



Spotlight

HIV prevention relay race

Researchers gathered at the International AIDS Conference focused on long-term efforts to control the spread of HIV

If there is one thing researchers have come to realize in their search for a safe and effective AIDS vaccine, it's that the virus doesn't allow its victims—or science—much time to mount a successful defense.

Within six days after exposure to HIV—the length of time the approximately 25,000 researchers, healthcare workers, and activists gathered at the XVII International AIDS Conference in Mexico City, August 3-8—the virus overcomes the body's initial defenses and spreads rapidly through the blood, turning HIV into the biological equivalent of a runaway train.

This early, yet crucial, chapter in the life cycle of the virus was referenced in a number of key talks at the sprawling conference. “We refer to [those six days] as a window of vulnerability,” said Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), who spoke about new directions in HIV prevention research. “But [those days] can also become a window of opportunity,” he added. “Our success or failure with vaccines, as well as with our ability to ultimately control [and] perhaps even cure HIV, will rest in that very short time frame.”

Recent setbacks in the HIV prevention field, as well as the latest statistics regarding the spread of the virus, pushed prevention research to the forefront of many discussions at this year's conference,

reminding attendees why vaccines and other biomedical methods of preventing HIV transmission represent enormous and thus far unmet challenges for scientists. Much of the focus was on vaccines, microbicides, and oral pre-exposure prophylaxis (PrEP), as well as the implementation of safe male circumcision programs.

A clearer picture of the epidemic

Though major strides have been made in the past decade in both the development of new antiretrovirals (ARVs) and in providing ARV treatment to more people living with HIV/AIDS, countries have been less successful in controlling the spread of new infections, particularly in high-risk populations. The US Centers for Disease Control and Prevention (CDC) released updated HIV incidence estimates at the conference showing that the annual number of new infections has been more than 16,000 higher in the US than the estimated 40,000 new infections each year that had been continuously reported since the mid-1990s (see *VAX* May 2008 *Spotlight* on *A static epidemic*).

The most recent estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS), which were released just prior to the start of the conference, indicate that 33 million people are currently living with HIV/AIDS and that 2.7 million new HIV infections occurred globally last year. Although the rate of new HIV infections has fallen in some countries, including in some of the hardest-hit regions of sub-Saharan Africa, this has been offset by increases in new infections in other countries, according to the UNAIDS report.

Moreover, the cost of treatment has grown astronomically since the advent of highly active antiretroviral therapy (HAART). To meet the goal of universal

access, UNAIDS estimates it will cost approximately US\$54 billion each year to provide ARVs to those in need in low- and middle-income countries by 2015.

A shifting pipeline

“We have absolutely no choice but to continue to develop the science required for an HIV vaccine no matter how long it takes,” said Myron Cohen, associate director of the University of North Carolina's Center for AIDS Research during his plenary talk on preventing the sexual transmission of HIV. The failure of Merck's cell-mediated adenovirus serotype-5 (Ad5) vector-based candidate to show any efficacy in a large Phase IIb test-of-concept trial last September has steered AIDS vaccine researchers back to basic science, and the conference unexpectedly became a forum to showcase these shifting priorities.

The most vibrant example of this shift occurred last month when Fauci decided not to move forward with another Phase IIb test-of-concept trial known as PAVE 100A, which was to evaluate an Ad5 vector similar to Merck's as a boost vaccination following multiple immunizations with a DNA-based vaccine candidate (see *PAVEing the way to a smaller trial*, *LAVI Report*, July-August, 2008). Although Fauci is considering a smaller trial in place of PAVE 100A, the pipeline of vaccine candidates could still shrink in coming months. In its biennial *2008 AIDS Vaccine Blueprint*, IAVI recommended that less promising vaccine

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candidates get weeded from the current clinical pipeline and that the freed-up resources be shifted instead to basic discovery efforts that will help researchers develop improved AIDS vaccine candidates (see *Global News*, this issue).

While the results of the STEP trial may have slowed interest in the development of AIDS vaccine candidates that induce primarily cellular immune responses against the virus (see *VAX* July 2008 *Special Issue, Understanding the Immune System and AIDS Vaccine Strategies*, and *VAX* April 2008 *Primer on Understanding Cellular Immune Responses*), clinical investigators say there is still much to be learned from the trial volunteers. Susan Buchbinder, of the San Francisco Department of Public Health and a principal investigator of the STEP trial, said researchers are still awaiting data from trial volunteers that may help researchers determine what contributed to the candidate's lack of efficacy, including behavioral factors such as the possibility of sexual networks among uncircumcised men at certain trial sites that led to higher rates of HIV infection. Investigators are also still trying to determine why some vaccinated volunteers—uncircumcised men who have sex with men (MSM) who had immunity to the modified cold virus used in the vaccine candidate because of natural exposure—seemed to be at a higher risk of HIV infection.

