Ratcheting up T-cell responses

A crop of vaccine candidates that are capable of inducing robust cellular immune responses garner attention at this year’s AIDS Vaccine conference

By Kristen Jill Kresge

The audience of close to a thousand researchers who gathered at the start of the annual AIDS Vaccine conference in Amsterdam from August 29 to September 1 was greeted with a level of optimism that has become quite unusual in this field. Lawrence Corey of the HIV Vaccine Trials Network in Seattle called 2006 “a vintage year for vaccine development” when he gave an overview presentation on the current status of the HIV vaccine pipeline at the opening plenary session.

Over the following days support for his statement came from several presentations that showed promising immunogenicity data for some of the vaccine candidates currently in clinical trials, a welcome shot of good news for a field that has struggled for many years to develop candidates that invoke promising levels of immune responses in humans. “A few years ago it was hardly possible to stimulate T-cell responses with vaccination,” said Andrew McMichael of the University of Oxford, UK. Now several Phase I and II trials with candidates based on adenovirus alone or in prime-boost combination with DNA plasmids, modified vaccinia Ankara virus, and poxvirus vectors containing HIV genes are providing encouraging results.

Researchers have been able to increasingly ratchet up the level of CD4+ and CD8+ T-cell responses; those induced by the current crop of candidates are three times higher than those possible just a couple of years ago, said Corey, and he is hopeful that this progress will continue in the coming years. While efforts to stimulate a neutralizing antibody response with immunization are still largely unsuccessful, researchers suggest advances in cellular-based vaccines may bring the field closer to a vaccine that may either prevent HIV infection or, perhaps more likely, lower viral load and therefore ameliorate disease progression and lower the infectivity in individuals who do become infected.

HIV prevention picks up momentum

Discussion of microbicides, vaccines, and other new prevention technologies tops the bill at international AIDS conference

By Kristen Jill Kresge

Over the past several years the number of people 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), which are bringing treatment to developing countries. But the number of new HIV infections continues to be high, with four million individuals becoming newly infected last year, and this has shifted attention back to halting transmission of the virus. The need for a concomitant improvement and scale-up of treatment and prevention services was never more emphasized than when a record 26,000 delegates from around the world gathered in Toronto from August 13-18 for the International AIDS Society’s (IAS) XVI International AIDS Conference.

The conference kicked off with speeches from Bill and Melinda Gates and former US president Bill Clinton. The trio recently vis-
infected. “There’s cautious optimism now” about the ability of T-cell based vaccines, said Corey.

But others who addressed the conference delegates painted a less rosy picture of the current state of research. Jaap Goudsmit of the Netherlands-based biotechnology company Crucell reminded researchers that there is yet to be a vaccine against any disease licensed on the basis of results from T-cell assays. He also recounted that the late vaccinologist Maurice Hillemann wrote in one of his last published articles that any vaccine based on cellular immunity was unlikely to be effective (Proc. Natl. Acad. Sci. USA 101, 14560, 2004).

Even with the encouraging immunogenicity data in hand there are still several potential pitfalls with the current candidates. Debate continues over including the highly variable HIV env gene as a vaccine insert, which John Moore of Weil Medical College at Cornell University called “one of the most hyper-glycosylated proteins vaccinologists have ever had to deal with.” And although many of the concerns about the potential for pre-existing immunity to viral vectors like adenovirus seem to have subsided somewhat, research into new vectors like cytomegalovirus (CMV) or other serotypes of adenovirus are a clear priority for the field. Several speakers also underscored other key challenges, including establishing a better pre-clinical system for evaluating vaccine candidates and streamlining the clinical trials process to expedite the development of vaccines.

**Vintage data**

Much of the promising immunogenicity data presented at the conference came from trials administering vaccine candidates in a prime-boost combination and several utilize DNA plasmid vaccines for the initial immunization. “Don’t consider DNA as not immunogenic because they [DNA plasmid vaccines] are priming very well,” said Giuseppe Pantaleo of the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland.

One of the earliest presentations on a DNA vaccine candidate was by Eric Sandström of the Karolinska Institute, Sweden, who presented for the first time immunogenicity data from a Phase I trial that is ongoing in Stockholm with a seven plasmid DNA vaccine developed at the institute in collaboration with the Swedish Institute for Infectious Disease Control. The candidate contains env genes from clade A, B, and C; rev from clade B; gag from clade A and B; and RT from clade B. Forty volunteers in the trial were randomized to receive three injections with one of three doses (1mg, 2mg, or 3.8mg) of the DNA vaccine administered either intradermally (via the needle-less system developed by Bioject) or intramuscularly. Half of the participants also received a 0.5ml injection of the cytokine granulocyte-macrophage colony-stimulating factor (GMCSF).

Six months after the final DNA immunization, all but two volunteers also received a booster immunization with a modified vaccinia Ankara (MVA)-based vaccine candidate developed by the US National Institutes of Allergies and Infectious Diseases and manufactured by the Walter Reed Army Institute of Research (WRAIR). Side-effects in vaccine recipients were limited to fatigue and general flu-like symptoms after the DNA prime and only mild adverse events were reported after the MVA injection.

Researchers measured the level of immune responses by IFN-γ ELISPOT assay and positive responders in this trial were defined as those with greater than 55 spot forming cells (SFC) per million cells. After the third DNA immunization, 11 of the 38 vaccinees had positive immune responses. But after the MVA immunization there was a significant immune response boost to both Gag and Env, with 33/36 of participants having positive ELISPOT results. The MVA vaccine appeared highly immunogenic despite several of the trial volunteers having been previously exposed to vaccinia virus through smallpox vaccination.

Based on the results of this trial Sandström and colleagues are preparing for a Phase I/II trial in Tanzania with the same candidates, excluding GMCSF, since the DNA plasmid vaccine is based on HIV strains circulating in that country.

Results from a Phase I trial conducted by the EuroVacc consortium with another DNA plasmid vaccine tested in combination with NYVAC, a modified poxvirus vector vaccine, were also presented. A total of 40 volunteers—20 male, 20 female—were recruited for this trial at two sites in the UK and in Lausanne. Half of the participants received...
two injections of a DNA plasmid vaccine containing HIV clade C env, gag, pol, and nef genes and all volunteers received two doses of NYVAC containing the same genetic inserts. The combination was more immunogenic than NYVAC alone, which induced positive ELISPOT responses in only 40% of volunteers and these tended to disappear by 48 weeks after immunization. Of the 20 volunteers who received the DNA/NYVAC combination, 90% had positive responses (>55 SFC). Responses to env averaged around 120 to 180 SFC after DNA priming and boosting with NYVAC, with the highest responder reaching 300 SFC. Some volunteers also generated more diverse responses to gag and pol but at much lower levels, and the immune responses induced by this vaccine regimen were maintained through 48 weeks. "These responses are in the range of what we see in long-term non-progressors," said Pantaleo. However they are primarily directed to env, which, he pointed out, is not the case in people who are HIV infected.

