



## Spotlight

### Injection of hope

*Wider implementation of harm-reduction programs may help curb HIV's spread*

Alex Wodak, a physician in Sydney, Australia and former president of the International Harm Reduction Association, is thankful that his country responded rapidly to a growing HIV epidemic among injection drug users (IDUs). As a result only 5% of the country's new HIV infections in 2003 occurred within the IDU community. In the US that same year, 33% of new infections were among IDUs or their sex partners.

This discrepancy in HIV prevalence among IDUs between the two countries can be at least partly attributed to the introduction of harm-reduction programs that aim to reduce the spread of HIV among IDUs. The package of programs includes education, needle or syringe exchange so that IDUs aren't injecting with contaminated needles, supervised injection facilities that provide both clean needles and help prevent overdose, and drug replacement therapy to help wean individuals from the addiction of illegal drugs.

Studies show that these programs are an effective way to reduce HIV transmission among this highly vulnerable group. This has positive effects well beyond IDUs. Researchers have observed that more generalized HIV epidemics in several countries often start among IDUs, so reaching this population can have a much broader impact on HIV prevention efforts.

These programs also establish a vital link between public health workers and

IDUs, who are often isolated. "Needle and syringe programs are a stand-in for the larger issue of how to reach the people who are the least engaged in society yet are at the greatest risk," says Daniel Wolfe, the deputy director of International Harm Reduction Development Program at the Open Society Institute. Yet harm-reduction programs are not implemented widely because drug use is a difficult issue to confront. There are legal and moral sensitivities about drug use, just as there are around the sexual transmission of HIV. "Thank God that Australia was settled by convicts, whereas the United States was settled by puritans and has been dealing with it ever since," says Wodak.

Because of their high risk, IDUs can also be important volunteers for AIDS vaccine trials. But it is an ongoing question whether it is ethical to test vaccine candidates in IDU cohorts without providing sterile needles and syringes.

#### A growing problem

The HIV epidemic among IDUs is a serious problem. Globally, 10% of all HIV-infected individuals are IDUs and, outside of sub-Saharan Africa, an estimated one in three new HIV infections is due to injection drug use.

Even in Africa, where the epidemic has been driven almost exclusively by sexual transmission, injection drug use is now a documented source of HIV transmission in 10 countries. Contaminated needles cause the largest share of new infections in some 20 nations and are fueling several of the world's growing epidemics, including those in Russia, Ukraine, China, Indonesia, central Asia, and much of south and southeast Asia. In the countries of the former Soviet Union roughly 70% of HIV infections occur among IDUs.

These alarming statistics highlight the overwhelming need for harm-reduction programs, especially in areas with exploding epidemics. A comprehensive approach is required to combat the spread of HIV within communities of IDUs, including programs to reduce the number of individuals who inject drugs, promote safe injection practices and discourage unsafe sex, and roll back the legislation that outlaws the sale or possession of injection paraphernalia.

Some of the most well-studied of these programs, and of HIV prevention strategies overall, are needle and syringe provision or exchange programs that supply IDUs with sterile injection equipment. These come in a variety of forms, including supervised injection sites, a one-to-one exchange of needles, or sale of sterile needles and syringes at pharmacies, clinics, or vending machines. The majority of studies have shown that needle and syringe programs reduce HIV transmission in a safe manner and are very cost-effective.

Since the first needle-exchange program began in Edinburgh, Scotland, in the early 1980s, many such programs have started up around the globe. There are now safe injection facilities operating in over 20 European cities. These sites provide IDUs with clean injection equipment and allow them to inject drugs in a supervised setting. These sites also usually offer education and condoms, access

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to drug rehabilitation, and health services, and are able to connect IDUs with a larger support network that can influence positive behavior change. There is currently only one safe injection site in North America. This site in Vancouver, Canada, opened in 2003 and was recently given permission by the Canadian government to continue operating until at least the end of next year.

### US opposition

Despite the evidence in support of needle and syringe provision as an effective HIV prevention strategy, the programs are still reaching a miniscule number of people. In 2004 HIV prevention activities for IDUs reached at most 5% of all users globally.

