



Spotlight

Prevention gains momentum

Discussion of HIV prevention technologies tops the bill at international meeting

Over the past several years the number of people in developing countries receiving antiretroviral (ARV) therapy has steadily increased due to efforts mounted by the Global Fund to Fight AIDS, Tuberculosis, and Malaria and other international programs, including the US President's Emergency Plan for AIDS Relief (PEPFAR). But the number of new HIV infections continues to be high—four million individuals were newly infected last year—and this has shifted attention back to halting transmission of the virus. The need to focus on improving prevention services was fully emphasized at the International AIDS Society's (IAS) XVI International AIDS Conference in Toronto from August 13-18, where a record 26,000 attendees from around the world gathered. Bill Gates, who addressed the conference during the opening session, said "the goal of universal treatment—or even the more modest goal of significantly increasing the percentage of people who get treatment—cannot happen unless we dramatically reduce the rate of new infections."

Expanding HIV prevention programs and research into new approaches for preventing transmission, including discussion of the ongoing microbicide, male circumcision, and pre-exposure prophylaxis (PrEP; see *VAX* May 2006 *Spotlight* article, *Treatment as prevention*) trials, held prominence in the following

days. The efficacy of some of these approaches is still being tested, but there is a shared optimism among researchers that a combination of these strategies, along with continuing education efforts, will help curtail the epidemic's spread. Few speakers, including former US President Bill Clinton who made several appearances during the first days of the conference, failed to note the overwhelming need for new prevention technologies and ultimately a preventive vaccine. "It's going to be a rocky road until we have a vaccine," said Clinton.

Alphabet soup

The promotion of ABC—abstinence, being faithful, and using condoms—has long been a point of controversy in the HIV prevention field since it offers few options to women, who are often not able to negotiate condom use, even within marriage. Now that newer prevention technologies are in development, researchers are introducing a new series of prevention acronyms. The latest, referred to as CBS—circumcision, barrier methods (such as the female diaphragm), and syringe exchange—are the next crop of options that researchers hope will enter the prevention arsenal and be implemented more broadly.

The results of the first prospective study from South Africa showing that adult male circumcision could reduce the risk of HIV transmission to men were reported a year ago at the IAS meeting in Rio de Janeiro (see *VAX* August 2005 *Spotlight* article, *A comprehensive response*). Three other circumcision trials are ongoing in Kenya and Uganda and interim data from two of these trials sponsored by the US National Institute

of Allergy and Infectious Diseases (NIAID)—one in Uganda and one in Kenya—were recently analyzed by a data safety monitoring board. The efficacy data at this point are not sufficient to warrant stopping either trial but another analysis was recommended before the trials conclude in September 2007. Many public health officials, including those at the Joint United Nations Programme on HIV/AIDS (UNAIDS), took advantage of the opportunity provided by the conference to say that governments and communities should delay recommending this surgical procedure to men in regions with high HIV prevalence rates until further evidence is accumulated. Still, the topic was mentioned often by speakers and was the focus of lively discussion among attendees.

Researchers also eagerly await the results from an ongoing Phase III trial to evaluate the efficacy of the female diaphragm in preventing HIV transmission. An update on this study was provided in a plenary session by Gita Ramjee of the HIV Prevention Research Unit in Durban, South Africa, who reported that enrollment of volunteers is now complete at sites in Harare, Zimbabwe, as well as in Durban and

In This Issue

Spotlight

- **Prevention gains momentum**

Global News

- **Phase I vaccine trial ongoing in Russia**
- **IAVI's AIDS vaccine blueprint promotes innovative approaches to evaluating lead candidates**

Primer

- **Understanding Long-term Nonprogressors**

Johannesburg, South Africa.

The implementation of syringe-exchange programs was covered in a plenary talk by Alex Wodak of St. Vincent's Hospital in Sydney, Australia. Wodak reported that 10% of all new HIV infections globally last year occurred among injection-drug users (IDUs). This route of HIV transmission is responsible for 68% of new infections in the Ukraine and is also reported now in at least 10 countries of Africa, where the epidemic has so far been fueled almost exclusively by sexual transmission. Although harm reduction programs that promote syringe exchange or provide safe-injection facilities to IDUs are among what Wodak calls the "most effective interventions in the HIV/AIDS repertoire" they remain under-utilized.

