



# IAVI Report

## Contents

**1** And the winner is... HIV treatment and prevention

**1** Molecular snapshots from CROI 2007

**10** An interview with Dennis Burton

**14** Advisory panel considers complexities of HIV prevention trials

**17** In memoriam: Prof. Job Bwayo

**18** In memoriam: Dr. Kenneth Anthony Kalanyi Kebba

**19** Vaccine Briefs

## And the winner is... HIV treatment and prevention

*The red carpet was rolled out at CROI, where talk centered on exciting new treatments and prevention strategies and the need to continue progress on both fronts*

**By Kristen Jill Kresge**

The 79th Annual Academy Awards were the big news in Los Angeles on the evening of Sunday, February 25. Headlines around the world focused on this year's Oscars ceremony—who won, who lost, and what everyone was wearing. American film director Martin Scorsese finally won an Oscar and former US Vice President Al Gore also took home a gold statuette for his documentary film about global warming, *An Inconvenient Truth*. But on that same night a red carpet was also rolled out at another ceremony across town.

This affair, though decidedly less glitzy and glamorous, also grabbed its share of headlines in the following days, including a front-page article in the *New York Times*. The occasion was the 14th annual Conference on Retroviruses and Opportunistic Infections (CROI), and instead of attracting movie stars from Hollywood it drew nearly 4000 HIV researchers and clinicians from around the world.

Although CROI may not attract the same level of celebrity as the Academy Awards, it is still a highlight on the conference calendar of researchers working in the HIV/AIDS field—an opportunity to showcase the latest advancements in prevention and treatment. This year's conferences satisfied all of those interests, ushering in two new classes of antiretrovirals (ARVs) to the treatment armamentarium and focusing on several HIV prevention strategies of the past, present, and future. Prevention of mother-to-child transmission (PMTCT), male circumcision, suppression of herpes simplex-2 virus (HSV-2), and vaccines topped the agenda while many other presentations at the meeting covered the nitty-gritty of HIV transmission and pathogenesis. Researchers shared their gains in the fundamental understanding of HIV biology and possible ways to exploit the dynamics of infection in order to control the virus (see *Molecular snapshots from CROI 2007*, this page). And although the Oscars probably inspired better afterparties, the research presented at CROI could have much more profound and enduring effects.

*continued on page 2* 

## Molecular snapshots from CROI 2007


*Highlights in virology and immunology, from HIV variation and endogenous retroviruses to T-cell memory and exhaustion*

**By Richard Jefferys**

Historically, the annual CROI meeting has concentrated heavily on virology, while immunology and vaccines commanded the attention that you might expect for, say, the Oscar for best animated short film. But the first day of this year's CROI offered two parallel morning

sessions on virology and immunology and, surprisingly, it was the latter session that was standing room only. In a similar shift, vaccines commanded a special symposium that lasted the entirety of Tuesday afternoon. The increased balance of the program is perhaps a welcome sign that

the relative success of antiretroviral therapies has sharpened the focus on the complex immunological questions that confront researchers in the disparate fields of AIDS pathogenesis, preventive vaccine research, and immune-based therapy development.

*continued on page 6* 

### 'A convenient truth'

The Bernard Fields Lecture on the opening night of CROI was delivered by Edward Berger of the US National Institute of Allergy and Infectious Diseases (NIAID), who told the story of the seminal discovery of the cellular co-receptors on the surface of CD4<sup>+</sup> T cells that HIV uses during entry into the cell. Early work in this area was motivated by the study of some rare individuals that were immune to HIV infection, and this immunity was eventually attributed to a genetic deletion, known as a  $\Delta 32$ , in their CCR5 gene. The lack of CD4<sup>+</sup> T cells expressing CCR5 at the surface is still the only molecular explanation for resistance to HIV infection, despite repeated exposure to the virus.

Subsequent work has illustrated the precise interaction between gp120 and CD4<sup>+</sup> T cells, which triggers fusion of the virus and therefore subsequent infection. This original discovery held great promise for both prevention and therapy and recently significant advances occurred in both areas.

Just a few weeks ago AIDS vaccine researchers came a step closer to understanding how this interaction between CD4<sup>+</sup> T cells and a highly conserved region of the viral surface protein gp120 can be disrupted by a broadly neutralizing antibody known as b12 (*Nature* 445, 732, 2007). Dennis Burton of Scripps Research Center in La Jolla, California who participated in this research with Peter Kwong and colleagues at the Vaccine Research Center (VRC) at NIAID said, "This provided us for the first time with very detailed molecular information," which can now be used to design improved immunogens. "That's still an enormous structural challenge," said Burton, "but we have some of the best structural scientists in the world working on this." (See *Interview with Dennis Burton*, page 10.)