This is partly due to the US's opposition to needle and syringe exchange programs, both at home and abroad. As the largest provider of funds for international AIDS prevention programs, the US also has great sway over programs in other countries. Restrictions in the President's Emergency Plan for AIDS Relief (PEPFAR) prevent any of the US\$34 million from being used to fund needle-exchange programs. The US government's stance stems from concerns that providing people with injection equipment will only promote illegal drug use.

Within the US, several states have found ways around the federal funding ban and operate needle and syringe programs using state and local government funding, or private donations.

### Implementation

One challenge in needle syringe programs is determining how many needles are enough to stem HIV transmission. The World Health Organization (WHO) approximates that providing 200 sterile needles and syringes per drug injector each year is likely to control the spread of HIV. Another often quoted target accepted by a range of agencies, including the WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS), is that 60% of all injections need to be done with a sterile needle and syringe. Australia established its first needle and syringe program in 1986 and annually distributes 30 million needles in a country with a population of less than 20 million. By contrast, the US distributes only about 25 million needles each year for a population of 300 million.

Implementing these programs early in the course of an HIV epidemic is also critical to success. For many countries in Eastern Europe and southeast Asia, therefore, the optimal time to implement such programs is now. According to UNAIDS, Russia's HIV epidemic is the fastest growing in the world. Most infected individuals are under the age of 30 and nearly 90% are IDUs, yet needle and syringe programs reach perhaps 2% of the Russian IDU population. Most of these are funded by non-governmental organizations (NGOs). Moscow has no needle-exchange program, syringes are not available for purchase, and possession of a syringe containing drug residue is a punishable offense.

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Other former Soviet states have more progressive drug policies. Ukraine hosts about 250 projects sponsored by the Global Fund that reach about 70,000 IDUs. Among the central Asian countries of the former Soviet Union, where about 70% of the HIV infections are among IDUs, only Kyrgyzstan and Tajikistan offer drug treatment and needle and syringe programs.

China has also made recent strides in its commitment to stemming the HIV epidemic among IDUs, which make up about 44% of the 650,000 people officially estimated to be HIV infected. The Chinese government plans to spend approximately \$185 million on HIV prevention, doubling current spending, between 2005 and 2007. Over the next five years, the Global Fund also plans to disburse more than \$60 million in funds to prevent HIV transmission among IDUs and sex workers in the seven Chinese provinces that harbor 90% of the HIV-infected IDUs.

Indonesia, a country with strict drug laws, is making attempts to stem its injection-driven HIV infection rate of

44%. Vietnam made a strong national commitment in 2005 to provide sterile needles and drug substitution therapy for its IDUs, which make up 52% of the nation's total number of HIV-infected individuals. Despite this, harsh anti-drug laws have resulted in the executions of 44 people in 2004, according to Amnesty International. UNAIDS estimates that more than 55,000 drug users are currently held in rehabilitation centers in Vietnam that human rights activists say more closely resemble labor camps.

### Vaccine trials

IDUs would benefit greatly from access to a preventive AIDS vaccine and so their participation in clinical trials is especially important. Many trial sponsors and researchers agree that if IDUs are enrolled in a vaccine trial, the sponsor is ethically required to provide the volunteers with sterile injection equipment. "Needles and syringes should obviously be provided. It is good research ethics and good public health," says Chris Beyrer, director of the Fogarty AIDS International Training and Research Program at Johns Hopkins Bloomberg School of Public Health.

The Thai Drug Users Network (TDN) is an activist group that has lobbied for the provision of sterile needles and syringes to IDUs participating in HIV prevention trials in the country, many of which are sponsored by US-based organizations. So far they have been unsuccessful and the TDN has now taken their case to the Thailand National Human Rights Commission.

Needles and syringes are available for purchase at pharmacies in Thailand but, according to Karyn Kaplan of TDN, the drug users her group talks with say that obtaining needles is not that easy. They cost about 12 cents each and many pharmacists refuse to sell needles to people they perceive as drug users. "Clearly the US policies against needle exchange and harm reduction itself are hampering individuals' ability to protect themselves," says Kaplan. Since the US is not likely to begin funding needle and syringe programs in the near future, Beyrer suggests that an NGO could provide them.

