



IAVI Report

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Brazil's model approach

Recent international conference highlighted the need to partner prevention and treatment in the response to the epidemic

by **Kristen Jill Kresge**

The 3rd International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment was recently held in Rio de Janeiro. But Brazil's opportunity to host this large international meeting was not only due to the impressive landscape of this seaside city. The country has become a leader among developing countries for its progressive and comprehensive response to the epidemic. And long before thousands of delegates arrived, Brazil was stealing headlines with its defiant attitude towards drug pricing (see *Brazil battles over drug pricing*, page 3).

Lauded as one of the first to adopt a national treatment program, Brazil is also a leader in HIV prevention and simultaneously working on both fronts is what Pedro Chequer, director of the National AIDS Program, calls the cornerstone of their success. In addition to universal access to life-saving antiretrovirals (ARVs), the government also acted quickly to implement a needle-exchange program for intravenous drug users (IDUs) and to create outreach programs that collaborated with highly-affected communities like commercial sex workers and men who have sex with men. "Treatment, prevention, and care are all part of the same package and each is equally important," says Chequer.

The significance of linking HIV prevention efforts with access to treatment emerged throughout several sessions at the conference. Mauro Schechter of the Rio de Janeiro Federal University and a conference co-chair associated the renewed emphasis on prevention with advancements in the scale up of ARV programs. Discussing prevention had been difficult because of its obvious link with HIV testing, which is a hard sell when there was nothing to offer people who were infected. But since 2000, when the world AIDS conference was held in Durban, there has been a sustained international interest in making treatment programs available in developing countries. Schechter emphasizes that now that progress is finally occurring on this front—thanks to a collection of global initiatives including the Global Fund to Fight AIDS, Tuberculosis, and Malaria and the World Health

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Cutting HIV transmission

Male circumcision as a potential HIV prevention strategy


by **Sheri Fink**

While the ultimate hope for stopping the AIDS epidemic, a vaccine, remains years away there may already be a way to effectively cut the sexual transmission of HIV—male circumcision. Scientists in eastern and southern Africa have been studying whether the surgical procedure can protect against HIV infection, and also what it would mean to promote for medical reasons a prac-

tice that has long held cultural significance.

Results from the first of three major randomized, controlled trials of circumcision were announced at the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment in Rio de Janeiro in July (see *Brazil's model approach*, page 1). The French National Agency for Research on AIDS and Viral Hepatitis

(ANRS) sponsored the study involving over 3000 volunteers in Orange Farm, an urban area within South Africa's Gauteng Province. The men were randomized to either receive circumcision immediately or defer the procedure for 21 months. Circumcision proved markedly protective. At the interim study evaluation three times fewer circumcised participants (18) had acquired HIV com-

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Chris Beyrer

Organization's (WHO) '3 by 5' initiative—reinforcing prevention messages has become a necessity.

Several talks throughout the four-day meeting also underscored the inability of treatment alone to control the epidemic. Researchers repeatedly acknowledged that even as the availability of ARVs improves, countries must remain vigilant in providing prevention services. Treatment programs and ARV trials provide an opportunity for health-care workers to discuss risk-reduction strategies and offer a variety of prevention services, including voluntary counseling and testing (VCT), according to Marie Laga from the Institute of Tropical Medicine in Antwerp, Belgium, who spoke about the synergy of prevention and care in Africa. A recent report (www.who.int/3by5/progressreportJune2005) from the WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) illustrated the positive effect treatment has on the uptake of VCT—people are more likely to get tested if they know they will have access to therapy. One district in Uganda witnessed a 27-fold increase in VCT services after the introduction of ARVs. Laga also credits the provision of drug therapy with helping to reduce the stigma associated with HIV and therefore increasing disclosure within communities. In his speech at the conference, Stephen Lewis, UN special envoy to Africa, heaped praise on the '3 by 5' initiative for making such a difference not only for treatment but also for prevention efforts (For more on Stephen Lewis see interview, page 14).

Among the prominent prevention strategies discussed during the meeting were the increased importance of tailoring risk reduction efforts for IDUs, exploring novel strategies like male circumcision, the diaphragm, and ARV prophylaxis, as well as the importance of long-term options like vaccines.