Next generation

The next generation of prevention options, called MTV—microbicides, treatment or PrEP (providing ARVs to uninfected individuals to try to prevent infection), and vaccines—are also under evaluation in several ongoing clinical trials. Currently 5 microbicide candidates are in large-scale efficacy trials, with results expected as early as next year, and another 14 are now in earlier safety studies. "We're not a long way from finding out if a microbicide will work or not," said Ramjee.

Five trials are also ongoing to test the efficacy of PrEP to prevent HIV transmission (see *VAX* May 2006 *Spotlight* article, *Treatment as prevention*). Leigh Peterson, a principal investigator from the US-based organization Family Health International (FHI), presented the first preliminary safety data from a PrEP trial involving women at high risk of HIV infection in Ghana. In a late-breaker presentation Peterson reported that so far no serious adverse events were associated with taking tenofovir, the ARV being tested in this trial. Peterson also reported that among the 936 women enrolled in this study only 2 HIV infections occurred in the group of women receiving tenofovir, compared to 6 in women receiving placebo. But since the overall number of new infections was so small it is not possible for researchers to conclude yet whether this approach will be effective.

Another late-breaker presentation on PrEP involved a survey, conducted by

researchers at the San Francisco Department of Health, to gauge the use of PrEP amongst men who participated in gay pride events or visited sexually-transmitted disease clinics in San Francisco. Only one of the 851 men who completed the questionnaire between February and June reported already using PrEP in an effort to prevent HIV infection and only 2% of responders said they knew of someone else who was using PrEP. The majority of men surveyed (68%) said they would be willing to take ARVs to try to prevent HIV infection if this method were proven safe.

Researchers also stressed the advancements researchers are making in developing and testing AIDS vaccine candidates. In a plenary session on the dynamics of HIV/AIDS vaccine research, Françoise Barré-Sinoussi of the Institut Pasteur in Paris highlighted the 85 Phase I and II trials that have taken place since 1987 with more than 30 different vaccine candidates, and summarized the key challenges that remain.

Less than the best

Many of the vaccine candidates currently in clinical trials are only capable of inducing HIV-specific cellular immune responses, and not the neutralizing antibodies that most researchers consider will be a necessary component of the immune response if a vaccine is to completely protect a person from HIV infection. This raises questions about what to expect from a vaccine that primarily induces cellular immunity. "The best thing we can hope for at this point is vaccines that impact viral load," said Ronald Veazey of the Tulane National Primate Research Center in the US. This type of vaccine is often referred to as partially effective since it wouldn't provide sterilizing immunity that is capable of completely preventing HIV infection.

Disease course in HIV-infected humans is partly predicted over the long term by the amount of virus that is circulating in the blood, a measurement known as viral load. A vaccine that could lower viral load in someone who was subsequently HIV infected could therefore extend the amount of time it takes for that person to progress to AIDS (see *Primer*, this issue). Lowering viral load would also lower the likelihood

that an HIV-infected individual could then transmit the virus to others and could help limit the epidemic's spread.

Two presentations by Lisa Jacobson and Thomas Quinn from Johns Hopkins University focused on how a partially-effective AIDS vaccine, which didn't protect against HIV infection but reduced viral load, would influence the number of new HIV infections. HIV viral load is the major predictor of HIV transmission from mother-to-child and is also a key determinant in sexual transmission, although Quinn acknowledges that this route of transmission is far more complicated.

Studies from Rakai, Uganda with discordant couples—where one partner is HIV-infected and the other is not—showed that transmission between partners did not occur when the HIV-infected individual had an undetectable viral load, meaning it was lower than could be measured by conventional tests. "It's the dominating factor in transmission," said Quinn. "If you can modify transmission, you can control the epidemic."

This gives scientists hope that a partially-effective vaccine could still reverse the course of the epidemic. According to Quinn, even a vaccine that is only 50% effective at lowering viral load (by 0.5-1.0 log) would dramatically reduce the HIV prevalence in 20 years, as long as efforts were made simultaneously to bolster existing HIV prevention strategies to counteract any increased level of risk behaviors (behavioral disinhibition) among those who received the vaccine.

Several researchers, including Sally Blower of the University of California in Los Angeles and her colleagues, also work on modeling the effects of partially-effective AIDS vaccines on the spread of the epidemic. These models help researchers predict how variables like the degree of protection offered by the vaccine, the number of people who receive it, the duration of protection, and the vaccine-induced reduction in viral load (which corresponds to a reduction in transmissibility and increased survival time), would influence HIV prevalence.

