



Spotlight

A comprehensive response

International conference highlights need for simultaneous treatment and prevention efforts.

Since the World AIDS conference was held in Durban more than five years ago, there has been a sustained international interest in making anti-retroviral (ARV) therapy available to people in developing countries. Thanks to a collection of global initiatives, including the World Health Organization's (WHO) '3 by 5' Initiative and the Global Fund to Fight AIDS, Tuberculosis, and Malaria, the scaling up of treatment programs is finally occurring. Now researchers are reinforcing the importance of prevention messages and new prevention strategies for slowing the spread of HIV.

Thousands of delegates gathered recently in Rio de Janeiro, Brazil for the 3rd International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment. Speakers throughout the four-day conference emphasized how treatment access can promote HIV prevention efforts.

When ARVs are unavailable fewer people are willing to be tested for HIV infection and this makes it more difficult to emphasize prevention messages. Both treatment programs and ARV trials provide an opportunity for healthcare workers to offer a variety of prevention services and to discuss ways that individuals can reduce their risk (see *Primer*, this issue). This includes offering people voluntary counseling and testing (VCT; see April *Primer* on *Understanding Research*

Voluntary Counseling and Testing). The positive effect that treatment access has on VCT rates is illustrated in the recent report (www.who.int/3by5/progressreportJune2005) from the WHO and the United Nations Joint Programme on HIV/AIDS (UNAIDS). The report highlights a district in Uganda where there was a 27-fold increase in the number of people coming in for VCT services when ARV therapy was introduced.

The researchers and community representatives in Rio repeatedly acknowledged that even though the need for treatment remains great, HIV prevention efforts should occur at the same time because ARVs alone will not control the epidemic. The conference highlighted several areas of prevention, including the increased importance of risk reduction efforts for injection drug users (IDUs), exploring novel strategies like male circumcision, and the need to continue research into the development of long-term options like vaccines.

Risk among IDUs soars

In a plenary talk on emerging HIV epidemics Chris Beyrer of Johns Hopkins University in the US offered a sobering description of the dire conditions facing IDUs in several countries in Eurasia (Eastern Europe and Central Asia). Despite an exploding number of new HIV infections in this region there are very few treatment and prevention programs.

Beyrer pinpointed 11 countries as places where explosive HIV epidemics are in progress. Official statistics estimate that currently 1.4 million people in the former countries of the Soviet Union are HIV infected, along with 1.1

million in China and Eastern Asia. The majority of these new infections are occurring among IDUs and the spread of the epidemic is aggravated by the lack of prevention programs to discourage IDUs from sharing syringes.

Tajikistan, the poorest country of the former Soviet bloc, is struggling to cope with a growing epidemic among IDUs yet there are currently no programs offering free access to ARVs and only a single non-governmental organization (The Open Society) is working on HIV prevention. The gross domestic product per capita was only US\$179 in 2000, making it poorer than many African countries, and as much as half of all economic activity there is linked to drug sales. "While we are responding globally with access to treatment, HIV is spreading in new regions," says Beyrer. "A very rapid HIV epidemic is now unfolding where very little prevention is happening."

Needle-exchange programs or drug substitution programs that use non-addictive drugs like methadone or buprenorphine to wean people from heroin addiction are effective in reducing the transmission of HIV among IDUs. But only an estimated 10% of IDUs worldwide have access to needle-exchange programs, even with the recent expansion of prevention

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efforts in some countries like China where the government just recently loosened restrictions. The availability of programs is also limited by funding restrictions such as those in the US President's Emergency Plan for AIDS Relief (PEPFAR) that restrict grant money from being used to fund syringe exchange. "We need to implement programs that we already know work. Unfortunately they have been very hard to start, despite mounds of scientific evidence that show they are effective," says Beyrer.

Beyrer is also discouraged by the exclusion of IDUs from many of the global treatment programs. He points out that throughout Eurasia IDUs were the first groups to become HIV infected and therefore should be overrepresented in the populations receiving treatment, but this is not the case. "Even where policy allows, the de facto reality is that people don't get into treatment programs. It's a terrible way to approach public health because you are isolating the people at highest risk."

Some countries, such as Canada, are exploring innovative options to make injection drug use safer. Vancouver opened the first supervised injection facility in the Americas to address risk behaviors among the city's large IDU population. In Rio Mark Tyndall of the BC Center for Excellence in HIV/AIDS provided an update on the center's first 18 months. He reported that there were 15,000 different visitors to the site, which offers needle exchange, provides visitors with information on safe injection practices, and has nurses on hand to supervise injections. Counselors are also available and they can provide referrals to drug detoxification centers in the city.

The Vancouver site is modeled after similar locations in Europe and Australia, which have a good track record at reducing HIV transmission among visitors to the sites. In Vancouver the HIV transmission rate among IDUs that come to the site continues to be high at around 30%. Visitors are, however, one third less likely to share needles.

