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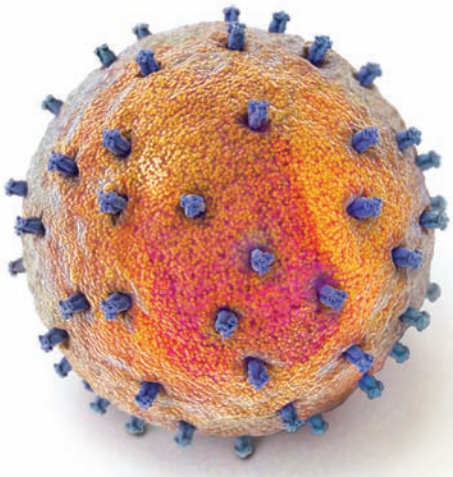

[SPOTLIGHT]

Everything from Cause to Cure

Research presented at the biannual International AIDS Society Conference ran the gamut from early HIV infection to the search for a cure

By Daisy Ouya and Kristen Jill Kresge

With the theme "From Cause to Cure," the 5th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention, which was held from July 19-22 in Cape Town, South Africa, brought together more than 7,500 delegates to discuss a range of questions regarding everything from the earliest events of HIV infection to how best to eradicate HIV from an infected individual. Françoise Barré-Sinoussi, co-recipient of the Nobel Prize for the discovery of HIV, spoke at the opening ceremony and cited two main challenges plaguing researchers. "One challenge we have is to develop a vaccine, another is to have a cure for AIDS," she said.

Researchers continue to focus on developing new biological interventions to prevent the spread of HIV, including a vaccine, as well as implementing those already available, such as adult male circumcision. There was also a chorus of support for sustaining and increasing the availability of antiretroviral therapy (ART) and initiating treatment earlier in the course of HIV infection, both to save lives and prevent new infections from occurring (see *VAX* July 2009 *Spotlight* article, *Test and Treat on Trial*).

These themes are not new, but in the midst of a global economic crisis that threatens the sustainability of HIV/AIDS funding, the need to continue battling HIV through both treatment and prevention seemed an even more pervasive message. "HIV is not in recession," emphasized Barré-Sinoussi. Stephen Lewis, co-director of AIDS-Free World, noted that HIV/AIDS programs have objectively strengthened health care systems, and he warned that a reduction in funding could "derail the gains" in preventing and treating HIV in poor countries.

When to start

The approach to treating HIV has changed dramatically over the past 25 years. There are now more than 30 licensed antiretrovirals (ARVs), and combination regimens of these drugs, which work remarkably well at controlling the virus. Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases, said that now a newly HIV-infected 20-year-old who receives appropriate treatment has a life expectancy of at least 69 years. "The results are striking, historic, and to some degree unprecedented," Fauci said.

Over time, the way ARVs are administered has also changed. Early on, researchers thought the best approach was to treat an HIV-infected individual as early as possible. However, clinicians eventually became concerned about the toxicity of ARVs, as well as their cost, and tended to delay initiation of therapy until a person's health began to decline. Also, because the availability of ARVs was severely limited in developing countries, guidelines were devised so that therapy was not administered until a person developed AIDS.

Now, evidence is accumulating that suggests starting therapy much earlier in the course of HIV infection may be beneficial, leading many researchers to call into question current treatment guidelines. "Everything seems to point toward earlier therapy," said Fauci. This was a recurrent theme at the conference but was tempered by warnings about potential drug shortages in some countries that could jeopardize access to therapy, even for individuals already on treatment.

ALSO IN THIS ISSUE

Earlier initiation of therapy may be beneficial because HIV can wreak havoc even when the immune system is effectively keeping the virus in check. Following HIV infection, it typically takes 8-10 years before a person's immune system becomes exhausted by the virus and weakened to the point that a person develops AIDS. It was long thought that during this period when the immune system is battling the virus, HAART was not necessary. But researchers are now finding that the decade following infection is not benign. HIV continues to reproduce or replicate during this time, and the body's immune system is chronically activated. This induces "inflammatory changes that are associated with an increased risk of mortality," according to Wafaa El-Sadr, a professor in the department of epidemiology at Columbia University. "HIV is much more toxic than any drug you can throw at it," said Julio Montaner, president of IAS.

