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OCTOBER 2003
Vol.1 ■ Num.3

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◆ Challenges Highlighted at AIDS Vaccine 2003

Coordination and challenges were major themes at the AIDS Vaccine 2003 conference held 18-21 September in New York City, an annual meeting sponsored by the US National Institutes of Health, the French research program ANRS, and the World Health Organization. The meeting featured updates on vaccine science and clinical trials. Many presentations described continuing progress in these areas but there were no major breakthroughs announced. Instead participants reflected on the challenges facing the AIDS vaccine field and emphasized the need for continued work on 'basic science' (laboratory studies of vaccines and immune responses), clinical trials site development, and studies aimed at finding a correlate of protection that could be used to swiftly identify effective vaccines in animal and human studies. Gary Nabel, head of the US Vaccine Research Center, said that a trial that identified a correlate of protection would be a "transforming event" for the field.

Many speakers emphasized the need for increased collaboration and coordination between US and Europe and between the industrialized world and developing countries. "We need teams of the best and brightest people working in problem-solving mode to overcome scientific obstacles," said IAVI's Senior VP for Research and Development Wayne Koff.

One source of this coordination could be the Global HIV Vaccine Enterprise which was recently proposed by a coalition of vaccine researchers, including Richard Klausner of the Bill & Melinda Gates Foundation. Larry Corey, head of the US HIV Vaccine Trials Network, reviewed planning activi-

ties for the Enterprise including an August meeting in Washington DC. At that meeting working groups on regulatory issues, organization and funding, clinical trials capacity, manufacturing issues, product development, and vaccine discovery were formed. These groups will help develop a plan for action.

Corey said that "the real challenge and real work will be to get agreement that there is a good enough plan [from the working groups] ... so that the people who actually provide the money agree" that there is broad support from AIDS vaccine developers. The enterprise has not yet received any funding and does not have a set membership. Jose Esparza, head of the WHO-UNAIDS Joint Vaccine Initiative, emphasized the openness of the project. "The Enterprise doesn't exist beyond a vision. It is not an organization. This is not a club," he said. "The intention is to involve the whole community globally."

Correlate of protection: An immune response (immune cells or antibodies) that corresponds to a high degree of vaccine protection. We do not yet know which type or level of immune response indicates protection against new HIV infection. A correlate will be identified by testing vaccines in human trials and studying the immune responses from people who are protected from HIV infection.

GLOBAL NEWS

◆ AIDS Vaccines at ICASA

On 20 September nearly 100 African scientists, trial volunteers, community advisory board members and AIDS NGO representatives from Africa participated in "Community Matters: Preparing for a Vaccine to Prevent AIDS," an all-day workshop on the ethics and science of AIDS vaccine development co-

A PUBLICATION OF THE IAVI REPORT

[The Newsletter of the International AIDS Vaccine Initiative]

sponsored by IAVI, **AfriCASO**, **ICASO**, **KANCO** and **AAVP**. The workshop was an official satellite of the International Conference on AIDS and Sexually Transmitted Diseases in Africa (ICASA) held in Nairobi from 21-26 September. Kenyan Minister of Tourism and Information Raphael Tuju opened the satellite session and reminded the audience that “no epidemic of this magnitude has ever been rolled back without a vaccine.” He urged African AIDS organizations, governments and research groups to place AIDS vaccine research on their agendas alongside treatment, condoms and other prevention strategies.

The satellite meeting featured an in-depth discussion of new policies on treatment for HIV-negative vaccine trial volunteers who become infected with HIV through high-risk behavior during the study. (AIDS vaccines cannot cause HIV infection but some volunteers may become infected with HIV during the course of a study through their high-risk behavior.) Representatives from HIV Vaccine Trials Network, IAVI and the South African AIDS Vaccine Initiative each outlined policies that include payment for several years of antiretroviral therapy for volunteers who become infected during AIDS vaccine trials. Other sessions explored ways to explain AIDS vaccine research to nonscientific audiences. This topic was also examined at an IAVI-sponsored skills building workshop on AIDS vaccine materials and education programs on 22 September.