Risk among IDUs soars

In a plenary talk on emerging HIV epidemics, Chris Beyrer of Johns Hopkins University offered a sobering description of the dire conditions facing IDUs in several countries in Eurasia (Eastern Europe and Central Asia), where the number of new HIV infections is exploding but access to treatment and prevention remains minimal. Official statistics estimate that currently 1.4 million people in the former countries of the Soviet Union are HIV infected, along with 1.1 million in China and Eastern Asia.

Beyrer pinpointed 11 countries where explosive HIV epidemics—defined as a 30-40% prevalence—are in progress. The majority of these new infections are occurring among IDUs and the spread of the epidemic is facilitated by close proximity to known heroin trading routes, the continued criminalization of risk behaviors, and the limited access to prevention programs that discourage IDUs from sharing syringes or injection equipment.

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

Prevention programs like needle exchange or drug substitution, which use methadone or buprenorphine to wean people from heroin addiction, are effective in reducing the transmission of HIV among IDUs but remain limited in number and reach. Despite the expansion of harm reduction efforts in some countries, including China where the government just recently loosened restrictions on methadone programs, only an estimated 10% of IDUs worldwide have access to needle-exchange programs (NEPs). Access is also limited by funding restrictions like those in the US President's Emergency Plan for AIDS Relief (PEPFAR) that restrict grant money from being used to fund syringe exchange. "We need to implement programs that we already know work. Unfortunately they have been very hard to initiate, despite mounds of scientific evidence that show they are effective," according to Beyrer.

What is even more disconcerting to Beyrer is the exclusion of IDUs from many of the global treatment programs. He points out that throughout Eurasia IDUs were the first groups to become HIV infected and therefore should be overrepresented in the populations receiving ARV treatment, but according to Beyrer this is not the case. "Even where policy allows, the de facto reality is that people don't get into treatment programs," he says.


Brazil battles over drug pricing

The recent IAS meeting also furthered the debate about the pricing and availability of antiretrovirals (ARVs) and several representatives from Brazil seized the opportunity of hosting the meeting to further the very public debate between the Ministry of Health and three US-based pharmaceutical companies on securing reduced drug prices for the country's national treatment program. The most heated negotiations have occurred between the ministry and Abbott over the pricing of its patented drug lopinavir/ritonavir (Kaletra), which eats up almost a third of Brazil's annual treatment budget. In response, the government threatened Abbott that if they didn't lower the price, Brazil would begin manufacturing the drug domestically. This tactic, known as compulsory licensing, is permitted within the international regulations of the World Trade Organization for

member countries that are acting in the public interest. Pharmaceutical lobbying groups in the US heavily criticized Brazil's stance, arguing that compulsory licensing would limit future investment into novel therapies. However within Brazil this move was viewed as a necessary step to sustain the universal treatment policy in the face of escalating expenses. Manufacturing capacity for lopinavir/ritonavir could be up and running by next year and would cost approximately US\$0.40 per pill, according to Chequer.

Negotiations seemed to reach resolution before the start of the conference but within days of announcing an agreement Brazil's health minister resigned, throwing a wrench into the works. At the conference the new minister, Jose Saraiva Felipe, defended Brazil's right to manufacture the drug generically and was dismissive of any arrangement reached prior

to his accepting the post. Chequer used his speaking engagements at the conference to emphasize his opinion that the Brazilian government should move forward with compulsory licensing to ensure the best care for its citizens. He argued that the details of the deal with Abbott required the country to spend \$70 million on Kaletra regardless of the number of people who need the drug as part of their regimen. Chequer accused Abbott of overestimating the future demand in order to overestimate potential savings.

Many of the nation's prominent activists agreed with Chequer. "The agreement with Abbott is a step backwards for Brazil," said community activist Octavio Valente Jr. at the opening session of the conference. The ministry is also negotiating with Merck on pricing of the drug efavirenz (Sustiva) and Gilead Sciences on tenofovir (Vi read). 

"It's a terrible way to approach public health because you are isolating the people at highest risk."

The spread of hepatitis C virus (HCV) in IDUs is a useful marker for emerging HIV epidemics because it indicates that risk behaviors like needle sharing are occurring. Epidemics of HCV tend to precede HIV in some populations because of the infectiousness of the virus during blood-to-blood contact—sexual transmission of HCV is rare—and therefore an HCV epidemic could be an important signal that aggressive prevention efforts are needed.