Rick Koup presented an update on the DNA plasmid vaccine and adenovirus serotype 5 (Ad5) vector-based vaccine developed by the Vaccine Research Center (VRC) at the US National Institutes of Health (NIH) that is currently in Phase I/II clinical trials (see On trials, IAVI Report 10, 2, 2006). Enrollment for these trials is now two-thirds complete but is still ongoing at HIV Vaccine Trials Network (HVTN) sites in North and South America and South Africa and at WRAIR sites in Africa. Data from several previous trials with this combination of vaccine candidates show that the DNA priming produces higher CD4+ and CD8+ T-cell responses up to the third DNA immunization and Koup reported that the CD8+ T-cell responses are boosted 5-fold after administration of the Ad5 vaccine. The T-cell responses after boosting are also more polyfunctional, as determined by expression of the cytokines IFN-γ, interleukin-2 (IL-2), MIP1β, and TNFα, and expression of CD107. Some immunizations in these trials were given with the Bioject system and Koup hinted that data comparing this route of administration with traditional intramuscular injection would be available soon. For now the VRC, WRAIR, and IAVI are preparing to move these candidate vaccines into a Phase Ib test-of-concept trial, known as PAVE 100.

‘Nature’s adjuvant’

Adenovirus-based vaccine candidates have produced the most impressive cellular immune responses seen so far, and Gary Nabel of the VRC referred to the viral vector as “nature’s adjuvant.” Another advantage of this vector is that it can be administered at much higher doses than other viral vectors—1000 to 10,000-fold more particles than can be safely used with MVA, for example. But results from a Phase I safety trial, HVTN 054, indicate that at higher doses the reactogenicity of Ad5 vaccines increases without any further gain in immunogenicity. Laurence Peiperl of the University of California School of Medicine in San Francisco presented data from this trial that evaluated a single injection of the VRC’s Ad5 vaccine candidate at a dose of either 1010 or 1011 particle units (PU). The recombinant Ad5 vaccine encoding HIV Env from clades A, B, and C and clade B Gag/Pol was administered to 20 volunteers at each dose. Systemic reactogenicity and flu-like symptoms or reactions at the injection site were reported in four volunteers, all of whom received the dose of 1011 PU. The side-effects peaked one or two days following injection and trailed off within a week and although none of the serious adverse events were considered related to the vaccine, Peiperl concluded that the safety profile of the lower dose seemed more favorable.

Additionally the immune responses measured by intracellular cytokine staining assay were actually higher in volunteers who received the lower dose—95% were considered responders compared to 90% at the 1011 PU dose. “It appears that less is more for immune responses to adenovirus,” said Robert Seder of the VRC.

The same dose of Merck’s Ad5 vaccine candidate is also being evaluated in the company’s ongoing Phase Ib test-of-concept trial in collaboration with the HVTN (see Renewed promise, IAVI Report 9, 4, 2005). The highly anticipated efficacy data from this trial won’t be available until 2008 but Michael Robertson of Merck provided some preliminary information about the safety of the vaccine candidate. The majority (74%) of volunteers reported mild or moderate adverse events, most of which
were headache, fever, fatigue, or pain at the injection site. Serious adverse events occurred in 13 individuals and 3 of these were attributed to the vaccine, including a severe case of fever, diarrhea, and a report of possible anaphylaxis. The number of adverse events decreases after the second and third immunizations, which Robertson credited to anti-vector immunity.

Another focus of his presentation was on the experiences of conducting the trial in individuals at high risk of HIV infection either through sexual activity or injection drug use. Conducting trials in these populations will allow researchers to get preliminary efficacy results with smaller, faster, and cheaper studies, said Robertson, but some have speculated that it will be more difficult to both recruit and retain high-risk individuals in long-term vaccine trials. So far, at least, this has not been Merck’s experience. Approximately 2000 of an intended 3000 volunteers were enrolled in the study at the end of July—enrollment should be complete by the end of this year—and volunteers have completed 95% of scheduled visits.

Robertson presented data collected about the reported risk behaviors of the individuals to establish the level of risk in this cohort. Men screened for the Phase IIb study across all sites reported a median of 6 different sexual partners in the last 6 months, and 12% of them reported having unprotected anal intercourse with a partner who they knew was HIV infected. Women reported an average of 28 different sexual partners over the previous 6 months and 5% had unprotected vaginal intercourse with an HIV-infected partner. Also, 15% of the women screened for the trial reported having another sexually-transmitted disease in this same time period. During the screening process the HIV prevalence rates among males was 4% and for females was around 3%, though Robertson explained that these figures vary greatly from site to site.

**Pre-existing anxiety**

By the time the Merck trial is fully enrolled there will be an equal number of volunteers with both low and high levels of pre-existing antibody immunity to Ad5. This will allow researchers to draw conclusions about how the immunogenicity of the vaccine is compromised by anti-vector immune responses. As many as 95% of people in sub-Saharan Africa and southeast Asia have high antibody titers to Ad5 and this has been a major concern for the AIDS vaccine field. However preliminary data suggests that the immune responses induced by current vaccine candidates are only modestly affected by prior Ad5 infection. Immune responses to the VRC’s DNA/Ad5 vaccines remain high even in volunteers with very high anti-Ad5 antibody titers (>1:7000).

Data from Merck’s earlier Phase I and II trials also show that the immune responses in volunteers with high levels of pre-existing immunity are only blunted by an average of 15% when compared to volunteers without Ad5 seropositivity. This is encouraging to many researchers. “The data is limited, but it doesn’t look like pre-existing immunity is going to be a show stopper,” said Koup.

Still, many research groups are continuing to develop vectors based on other serotypes of adenovirus. Both Nabel and Dan Barouch of Beth Israel Deaconess Medical Center in Boston presented on recombinant adenovirus vectors that retain the immunogenicity of Ad5, yet can circumvent problems with pre-existing immunity. Nabel and colleagues at the VRC are studying the mechanism by which Ad35, a serotype of adenovirus with a much lower seroprevalence worldwide, targets dendritic cells to see if this influences its immunogenicity. “If we understand it, we may be able to engineer our way around it,” he said.

Nabel also argued that researchers might not gain anything using Ad35 as a vector, especially if its immunogenicity is further compromised in people previously infected with Ad5. But for now there is a paucity of data in non-human primates. “Human data is the only thing that’s going to matter here,” said Jerald Sadoff of the US non-profit Aeras Global TB Vaccine Foundation, “and it’s immunogenic enough to move forward.”

Other groups are attempting to develop novel viral vectors. Louis Picker of the Oregon Health and Science University in the US presented on the development of cytomegalovirus (CMV) vectors for AIDS vaccines. CMV is a herpesvirus that is ubiquitous throughout the world and, once established, infection persists indefinitely. Infection with CMV has very few conse-
quences in healthy individuals and there are rarely any symptoms but it can cause serious disease in immunocompromised individuals, including those with HIV/AIDS.

Attributes of CMV that make it attractive to AIDS vaccine researchers are its immunogenicity and the induction of T-cell responses at mucosal surfaces. Reinfection with the virus is also highly efficient so it easily avoids any potential problems with pre-existing immunity. The virus also has a large genome that could be customized to both increase immunogenicity and attenuate the virus to enhance safety, which would be an important issue moving forward with this viral vector. “We’re hoping to manipulate these viruses to make them unquestionably safe,” said Picker.

Moving forward

Researchers are also now focusing on ways to streamline the AIDS vaccine pipeline and push promising candidates forward as quickly as possible (see Vaccine Briefs, this issue). One way to accomplish this is to improve the ability to evaluate preclinical candidates so that fewer non-immunogenic candidates are moved into costly Phase I trials. Advancements in this area were reported in Amsterdam by J. Victor García-Martínez of the University of Texas Southwestern Medical Center, who has developed a humanized mouse model that can be used to test vaccine candidates.