IAVI President and CEO Seth Berkley facilitated an AIDS vaccine “roundtable” discussion at the main conference. Berkley highlighted the accomplishments of Uganda and Kenya which were the first African countries to approve and complete AIDS vaccine trials, saying “East Africa has shown remarkable commitment and leadership on AIDS vaccines. These efforts should be applauded and expanded so that we move as rapidly as possible towards an effective AIDS vaccine, which is so desperately needed in these countries and in the rest of the world.”

AfriCASO: African Coalition of AIDS Service Organizations

ICASO: International Coalition of AIDS Service Organizations

KANCO: Kenya AIDS NGO Consortium

AAVP: African AIDS Vaccine Programme

SPOTLIGHT

◆ The Search for an AIDS Vaccine in Russia

Today, Russia is at the heart of the fastest growing AIDS epidemic in the world. It is an epidemic that is spreading mainly through intravenous drug use. (Intravenous drug users (IDUs) sometimes share needles that have been contaminated with HIV-infected blood and this leads to new infections.) In some parts of Russia more than 60% of IDUs are infected with HIV and the epidemic is not showing any signs of slowing down. Between 1998 and 2002, for example, there was a 22-fold increase in HIV among pregnant Russian women. If this epidemic continues unchecked, experts warn that 1 in 25 Russians could be HIV positive by 2008.

At first glance there is reason to hope that Russia can respond to its epidemic. The country has a large number of doctors and nurses and well-developed systems for conducting scientific research and approving new products. It is also a country with a long history of developing and manufacturing its own vaccines and medications. During the Soviet era, for example, Russian facilities produced one-third of the supplies of smallpox vaccine used in the worldwide campaign to wipe out the disease.

Many of the Soviet era vaccine manufacturing plants are now out of date and do not meet international standards. But these facilities and their staffs are still a potential foundation for AIDS vaccine efforts. A small group of Russian researchers and international collaborators are now attempting to build on this foundation to respond to the expo-

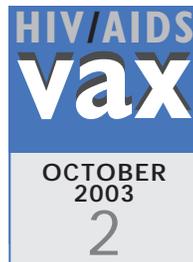
sive AIDS epidemic there.

It is a challenging task. Russia has been slow to respond to its epidemic. President Vladimir Putin has yet to make an urgent call for a coordinated response to the crisis and government funding levels for AIDS treatment and care remain low. One reason for the slow response may be the public opinion that AIDS is limited to highly-stigmatized groups of people like IDUs and commercial sex workers. In fact the disease is not confined to isolated groups. Reports of sexual transmission of HIV among non-IDUs are increasing. This is a warning sign that HIV is circulating in the general population.

In spite of the slow overall response Russian scientists have gained some support for AIDS vaccine research. At present three groups have small government grants to develop vaccine candidates. US and UK governments and academic institutions are also providing support for vaccine research and related activities including studies of who is infected, how rapidly HIV is spreading in different communities, how people are becoming infected (routes of transmission, see *Primer*), and what ‘clades’ (types) of HIV are found in Russia.

The first **incidence** study in Russian IDUs is currently underway at the “8 Plus Clinic” at the Biomedical Center in St Petersburg. The study is co-funded by the US HIV Prevention Trials Network (HPTN). It has enrolled 520 HIV-negative IDUs who will be followed for 12 months and tested for HIV every six months. Half-way through the trial more than 80% of the original volunteers are still enrolled. This is a strong start for this type of research. Biomedical Center head Andrei Koslov hopes the current study will help prepare the IDU community for future vaccine trials.

The study at the 8 Plus Clinic is helping to challenge stereotypes about IDUs, who are often seen as difficult to recruit and retain in



studies. With the exception of Thailand, most countries with serious HIV epidemics in IDUs have failed to study or work with these communities.

