The last time the International AIDS Conference was held in Washington, D.C., the number of antiviral drugs licensed to treat AIDS was zero. That was in 1987, and US regulatory approval for zidovudine (AZT) was still a year away. But it was already clear that the pandemic was escalating at a frightening pace, and the US Public Health Service placed national travel and immigration restrictions on people with HIV. Activists in the country, meanwhile, mobilized to form the AIDS Coalition to Unleash Power—or ACT UP—to push researchers to find effective treatments for their dying loved ones. Half a world away, Ugandans established the first AIDS clinic in Africa and, in 1987, The AIDS Support Organization (TASO) began providing quality care for HIV-infected people.

A quarter century later, with the biennial conference once again at the doorstep of the US Capitol, the landscape and mood of the 19th International AIDS Conference—AIDS 2012 for short—will look and feel profoundly different, even if the ultimate message of both meetings remains the same. For one, the 25,000 attendees expected to attend the event, which will take place July 22-27, and will include keynote talks from Elton John, Bill Clinton, and Bill Gates—is a much larger group than the 6,000 who attended the 1987 meeting, though it could be argued the 1987 conference was more newsworthy. An astounding 900 journalists covered those proceedings.

The location of the conference is also seen as symbolic, and not because a US presidency hangs in the balance. The last time the conference was held in the US was in 1990. The International AIDS Society—which sponsors the meeting—decided to host the conference in Washington, D.C., after the Obama administration announced, in December 2009, that it was lifting the controversial travel ban on HIV-infected people. Former International AIDS Society (IAS) president Julio Montaner had previously noted that the ban had no scientific or public health merit (see VAX Dec. 2009 Spotlight article, A Year of Progress).

IAS president Elly Katabira, who helped start TASO, is presiding over AIDS 2012. It is billed as the largest conference dedicated to a single issue and its theme this year is “Turning the Tide Together.”

There has been much progress in HIV treatment since the conference was last held here. Today, an arsenal of some 30 antiretroviral drugs are available for the treatment of the HIV-infected. The drugs have been highly effective in suppressing HIV in those fortunate enough to have access to them. Some have even been found to be effective, in some instances highly effective, in reducing HIV transmission. The US Food and Drug Administration is expected to rule in September on whether the ARV known as Truvada—a combination of the drugs tenofovir and emtricitabine—may be used for HIV prevention in certain high-risk populations (see Primer, this issue). Further, a recent international trial found earlier ARV treatment of HIV-infected individuals reduced HIV transmission to their HIV-uninfected partners by 96%.

ARVs are not the only bright spot. Adult male circumcision, another effective strategy for curtailing HIV transmission, is expanding in sub-Saharan Africa. The arduous hunt for an effective vaccine has been buoyed in recent years by a series of clinical and preclinical breakthroughs. And scientists are even launching research programs to accomplish what was until relatively recently considered pretty much impossible—curing HIV infection.
Dr. Anthony Fauci, the director of the US National Institute of Allergy and Infectious Diseases (NIAID) and a speaker at the 1987 meeting, recalled how bleak the atmosphere was back then. “AZT wasn’t widely used and it was only a single drug. Its effect was short-lived,” he says. “We had a raging epidemic with an infection rate exploding in front of our eyes. And we didn’t even fully realize what it was like in the developing world.”

Fauci will be giving the opening plenary talk at AIDS 2012 on July 23, and he’ll have far more scientific tools to highlight this time around, though the global economic slump threatens funding for their development. “Our challenge is to work collectively to implement these proven interventions in order to make an AIDS-free generation truly possible,” wrote Fauci and his chief of staff, Gregory Folkers, in a recent blog post in advance of the conference. “This will require increased financial resources, innovation, political will, an overall strengthening of health systems, fighting stigma, and greater ownership by all countries of HIV/AIDS efforts within their borders.”