His research group transplanted human CD34+ stem cells into immunodeficient NOD/SCID mice that had already received implants of human thymus and liver tissues. This resulted in long-term repopulation of human B cells, monocytes/macrophages, T cells, and dendritic cells in the mice. When infected with HIV, these mice produced HIV-specific human antibodies and experienced progressive disease, marked by a depletion of CD4+ T cells and an increase in CD8+ T cells, which mirrors human infection.

Further analysis showed that CD4+ T cells in the humanized mice were also depleted in the lung and gut, which is now known to be a primary site of HIV replication early in human infection. Models like this could vastly improve the ability of researchers to understand a candidate’s immunogenicity since it more closely mimics human HIV infection.

In the meantime, the field is eagerly anticipating the results of the ongoing trials to answer some of the critical questions about cellular immunity. “The next few years are going to be very interesting in this field,” said Robertson. “Hopefully we will have good news on T-cell based vaccines.”

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Michael Robertson

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ited Africa to gather a first-hand picture of the toll that HIV/AIDS is taking there, and between them they made several appearances in the first days of the meeting. At the opening ceremony Bill Gates emphasized the need for focusing on HIV prevention, saying, “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.” Measures to expand HIV prevention programs and research into new approaches to prevent transmission of the virus, including new technologies like vaccines and microbicides, held prominence in the days to follow. Helene Gayle, who left her post as president of IAS following the conference, said this meeting will undoubtedly be remembered as the one that placed HIV prevention back on the agenda.

Late-stage clinical trials with several microbicide candidates were highlighted by scientists and activists, and other HIV prevention strategies like pre-exposure prophylaxis (PrEP; see Treatment as prevention, LAVI Report 10, 3, 2006) and male circumcision (see Cutting HIV transmission, LAVI Report 9, 3, 2005) were touted by Gates, Clinton, and many others. There is a shared optimism among researchers that a combination of these strategies could help curtail the epidemic’s spread, although conclusive research on their efficacy is still unavailable. And despite the scientific obstacles to developing an AIDS vaccine the number of candidates is expanding and the Vaccine Research Center at the US National Institutes of Health (NIH) is now moving towards advancing its lead candidate into a preliminary efficacy trial. “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 disempowered women, particularly those who are victims of abuse. Now that newer prevention technologies are winding through development, researchers are ushering in a new era of prevention acronyms. The next generation, referred to as CBS—for circumcision, barrier methods (such as the female diaphragm), and syringe exchange—are the next crop of options that researchers hope will enter the prevention armamentarium 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 (PLoS Med., 7, e262, 2006). Three other circumcision trials are ongoing in Kenya and Uganda and interim data from two of these trials—one in Uganda, one in Kenya—sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID) were recently analyzed by a data safety monitoring board. The efficacy data at this point were not sufficient to warrant stopping either trial, but another interim analysis was recommended within the next year. Both trials are scheduled for completion by September 2007 and many public health officials, including some from the Joint United Nations Programme on HIV/AIDS (UNAIDS), took the opportunity provided by the conference to reinforce messages 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 covered 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. Enrollment of volunteers is now complete in Harare, Zimbabwe, as well as in Johannesburg and Durban, South Africa. Researchers at the University of California in San Francisco expect the trial will be completed by June of next year (see Capping infection, page 15).

An update on syringe-exchange programs was also a topic of two plenary talks, delivered by Alex Wodak of St. Vincent’s Hospital in Sydney, Australia and Chris Beyrer of Johns Hopkins University in the US. Wodak reported that in 2005, 10% of all new HIV infections globally occurred among injection drug users (IDUs). This route of HIV transmission is responsible for 68% of new infections in Ukraine and is also reported in at least 10 African coun-
tries, where the epidemic has until now been driven solely by sexual transmission.

Harm reduction programs that promote syringe exchange or provide safe-injection facilities to IDUs (see Injection of hope, page 9) are among what Wodak calls the "most effective interventions in the HIV/AIDS repertoire," but they remain severely under-utilized. In most countries IDUs also lack access to ARVs. Beyrer noted that 34,000 IDUs in developing countries are currently receiving treatment, but only 4000 of these are outside of Brazil.

Beyond CBS

The next generation of prevention options, called MTV—for microbicides, treatment or PrEP (providing ARVs to try to prevent infection), and vaccines—were also widely discussed. Currently five microbicides are in large-scale efficacy trials with results expected as early as next year. "We're not a long way from finding out if a microbicide will work or not," said Ramjee, who emphasized in a plenary talk on HIV prevention technologies that this progress has occurred without any investment from the private sector. Funding for these advanced trials has been provided by the Bill & Melinda Gates Foundation, the NIH, the United States Agency for International Development (USAID), and the Department for International Development (DFID) in the UK. Another 14 microbicides are in early safety trials and several of these second-generation candidates are gel formulations of ARVs that have a more specific mechanism of action and may be longer lasting.

Even as five trials are ongoing to test the efficacy of PrEP to prevent HIV transmission (see Treatment as prevention, LAVI Report 10, 3, 2006), researchers presented the preliminary safety data from one trial involving women at high risk of infection in Ghana, which is sponsored by the US-based organization Family Health International (FHI). In a late-breaker presentation Leigh Peterson of FHI, principal investigator of the trial, reported that so far no serious adverse events were related to receipt of tenofovir, the nucleoside reverse transcriptase inhibitor being tested in this trial. Peterson also reported that among the 936 women enrolled in this study only two HIV infections occurred in the group of women receiving tenofovir, compared to six in women receiving placebo. But since the infection rate was so low it is still unclear whether this approach will be prove effective.

Another late-breaker presentation on PrEP detailed 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 a sexually-transmitted disease clinic in San Francisco. Only one of the 851 men who completed the questionnaire between February and June of 2006 reported already using PrEP in an effort to prevent HIV infection, and only 2% of responders said they knew someone who is HIV uninfected and is already taking ARVs to try to prevent HIV infection. The survey showed that the majority of men surveyed (68%) would be willing to take ARVs to try to prevent HIV infection if this method were proven safe.

As microbicide and PrEP trials continue, researchers also stressed the advances researchers are making in developing and testing AIDS vaccine candidates. In a plenary session on the dynamics of HIV/AIDS vaccine research, Francoise Barre-Sinoussi of the Institut Pasteur in Paris highlighted progress, including the 85 Phase I and II trials that have taken place since 1987 with more than 50 different vaccine candidates. She also summarized the key challenges that remain. In another vaccine session at the conference Jose Esparza of the Gates Foundation applauded the announcement of a Russian vaccine center that will coordinate regional AIDS vaccine research for Eastern Europe and central Asia. The first vaccine candidate developed by Russian researchers, known as Vichrepol, at the Institute of Immunology in Moscow is now in Phase I clinical trials (see Vaccine Briefs, this issue).

Less than the best

The majority of the vaccine candidates currently in clinical trials primarily induce cellular immune responses rather than neutralizing antibodies, and researchers are now questioning what they can expect from this type of vaccine. "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. In a satellite symposium preceding the official opening of the conference several researchers discussed and debated the use of clinical trials to evaluate a partially-effective
A vaccine is the only way, conclusively and categorically, to end the pandemic

Stephen Lewis

A vaccine, one that may not prevent HIV infection but rather delay disease progression or viral set point, and how it might affect the course of the pandemic. This session, sponsored by the Postgraduate Institute for Medicine, was hosted by Larry Corey of the HIV Vaccine Trials Network (HVTN) and focused on viral load as a surrogate marker for vaccine efficacy.