Buchbinder noted that the retention rate in the STEP study, even after the immunizations were suspended and volunteers were unblinded—told whether they received the vaccine candidate or placebo—is still about 95%. “We explained to the study volunteers that this is a pivotal trial and that we need their continued participation and our retention rates have been very, very high,” said Buchbinder, adding that this was “a testament to the incredible dedication of our study volunteers.”

A number of sessions at the conference also focused on ways to attract a new generation of researchers into the AIDS vaccine field, an issue that has become in vogue lately. “Everywhere you go it is the same faces,” said Mauro Schechter, chief of AIDS research at the Universidad de Federal do Rio de Janeiro in Brazil. “Where is the next generation? We are not giving the right message if we do not tell all the researchers that this is a relay race,” he said.

A pill to prevent HIV?

With no AIDS vaccine looming on the horizon, there is increasing attention being placed on the growing array of clinical trials evaluating PrEP—the administration of ARVs to uninfected individuals to prevent HIV infection (see *VAX* May 2006 *Spotlight on Treatment as prevention*). Nowhere was this more evident than at the conference, where the status of PrEP trials and future concerns about its effectiveness and implementation were discussed at a broad range of sessions and received considerable media coverage.

There is no evidence yet from trials evaluating whether daily administration of the ARV tenofovir or a combination pill of two ARVs known as truvada will be effective at preventing HIV transmission, but researchers and advocates are

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Mitchell Warren

gearing up for the results. If effective, there will be many obstacles to successful implementation of PrEP programs. “We may have an answer in 2-3 years and we have to make sure we are ready for the data,” said Mitchell Warren, executive director of the AIDS Vaccine Advocacy Coalition, which released a report on PrEP at the conference.

Seven PrEP trials are currently underway or in the planning stages, including one involving 4,200 women in southern Africa to evaluate a gel-based microbicide containing tenofovir to determine its ability to block HIV infection. The furthest along of the oral PrEP trials, being conducted by the CDC, is testing tenofovir in 400 HIV-uninfected MSM in the US. Results are expected next year, according to Timothy Mastro, senior director of research at Family Health International, a sexual and reproductive health organization that is funding another PrEP trial that will begin enrolling volunteers in Africa this year.

Mastro said the primary purpose of the current batch of studies is to determine whether an ARV-based intervention prevents HIV infection and whether it is safe. Only then will researchers tackle some of the thornier issues. “Then we will evaluate risk behaviors, adherence, alteration of disease progression, and whether or not [HIV] resistance develops in those that become infected [during the] trial,” he said.

In total, the seven PrEP studies will include close to 18,000 volunteers, and that number is likely to get even higher because study investigators for at least two of the trials have decided to expand enrollment after observing a lower HIV incidence rate than what was previously estimated for the study population (see *VAX* July 2007 *Primer on Understanding HIV Incidence*).

An underutilized strategy

Meanwhile, questions are mounting about why the implementation of male circumcision programs is lagging. Three years ago, researchers halted two large randomized controlled trials after data showed that male circumcision reduced HIV transmission by as much as 65% in heterosexual men. Despite the plethora of favorable data, researchers and AIDS advocates at the conference reported that the intervention is underutilized, particularly in regions of sub-Saharan Africa where heterosexual sex is the primary mode of HIV transmission.

Robert Bailey, an epidemiologist from the University of Illinois, reported at the conference that male circumcision did not appear to increase HIV risk behavior in a randomized control trial of 1,319 men in Kenya. Bailey, who has been studying circumcision for more than a decade, also presented data based on surveys of men in a Kenyan cohort, which suggested that circumcision actually increases penile sensitivity and results in an enhanced ease of reaching orgasm among newly circumcised men as compared to men in an uncircumcised control group.

Still, efforts to provide the procedure to men have faced a number of cultural, religious, and even political barriers.