El-Sadr presented data from the SMART study, conducted at more than 300 clinical research centers in 33 countries, which compared the clinical outcomes of nearly 5,500 HIV-infected individuals who were randomized to start ART early in the course of their infections, or later, when their levels of critical infection-fighting CD4+ T cells fell below 250 in a microliter of blood. The clinical definition of AIDS is when an HIV-infected person's CD4+ T-cell level reaches 200. The study aimed to maximize the benefits of ART, while minimizing its risks, which can include serious adverse effects such as renal failure, heart disease, and cancers. The results of the SMART study showed that later initiation of therapy increased an individual's risk of serious AIDS- and non-AIDS-related events.

Another study presented at the conference provided additional evidence that starting therapy earlier can improve clinical outcomes. The study, known as CIPRA HT 001, involved 816 HIV-infected adults in Haiti with CD4+ T-cell levels between 200 and 350. Half of the participants were randomly selected to start treatment within two weeks of enrollment, while the remaining volunteers did not receive ART until their CD4+ T-cell counts dropped below 200, in accordance with the current treatment guidelines set by the World Health Organization. At an interim review, the study's data safety monitoring board (DSMB) found that early treatment improved survival rates—nearly four times as many volunteers who started therapy later had died compared to those who started earlier. Twice as many people in the group that received delayed therapy also had developed tuberculosis during the study. Based on these findings, the DSMB recommended the trial be stopped and that all volunteers be offered ART.

Together these studies suggest that perhaps the current treatment guidelines need to be reconsidered. If the CD4+ T-cell threshold is raised, many more people would need ART, dramatically increasing global treatment costs. But others argue earlier therapy is still a cost-effective strategy. "It doesn't actually cost more money," said Fauci, "it's twice as expensive to care for people who don't start early."

As researchers reconsider the optimal time to begin therapy, there is also an ongoing push to expand availability of ARVs to help stem the spread of the virus. Although there is little clinical evidence, many researchers suggest that expanding access to therapy and initiating it as early as possible can be an effective prevention strategy. HAART lowers the amount of virus circulating in an infected individual, making it less likely they could transmit HIV to others. "HAART is an essential tool to curb the growth of the pandemic," said Montaner, who called HIV therapy a "cost-averting intervention even in a fiscally challenging environment."

The status of HIV prevention

Ronald Gray, professor in population and family planning at Johns Hopkins University, gave a thought-provoking plenary talk on the state of biomedical prevention. He pointed out that out of 29 trials evaluating the efficacy of different biomedical interventions, only four had shown significant success (three evaluating adult male circumcision and the other evaluating treatment of sexually transmitted infections to reduce HIV risk). Five showed possible harm. As such, Gray challenged the prevention community to urgently improve the design of clinical trials and to do a better job of screening candidates and strategies so that fewer large-scale trials, which are difficult and expensive, are conducted.

He challenged the microbicide field to improve preclinical testing of candidates. Citing Thomas Huxley's famous quote, "The greatest tragedy of science is the slaying of a beautiful hypothesis by an ugly fact," Gray suggested that researchers reassess the hypothesis that treating sexually transmitted infections such as herpes simplex virus-2 could lower the risk of HIV infection after multiple clinical trials have shown otherwise.

Gray also spoke about vaccine research and questioned the validity of current lab assays that are used in clinical trials to measure people's immune responses to vaccine candidates. As for future work, he suggested that a priority for vaccine researchers should be exploring candidates that would act quickly at the mucosal surfaces, the most common entry point for HIV.

Fauci pointed out that vaccine researchers have already started focusing more on understanding the basic immunology of HIV and are using this to design improved vaccine candidates. And although the field is moving

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MANAGING EDITOR
Kristen Jill Kresge

SENIOR SCIENCE WRITER
Andreas von Bubnoff, PhD

SCIENCE WRITER
Regina McEnery

PRODUCTION MANAGER
Nicole Sender

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more toward basic research, Fauci said, "It's not going to slow things down, I think it's [actually] going to speed things up."

Implementing circumcision

Ever since adult male circumcision (AMC) was shown to reduce a man's risk of HIV infection, public health officials and researchers have been working to devise the best way to quickly offer this surgical procedure in regions where HIV infection rates are high and circumcision rates are low. Kawango Agot, of the Universities of Nairobi, Illinois, and Manitoba Project, gave an overview of progress on this front in the Kisumu district of Kenya. Since the Kenya National Voluntary Male Circumcision Program was initiated in November 2008, around 30,000 males have been circumcised through the public system, largely with support from donor agencies. One obstacle to implementing circumcision programs was the lack of trained medical professionals. In June, Kenya revised its health regulations to allow nurses to conduct the surgical procedure, and Agot's group has found that after training and supervision, adverse events following AMC did not differ if the procedure was performed by nurses.