Noam Letvin of Beth Israel Deaconess Medical Center in Boston opened this provocative session by seeing how administration of a cellular-immunity based vaccine would affect progression of simian-immunodeficiency virus (SIV) in rhesus macaques (Science 312, 1530, 2006). Macaques were vaccinated with a two-part DNA prime and adenovirus serotype 5 (Ad5) vaccine boost, containing gag, pol, and env genes from SIVmac239. All vaccinated animals had robust T-cell responses to all three viral proteins encoded, but no neutralizing antibodies were elicited.

Disease course in HIV-infected humans is best predicted over the long term by plasma viral load, so in these studies Letvin and colleagues were interested in comparing the SIV viral loads between vaccinated and control animals. Throughout 112 days following immunization the vaccinated macaques maintained significantly lower viral loads as compared to controls, but soon after the difference was lost and viral loads of animals in both groups were comparable.

Letvin continued monitoring these animals through 850 days and saw that even though vaccinated macaques lost the ability to suppress viral replication they still had improved survival rates over the unvaccinated control animals. When researchers looked more closely at the sub-populations of CD4+ T cells in both groups of macaques they found that the central memory CD4+ T cells were more highly preserved and the Gag-specific CD4+ and CD8+ T-cell responses were stronger in vaccinated animals. These differences conferred a survival advantage, even though there was only a transient reduction in viral load, indicating that using viral load as a surrogate marker for vaccine efficacy may not in itself be sufficient.

**Partially-effective vaccines**

Two other presentations by Lisa Jacobson and Thomas Quinn from Johns Hopkins University focused on how an AIDS vaccine that reduces viral load could reduce transmission rates. HIV viral load is the major predictor of HIV transmission from mother-to-child. Quinn acknowledged that sexual transmission is far more complicated but there is evidence from a study of discordant couples in Rakai, Uganda that transmission from HIV-infected to uninfected partner did not occur when their viral load was undetectable. “It’s not always viral load, but it’s the dominating factor in transmission,” said Quinn. “If you can modify transmission, you can control the epidemic.”

If a 50% efficacious vaccine could reduce viral load by 0.5-1.0 log in individuals who eventually become infected, the prevalence of HIV would drop dramatically in 20 years, according to Quinn, as long as efforts are made simultaneously to bolster existing HIV prevention strategies to counteract any behavioral disinhibition among those that receive the vaccine.

But according to Sally Blower of the University of California in Los Angeles, even if vaccinated individuals don’t increase their risk behavior a partially-effective vaccine could still make the epidemic worse because as infected individuals live longer there is a greater potential for them to transmit the virus to others, as long as their viral load remains at detectable levels (>50 viral copies/ml blood). Blower and her colleagues 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 take it, the duration of protection, and the vaccine-induced reduction in viral load (which is associated with a reduction in transmissibility and increased survival time) would influence HIV prevalence.

“What we’ll need with partially-effective vaccines is very high coverage,” said Blower. Based on models of the incidence rates in communities of men who have sex with men (MSM) 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.”
Injection of hope

Needle and syringe programs can lower HIV infection rates and provide important outreach to injection drug users

By Catherine Zandonella

In Vancouver’s downtown eastside, tucked away on a side street, is North America’s only supervised injection facility for intravenous drug users. Upon entry, visitors receive a tray with alcohol swabs and sterile needles and syringes to inject the illegal drugs that they have brought with them. The 12 injection booths equipped with mirrors and lights give the impression of a beauty parlor, prompting the facility’s nickname—the ‘Hair Salon.’

Since opening in 2003, the facility has provided sterile injection equipment to about 7000 registered users and oversees about 20,000 injections a month.

“That is 20,000 injections that don’t occur in a public site, that are done with clean equipment not shared and is disposed of appropriately,” says Dan Small, director of the Portland Hotel Society, a community group that helped to establish the facility.

The safe injection site is one type of program aimed at reducing the risk of HIV transmission by providing injection drug users (IDUs) with sterile needles and syringes. Since the first needle-exchange program began in Edinburgh, Scotland, in the early 1980’s, many such programs have started up around the globe. These programs may also offer education and condoms, access to drug rehabilitation, and health services.

Unfortunately these efforts reach only a fraction of the IDUs at risk of HIV infection around the world. HIV prevention activities for IDUs reached at most 5% of all users globally in 2004. About 65 countries have needle and syringe programs but coverage is poor. In some countries these programs are banned due to concerns that they promote drug use. The US, the largest provider of funds for international AIDS prevention programs, refuses to finance needle-exchange programs at home or abroad and has tried to impose restrictions on such programs in United Nations (UN) policies.

Yet studies show that needle and syringe programs are effective at reducing HIV transmission risk. Throughout the world the lack of needle and syringe programs is fostering the transmission of HIV among needle sharers, their sexual partners, and their children. IDUs are often regarded as being at the margins of a society and all but excluded, but that might not be as true as some might like to believe and a growing HIV epidemic among IDUs within a community always has the potential to spill over into the greater population.

As well as directly reducing HIV transmission risk these programs are important outreach mechanisms that establish relationships between public health workers and a marginalized population, and can offer other benefits including improved access to health care and drug treatment, prevention of other blood-borne diseases, and education about how to avoid sexual transmission of HIV. “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. Because of their high risk these individuals can 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 epidemic

Globally, IDUs make up 10% of all HIV cases and, outside of sub-Saharan Africa, an estimated one in three new HIV infections is due to injection drug use. Contaminated needles cause the largest share of new infections in some 20 nations and are fueling some of the world’s burgeoning 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 cases are among IDUs. “The biggest problem with HIV infection among IDUs is now occurring in developing and transitional countries, mainly in Asia and Eastern Europe where HIV has spread very rapidly over the last 5 to 10 years,” says Don Des Jarlais, research director at the Center for Drug Use and HIV Research in New York City.
To combat these escalating epidemics, most agree that a comprehensive approach is required that includes strategies to reduce the number of individuals who inject drugs, promote safe injection practices and discourage unsafe sex, and provide antiretroviral therapy and other health support for IDUs living with HIV. Programs must include education and community outreach, drug dependence treatment, condom distribution and prevention of sexually-transmitted infections, legislation reform, and public education to create support for harm reduction.

Still, experts say these efforts won’t significantly reduce HIV transmission without clean needles. “You don’t reduce HIV transmission among IDUs unless you have a good supply of injection equipment,” says Des Jarlais. Programs that supply sterile needles and syringes come in a variety of forms, including supervised injection sites—which operate in over 20 European cities—and programs that offer a one-to-one exchange of needles. Other important initiatives include pharmacy and vending machine sales of needles and the roll-back of punitive legislation for the sale or possession of injection paraphernalia.

Effective programs

Needle and syringe provision is one of the most studied HIV interventions. The majority of studies find that needle and syringe programs reduce HIV transmission in a safe and cost effective manner, according to a recent meta-analysis of 45 studies conducted from 1989 to 2002 (Int. J. Drug Policy 16, 33, 2005). Twenty-three of 33 studies that looked at HIV risk behavior outcomes showed a positive reduction in syringe sharing, borrowing, lending, or reuse. For example, a study of 5000 IDUs in New York City from 1990 to 1997 found that injection risk behaviors declined significantly accompanied by a substantial increase in syringe exchange participation. HIV seroprevalence in this population also declined from about 45% in 1991 to about 30% in 1996.