Researchers agree that enhancing the ease of access to clean needles and syringes will help IDUs protect themselves and their partners, and perhaps help head off some of the world's rapidly expanding epidemics.

## Global News

### UNAIDS and WHO release new report on global epidemic

In advance of World AIDS Day, which was observed on December 1, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) released a report detailing updated global and regional estimates of the number of people newly HIV infected in 2006 ([www.unaids.org/en/HIV%5Fdata/epi2006/](http://www.unaids.org/en/HIV%5Fdata/epi2006/)). Twenty-five years after the first cases of AIDS were reported the epidemic is still spreading relentlessly around the globe. In 2006 alone, 4.3 million people were newly infected with HIV, bringing the total number of people living with HIV/AIDS to 39.5 million.

Since 2004 the number of people living with HIV increased in every region of the world. In some regions these new infections are disproportionately occurring in young people. In the Russian Federation, 80% of HIV-infected individuals are younger than 30 years old. The primary route of transmission in the countries of Eastern Europe and Central Asia is still injection drug use and 67% of HIV infections in 2005 were a result of people injecting drugs with contaminated needles and syringes (see *Spotlight* article, this issue).

However, in eight African countries where sufficient data was available, HIV prevalence has declined among young people since 2000/2001. This trend is attributed to the success of HIV prevention messages targeting this age group that encourage young people to avoid behaviors that place them at risk of HIV infection. Throughout the world women are also continuing to bear the brunt of the HIV epidemic. In sub-Saharan Africa 59% of the people living with HIV/AIDS are now women.

Despite promising advancements in the availability of HIV treatment in developing countries, 2.9 million people died from AIDS in 2006—the highest number ever reported for a single year. The vast majority of these deaths (72%) occurred in sub-Saharan Africa where the epidemic is still hav-

ing the greatest impact, but worldwide AIDS is now the leading cause of death in people between the ages of 15 and 59.

The theme of this year's World AIDS Day was accountability and Kofi Annan, secretary-general of the United Nations, said in a *USA Today* editorial that, "as the number of infections continues unabated, we need to mobilize political will as never before." He called on every prime minister, president, parliamentarian, and politician to strengthen protections for vulnerable groups, including people living with HIV, young people, commercial sex workers, injection drug users (IDUs), or men who have sex with men. Both UNAIDS and WHO emphasize the need to increase and improve prevention efforts that target people who are at greatest risk of HIV infection.

### Mounting data on benefits of male circumcision

Results from two randomized, controlled clinical trials show that circumcision of male adults reduced their risk of acquiring HIV by approximately 50%. These results were released on December 12, 2006 after an independent committee of clinical research experts, statisticians, ethicists, and community representatives reviewed the interim data collected in these trials. Based on the substantial benefit offered by circumcision, male volunteers in the control group will now also be offered the surgical procedure. Researchers will continue to monitor the HIV infection rates among all volunteers and will also study how the procedure affects their behaviors.

Both of these trials, one which took place in Rakai, Uganda, and the other in Kisumu, Kenya, were sponsored by the US National Institute of Allergies and Infectious Diseases (NIAID), part of the National Institutes of Health. They confirmed the results of a previous circumcision study conducted in South Africa, which was the first to show that removal of the foreskin offered some protection against HIV infection (see *VAX* August 2005 *Spotlight* article, *A comprehensive response*). According to NIAID, studies in Africa have found that circumcision is an

accepted practice, with 50-86% of those surveyed saying they would either have the procedure or want their partner to undergo circumcision if it was known to be safe, affordable, and have minimal side effects.

Organizations like UNAIDS and WHO are currently working on recommendations for the implementation of adult male circumcision in countries where sexual transmission of HIV predominates. Another study sponsored by US-based Johns Hopkins University is still ongoing to determine if male circumcision reduces HIV transmission from men to women. However, public health experts agree that any intervention that reduces HIV rates in men by 50% will also benefit women.



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## How can animal models be used to identify the correlates of protection for an AIDS vaccine?