If Russia is able to build IDU cohorts (groups of volunteers for studies) it will be a valuable contribution to AIDS vaccine research. It is important to include IDUs in trials to learn whether vaccines offer similar protection against both intravenous and sexual exposure to HIV (see *Primer*). Since sexual transmission is now increasing in Russia, the country could be an important site for trials that compare vaccine effects in IDUs and people exposed through sexual contact.

International partners are also hoping to strengthen Russian vaccine manufacturing capacity. One project aims to convert former bioweapons facilities to medicine and vaccine production. "When an AIDS vaccine is finally licensed, Russia could play a key role in manufacturing for many parts of the world," says Don Burke, head of the Center for Immunization Research at Johns Hopkins University.

Obstacles to progress

Sadly, projects like the 8 Plus Clinic remain rare in Russia. In 2002 the government budget for AIDS spending was just US\$ 5.5 million. In contrast, the US spends roughly \$15 billion per year on domestic HIV/AIDS programs.

Stigma and discrimination also remain major problems. Active IDUs are ineligible for most health care including HIV treatment. Russian law requires that people with HIV are registered by name with the national authorities. This requirement may stop some people from seeking HIV testing. (At the 8 Plus Clinic each volunteer is assigned a numerical code. Staff doctors never learn their patients' names and so avoid the requirement of reporting

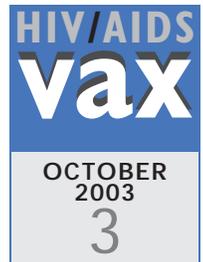
volunteers' HIV test results to the authorities.) The government also does not support prevention strategies such as **syringe exchange** and drug replacement programs that provide a substitute to illegal intravenous drugs.

The handful of initiatives that do exist cannot solve the problem alone but they are a sign of what is possible in Russia should the government choose to respond. In a promising step the Russian government recently launched an AIDS advisory council that could coordinate a national research agenda.

This progress should have been made much earlier, Russian scientists say. "Recently we attended parliamentary hearings where the Russian authorities all started their speeches by saying, 'Attention, attention, we are on the edge of disaster. Our house is on fire,'" says Eduard Karamov, a researcher at Moscow's Ivanovski Institute for Virology. "I said, 'Calm down, sit back, the fire started many years ago.'"

Incidence: *The rate of new infections per year, measured by determining the number of new infections in a specific population over a given period of time. HIV incidence rates are often expressed as percentages (the percentage of people in the population who acquired HIV in one year).*

Syringe exchange: *Syringe exchange is a 'harm reduction' strategy designed to reduce the risks associated with intravenous drug use. Syringe exchange sites allow IDUs to swap used needles for clean ones and reduces the risk that IDUs will share or re-use needles that are contaminated with HIV and other diseases such as hepatitis.*



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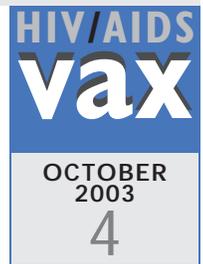
The Spotlight and Primer articles in this issue of VAX are based on articles by Emily Bass and Chris Beyrer which originally appeared in the May-August 2003 and May-June 2002 issues of the *IAVI Report*. All other articles are by Emily Bass.



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IAVI is a scientific organization founded in 1996 whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI focuses on four key areas: accelerating scientific progress; education and advocacy; ensuring vaccine access and creating a more supportive environment for industrial involvement in HIV vaccine development.

WHY DO VACCINES NEED TO BE TESTED IN DIFFERENT POPULATIONS?



Instead of conducting one large trial to see if an AIDS vaccine is successful, most vaccine developers plan on multiple trials of vaccines. One important reason for this strategy is that there are several different ways that people can become infected with HIV. HIV is passed or 'transmitted' from one person to another through close contact with body fluids that contain the virus (blood, semen, vaginal secretions or breast milk). Only certain types of contact with these fluids can lead to infection. These include unprotected vaginal or anal sex (sex without a condom); breastfeeding; and the use of a needle that has been contaminated with HIV-infected blood, as can happen when illegal drugs, such as heroin, are injected into the blood. This is called 'intravenous' (IV) drug use. The particular way that HIV enters and infects the body is known as the 'route of transmission.'