"What we'll need with partially-effective vaccines is very high coverage," says Blower. Based on models of the

incidence rates in communities of men who have sex with men in San Francisco, she calculates that 100% of people in highly affected communities would need to be vaccinated for a 50%

effective AIDS vaccine to blunt the epidemic in these highly-affected groups.

But with the continuing expansion of the epidemic, the need for a preventive vaccine remains stronger than ever and

this was echoed by Stephen Lewis, United Nations special envoy for HIV/AIDS in Africa, who said “a vaccine is the only way, conclusively and categorically, to end the pandemic.”

Global News

Phase I vaccine trial ongoing in Russia

The first AIDS vaccine candidate developed by Russian scientists, known as Vchrepol, is now in Phase I clinical trials. Descriptions of this candidate and the ongoing study were presented in posters at both the International AIDS Conference in Toronto (see *Spotlight* article, this issue) and the AIDS Vaccine 06 conference held from August 29 to September 1 in Amsterdam. Vchrepol is a recombinant protein vaccine comprised of fragments of HIV proteins administered with an adjuvant known as polyoxidonium, which is already used with a licensed influenza vaccine.

The ongoing clinical trial involves 15 volunteers who receive 3 intramuscular injections of the vaccine candidate at 5 different doses. The dose is only escalated once the safety and tolerability of the lower dose is established. So far two of the five doses have been evaluated and no side effects or safety issues have been reported. The poster presented at the AIDS Vaccine 06 conference reported that the vaccine candidate induced antibody responses and suggested that subsequent studies will be needed to fully evaluate its safety and immunogenicity.

By the end of last year there were 350,000 documented HIV infections in Russia and the epidemic continues to expand at an alarming pace. As in many other countries in Eastern Europe and Central Asia, the majority of new HIV infections in Russia are occurring amongst injection drug users. Russia recently announced plans to create a vaccine research center for Eastern Europe and Central Asia to work on developing and testing other AIDS vaccine candidates (see *VAX* July 2006 *Global News*).

IAVI's AIDS vaccine blueprint promotes innovative approaches to evaluating lead candidates

IAVI's flagship publication, the *AIDS Vaccine Blueprint 2006: Actions to Strengthen Global Research and Development*, was released on August 15 during the International AIDS Conference in Toronto (www.iavi.org/viewfile.cfm?fid=41059). This biennial publication outlines a series of new scientific and policy initiatives to accelerate the development of an AIDS vaccine through the involvement of industry, building research and clinical trials capacity in developing countries, and a new vaccine development model that will promote the rational design of vaccine candidates as well as an accelerated approach to clinical trials. “The challenges to developing an AIDS vaccine are enormous,” said Seth Berkley, Chief Executive Officer and President of IAVI. “We're trying to accelerate every component.”

Industry's involvement in the development of an AIDS vaccine is seen by many in the field as imperative since much of the expertise in testing and manufacturing licensed vaccines is found within large pharmaceutical companies. Although several companies are actively engaged in AIDS vaccine research and development, the *Blueprint* calls for an increased level of commitment.

Another area highlighted in the document is the continued need to enhance the ability of developing countries to conduct AIDS vaccine clinical trials, including the development of networks of excellence for both research and clinical trials in the countries hardest hit by the epidemic. “We need more clinical trial capacity and we also hope that more vaccine research will be done in developing countries,” says Pontiano Kaleebu, Assistant Director of the Uganda Virus Research Institute.

The *Blueprint* also recommends that the AIDS vaccine field implement an accelerated approach to clinical trials that will provide researchers with pre-

liminary data about a candidate's efficacy earlier in development. The proposal would entail running several Phase II trials involving around 500 volunteers in parallel, rather than a single Phase IIb test-of-concept trial with up to 3000 volunteers. Only those candidates that show some degree of efficacy and improve upon the best current products would then go into more advanced trials.



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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 23 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 can AIDS vaccine researchers learn from studying people who are HIV infected but progress more slowly to AIDS?