Studies involving IDU cohorts are often not simple to interpret though. Six of 10 studies that evaluated HIV seroconversion or seropositivity as outcomes found that needle and syringe program use was protective, but the other four studies found that individuals using needle and syringe programs had higher HIV seroconversion rates. Shortcomings in study design may explain these results, say the authors. Needle and syringe programs tend to attract high-risk individuals with no access to clean equipment elsewhere and some studies failed to note whether an individual was a regular or intermittent attendee. Irregular attendees may be at higher risk of HIV seroconversion because they have less access to sterile equipment and prevention messages.

Making comparisons across studies can also be complicated by the fact that they are often conducted at different stages of HIV epidemics with wide variations in HIV seroprevalence and risk; high seroprevalence will tend to lead to new infections from both needle sharing and sexual behavior, and the relative success of a needle and syringe program may therefore be masked by sexual transmission.

The majority of studies show that needle syringe programs are cost effective. One study in New York City found that the cost per HIV infection averted for a year was estimated to be less than US$3000, far below the then-estimated lifetime cost of medical treatment for an HIV-infected individual of $56,000 to $80,000. Rolling back punitive drug laws can also help decrease HIV transmission risk, according to studies conducted in the US indicating that legal restrictions on syringe and needle availability are correlated with higher HIV seroincidence and seroprevalence.

Drug substitution with methadone or buprenorphine does reduce the sharing of injection equipment, and may also result in fewer exchanges of sex for drugs or money. While methadone programs are available in the US, Canada, Europe and Australia, fewer than 13,000 of the 5.2 million IDUs who live in countries where contaminated needles are the main source of HIV infections have access to substitution treatment.

One thing is clear—studies have failed to show that needle and syringe programs increase illicit drug use or cause migration of IDUs to cities that offer such programs. Nor have they documented greater numbers of discarded needles on city streets.

How much is enough?

One of the biggest hurdles in needle syringe programs is how to determine how many needles are enough to stem HIV trans-
mission. “It is all really about coverage,” says Alex Wodak, former president of the International Harm Reduction Association, “reaching the maximum number of people you can reach with the maximum number of needles you can provide in a framework that is attractive to the population that you are trying to reach.”

The World Health Organization (WHO) approximates that providing 200 sterile needles and syringes per drug injector per year is likely to control HIV infection, with higher targets where seroprevalence has already reached unacceptable levels. 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 be done with a sterile needle and syringe.

Implementing these programs early in the course of an HIV epidemic is critical to success. 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 about 25 million needles each year for a population of 300 million.

The annual AIDS incidence in the US in 2003 was 14.7 per 100,000 population, with 25-33% of the cases among IDUs or sex partners of IDUs, compared with Australia’s 1.2 per 100,000 population with about 5% of cases from the IDU community. “Thank God that Australia was settled by convicts and we are a fairly practical country, whereas the United States was settled by puritans and you’ve been dealing with it ever since,” says Wodak.

**Around the globe**

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) or are supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria. Moscow has no needle-exchange program, syringes are not available for purchase, and possession of a syringe containing drug residue is a punishable offense. Drug substitution therapy is also illegal in Russia.

Other former Soviet states are more progressive. 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 cases are among IDUs, Kyrgyzstan offers substitution treatment and needle and syringe programs, including for prisoners. Tajikistan, which shares a long border with the opium-producing Afghanistan, has NGO-sponsored programs where volunteers travel the mountainous border region offering drug treatment programs and clean needles.

China has 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 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. As of November 2005, 91 needle-exchange projects were operating throughout China and the National Center for AIDS/STD Prevention and Control plans to provide sterile injection equipment to 105,000 IDUs by 2010. About 6,500 patients receive methadone in 58 treatment programs around the country. However, concerns remain about the human rights of drug users, who may be forced to enroll in treatment programs.

Indonesia, a country with strict drug laws, is making attempts to stem its injection-driven HIV infection rate of 44%. Limited drug substitution pilot programs and needle and syringe programs operate in Jakarta and Bali, including a pilot prison program. However, efforts vary widely from island to island in the archipelago. In the past two years about 80% of new HIV cases have been due to unsafe injection practices, an infection rate among IDUs second only to the former Soviet Union. Injection-related infections are on the rise in Afghanistan, Cambodia, and Pakistan, countries where most HIV infections to date have been sexually transmitted.

Vietnam in 2005 made a strong national commitment to providing sterile needles...
The condom equivalent for IDUs is clean needles and syringes… [they] should obviously be provided. It is good research ethics, and good public health

Chris Beyrer

and drug substitution therapy for its IDUs, which make up 52% of the nation’s HIV cases. Roughly 30 needle and syringe programs operate in the country, which receives influxes of illegal drugs across its borders with China and Myanmar. On Vietnam’s northern border with China, HIV infection rates have declined in some areas due to a program offering 25,000 needles/syringes per month, which is funded by the Ford Foundation and is being studied for efficacy by the US National Institute on Drug Abuse. At the same time 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 that human rights activists say more closely resemble labor camps.

**US policy, global impact**

The US is the largest donor for AIDS prevention programs worldwide but the current administration views providing needles and syringes as promoting drug use. This is despite seven reviews conducted by US-funded agencies concluding that such programs reduce HIV transmission and do not increase the use of illegal drugs. Within the US needle and syringe programs have found ways around the federal funding ban and operate in most major cities, using state and local government funding, or private donations.

Outside the US, however, the refusal to support needle and syringe programs could have far-reaching consequences. During a March 2005 meeting of the UN Commission on Narcotic Drugs (CND) the US delegates successfully lobbied to exclude the men-
tion of needle exchange or the human rights of drug users from any CND resolutions. The US policies were criticized by numerous NGOs, foreign governments, and on the pages of the New York Times and Washington Post. US delegates made the same arguments later that year at the UNAIDS global HIV prevention strategy meeting in Geneva, but the final language of the UN resolution recognized the importance of access to sterile injection equipment and measures to protect the human rights of drug users.

Vietnam is the only country selected by the US President’s Emergency Plan for AIDS Relief (PEPFAR) in which injection drug use comprises the majority of new HIV infections. None of the $34 million that PEPFAR provides may be used for needles or syringes, although some funds will go to a drug-substitution program. Other US aid programs find ways to work around the ban. For example, while the United States Agency for International Development (USAID) cannot provide funding for needle and syringe programs, it partners with providers of those services.

**Vaccine trials**

IDUs are considered important participants in HIV prevention trials because of their elevated risk of acquiring HIV. Yet while sex workers who participate in clinical trials are given condoms and education it is not considered necessary to give IDUs sterile needles and syringes. Some researchers think this is ethically questionable. “The condom equivalent for IDUs is clean needles and syringes,” says Chris Beyrer, director of the Fogarty AIDS International Training and Research Program at Johns Hopkins Bloomberg School of Public Health. “Needles and syringes should obviously be provided. It is good research ethics, and good public health.”

The Thai Drug Users Network (TDN) has lobbied for the provision of sterile needles and syringes to IDUs participating in a US-sponsored clinical trial of tenofovir for HIV prevention in Thailand, where the HIV incidence among IDUs is 37-50%. The trial, sponsored by the US Centers for Disease Control and Prevention (CDC), is enrolling 1600 HIV-uninfected IDUs in Bangkok during the period from 2005-2007. IDUs will receive safe injecting education and access to methadone but not clean needles.

Needles and syringes are available for purchase at pharmacies 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. “The main issue, of course, is the criminalization of people who use drugs, rendering it highly unsafe to carry any drug paraphernalia, clean or not,” says Kaplan.