Also at CROI, the field of HIV treatment was reenergized by news of the first drugs in two novel classes of ARVs. The first is a small molecule designed to obstruct the CCR5 receptor-binding pocket and effectively block attachment. This CCR5 inhibitor, known as maraviroc, dramatically reduced the level of viral replication in HIV-infected individuals (Abstract 104aLB and 104bLB, [www.retroconference.org/2007](http://www.retroconference.org/2007)). The data presented at CROI is now also being considered by the US Food and Drug Administration as the basis for licensure.

Another novel ARV is also a step closer to becoming a reality. For more than a decade researchers have been trying to interfere with HIV's integrase to prevent the virus from inserting its genetic material into chromosomal DNA, but identifying safe and effective compounds has proven an arduous task. Now, based on Phase III trial results presented by US pharmaceutical company Merck, a new drug called raltegravir is highly effective at lowering viral replication, as measured by a significant drop in viral load in individuals given the drug in addition to their highly-active antiretroviral therapy (HAART) regimen (Abstract 105aLB and 105bLB).

News of these novel ARVs caused quite a stir at CROI and many insisted that there hasn't been this much enthusiasm since the first studies showed that HAART was an effective strategy for controlling HIV infection.

### And the nominees for HIV prevention are ...

In the prevention sessions the enthusiasm was more tempered. "This has been quite a remarkable year in the study of HIV interventions," said Judy Wasserheit of the University of Washington in Seattle. She mentioned both the highs—the very encouraging results of the circumcision trials—and the lows, including the recent results from the cellulose sulfate trial that show the candidate microbicide may actually enhance risk of HIV acquisition (see *Advisory panel considers complexities of HIV prevention trials*, page 14).

### ...Circumcision

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 (Abstract 155aLB). This trial was stopped prematurely by the data safety monitoring board in December 2006 because of indications that the intervention could lower the risk of HIV acquisition by greater than 50%, supporting earlier results from another randomized, controlled clinical trial of circumcision in South Africa (see *Cutting HIV transmission*, *LAVI Report* 9, 3, 2005).

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.

  
**This has  
been quite a  
remarkable  
year in the  
study of HIV  
interventions**

Judy Wasserheit

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 this may be due to complete keratinization of the wound, 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 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 was not a dominant influence in this trial.

The investigators also found that circumcised men who reported multiple sexual partners or partners outside of marriage 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 (Abstract 155bLB); researchers observed a 0.6% HIV incidence among circumcised men who reported a genital ulcer disease and 1.8% in those who didn't, compared to 1.1% and 6.3% among uncircumcised men with or without genital ulcer diseases respectively. Overall, circumcision reduced the rate of symptomatic genital ulcer diseases by 47%. Although circumcision is protective irrespective of co-infection with these 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 HSV-2, the cause of genital herpes. There are currently several ongoing studies to test whether treating HSV-2 with acyclovir or valacyclovir can reduce the levels, or frequency, of HIV shedding in the genital tract or reduce transmission of the

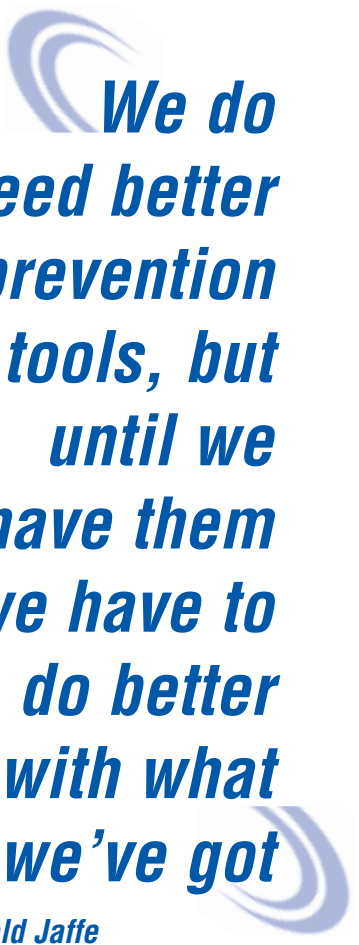
virus by reducing the symptomatic ulcerations (see *HIV prevention in a pill?*, *LAVI Report* 9, 4, 2005).

Two studies presented at CROI looked specifically at the genital shedding of HIV in 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 HIV shedding (-0.4 log copies of virus) as determined by cervical vaginal lavage (Abstract 30). 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 symptomatic HSV-2 infection or in those who are more severely immunocompromised and therefore have higher viral loads.