Next-generation microbicides

The development of topical microbicides that women can apply before intercourse to prevent HIV transmission was a hot topic at the 2006 AIDS conference in

Toronto, particularly after Bill and Melinda Gates specifically called for increased research efforts into their development. But the announcement earlier this year that the microbicide gel Carraguard had no effect on HIV infection rates in women enrolled in a Phase III clinical trial made it just the latest in a string of candidates that have failed to provide protection against HIV (see *Vaccine Briefs*, *IAVI Report*, March-April, 2008).

Zeda Rosenberg, chief executive officer of the International Partnership for Microbicides, spoke at a number of sessions about the development of a new generation of microbicides, based on existing ARVs, which many researchers consider more promising than those previously tested.

The results from the first efficacy trial of one of these second-generation candidates are not expected until

2010, when a Phase IIb test-of-concept trial testing a gel containing the ARV tenofovir will be completed in South Africa. However, a study released at the conference was cause for optimism. Researchers at the CDC showed that a microbicide candidate consisting of two ARVs provided almost complete protection in rhesus macaques against the monkey equivalent of HIV. —*Regina McEney*

Global News

AIDS Vaccine Blueprint launched: A challenge to the field

The *AIDS Vaccine Blueprint 2008*, IAVI's biennial report on the state of AIDS vaccine research and development and a roadmap for the field, was released at the XVII International AIDS Conference in Mexico City, August 3-8. It issues several challenges to AIDS vaccine researchers and outlines interim goals toward overcoming many of the obstacles impeding vaccine development, as well as milestones by which the field can measure its progress.

The *Blueprint*, which IAVI has been producing since 1998, strikes a different theme and tone than two years ago when more than two dozen AIDS vaccine candidates were moving through the pipeline, including Merck's cellular immunity-based vaccine, known as MRKAd5, which many researchers regarded as the most promising.

Merck and the US National Institute of Allergy and Infectious Diseases stopped immunizations in the Phase IIb test-of-concept trial of this candidate last September after it failed to provide any protection against HIV infection. "Two years ago, we all thought we had a signal of hope from Merck," said Seth Berkley, the founder and CEO of IAVI. "What has happened is we've learned a lot about the science."

Because most of the AIDS vaccine candidates currently in clinical trials employ strategies similar to MRKAd5, the IAVI *Blueprint* urges stakeholders to "review their portfolios and drop candidates considered to have a low probability of success."

IAVI suggests that the resources be spent instead on research efforts to develop a more diverse clinical pipeline of

AIDS vaccine candidates that can induce both cellular immune responses and antibodies against HIV (see *VAX* July 2008 *Special Issue on Understanding the Immune System and AIDS Vaccine Strategies*).

Other recommendations in the *Blueprint* include establishing incentives to enhance innovation in AIDS vaccine discovery, and training the next generation of researchers. "Science is not a straight line," said Alan Bernstein, president of the Global HIV Vaccine Enterprise, commenting about the recent setbacks in the AIDS vaccine field. "It's clear after 25 years that we are on a long journey." —*Regina McEney*

Passage of PEPFAR

US President George Bush recently signed into law a revised version of the President's Emergency Plan for AIDS Relief (PEPFAR) authorizing US\$48 billion in funding over the next five years to expand existing HIV/AIDS prevention, treatment, and care efforts worldwide. The original five-year, \$15 billion plan, which has supported the provision of life-saving antiretroviral (ARV) treatment for approximately 1.7 million HIV-infected people, was due to expire in September.

The revised version more than doubles the amount of funding for HIV/AIDS prevention, treatment, and care programs, and also authorizes \$9 billion in funding for malaria and tuberculosis programs.

A section of the new PEPFAR bill also contains provisions related specifically to facilitating the development of vaccines, including those against HIV/AIDS, tuberculosis, and malaria. The US President is required to report to Congress within one year on a strategy for accelerating the development of these vaccines, including details on creation of economic incentives for research, development, and manufacture, as well as the efforts taken by the US to support clinical trials of vaccines in

developing countries and to prepare these countries for the introduction of new vaccines. —*Jonathan Grund, contributing writer*



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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.

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What are the implications of the genetic diversity of HIV for AIDS vaccine development?

Over the past century, scientists have assembled an impressive arsenal of vaccines to combat germs. Such vaccines have helped eradicate deadly scourges like smallpox and also shield millions of people each year from contracting the flu.