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

Tyndall reported that there were 15,000 different visitors to the site, and while transmission rates among frequent visitors at safe injection sites in Europe have declined, the rates in Vancouver continue to be high at around 30%. More impressively however, visitors were one third less likely to share needles. The idea of expanding the number and reach of these sites throughout the country is resting on Vancouver's site, said Tyndall, who argues that the best results


can only be achieved when there are multiple sites in each city.

A short cut on the road to prevention

One of the biggest news stories at the conference came when a group of French researchers presented results from the first prospective study on the effect of male circumcision on female-to-male transmission of HIV. Bertran Auvert of INSERM, the French National Institute for Medical Research, presented data from study ANRS 1265 sponsored by the French National Agency for AIDS Research that showed that adult male circumcision offered a 65% rate of protection from HIV infection.

Researchers have long thought that circumcision could be protective because it reduces the surface area available for transmission and encourages a keratinization of the surrounding skin. The foreskin is also home to a high density of dendritic cells that could facilitate transmission of HIV. This cross-sectional study confirmed the results of more than 30 previous observational studies on the benefits of circumcision, but few had expected such a profound effect. A previous meta-analysis of the numerous observational studies found a 42% reduction in the risk of HIV infection.

This study enrolled over 3,000 men between the ages of 18 and 24 in an urban area on the outskirts of Johannesburg, known as Orange Farm, who were randomized to be circumcised immediately or to defer circumcision until after 21 months. Both groups received intensive counseling on risk reduction at each study visit (planned for 3 months, 12 months, and 21 months following their



**More
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cultural
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Catherine Hankins



initial visit) and were treated for sexually-transmitted infections (STIs). Of 69 new HIV infections during the trial, 51 occurred in the control group and only 18 in the circumcised men.

While many in the prevention field were excited by this result, the researchers as well as officials from the WHO and UNAIDS stressed the need for caution by urging governments to await the results of other ongoing prospective studies before making recommendations on circumcision. "More research is needed to confirm the reproducibility of these results in differing social and cultural contexts," says Catherine Hankins of UNAIDS.

Three similar studies to the ANRS trial are currently in progress, two in Uganda and one in Kenya. The US National Institutes of Health is sponsoring one in each country and the Bill & Melinda Gates Foundation is sponsoring another in Uganda that is enrolling 800 HIV discordant couples to monitor the effects of circumcision on male-to-female transmission. The NIH trial in Uganda, the largest to date, has already enrolled 5,000 men, but the earliest results of these trials are not expected until 2007. No trials have yet looked at the effect of circumcision on transmission in men who have sex with men.

A recently-published cross-sectional study (*J. Acquir. Immune Defic. Syndr.* **39**, 576, 2005) conducted by the Centers for Disease Control and Prevention (CDC) provides additional support to the protective effect of circumcision. This study found that men in HIV-infected male/female concordant couples were 11 times more likely than men in discordant couples to be uncircumcised. This study included 126 discordant couples and 40 sero-concordant couples in Kampala, Uganda.

Although Auvert emphasized the simplicity of the procedure in the context of the study—"You just pull it, clamp it, and cut it"—offering this intervention on a large scale would be difficult. Many public health experts fear that the high rate of protection offered in the South African study could encourage men to have circumcisions outside of a supervised medical facility, putting them at greater risk of HIV infection. WHO is currently formulating guidelines on safe circumcision practices to avoid this situation.

Researchers are also concerned that circumcised men will feel a false sense of protection and increase their risk behaviors—discontinuing use of condoms or increasing their number of sexual partners—referred to as

disinhibition. There are also many lingering questions about how acceptable circumcision will be in cultures and religions that typically discourage the practice. "If this trial is confirmed by others, then it would be an important advance for prevention," says Helene Gayle, president of the IAS. "But it should not be implemented until we have further information. There is no one thing that is going to make all the difference in prevention."

More prevention alternatives

Of equal importance is reducing male-to-female transmission, and for this scientists are testing an old mainstay in the field of reproductive health: the diaphragm. A Gates Foundation-funded study to evaluate the diaphragm's ability to protect women from becoming HIV infected is being led by Nancy Padian of the University of California, San Francisco and is approaching full enrollment at sites in South Africa and Zimbabwe. A total of 4,500 women will be randomized to either the diaphragm or the control group and followed for four years. Both arms of the trial will receive risk-reduction counseling and be encouraged to use condoms.