Using animal models to study HIV infection and the progressive development of AIDS is an important way for researchers to analyze how the virus behaves in humans (see *VAX* October 2006 *Primer on Understanding AIDS Vaccine Pre-clinical Development*). Despite its limitations, the non-human primate model is immensely useful to researchers. Studying the related simian immunodeficiency virus (SIV) in non-human primates, typically rhesus macaques, provides important information about HIV, even though these studies involve a different virus. Many discoveries about how SIV interacts with the immune system and causes disease, a principle known as pathogenesis, in macaques have later been shown to also be true for HIV in humans. For example, the finding that HIV preferentially kills CD4<sup>+</sup> T cells, a critical subset of immune cells, at the mucosal surfaces of the intestine or gut early in the course of infection was first observed with SIV infection in rhesus macaques (see *VAX* April 2006 *Primer on Understanding the Early Stages of HIV Infection*).

Non-human primate studies are also an important tool for researchers who are studying the immune correlates of protection so that they can design improved AIDS vaccine candidates (see *VAX* November 2006 *Primer on Understanding Immune Correlates of Protection*). If they can successfully identify the specific types of immune responses (antibodies, CD4<sup>+</sup> or CD8<sup>+</sup> T-cell responses, other natural immune responses, or some combination of these) that protect rhesus macaques from SIV infection, it will most likely provide vital clues about the types of responses that would be protective against HIV infection in humans.

### Sterilizing protection

Working with non-human primates also allows researchers to conduct studies that would be impossible to do in humans. Due to safety concerns, researchers have not tested any AIDS vaccine candidates in humans that con-

tain either a killed version of HIV or a live but weakened version of the virus. However, researchers are able to test live-attenuated SIV vaccine candidates in rhesus macaques and then try to infect or challenge them with SIV and see if they are protected. These challenge studies would never be conducted with human volunteers, but the results of these animal studies may be important in the identification of the correlates of protection.

When rhesus macaques are given a live-attenuated SIV vaccine and then challenged with exactly the same viral strain, the majority of animals are protected from SIV infection. So far this is the only model where researchers have been able to induce sterilizing immunity against the virus.

This indicates that there is an immune response, or a combination of responses, which are capable of protecting macaques. Now researchers have to identify the exact immune responses that are responsible for this protection. Work in this area is ongoing and researchers, many of whom are working as part of larger scientific consortia, are now studying this question. Researchers have already identified an antibody that is directed to the envelope protein on the surface of the specific SIV strain used in these experiments. This antibody is capable of neutralizing the virus and therefore is correlated with protection, but it is still unknown if this response is actually responsible for the protection.

Researchers are also studying other immune responses induced at specific sites, like the intestine, and the genetic makeup of the macaques to see if these factors are also contributing to protection. Defining the precise correlates of protection is an incredibly difficult and time-consuming task. Since many different laboratories are working in this area, it is also important that researchers use the same tests or assays to evaluate the immune responses so that their data can be compared.

### Mechanism of protection

Even after researchers identify the antibodies or cellular immune responses that correlate with protection there are still

many other questions. These responses are still just correlated or associated with protection and often researchers don't know specifically how these immune responses interact with HIV. Pinpointing the precise method by which these immune molecules and cells kill the virus and block HIV infection is also an important area of research. This mechanism of protection can be particularly instructive when researchers are considering how to induce these responses with vaccination.

There are several complications with determining the mechanism of action between these immune responses and the virus. In some cases the immune responses that researchers identify as the correlate of protection may only be masking another antibody or cellular immune response that is actually the one responsible for protection. It is also possible that another genetic factor not related to the immune system provides protection.

### Relevance

If researchers are able to define the correlates of protection in non-human primate models, developing an AIDS vaccine candidate that can provide sterilizing immunity in humans will still be a complex process. It may be difficult to stimulate similar immune responses without using a live-attenuated AIDS vaccine candidate, and it is unlikely that this approach will ever be tested in humans.

Most of the vaccine candidates that are currently in clinical trials trigger primarily cellular immune responses and specifying the correlates of protection with these types of vaccines will be even more difficult, in both animals and humans. Some researchers think it is possible that different vaccine candidates may even stimulate different CD4<sup>+</sup> or CD8<sup>+</sup> T cell responses, and therefore have different correlates of protection.

Despite these challenges, working with non-human primates is still the best model available to AIDS vaccine researchers and it is likely to provide them with critical clues that will help improve the design of novel candidates.