“Clearly, the US policies against needle exchange and harm reduction itself are hampering individuals’ ability to protect themselves.”

After unsuccessfully lobbying the CDC and the Thai Minister of Public Health, the TDN has taken their case to the Thailand National Human Rights Commission. Over the last three years Thai IDUs have been terrorized by a brutal anti-drug policy that has resulted in massive arrests and a reported 3000 extra-judicial killings. TDN has won a Global Fund grant to support involvement of drug users in the planning and implementation of harm reduction services and policy advocacy.

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. Providing syringes and needles in clinical trials will reduce the HIV transmission rate, so trial design will have to include enough participants to compensate for that reduction.

**Barriers to access**

Many researchers agree that the success of needle and syringe programs rests on easy availability. Down the street from Vancouver’s safe injection facility, volunteers patrol the streets in the predawn hours passing out needles. This ‘low threshold’ approach makes it far easier to get needles than it would be at a health department or pharmacy that requires patients to sign forms and wait in line, says Dan Small. “Can you imagine a person living in the shadow of life, in active addiction, waiting 15 minutes for a needle?”

Users at the safe injection site have to register but proof of identification or form filling is not required. Patients are selected at random for participation in ongoing trials of the facility’s efficacy. Already, several published papers demonstrate that the facility has lessened the number of

**Clearly, the US policies against needle exchange and harm reduction itself are hampering individuals’ ability to protect themselves**

Karyn Kaplan
littered in the community, reduced the number of addicts shooting up in doorways, prevented overdoses, and referred people for treatment. About 2500 IDUs are enrolled in an ongoing study to determine if the site is helping reduce the HIV seroconversion rate.

Despite these successes, the threat of closure has been hanging over the ‘Hair Salon.’ Happily, on September 1, 2006 Federal Health Minister Tony Clement announced that the Canadian government had “deferred the decision” on continuing the facility’s operating exemption from the Controlled Drugs and Substances Act until December 31, 2007. During that time the supervised injection site will be allowed to continue operations and additional studies will be conducted on the effects on crime, prevention, and treatment.

Many questions remain about the best way to implement needle and syringe programs. Since it is impossible to ensure that every IDU uses a clean needle every time, researchers would like better information about the degree of coverage necessary to significantly reduce HIV transmission. 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 burgeoning epidemics.

Catherine Zandonella, MPH, is a freelance writer whose work has appeared in Nature and New Scientist.
Capping infection

An ongoing clinical trial is testing whether the contraceptive diaphragm can help lower women’s risk of HIV infection

By Sheri Fink

An old-fashioned birth control method, the diaphragm, could one day soon make a comeback as a woman-controlled HIV prevention method. That’s the hope of researchers conducting a randomized, controlled HIV prevention study funded by the Bill and Melinda Gates Foundation and known as Methods for Improving Reproductive Health in Africa (MIRA) that has enrolled women in Harare, Zimbabwe and in Durban and Johannesburg, South Africa. Investigators from the University of California at San Francisco (UCSF), University of Zimbabwe, Ibis Reproductive Health, Medical Research Council of South Africa, and the Perinatal HIV Research Unit of South Africa are assessing whether latex diaphragms used during intercourse can protect women from contracting HIV.

“Biologically, it’s very plausible that it will work,” says MIRA Principal Investigator Nancy Padan. Contraceptive diaphragms cover the cervix, the lower opening of the uterus, and prevent access to the upper genital tract, both thought to be key sites of entry for HIV. Cervical tissue is much thinner than vaginal tissue and observational studies have suggested that other sexually-transmitted pathogens, including those causing gonorrhea and chlamydia, preferentially infect cervical as opposed to vaginal cells and that diaphragms used with spermicide can prevent the transmission of some sexually-transmitted infections (STIs). Analogous to the male foreskin, the cervix also contains some of the same target cells for HIV—Langerhans cells, a type of antigen-presenting dendritic cell. A recent prospective study in South Africa showed that male circumcision removing the foreskin may significantly reduce men’s chances of acquiring HIV.

Although women can still acquire HIV after hysterectomy, these other findings suggest that shielding the cervix with a diaphragm might lower the risk of a woman contracting the virus. In addition, because relatively high amounts of HIV are shed by cervical cells, covering the cervix during intercourse might decrease a woman’s infectiousness if she already has HIV.

Current prevention methods fall short

With effective AIDS vaccines and microbicides still years away, male and female condoms remain the most reliable method for HIV prevention. But condom use remains extremely low—one study in the US found that condoms were used consistently during heterosexual intercourse only about 19% of the time. Female condoms, comparable in efficacy to the male condom in preventing STIs other than HIV and on the market for more than a decade, have been inadequately supplied and adopted—in 2005, only 14 million female condoms were available worldwide, compared with 6 to 9 billion male condoms.

Male circumcision is showing some promise in trials as an HIV prevention method but, even if proven effective, will require years to implement widely. Female-initiated methods are seen as particularly important in light of the fact that young, married women are the fastest-growing group of new HIV infections in many countries, and they often have difficulty negotiating condom use. Both HIV professionals and at-risk populations have shown a keen interest in expanding HIV prevention options, particularly those that are woman-controlled and already approved for use.

The diaphragm fits both of these criteria but its low usage worldwide and its labor-intensive initial fitting process cast doubt on whether women and health care providers will find the method acceptable. In the US and other countries where oral hormonal contraceptives are affordable and widely available, diaphragms have fallen out of favor as a birth control method. In 1995 only 2% of contraceptive users between the ages of 15 and 44 in the US used the method. Standard diaphragms come in nine different sizes and must be fitted in a health clinic and inserted prior to intercourse. Many health care providers stopped recommending them. “There’s somewhat of a provider bias,” says Padan. “Health care providers assume women won’t use them.”

Padan’s recent research, however, has been finding the oppo-
The problem we did have with some women is the partner would say if she can use it without me knowing, then she can be unfaithful

Agnes Chidanyika

site. “They’re highly acceptable,” she says. Her group conducted a six-month diaphragm acceptability study in Zimbabwe prior to the launch of the HIV prevention study. Nearly all of the 186 participants reported having tried the diaphragm during the study period. At the study’s conclusion 96% had used the diaphragm during the previous two months, however consistent diaphragm use between visits was low—only 13-16%.

**Zimbabwe study**

On a recent afternoon at the MIRA study site in Epworth, a densely-populated suburb of Harare, Zimbabwe, a dozen or so women arrived for their final study visit. Outside in the dusty sunshine, music blared from a saloon next door and peddlers squatted before small piles of tomatoes and carrots. Here in Zimbabwe the researchers have enrolled 2505 women ages 19–49, randomized them into diaphragm and no diaphragm arms (both receive condoms and prevention education), and are following them for at least 12 months. During quarterly visits the researchers test the participants for HIV and STIs and ask them about their experiences with the diaphragms. The women fill out computer surveys and meet with counselors and clinicians. All women completing their final visits are offered a diaphragm. “Most women are accepting it,” says Project Director Agnes Chidanyika. “They look forward to using it, especially those in the condom arm who haven’t used it.”

In a counseling room at the clinic, a young woman in the diaphragm arm of the study demonstrated diaphragm use on a plastic pelvic model. She grasped the latex, cup-shaped diaphragm by its firm, springy lip, squeezed it in two, and inserted it easily into the model. “To be eligible to be in the study you have to be able to insert the diaphragm within five attempts,” says Chidanyika. “We had one or two out of those 2500 women who couldn’t insert the diaphragm in five attempts. It was fairly easy once they knew how it was done for them to be able to insert it.”

