune system is able to effectively control HIV replication. This control lasts, on average, 10 years. During this time there are often no symptoms associated with infection, which is why many people may not know they are actually infected. Eventually HIV overtakes the immune system and an infected person should begin antiretroviral (ARV) therapy. This temporary, but prolonged, control of HIV infection shows that the immune system can mount an effective response against the virus, although it is insufficient to prevent infection or eventual disease progression.

There are also some individuals, known as long-term nonprogressors (LNTPs), who are able to control viral replication for much longer than 10 years without ever taking ARVs (see *VAX* September 2006 *Primer* on *Understanding Long-term Nonprogressors*). There are several different categories of LTNPs and probably many different explanations for why these individuals can effectively control HIV. Studying these individuals can provide information about the type of immune responses or the genetic characteristics that are capable of keeping HIV infection in check.

Live-attenuated vaccines

Studies of simian immunodeficiency virus (SIV) infection in non-human primates (see *VAX* October 2006 *Primer* on *Understanding AIDS Vaccine Preclinical Development*) show that a live but weakened, or live-attenuated, version of SIV can protect against subsequent SIV infection. So far this is the only type of vaccine candidate in human or non-human primate studies that provides complete protection against infection. Again, such studies suggest that protection against HIV is possible and researchers are now trying to learn precisely what immune responses are responsible for protection in non-human primates (see *VAX* December 2006 *Primer* on *Understanding Immune Correlates of Protection, Part II*).

Broadly neutralizing antibodies

Currently none of the vaccine candidates being developed or tested are capable of inducing broadly neutralizing antibodies against HIV (see *VAX* February 2007 *Primer* on *Understanding Neutralizing Antibodies*). However several antibodies that occur in natural infection have been isolated from HIV-infected individuals that, in laboratory experiments, can neutralize many strains of HIV. Also, giving high doses of neutralizing antibodies to non-human primates can protect them from subsequent SIV infection. These studies suggest that the immune system is able to make neutralizing antibodies against HIV and that these antibodies are able to prevent infection. Now researchers need to design the right immunogen, or piece of HIV protein that can be used in a vaccine to cause such an immune response. Unfortunately, designing such an immunogen has proven extremely difficult.

Long road ahead

Information collected from studying ESNs, LTNPs, and the protection of non-human primates from SIV infection will help in the design of better AIDS vaccine candidates. There are still many scientific obstacles to the development of an effective AIDS vaccine but progress in understanding how certain individuals and animals control the virus will help researchers overcome these challenges.