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, indicated that there was no statistically significant difference in the levels of HIV in the genital tract of women given acyclovir over a four-month period (Abstract 154LB). Acyclovir therapy did however seem to reduce the periodic frequency of HIV shedding in the genital tract. Delany said further study is required to determine whether acyclovir therapy can limit the HSV-2 ulcerations and thereby lower HIV transmission rates. Results from these ongoing trials won't be available until 2008.

#### **...PMTCT**

If interventions like HSV suppression or pre-exposure prophylaxis (see *Treatment as prevention*, *LAVI Report* 10, 3, 2006) are found to work, the big challenge will be delivering them. That's where the provision of ARVs for PMTCT can provide a sobering lesson (see *New strides in protecting infants from HIV*, *LAVI Report* 9, 2, 2005). The first trial showing that this simple intervention could protect infants from contracting HIV was completed 13 years ago but currently only 9% of pregnant women globally have access. 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."

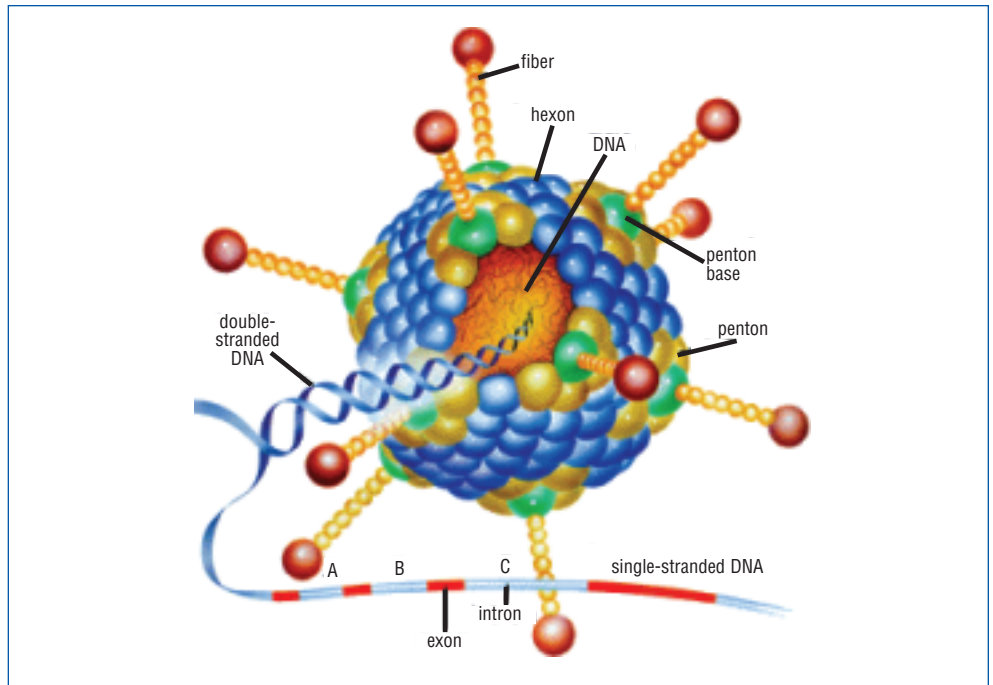


**We do  
need better  
prevention  
tools, but  
until we  
have them  
we have to  
do better  
with what  
we've got**

**Harold Jaffe**

*We really are entering a new era of vaccine development. We have vaccines now that are immunogenic, at least in early phases of development*

**Scott Hammer**



**Figure 1. Adenovirus particle.** Adenoviruses are non-enveloped, double-stranded DNA viruses with icosahedral symmetry. The viral capsid is composed of 240 hexon proteins (shown in blue) and 12 penton base proteins (shown in green). The fiber spike associated with each penton base allows the virus to attach to human cells using the coxsackie-adenovirus receptor. There are 51 serotypes of human adenoviruses identified so far, three of which are currently in or soon to enter clinical trials as AIDS vaccine vectors (Ad5, Ad35, and Ad26). To circumvent pre-existing immunity to these vectors, Dan Barouch and colleagues have constructed a chimeric Ad5/Ad48 virus where the hexon proteins, the primary target of antibodies, are substituted with the corresponding proteins from Ad48.

**Measure twice, cut once**

Researchers are now facing this challenge as they begin to consider recommending and implementing safe 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 the control arm actually tried to re-enter the trial under false names in the hope of getting circumcised, 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 HIV 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 a clinical trial.

**The HIV envelope please**

Interest in the somewhat beleaguered research into AIDS vaccine candidates that

induce potent humoral immune responses was boosted by recent structural work by Peter Kwong of the VRC and colleagues and some of this excitement spilled over into CROI. Burton summarized the importance of this study in a plenary talk entitled “Toward broadly neutralizing antibodies against HIV,” but also made it clear that it’s a long way until this work is translated into the design of better vaccine candidates (Abstract 99). “Studying natural infection doesn’t give the answer.” Instead, he said, AIDS vaccine researchers are left to “make up new rules.”