The young woman said she found her own diaphragm comfortable and had used it throughout the study period except when she tried to get pregnant. As with all barrier methods, the importance of child-bearing in many societies may be an obstacle to widespread adoption of the diaphragm as an HIV prevention method.

Those championing the diaphragm claim that its great advantage over the condom is the fact that women can typically use it without their partners’ knowledge. Chidanyika said that was only partly true in the MIRA study, because participants are asked to use Replens gel when inserting their diaphragms. “There’s this myth about dry sex in African countries, so we were worried they might not want to use the diaphragm because they would have to use the gel to ease the insertion,” she says. “But we actually found the gel became quite popular.” Chidanyika says the diaphragms were acceptable among the male partners of most women, who were happy to let their female partners use a potential HIV prevention method that their partners were responsible for and they could not feel. However, this sentiment was not universal, says Chidanyika. “The problem we did have with some women is the partner would say if she can use it without me knowing, then she can be unfaithful.”

**Challenging study environment**

The MIRA study is being conducted at the epicenter of the HIV epidemic. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2006 Report on the Global AIDS Epidemic, HIV prevalence among adults ages 15–49 in Zimbabwe is 20.1% and in South Africa it’s 18.8%. If diaphragms prove to be acceptable and effective against the transmission of HIV and STIs at these sites, chances are that they will prove useful in other countries hit hard by HIV/AIDS.

In Zimbabwe in particular, researchers could scarcely have chosen a more challenging situation in which to conduct their study. The country is currently experiencing epic inflation and joblessness. The Epworth study site sits just a few feet away from the rubble of countless shanties destroyed by order of the Zimbabwean government in the summer of 2005 in a campaign called Operation Murambatsvina or “Drive out Trash.” According to a UN-Habitat study, an estimated 700,000 people lost their dwellings or businesses in the campaign.
Over a quarter of the MIRA study participants in Zimbabwe were displaced by Operation Murambatsvina. This could have devastated the study, but MIRA researchers temporarily stopped enrolling new participants and channeled all of their energy and resources into tracking participants in order to keep them in the study. “We went to everybody, regardless of whether we just saw them yesterday or we last saw them last year,” says Chidanyika. “We just tried to find out if they were going to be evicted by Murambatsvina and, if they were, which places they were most likely to move to.”

The researchers managed to retain a stunning 99% of the participants by visiting homes, villages, and displaced persons camps, reaching out to alternative contacts, and launching a radio and poster campaign. The researchers now provide many participants with bus fare to reach the study site from their new locations. Chidanyika says the high retention rate also reflects the enthusiasm of the diaphragm study participants. “The participants themselves, they were very interested in participating in the study and coming back,” she says.

A look to the future

Results from the MIRA study are expected in 2007. If diaphragms prove effective at lowering HIV transmission, however, those wishing to promote wide-scale adoption of the method will need to contend with several difficulties.

The major fear with diaphragms and indeed all female-controlled methods is that they will lead to lower condom usage. “I don’t think anyone thinks diaphragms will be more effective than condoms,” acknowledges Padian, “but we’re doing the study in the situation where many women cannot use condoms.” There is also a fear that behavioral disinhibition will result from women believing that they can stop worrying about contracting HIV if they are using a diaphragm, but this is a consideration with all HIV prevention mechanisms and even HIV treatment. The potential problem will need to be countered by education.

Perhaps the most serious obstacle to future use of diaphragms is the possibility that they will be less acceptable in real settings than they are in the research environment. Over-optimism about the prospects of the female condom, another woman-controlled contraceptive and HIV prevention method, is an important cautionary case. While evidence suggests that the female condom is effective and easy to use, it has taken a long time to increase uptake for this unfamiliar contraceptive method.

On the positive side, however, female condoms have been successfully marketed in some high-prevalence countries. Furthermore, the diaphragm may be more attractive economically for some women; a single diaphragm, though initially more expensive than a female condom, may be used for several years.

The main problem with traditional diaphragms is the cumbersome way they are fitted. The traditional, labor-intensive method uses rings. The MIRA study, instead, has used a method that its directors term a “modified fitting scheme.” All women start with one size of diaphragm, then the fit is assessed using digital examination and other sizes are tried as necessary.

Even this simpler method, however, requires a health clinic attendance for a diaphragm fitting, a potentially costly prospect that may be associated with stigma. This limitation has led developers to pioneer alternate forms of cervical barriers. Maggie Kilbourne-Brook, program officer with the group Program for Appropriate Technology in Health (PATH), says a single-sized device is the main improvement needed. “It needs to be ‘one size fits many,’” she says, “which will reduce the procurement cost, the training cost, and has the potential to become an over-the-counter device.”

This conclusion is based on detailed research that PATH, in conjunction with the Contraceptive Research and Development Program (CONRAD), has conducted on the acceptability of cervical barriers. Women who had used barriers were asked what they did and did not like about them. Providers, too, were asked why barriers were not being used in their clinics and what it would take to bring them into wider use. Donors and those in charge of procurement were also surveyed. The goal was to uncover the roadblocks to greater use of cervical barriers, opening the possibility to create better products. “They’d been around 100 years and hadn’t really been improved in that time,” says Kilbourne-Brook. “We now understand much more

I don’t think anyone thinks diaphragms will be more effective than condoms, but we’re doing the study in the situation where many women cannot use condoms

Nancy Padian
about vaginal anatomy. Manufacturing practices have changed. New materials have been developed."

In addition to needing a one-sized product, the researchers concluded that several other modifications would make diaphragms much more acceptable. “What we need to be able to achieve is to make a device that is easier to insert and remove than standard products, and easier to use and learn to use than the currently available product,” says Kilbourne-Brook. “It needs to be comfortable for both partners.”

The PATH researchers used this information to develop an improved diaphragm. Their development process was further informed by user feedback from women and their partners in Thailand, South Africa, and the Dominican Republic. The resulting product, SILCS, is a single-sized silicone diaphragm with a nylon or polymer spring that fits most women across all of these countries. The researchers expect to begin testing the product for contraceptive effectiveness in late 2006.

A number of other cervical barriers are also in the process of being developed and approved. The single-sized Lea’s Shield is a silicone cervical barrier contraceptive already FDA approved for up to 48 hours of continuous use in the US and Europe. Another product being tested, the BufferGel Duet, is a disposable, one-size diaphragm pre-filled with the candidate microbicide and contraceptive BufferGel.

Indeed, if both microbicides and diaphragms prove to be partially effective at preventing HIV transmission then combining them could well offer higher protection. “We’re interested in evaluating whether the use of a physical barrier like a diaphragm could advance the effectiveness of a microbicide,” says Sharon Hillier, a microbicides researcher at the University of Pennsylvania. “Thinking of combinations of chemical agents like microbicides with physical barriers may present a real advance in effectiveness.”

Kilbourne-Brook believes it is important for advocates of various woman-controlled prevention methods, including cervical barriers, microbicides, and female condoms, to come together and devise strategic ways to look at research questions and procedural and regulatory hurdles. “Anything that we can do for one of these products will strengthen the future prospects for all of these products as well,” she says. “All of these products can offer a greater likelihood of protected sex for couples.” Padian agrees, “None of the methods we are looking at are 100% effective.”