Working with sero-discordant couples in Kampala, Uganda, in which the man is HIV uninfected, Kenneth Mugwanya and coworkers at Case Western Reserve University School of Medicine found a high level of knowledge among men about the ability of AMC to reduce HIV infection risk. But only 50% of the men were interested in having the procedure. In the Dominican Republic, where only about 5% of adult men are circumcised, Maximo Brito of the University of Illinois in Chicago and colleagues found that after attending information sessions, about two-thirds of a study group of 368 Dominican and Haitian men were willing to undergo the surgical procedure.

It is still unknown whether AMC reduces rates of HIV infection in men who have sex with men (MSM), but Tim Lane of the University of California in San Francisco presented data from a study in Soweto, South Africa, showing that uncircumcised MSM had 4.5 times higher HIV infection rates than their circumcised counterparts. Lane said that about 40% of men in the Soweto cohort also had sexual relations with women. Therefore, "reducing the risk of HIV among MSM could benefit entire communities," he said. Lane called for further research to assess the acceptability of an AMC trial for HIV prevention among MSM. ■

Daisy Ouya, contributing writer, is Program Manager, Information, Education, and Communication at IAVI in Nairobi, Kenya.

GLOBAL NEWS *By Kristen Jill Kresge*

South African AIDS Vaccine Initiative Launches Phase I Trial

The South African AIDS Vaccine Initiative (SAAVI) commemorated the launch of the South African arm of a Phase I AIDS vaccine trial at the Emavundleni Prevention Centre in Cape Town on July 20. The purpose of the trial is to evaluate the safety and immunogenicity of two vaccine candidates, developed by researchers in South Africa, which are administered sequentially in a prime-boost regimen.

The trial, known as SAAVI102/HVTN 073, is being conducted in collaboration with the HIV Vaccine Trials Network (HVTN) and the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health (NIH).

Researchers plan to enroll 36 volunteers at two clinical research centers in South Africa—the Emavundleni Centre in Cape Town and Chris Hani Baragwanath Hospital in Soweto. Twelve volunteers have already been successfully enrolled and vaccinated in the US arm of the study, which is being conducted at the Fenway Community Health Center in Boston.

The prime-boost regimen being tested is comprised of a DNA vaccine candidate followed by a modified vaccinia Ankara (MVA) vector-based candidate, both of which are modified by researchers to carry fragments of clade C HIV, the subtype that is predominant in South Africa, to induce an immune response against HIV. Both candidates were tested in the laboratory and in animal models prior to this study and neither can cause HIV infection.

The launch of the South African arm of the study was significant because the prime-boost regimen was developed by researchers in the country. "We're seen as the place to test vaccines, now we've developed one," said Anna-Lise Williamson of the University of Cape Town, who led the development of the vaccine candidates. "It usually happens the other way around."

The DNA vaccine candidate was constructed in South Africa using a plasmid provided by the Vaccine Research Center at NIAID. The MVA candidate was developed by researchers at the University of Cape Town with funding from SAAVI and the NIH. Both candidates were manufactured in the US. SAAVI is the lead program of the South African Medical Research Council (MRC) and was established by the South African government and the energy supply company Eskom in 1999 to coordinate the development of an HIV vaccine for southern Africa.

Anthony Mbewu, president of the MRC, called the launch of this trial a "scientific milestone," which he said "ensures that South Africa will be better able to design and develop vaccines against infectious agents in the future."

Anthony Fauci, director of NIAID, said that scientists in South Africa received more NIAID funding last year than any other country outside the US. "You have the intellectual capital and people who are passionate about health, especially in the arena of HIV/AIDS," he said. Fauci also discussed the "extensive challenges" facing AIDS vaccine researchers.

Despite these challenges, many speakers noted the importance of continuing AIDS vaccine research. "The cost of [HIV] treatment is very high," said Naledi Pandor, the South African Minister of Science and Technology. "I therefore cannot overstate the importance of the development of a vaccine for the South African population."