A July 25 plenary address will focus exclusively on AIDS vaccines (see VAX Q&A with Barton Haynes, this issue), and about two dozen talks will focus on vaccine science. But vaccines will not be a major presence at this meeting of 3,500 oral abstracts and dozens of satellite and special sessions.

Bill Snow, the Global HIV Vaccine Enterprise’s new director, says the limited number of vaccine talks isn’t surprising. “I think that it has always been the case that vaccines have been underplayed, largely because of IAS and because of who comes to these meetings,” says Snow. “There is always an immediacy to these conferences, always something people need to change right away. The social and political agenda has driven everything, which I do think is fabulous and really important.”

Snow says resources for AIDS research are clearly flat, which is overshadowing the scientific discussions, provoking calls for greater collaboration between researchers and funders, and forcing funders to make tough choices on which projects to keep funding and which ones to sideline. At the same time, he says, the field is increasingly focused on studying different prevention strategies together—such as pre-exposure prophylaxis (PrEP) with a vaccine candidate—because such approaches might dramatically lower HIV incidence in some high-risk populations.

“There is really a lot of work and thought going on into how trials will fit together, what the prevention package will be relative to the intervention tested, and how that is played out,” he says. “The funding crisis is really causing people to focus and prioritize, which is not a bad thing.”

Some advocates and researchers are now pushing for universal access to testing and treatment as a way to end the pandemic. But Mark Dybul, co-director of the global health law program at Georgetown University’s O’Neill Institute, who led the implementation of the President’s Emergency Program for AIDS Relief (PEPFAR) under US President George W. Bush, says there is no silver bullet that can eradicate HIV. “What a lot of us are talking about is combination prevention and really focusing on high transmission geographies and populations, because in different countries and in different parts of different countries, there are different drivers of the epidemic,” he says.

“There has already been a greater than 25% reduction in HIV incidence in 33 countries, 22 of them in sub-Saharan Africa,” says Dybul. “In some countries, the declines are as high as 40% to 60%.” He says countries need to be smart and focused on where the epidemics are occurring because there aren’t going to be resources to cover every country with every intervention.

Mitchell Warren, executive director of AVAC, based in New York, says the AIDS 2012 conference will predominantly be about making the right decisions about allocating resources for the future. “For instance, how do we optimize ARVs for treatment and prevention? How can we scale up adult male circumcision now? How can we bend the curve of the epidemic today?”

Warren says the global momentum to address the AIDS epidemic using scientifically proven methods, such as oral and topical ARV-based prevention and adult male circumcision, would undoubtedly save lives, prevent new infections, and lower the price tag for the global AIDS response over time. But he says a vaccine is still needed if the world wants to end the epidemic once and for all. “There will be people [at AIDS 2012] in D.C. who say that if we test and treat everyone who is HIV infected that will be enough to end the epidemic. Others will say that is not enough, that PrEP has a role. And male circumcision is important. The bottom line is they are all right, but how do we move beyond the technology that is specifically being championed and into a decision-making mode that pulls the pieces together?” wonders Warren.

At the same time, he says, sustained funding is needed for AIDS vaccine scientists to continue producing breakthroughs, such as the discovery of new and more potent broadly neutralizing antibodies that has helped breathe new life into antibody-based research. He also says the AIDS vaccine field needs to set and communicate milestones for measuring progress in order to keep the pipeline of vaccine candidates robust and flexible.

Warren says that, ideally, a vaccine would be cheap, easy to administer, and offer lifelong protection after a single immunization, unlike the more complex six-shot regimen that was tested in the RV144 trial that in 2009 demonstrated the first evidence of vaccine-induced efficacy (see VAX Sep. 2009 Spotlight article, First Evidence of Efficacy from Large-Scale HIV Vaccine Trial). “Someday, an AIDS vaccine might fit that description,” he says.
While the use of antiretroviral therapies to prevent HIV infection will likely dominate the scientific agenda at the 19th International AIDS Conference (AIDS 2012) in Washington, D.C., July 22-27, researchers are also paying attention to AIDS vaccines. VAX Science Writer Regina McEnery recently caught up with Barton Haynes, a Duke University professor who leads the virtual consortium known as the Center for HIV/AIDS Vaccine Immunology (CHAVI), to hear more about new findings from the RV144 trial in Thailand and the search for more potent and broadly neutralizing antibodies against HIV, which will be the subject of his July 25 plenary talk at AIDS 2012.