A route of transmission can be thought of as a pathway that the virus takes from one place in the body (the site of exposure) to another (the bloodstream that then carries HIV throughout the body). Each pathway has immune defenses that try to act against HIV and other infections. These can be thought of as border checkpoints and patrols designed to protect against foreign invaders.

Each route of HIV transmission has a different set of physical barriers and immune defenses, including immune cells and antibodies. These are tailored to different locations in our body. We can see and feel the differences in the physical barriers. The lining of our mouth, for example, is different from the skin on our arm. The differences we can't see with the naked eye include variations in the type and amount of immune defenses located at different sites in the body.

There are also variations in the immune defenses found in women and men, and adults and children. By themselves, these defenses are not enough to prevent HIV infection every time a person is exposed to the virus. This is why there is an urgent need for an effective, preventive AIDS vaccine.

Implications for vaccines

The ultimate goal is to develop an AIDS vaccine that prevents HIV infection no matter how someone is exposed to HIV. This is a challenging task since it is possible that the route of transmission will have an effect on how well a vaccine protects against HIV infection and disease.

A comparison of sexual versus IV routes of transmission shows why this is possible. Sexual transmission occurs across 'mucosal surfaces.' These mucosal surfaces are the boundaries between the outside world and the inside of the body, and include the inside of the mouth and nose, the lungs, the lining of the stomach, the vagina and the rectum. For infection to happen during sex, HIV must pass the physical barrier of the mucosal surface as well as the immune cells and antibodies that patrol that surface. Breastfeeding transmission of HIV also

happens across mucosal surfaces—the lining of the baby's mouth and stomach.

A syringe that pierces the skin bypasses the physical barrier and immune defenses designed to keep out foreign invaders.

When intravenous drug users (IDUs) share syringes that contain HIV-infected blood, a small amount of the virus is injected directly into their bloodstream. Once the virus is in the bloodstream it can spread rapidly throughout the body.

"We cannot assume that vaccines which prevent or reduce sexual transmission will necessarily work as well against spread through IV drug use," says Chris Beyrer, a researcher on vaccines and IDUs at Johns Hopkins University (US). This is not because IDUs will make different immune responses from other people. Most people who are vaccinated with an effective AIDS vaccine will make similar types of immune defenses. But these defenses may be more or less able to block HIV infection depending on the route of transmission of the virus.

There may also be variations in vaccine effects with different types of sexual exposure, such as anal and vaginal sex. The only way to find out how routes of transmission affect vaccines

is to test AIDS vaccines in communities where HIV-negative people are likely to be exposed to HIV through different routes, such as gay men exposed through anal sex and IDUs exposed through drug use. This strategy was used in the two large-scale 'Phase III' trials of an AIDS vaccine called AIDSVAX. In the US, Canada and Europe the trial tested the vaccine in just over 5400 people: 5108

HIV-negative men who have sex with men, and 309 HIV-negative women who were at high risk of heterosexual exposure. In Thailand the trial tested a closely-related version of the vaccine in roughly 2500 HIV-negative intravenous drug users. (The vaccine provided no overall protection in the North American-European trial; data from the Thai trial was not available as of October 2003.)

Today the need for vaccines that protect against sexual and IV transmission is greater than ever. There is a serious epidemic underway in intravenous drug users in Eastern Europe and Central Asia and the rate of new infections remains high in sub-Saharan Africa, where heterosexual contact is the most common route of transmission. It is crucial to conduct trials in people at risk for infection either via sexual contact or IV drug use. To do this, trial sponsors, governments and communities will have to work together to create research environments that are safe and welcoming to all people, including individuals who are discriminated against because of their behaviors, such as drug users and commercial sex workers. These trials will bring the world closer to the ultimate goal of a universal AIDS vaccine.

PRIMER UNDERSTANDING routes of TRANSMISSION