[PRIMER]

Understanding the Role of Social Science Research in Clinical Trials

What can researchers learn from studying communities in preparation for AIDS vaccine clinical trials? ***By Regina McEnery***

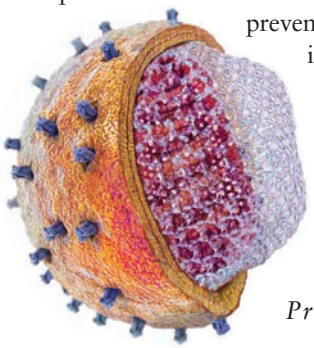
Volunteers are an essential component of AIDS vaccine clinical trials. Without the many individuals who are willing to participate in clinical studies, researchers would not be able to test candidate vaccines and determine if they are safe and effective. Recruiting thousands of volunteers for large Phase III efficacy trials is a daunting task. One way to effectively reach and engage potential volunteers for clinical trials is to gain a better understanding of the communities in which trials will take place. This is sometimes accomplished by conducting social science research.

Social science research, as its name implies, involves the study of human behavior and relationships. While more subjective than virology or immunology, social science research can include behavioral, health policy, and health systems research, as well as social epidemiology.

Social scientists have been studying HIV since the beginning of the epidemic. HIV is most often transmitted through sexual activity or injection drug use, and so developing a better understanding of the societal impact and drivers of the pandemic has been crucial to understanding HIV, particularly with regard to prevention. Social science research can also be used to collect information that can help ensure that AIDS vaccine clinical trials are conducted successfully.

Supporting volunteer recruitment and retention

If a trial is designed to show whether a particular candidate vaccine is effective at preventing HIV infection, individuals who participate in the trial must be at risk of HIV infection through natural exposure to the virus (see *VAX* May 2008 *Primer* on *Understanding the Recruitment of Volunteers at Risk of HIV Infection*). Importantly, volunteers in a vaccine trial are never purposely exposed to HIV and the vaccine candidates cannot cause HIV infection.



To ensure that at-risk volunteers are included, clinical trials are often conducted in areas where the rate of new HIV infections or incidence is highest. It is also in these areas or specific populations—such as men who have sex with men (MSM) or commercial sex workers—that a vaccine is needed most and would ultimately offer the greatest benefit, and so it is therefore important that these individuals are part of the clinical process.

Social scientists have employed in-depth interviews, focus groups, and anonymous surveys to gain information about these at-risk populations. To make sure the tools being used to collect the data—such as a questionnaire—are scientifically rigorous enough, social scientists will sometimes use independent auditors to review the language in the questionnaire and the method and settings in which the questions are asked.

The information collected from these surveys or interviews helps researchers identify factors that may impede recruitment, enrollment, and retention of at-risk individuals in clinical studies. There are different factors within these populations that affect a person's vulnerability with regard to HIV, and understanding these factors can help make the recruitment and enrollment process for clinical trials run more smoothly.

Several groups involved in AIDS vaccine research and development are currently engaged in social science research, including IAVI, the Kenya AIDS Vaccine Initiative, the Uganda Virus Research Institute, the Desmond Tutu HIV Foundation, the Aurum Institute, and the US National Institute of Allergy and Infectious Diseases, as well as many others. This research is helping to determine, for example, if certain populations are suitable for upcoming vaccine trials. Other research is focused on identifying barriers and opportunities for involving MSM or transgendered communities in HIV prevention research.

Gender issues

One particularly important avenue of social science research has focused on the role of gender in the HIV pandemic, and in AIDS vaccine research and development more specifically. Biological distinctions between men and women may impact the efficacy of a vaccine. Also, because HIV prevalence is so high among women, particularly in southern Africa, it is important that AIDS vaccine candidates be tested in adequate numbers of female volunteers (see *VAX* March 2008 *Primer* on *Understanding the Recruitment and Retention of Women in Clinical Trials*).

Social science research can help assess the barriers that discourage women in developing countries from participating in clinical trials. This knowledge can enable researchers to develop strategies that are aimed specifically at enrolling women. For instance, in a Kenyan study conducted by IAVI and the International Center for Research on Women, social scientists discovered that women were more vulnerable to HIV stigma than men, which may have affected their willingness to participate in a clinical trial. The study found that while men and women were both concerned that participating in a trial could potentially damage their personal relationships, the concern loomed larger for women, who are more likely to be dependent on a relationship for economic reasons.

By building a better understanding about the fears women and men have about clinical trials and HIV/AIDS and how their decision making processes may differ, researchers can hopefully strengthen outreach, recruitment, retention, and support systems within the context of AIDS vaccine clinical trials. ■