Even the most optimistic people feel an AIDS vaccine with sufficient efficacy is still years away. Will we get there? I'm hoping that we will and I’m optimistic that we will.

What will be the main highlights of your talk? The new findings that have energized the AIDS vaccine field. These findings will include identifying the immune correlates of infection risk in the RV144 trial, the elucidation of many transmitted/founder viruses (the viruses that cause infection in human to human transmission), the discovery of broadly neutralizing antibodies (bNAbs), and insights as to why bNAbs have been so difficult to induce. Everyone believes these new discoveries can provide important clues to speeding up the development of a preventive vaccine. Seven to eight years ago, the field was frustrated that we didn’t know what to do and we certainly didn’t know how to do it. What is different now is we have clues. We do know some people can make [potent] antibodies over long periods of time that we want to elicit over a shorter period of time in a vaccine.

Is the vaccine problem solvable? The observation that there appear to be antibodies that can hit the Achilles heel of the Envelope [HIV’s surface protein] and be made in certain people is one indication that this is a solvable problem. The immune correlates of infection risk found in the RV144 trial are also clues for further studies. I think there are strategies based upon these observations that the field is beginning to explore.

Can you describe one of those strategies? Most of the bNAbs are unusual in some respects. These unusual characteristics are in general indications that they are the products of either quite convoluted or disfavored developmental pathways. There are a series of technologies that have been developed whereby these pathways can be determined and studied with the goal of trying to recreate the pathways with a series of vaccine immunogens [active ingredients in vaccines] that can bypass these torturous pathways and follow more productive pathways.

Convoluted pathways? As antibody clones expand, they undergo changes. An antibody that travels down a short developmental pathway has fewer changes, whereas those traveling down longer pathways have more changes. Many of these bNAbs are among the [most] mutated and changed antibodies. Most of the vaccine [candidates] we have now induce antibodies that only have a few changes in their building blocks, whereas it takes several years of continuous stimulation of the immune system by the infecting virus to drive these mutations or changes in the bNAbs. We want to drive antibodies to have more mutations but to use a shorter pathway and we are just now exploring ways to do that.

This sounds complicated. HIV is different from other viruses for which successful vaccines have been made because, among these, HIV is the only virus that has the trait of integrating into the host genome. Unlike any other vaccine, we will have to have sterilizing immunity at the time of HIV transmission for a vaccine to be successful.

When will we be able to test a candidate derived from these strategies? We are in preclinical studies in non-human primates now. The timing of human studies will depend on the outcome of these preclinical studies.
Several novel strategies have in recent years shown promise in preventing HIV infection (see VAX July 2011 Spotlight article, *An Antiretroviral Renaissance*). Among these is pre-exposure prophylaxis, or PrEP—the administration of antiretrovirals (ARVs) either orally or topically to HIV-uninfected individuals.

One of those studies, known as iPrEx, revealed that Truvada—a combination of the ARVs tenofovir and emtricitabine—was 44% effective in preventing HIV infection among nearly 2,500 men and transgendered women who have sex with men. The study, which was conducted in six countries including the US, prompted Truvada’s maker, Gilead Sciences, to apply for regulatory approval from the US Food and Drug Administration (FDA) to expand the use of ARV as a therapy to prevent HIV acquisition, making it the first antiretroviral drug to be considered for such use.