It takes, on average, about a decade for an HIV-infected individual to develop AIDS. This progression occurs gradually as the virus attacks and destroys CD4⁺ T cells, a subset of immune cells that are an essential component of the body's immune response to pathogens such as viruses and bacteria. Other mechanisms are also implicated in the gradual depletion of these cells. Many CD4⁺ T cells are initially replenished by the immune system and as a result most HIV-infected individuals remain healthy with few, if any, symptoms for several years. But eventually the immune system begins to fail and the number of CD4⁺ T cells slowly declines. This is often accompanied by an increase in the HIV viral load, which physicians measure by quantifying the number of copies of virus in a sample of blood.

A person with a healthy immune system has between 600-1200 CD4⁺ T cells in a milliliter of blood. When the number of CD4⁺ T cells falls below 200, a person is clinically defined as having AIDS. At this point it is recommended that individuals begin taking antiretrovirals (ARVs) that can suppress the virus. Typically a person's CD4⁺ T cell count begins to rebound soon after starting ARV therapy and their viral load drops dramatically, often falling below the limit detectable by routine tests.

But some HIV-infected individuals are able to control the virus for much longer than a decade without ever taking ARVs. Researchers have even identified people who have been HIV infected for as long as 28 years and have never progressed to AIDS. These individuals are known as long-term nonprogressors, and they maintain very low viral loads and either don't progress to AIDS or do so much more slowly. Researchers estimate that 1% of all people who are HIV infected are long-term nonprogressors.

Just what makes these individuals able to control HIV for longer than others is still something of a mystery, and

it is further complicated because it could be due to different factors in different people. Several characteristics of the virus or the individual's genetic makeup could be partly responsible for this difference and researchers are actively studying long-term nonprogressors to determine exactly what enables them to control their HIV infection. AIDS vaccine researchers are particularly interested in determining the type of immune responses that are responsible for slowing disease progression because mimicking these responses might be the key to producing an effective vaccine.

This could be especially true for a partially-effective vaccine (see *Spotlight* article, this issue), one that would most likely not prevent HIV infection entirely but could lower viral load in people who do become infected. This lowered viral load would reduce the risk of them transmitting the virus to others, so a partially-effective vaccine could significantly reduce the number of new HIV infections. Long-term nonprogressors may hold important clues about what type of immune responses an AIDS vaccine would have to induce to keep HIV viral load under control.

Possible explanations

Researchers began studying long-term nonprogressors more than 15 years ago and they have identified several possible explanations for why some people have the ability to control HIV more effectively than others. One is that the virus that these individuals are infected with is weaker and therefore less able to infect and kill CD4⁺ T cells. Some people are infected with a strain of HIV that is missing a key viral protein, known as Vpr, which limits its ability to infect cells.

Another possible explanation is that people have CD4⁺ T cells that are resistant to HIV infection. Individuals have been identified who lack a receptor on the surface of these immune cells that is normally used by HIV to gain entry into and subsequently infect the cell. Researchers think there are probably also other genetic properties that

allow a person's immune cells to target and kill HIV more effectively.

But there are also many individuals who are long-term nonprogressors who are not infected with a weakened version of HIV or who do not have any of the known genetic properties that bolster their resistance to the virus. Researchers have studied these individuals to see if their immune systems are somehow able to mount more effective immune responses against HIV. So far none of the immune responses they've studied in long-term nonprogressors are any different than in people who progress to AIDS more quickly.

Elite controllers

To try to solve this puzzle and identify the particular immune response that might be important in controlling HIV infection, a team of scientists are now collaborating on a project to study specific subsets of long-term nonprogressors known as elite or viremic controllers. Elite controllers are HIV-infected individuals not taking ARVs who maintain viral loads that are considered undetectable (<50 copies of virus per ml of blood). About 1 in every 300 HIV-infected people is considered an elite controller. Viremic controllers are infected people not taking ARVs whose viral load remains below 2000 copies/ml of blood.

Bruce Walker and colleagues at the Harvard Medical School are now working with other AIDS vaccine researchers to identify a group of 1000 elite and viremic controllers around the world—they estimate there are about 2000 in the US alone, most of whom don't know it. They plan to analyze the immunologic and genetic characteristics of these individuals utilizing the information collected by the Human Genome Project that successfully mapped the thousands of human genes. By comparing this information across a larger cohort of controllers, researchers are hopeful that they will be able to identify the specific genes or immune responses that allow some people to control their HIV infection. Hopefully this will yield important clues for the future design of AIDS vaccines.