Influenza A and B viruses, which are responsible for seasonal flu epidemics, are constantly changing and evolving as they circulate throughout the population. This is a survival mechanism for viruses. Like many vaccines, those against influenza work by inducing antibodies—Y-shaped proteins that bind to viruses and prevent them from infecting human cells—against the virus that can effectively neutralize it (see *VAX* July 2008 *Special Issue, Understanding the Immune System and AIDS Vaccine Strategies*). An accumulation of changes or mutations at the site on the virus where these antibodies bind results in the formation of new strains of the virus that can effectively evade these antibodies, and therefore continue circulating within the population.

The amount of variation between strains of the same virus differs greatly. Influenza viruses change or mutate rapidly, forming new strains each year, which is why previously vaccinated individuals must get an annual flu shot to be protected. Vaccine developers study the mutation patterns of the virus and predict which strain will most likely be in circulation in a given season, and then update the influenza vaccine each year so that it will ideally protect against the predominantly circulating strain.

But compared to HIV, influenza's mutation rate is remarkably slow. The genetic variation of HIV in a single infected individual is about the same as the yearly genetic variation of influenza within the entire human population. Of all human viruses, only the hepatitis C virus mutates more rapidly than HIV.

The incredible genetic variation of HIV occurs because the virus reproduces or replicates so rapidly once inside a human. In a single HIV-infected person, between one billion and 10 bil-

lion HIV particles are produced every day. HIV makes several mistakes as a result of this rapid-fire replication rate. These mistakes are like a typing error—hitting the wrong key and therefore changing the spelling of a word. HIV's mistakes result in changes in its genetic sequence (see *VAX* July 2006 *Primer on Understanding HIV Clades*). Each change in the genetic sequence of the virus results in a unique version of the virus in an HIV-infected person, which in turn contributes to the extreme genetic variation of HIV globally. This variation could represent a significant challenge to AIDS vaccine researchers.

Sequencing technologies

Researchers have extensively studied the genetic variation of HIV in an attempt to inform AIDS vaccine design. Genetic sequencing, a process by which researchers can break down the virus into its genetic building blocks, has enabled scientists to distinguish different versions of HIV and classify them into different subtypes or clades. More efficient sequencing software has also begun to expose critical changes in the dynamics of HIV's evolution. With the help of more sensitive sequencing technologies, scientists can now better understand the full diversity of HIV that is currently in circulation, including low-frequency variants undetected by older sequencing methods. These hard-to-detect variants are also important to consider when designing AIDS vaccine candidates.

In recent years, researchers have also begun employing advanced genetic sequencing methods to mine areas of vulnerability in HIV's genome. One area of vulnerability are the sections of the virus that don't vary much between different clades, so-called constant regions. These areas are important targets for vaccine researchers who are trying to develop vaccine candidates that would provide broad protection against the majority of HIV variants in circulation. Another area of vulnerability is the specific location on the virus where antibodies bind. Knowing the genetic sequence of the virus at the point where the antibody binds can help researchers identify the best immuno-

gens—harmless pieces of HIV that are inserted into vaccine candidates in the hope of inducing an immune response against the virus. Researchers are also honing in on mutations that occur very early in the course of HIV infection.

Learning from trials

It is still unclear to what extent the genetic variation of HIV will matter in the context of AIDS vaccine development. Some AIDS vaccine candidates have included HIV immunogens from several clades to try to induce broad protection against several different clades of HIV, while others have included immunogens from a single HIV clade.

Researchers typically test AIDS vaccine candidates in geographical areas where the predominantly circulating clade of HIV matches the clade of the immunogens in the vaccine candidate. For example, the recently conducted STEP trial of Merck's MRKAd5 vaccine candidate, which contained clade B HIV immunogens, was conducted in countries where the predominant virus in circulation was HIV clade B. However, in a companion trial to the STEP study, known as Phambili, researchers were testing this MRKAd5 candidate with clade B HIV immunogens in South Africa, where clade C HIV is predominantly circulating. Immunizations in this trial were stopped ahead of schedule after results from the STEP trial showed that the candidate did not provide any protection against HIV infection.

To determine if genetic variation played a role in MRKAd5's inability to protect, researchers are carefully studying samples from the volunteers in the STEP trial who became HIV infected through natural exposure to the virus despite receiving MRKAd5. By analyzing the genetic sequence of HIV that infected these individuals, researchers can determine how different it was genetically from the immunogens that were included in MRKAd5. If the genetic sequence of the infecting virus and the immunogens are vastly different, researchers may determine that this played a role in the failure of the vaccine candidate to protect against HIV infection.