In June, an FDA advisory panel voted in favor of using Truvada as a preventive measure for HIV-uninfected men, the uninfected partners of those with HIV, and other at-risk individuals. The FDA is expected to rule on Gilead’s application in September.

Truvada could undoubtedly help some high-risk communities curb HIV transmission. Yet its approval could also present significant challenges to current and future studies evaluating other novel HIV prevention tools, not least AIDS vaccines. Even before the FDA took up Gilead’s application, AIDS vaccine researchers were discussing how best to deal with the ethical and scientific conundrums kicked up by the successes of PrEP.

In fact, those successes have had immediate implications for the AIDS vaccine trial known as HVTN505. This trial is currently enrolling 2,200 men who have sex with men (MSM) in the US who are circumcised and who have not been previously exposed to a common cold virus known as adenovirus serotype 5 (Ad5), a modified version of which is being used as the vector that delivers the active ingredients of the vaccine under evaluation (see VAX Sep. 2011 *Global News*). The Phase II trial has already signed up about 1,800 MSM and should meet its enrollment target soon. It is designed to determine if a DNA vaccine candidate followed by an Ad5 vector-based vaccine candidate in a prime-boost regimen is effective in either blocking HIV acquisition or lowering viral load among individuals who become HIV-infected through natural exposure despite vaccination (see VAX Sep. 2011 *Global News*).

When the results of the iPrEx study were unveiled in November 2010, the Seattle-based HIV Vaccine Trials Network (HVTN)—which is conducting the trial—consulted nearly 800 trial participants, scientists, community leaders, and other stakeholders to determine whether PrEP should be offered to some or all of the enrollees and, if the drug were offered, how participants should be monitored during and after the trial.

While studying the effect of the vaccine candidate remains the main focus of the study, trial organizers, after consultations with stakeholders, are providing volunteers information about PrEP in periodic risk-reduction counseling sessions that are standard in HIV prevention trials. They are also monitoring PrEP use among trial participants in two different ways. Trial participants who voluntarily choose to use PrEP are now being asked to report their PrEP use on a regular basis. To supplement this self-reporting tool, trial sites will also be analyzing the blood plasma levels of volunteers in order to obtain additional data on PrEP use among participants.

Should the FDA approve Truvada for the prevention of HIV—and the PrEP drug become a standard of care in some high-risk populations—it could further impact the design of AIDS vaccine trials.

**Vaccine vs. PrEP**

Not all the questions regarding the impact of PrEP have to do with ethics. For instance, if the HVTN505 trial shows that the vaccine regimen being evaluated is effective in reducing HIV transmission, it could raise questions about what part of the observed protection was due solely to the vaccine. This in turn could complicate efforts to determine the true efficacy of the vaccine. But researchers do not believe that PrEP use will cloud their results, since only a small percentage of trial participants are thought to be using Truvada and they are spread randomly between the vaccinated and placebo arms of the trial. The assumption could therefore be fairly made that any protective effect observed in the study can be attributed to the vaccine.

Researchers say the emergence of PrEP regimens, such as Truvada, will also likely mean that future AIDS vaccine trials will need to be larger and more expensive, particularly if a vaccine is studied in concert with PrEP. For instance, should a trial seek to evaluate the efficacy of a partially effective vaccine candidate combined with oral PrEP, it would require multiple arms to determine whether the overall efficacy of this combination strategy is greater than that of PrEP alone, the vaccine candidate alone, or a placebo (see VAX Aug. 2011 *Primer* on *Understanding the Rationale for Combination Prevention Trials*). With funds for HIV prevention research in short supply these days, that may well prove to be the most disruptive effect of PrEP’s recent successes.

---

**NEW VAX WEBSITE LAUNCHING THIS MONTH**

VAX, the bulletin on AIDS vaccine research, is moving to its own home this month. The new website, www.vaxreport.org, will showcase articles, podcasts, videos, and a searchable trials database. Look for additional website features in the coming months, and do let us know what you think of our new digs.