If the MIRA study indicates that traditional diaphragms are protective against HIV transmission, Padian believes there will be ways to extend the results to the new forms of cervical barriers that are being developed. “We’ll be able to generalize somewhat,” she says. “It would be crazy if you had to do a complete other trial.”

Her hope is that even partial protection against HIV by diaphragms will have a powerful effect on the epidemic. “Even though it’s not perfect, it’s better than nothing,” she says, “especially when woman can’t negotiate male condom use. For many women this is unequivocally one hundred percent out of the question.”

Sheri Fink, MD, PhD, is a freelance writer whose work has appeared in such publications as The New York Times and Discover Magazine, and the author of War Hospital: A True Story of Surgery and Survival.
Russia announces plan for vaccine research center

In a final report on infectious diseases—one of the three key areas considered by the leaders of the G8 nations when they gathered in St. Petersburg, Russia from July 15-17—there was a pledge for continued support of HIV prevention, treatment, and care programs. The document highlighted in particular the development of AIDS vaccines and microbicides as priorities in the fight against the pandemic, as well as vaccines that could prevent other diseases that enhance an individual’s risk of HIV infection. Other strategies promoted in the document included expanding the partnerships with developing countries to bolster capacity for research and development and ensuring that qualified healthcare workers are available in these regions.

In coordination with their hosting of this high-level meeting, Russia announced that it will request US$40 million to create a regional coordinating center for HIV/AIDS activities in Eastern Europe and Central Asia, with a portion of this funding being earmarked for the research and development of AIDS vaccine candidates. This proposal was introduced by the Russian Federation’s chief doctor, Gennady Onishchenko, and was endorsed by heads of state who participated in the summit. The use of federal funding for this project is now under examination by officials in the Russian Ministry of Finance.

Although clear plans for this coordinating center are still vague, between five and seven existing Russian research centers will be involved in implementing the program. One of these institutes, The State Research Center of Virology and Biotechnology (Vector) in Novosibirsk, has already been involved in the development of two AIDS vaccine candidates. Other institutions that will play a role, including the Institute of Immunology in Moscow and St. Petersburg University, are also currently developing AIDS vaccine candidates. By the end of last year there were 350,000 documented HIV infections in Russia, compared to just 200,000 four years ago, and the epidemic continues to expand. In Russia, as well as in many other countries in Eastern Europe and Central Asia, there continues to be an exploding number of new HIV infections occurring mostly amongst injection drug users (see Injection of hope, page 9). At sites in Estonia, Kazakhstan, Russia, and Belarus, HIV incidence rates among IDUs are reported at levels greater than 20%.

The first candidate developed by Russian scientists, known as Vichrepol, is now in clinical trials and information was presented in posters at both the International AIDS Conference in Toronto (see HIV prevention picks up momentum, page 1) and the AIDS Vaccine 06 conference in Amsterdam (see Rating up T-cell responses, page 1). The candidate is a chimeric recombinant protein, rec(24–41), encoding the p24 full length viral protein and a gp41 fragment. This chimeric protein is conjugated with the adjuvant polyoxiodonium, a synthetic polymer which is used in production of the influenza vaccine Grippo and was shown to enhance immune response in mice.

The ongoing clinical trial involves 15 volunteers who receive three intramuscular injections of Vichrepol at five different doses (2.5, 5, 10, 25, and 50 micrograms). The escalation of dose is only initiated 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 was found to induce antibody responses and suggested that subsequent studies will be needed to fully evaluate its safety and immunogenicity.
IAVI’s AIDS vaccine blueprint promotes innovative approaches to evaluating lead candidates

The AIDS Vaccine Blueprint 2006: Actions to Strengthen Global Research and Development (www.iavi.org/viewfile.cfm?fid=41059), IAVI’s flagship publication, was released on August 15 during the International AIDS Conference in Toronto. 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 an imperative, since much of the expertise in testing and manufacturing licensed vaccines is found within large pharmaceutical companies. Although some private sector entities are now actively engaged in AIDS vaccine research and development, the Blueprint calls for an increased level of commitment. “We’ve got to keep industry fully engaged,” said Berkley.

Another area highlighted in the document is the continued need to enhance the ability of developing countries to conduct AIDS vaccine clinical trials. The Blueprint suggests 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 who works at the Uganda Virus Research Institute, a partner organization of IAVI. He also emphasizes the need for increased political support in these settings.

The Blueprint also recommends that the AIDS vaccine field implement an accelerated approach to clinical trials that will provide researchers with answers about a candidate’s efficacy earlier in the development pipeline. This involves running several smaller Phase II trials in parallel with only those candidates that improve upon the best current products. These trials would be conducted in cohorts of individuals that are at high risk of HIV infection, allowing research to collect preliminary safety and efficacy data with a much smaller number of volunteers. Trials could therefore be run faster, providing answers in three to five years, and at a much lower cost. Berkley calls this strategy “a very bold design that requires a coordinated and prioritized effort.”

New funding for AIDS vaccine research ushers in new paradigm of collaboration

On July 19 the Bill & Melinda Gates Foundation awarded US$287 million in grants that will be disbursed over the next 5 years to 16 different research teams, encompassing 165 investigators from 19 countries, to support innovative approaches to overcoming obstacles in AIDS vaccine research (www.gatesfoundation.org/GlobalHealth/Pri_Diseases/HIVAIDS/Announcements/Announce-060719.htm). This funding will support basic scientific research to design vaccines that can stimulate both humoral and cellular immunity. But beyond these challenges, several of the grants will also help research teams develop infrastructure both in developed and developing countries to allow for consistent evaluation of the immunogenicity and efficacy of vaccine candidates and will be used to oversee the establishment of vaccine production and delivery systems.

This series of vaccine grants are the Foundation’s largest contribution to date for HIV/AIDS research and are in direct support of the scientific strategic plan established by the Global HIV Vaccine Enterprise, to which the Gates Foundation serves as the interim secretariat. This initiative brings together many of the leading teams that are currently working in the field and puts an even greater emphasis on collaboration and coordination of data between vaccine discovery teams at different institutions. Receipt of the grants is therefore contingent upon all groups agreeing to share data and intellectual property and working through a network of standardized laboratories to test their vaccine candidates. An editorial in the journal Nature Immunology referred to this new strategy as “a much-needed global experiment … that, if successful, could transform the process of vaccine design, development and delivery.” (Nat. Immunol. 7, 9, 2006)

Five of the grants are to laboratories that focus on research into vaccine candidates that can elicit broadly-neutralizing antibodies against HIV. The largest of these grants, $25.3 million, was awarded to Robin Weiss of the University College London, UK. Among the other recipients was Barton Haynes of Duke University in the US, who leads a team of researchers who were recently awarded a $300 million grant from the US National Institute of Allergy and Infectious Diseases to form the Center for HIV/AIDS Vaccine Immunology (CHAVI), which was another funding stream resulting from the establishment of the Enterprise.

Another six grants were issued to laboratories or consortia working on vaccine candidates aimed at inducing cellular immune responses to the virus. IAVI was the recipient of a $23.7 million grant in this category. Other grantees include David Ho of the Aaron Diamond AIDS Research Center in New York City and Juliana McElrath of the Fred Hutchinson Cancer Research Center in Seattle.

The remaining five grants were provided to researchers who will form centralized facilities for vaccine candidate evaluation and will be involved in measuring the immune responses generated by candidates developed through the vaccine discovery programs, as well as handling the data collection.