Meanwhile some of the leading cellular immunity-focused vaccine candidates are now, or will soon be, in preliminary efficacy trials. A summary of these candidates—including Merck’s adenovirus serotype 5 (Ad5) vaccine and the DNA and Ad 5 candidates developed at the VRC—was provided by Merlin Robb of US Military HIV Research Program (USMHRP) and was greeted with optimism (Abstract 103). “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.”

But David Ho of the Aaron Diamond AIDS Research Center in New York City cast some

doubt on this immunogenicity. In his overview presentation on the evidence to support possible clinical efficacy of T-cell based vaccines, he reminded the mixed audience of vaccine researchers and HIV clinicians that there is still no way of knowing if the number of spot-forming cells (SFCs) determined by the ELISPOT assay actually corresponds to T cells that can limit the virus's spread. "Reason tells us that they might, but formally this has not been documented." He was much more careful in his assessment of current research efforts. "Incremental progress is happening in the field, but it is happening at a rather slow pace," he said. "We should've appreciated earlier how difficult the task at hand is."

Even if the leading Ad-5 based candidates are immunogenic their efficacy in humans may be compromised by pre-existing immunity to the viral vector, which has motivated researchers to start looking at other serotypes or novel chimeric adenovirus vectors that can be used in heterologous prime-boost regimens with Ad5 (see Figure 1). Dan Barouch, of Beth Israel Deaconess Medical Center in Boston, and his colleagues determined first the seroprevalence of 51 known serotypes of human adenovirus in different countries in Africa and then the immunogenicity of four of these serotypes (Ad26, 48, 49, and 35) in rhesus macaques (Abstract 98) and found that Ad26 was the most immunogenic. They also constructed a chimeric Ad5 vector with all of the hypervariable regions of the hexon capsid protein—the viral protein to which antibodies are directed—replaced by the same regions of a much lower seroprevalent adenovirus, Ad48. They then tested the immunogenicity of both the Ad5/Ad48 chimera and the Ad26 vectors with HIV inserts in rhesus macaques who had already received two injections of an unadulterated Ad5 vaccine candidate. After boosting, the animals had T-cell responses that ranged from 1000 to 15,000 SFCs per million peripheral blood mononuclear cells (PBMCs), indicating that pre-existing immunity could be overcome with these non-Ad5 vectors.

Barouch also conducted a series of experiments with different heterologous prime-boost regimens, including Ad26/Ad5, Ad48/Ad5, and Ad49/Ad5. Data he presented at CROI showed that the Ad48 primed better than Ad49, but to a lesser extent than Ad26. The Ad26/Ad5 combination also "boosted remarkably well," Barouch said, with responses in the range of 2400 SFCs. This het-

erologous prime-boost was 5-fold more immunogenic than a homologous prime-boost with Ad5 in rhesus macaques.

Both the Ad26 and the Ad5/Ad48 chimeric vaccine candidates encoding clade A HIV *env* genes will go into Phase I clinical trials to assess their safety and immunogenicity in humans. Pending regulatory approval, Barouch expects these trials to start before the end of the year.

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 currently planning a Phase IIb test-of-concept trial with this prime-boost regimen, in partnership with IAVI, USMHRP, and the HIV Vaccine Trials Network (HVTN). This trial, known as PAVE 100, may start before the end of the year and the VRC is now also considering testing these candidates in a cohort of adolescent volunteers.

Merck's Ad5 vaccine candidate is already in two Phase IIb test-of-concept trials in the Americas, Caribbean, and Australia, as well as in South Africa (see *Vaccine Briefs, IAVI Report* 10, 6, 2006), and now the company is also preparing a protocol to evaluate the 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 at CROI that showed that replacing breastfeeding with formula feeding in developing countries, where women have limited access to clean water, can be equally problematic. For several years researchers have promoted formula feeding as a safer alternative to breastfeeding for infants of HIV-infected women; however, a study in Botswana found that use of infant formula increased a baby's chance of dying from a diarrheal disease by 50 times (Abstract 9).

Early weaning is another alternative strategy researchers tried to control the transmission of HIV through breastfeeding—instead of breastfeeding for more than a year women were asked to stop after four months. A study measuring the efficacy of this approach in Zambia found that early weaning had absolutely no effect on the number of HIV infections or mortalities by age two (Abstract 74LB). A trial with Sanofi Pasteur's canarypox vaccine candidate, vCP1521 is already being tested in infants born to HIV-infected mothers in Uganda. ■



**Incremental progress is happening in the field... We should've appreciated earlier how difficult the task at hand is**



**David Ho**