Cutting sexual transmission

One of the biggest news stories at the conference came when a group of

French researchers presented results from the first study to offer male circumcision to trial volunteers and then follow them to find out what effect this has on the female-to-male transmission of HIV. Bertran Auvert from the French national institute for medical research (INSERM) presented data from a study sponsored by the French National Agency for AIDS Research (ANRS) that found that adult male circumcision gave a 65% rate of protection from HIV infection.

Researchers have long thought that circumcision could be protective because it reduces the surface area available for transmission and encourages a toughening of the surrounding skin. The foreskin is also home to a high density of immune cells known as dendritic cells that could facilitate

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Helene Gayle

the transmission of HIV. This new study confirmed the results of more than 30 previous studies where researchers observed groups of both circumcised and uncircumcised men without actually performing the procedure. But these observational studies predicted a less dramatic effect.

This study enrolled over 3,000 men between the ages of 18 and 24 in an urban area on the outskirts of Johannesburg, known as Orange Farm. The men were selected randomly to either be circumcised immediately or to delay circumcision until after 21 months. Both groups received intensive counseling on how to reduce their risk for HIV infection and were treated for sexually-transmitted diseases at each study visit. Of 69 new HIV infections during the trial, 51 occurred in the uncircumcised group and only 18 in the circumcised men.

While many in the field of HIV pre-

vention were excited by this result, the study investigators stressed the need for caution. Officials from the WHO and UNAIDS urged governments to await the results of similar ongoing studies before making official recommendations on circumcision. "More research is needed to confirm the reproducibility of these results in differing social and cultural contexts," says Catherine Hankins of UNAIDS.

The Bill & Melinda Gates Foundation is sponsoring a trial in Uganda that is enrolling 800 HIV discordant couples where the man is HIV infected to monitor the effects of circumcision on male-to-female transmission. The other trials are sponsored by the US National Institutes of Health. Results from these trials are not expected until at least 2007.

Although circumcision is widely regarded as simple and safe, it is a surgical procedure and offering this intervention on a large scale would be difficult. The circumcisions in the setting of a clinical trial were done in proper medical facilities by trained surgeons, but this may not always be possible. Many public health experts fear that the high rate of protection offered in the South African study could encourage men to have unsafe circumcisions outside of medical facilities, which could put them at greater risk of HIV infection. WHO is currently formulating guidelines on safe circumcision practices to avoid this situation.

Researchers are also concerned that circumcised men could feel a false sense of protection after circumcision and therefore increase their risk behaviors. If circumcised men increase their number of sexual partners or stop using condoms it could moderate the protective effect. This is a concern for all HIV prevention trials. "Any new prevention tool should not undermine existing prevention programs," adds Hankins.

There are also many unanswered questions about how acceptable circumcision will be within cultures and religions that typically discourage this practice. The French researchers conducted studies to determine the acceptability of circumcision in this area of South Africa and found that 70% of men were willing to undergo this surgical procedure if it was

proven to prevent HIV infection.

"If this trial is confirmed by others then it would be an important advance for prevention," said Helene Gayle,

president of the IAS. "But it should not be implemented until we have further information. There is no one thing that is going to make all the difference

in prevention."

Global News

US government boosts funding of microbicide research

The US government's funding of the research and development of candidate microbicides to prevent transmission of HIV will increase by more than US\$12 million next year. The US Agency for International Development (USAID) will devote \$42 million annually to microbicides as part of the government's overall funding for HIV/AIDS initiatives, which totals more than \$2 billion.

Microbicides are creams or gels that can be applied topically in the vagina or rectum to block transmission of HIV. They are seen as an important preventive technology, particularly for women because they can be used without a partner's consent. The 2006 budget for microbicides is meant to fund research into new candidates and to support the testing of these candidates in clinical trials. The money will also be used to provide antiretrovirals (ARVs) to people in microbicide trials who happen to become HIV infected through exposure in the community.

The National Institutes of Allergies and Infectious Diseases (NIAID), part of the US National Institutes of Health, will also form a partnership with a non-governmental organization to develop vaginal microbicides. The International Partnership for Microbicides (IPM) will focus on candidates that are further along in development while NIAID will be more involved in the basic science and research of new microbicides. There are currently 5 candidates in various stages of clinical trials at sites in Africa and North America and 2 of them are already sponsored by NIAID. Emphasis has been placed recently on the need for collaborative partnerships between public and private organizations to speed the development of an

effective microbicide and vaccine to prevent the spread of the pandemic.

Indian ARVs are returned to WHO's arsenal of approved medicines

The World Health Organization (WHO) has returned seven ARVs manufactured by Indian drug companies to the approved list of medicines for use in developing countries. The WHO removed 3 of the generic or copied drugs from this list last year and 4 others were withdrawn by the companies after tests failed to prove that the ARVs were equivalent to those manufactured by European and US companies.

WHO also added 3 new drugs produced by the Indian company Aurobindo Pharma Ltd. The approval of these drugs allows them to be purchased and used by several international treatment programs and increases the options available to people in developing countries.

Progress report issued on Global Fund

The Global Fund to Fight AIDS, Tuberculosis, and Malaria funds 316 programs in 127 countries aimed at combating these life-threatening diseases. According to its annual progress report issued recently, these programs are providing 220,000 people with ARVs, far exceeding the target set for this year.

Within the report the Global Fund announced that it is suspending several of its grants to both Uganda and Myanmar. All 5 of the grants to Uganda, including 2 for HIV/AIDS, were temporarily stopped until the country's finance ministry can ensure that the approximately \$200 million will be handled effectively. The suspension of these grants should not interrupt treatment services or prevention programs in the country.

The Global Fund also chose to close its programs in Myanmar because of difficulty in delivering medicines and supplies. The grant was supposed to

provide the Southeast Asian country with \$98 million over 5 years and officials are now trying to convince the non-profit organization to reconsider its decision. The United Nations is now considering how to fill the gap in financial support to Myanmar.



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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.

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Why is risk-reduction counseling an important part of AIDS vaccine trials?

A key component of running AIDS vaccine clinical trials is providing the volunteers with education and counseling on how they can protect themselves from HIV infection. This process begins with voluntary counseling and testing (VCT). After this, volunteers who are eligible for participation in the trial are scheduled to return to the trial site repeatedly over several months or years.

At the start of the trial volunteers are given either the vaccine candidate or an inactive substance called a placebo. At each visit thereafter volunteers are tested for HIV infection and counseled on their behaviors. These sessions give volunteers an opportunity to talk with a counselor about how they can reduce their risk of becoming HIV infected. This process is known as risk-reduction counseling. This counseling is essential to AIDS vaccine trials as well as other HIV prevention trials because researchers do not know if the vaccine candidate will have any protective effect until large efficacy trials are completed. Also not all volunteers in the trial are receiving the vaccine.

Trained counselors can work with the participants to identify their risk behaviors and encourage them to avoid feeling any false sense of protection from the vaccine candidate. It is still very important during a clinical trial that volunteers continue practicing safer sex or injection practices and reduce behaviors that put them at risk of HIV infection as much as possible.

What is a typical risk-reduction counseling session?

During a risk-reduction counseling session the counselor will try to learn about the volunteer's past risk behaviors. This is referred to as collecting a "history" and can include information about their sexual practices and drug use. Counselors will ask volunteers about their number of sexual partners, their use of condoms

or other protective devices, and any special issues that may surround their previous behaviors, including sexual violence or domestic abuse. The type of counseling will depend on the targeted population enrolled in the study—the risk-reduction messages for injection drug users would be different from those at risk of sexual transmission.

A risk-reduction counseling session also provides volunteers with some basic information on HIV/AIDS and how it is transmitted. This may help to dispel any myths about how they can become HIV infected and can aid volunteers in identifying their true risk behaviors.

What is a risk-reduction plan?

During a risk-reduction counseling session the counselor works with each trial participant to develop an individualized plan for how to change his or her risk behaviors. Behavioral changes are often difficult for people to make so counselors should enquire about the volunteer's attitudes and beliefs to determine how these may be contributing to their HIV risk.

Counselors should also try to give volunteers several options for how to protect themselves because each volunteer is unique, even if they participate in the same risk activity. The risk-reduction plan that the counselor and volunteer create is personalized and each volunteer's questions and concerns should be considered so that the volunteer is more likely to adhere to it. The messages should also change over the course of the study so that volunteers don't get tired of hearing the same information.

In some studies risk-reduction counseling sessions are done with couples rather than individuals. This approach seems to work best for people who are at risk of becoming HIV infected through heterosexual transmission such as discordant couples, where only one partner is infected. Many women are still at risk of HIV infection in marriage, and for them risk-reduction counseling can be more effective if it addresses some of the

power struggles or violence that occurs in the home.

The counselor should try to create an environment that allows volunteers to be comfortable discussing their personal behaviors. Risk-reduction counseling sessions require counselors to dedicate large amounts of time and effort because many participants may initially be unwilling to discuss with strangers details about their sexual activities. But the more information the volunteers provide, the more likely their risk-reduction plan will be successful. One way counselors can put volunteers at ease is to use supportive verbal and body language. They should also remain objective and avoid judging the volunteer.

Does risk-reduction counseling work?

Several clinical trials in the US have shown that individual risk-reduction counseling sessions are effective in getting people to change their behaviors and reduce their risk. But little is known about how these results translate to other cultures.

Only one efficacy trial of a preventive AIDS vaccine candidate has been completed to date. During this trial volunteers in Thailand and the US were provided with risk-reduction counseling every 3 months for the first two years and then every 6 months for the final year. Researchers have heavily studied the risk behaviors of these participants over the course of the trial and their reasons for volunteering. In some cases the risk behaviors of the volunteers actually declined among both the vaccine and placebo groups, leading to a lower incidence of HIV infection than anticipated for the study period. This is one way a vaccine trial can benefit a community even if the candidate is found to be ineffective. Researchers also found that several people reported joining this trial specifically to learn about reducing their risk behaviors. This observation further supports the need for intensive risk-reduction counseling in the context of AIDS vaccine trials.