This study is sparking enthusiasm among prevention researchers because of the simplicity of using the diaphragm, which is already approved and available. It is much more discreet than male or female condoms, can be inserted without a partner's knowledge, and can be used repeatedly.

Researchers also hope that this study will answer critical questions about the role the cervix plays in HIV transmission. Diaphragms have proven effective at preventing other STIs like chlamydia and trichomoniasis because the rubber disc acts as a physical barrier that protects the cervix, which is also considered a focal point for HIV infection. The epithelium of the cervix has a much thinner surface than the vagina, making it more susceptible to infection. It is also packed with dendritic cells that can enhance HIV transmission. Padian hopes that shielding the fragile surface of the cervix and stopping viral particles in semen from reaching the upper genital tract will offer some protection against HIV.

Another innovative approach to prevent HIV transmission is using oral prophylaxis with ARVs, a strategy that is referred to as pre-exposure prophylaxis (PREP). The idea of taking ARVs to prevent infection is well established and short-term use after exposure to HIV—such as during childbirth or after acci-

dental contact with HIV-infected blood from a needle stick injury—is a common and effective way to avert HIV infection. PREP extends this approach by offering people ARVs even before exposure.

This concept received great attention at the Rio meeting, despite a dearth of data in human trials. Most of the discussion about PREP concerned the recent closure of two trial sites because of concerns among activists and participants about the ethics of the study. These trials were evaluating the efficacy of the drug tenofovir, manufactured by Gilead Sciences, to prevent individuals at high risk (men who have sex with men, commercial sex workers, and IDUs) from contracting HIV. One study being run by US-based Family Health International (FHI) involving sex workers in Cameroon was recently closed after a 5-month suspension, but both FHI and the CDC are sponsoring other Phase II studies with tenofovir.

Joep Lange of the University of Amsterdam explained the scientific rationale for PREP at a special session. The initial Gilead studies in 1995 showed prevention of infection in long-tailed macaques that received a daily subcutaneous injection of tenofovir (then called PMPA) for four weeks and were challenged with a single intravenous dose (10 ID₅₀) of SIV. Lange also highlighted the most recent animal data, which was presented earlier this year at the 12th Conference on Retroviruses and Opportunistic Infections. In this study Chinese rhesus macaques received an oral dose of tenofovir either once daily, once weekly, or not at all, and were then challenged weekly by rectal exposure to SHIV SF162P3. All animals eventually became infected, but the onset of infection was delayed in monkeys given tenofovir. Infection required at least six SHIV inoculations for monkeys receiving tenofovir, whereas only a single viral challenge was sufficient to infect the controls.

Lange refers to this recent data as “somewhat less rosy” and warns that “PREP is not a universal panacea” for HIV prevention. Still,


many in the public health field eagerly await the results of human trials. And the idea of PREP should extend beyond tenofovir, advises Kenneth Mayer of Brown University, who predicts that the future of PREP may rest in combination therapy. “Using a single drug to prevent infection may not work any better than using one drug for treatment.”

Understanding immune responses


Despite the lack of critical breakthroughs in the search for an effective AIDS vaccine, some studies presented in Rio did provide some insight into the nature of the immune responses that could be protective against HIV infection.

Sarah Rowland-Jones of Oxford University presented a study of post-natal HIV transmission through breast feeding to gain insight into whether a vaccine that induces cell-mediated immune responses might be able to prevent HIV infection. This collaborative trial with Julie Overbaugh's lab at the University of Washington enrolled 510 mother/infant pairs in East Africa. The women were all HIV-infected and received ARV prophylaxis during labor and delivery to prevent transmission to their children. Any women that chose not to breast feed in this study were offered a milk-substitution free.

The majority of infants that acquired HIV did so during the first month, making it difficult to determine if the infection was a result of exposure during childbirth or from breast milk. But of the children that remained uninfected at a month, Rowland-Jones and her colleagues found a direct correlation between their T cell responses and the likelihood of acquiring HIV through their first year of life, suggesting that the immune responses in the infants are able to protect them from HIV infection even during continual exposure to the virus. Rowland Jones is optimistic about this study. “It shows that young children can mount a cellular immune response and that it can be protective,” she says. “It's simply a correlation, but it's encouraging.”



***Pre-exposure
prophylaxis
is not a
universal
panacea***



Joep Lange

pared with control participants (51). The study's Data Safety and Monitoring Board halted the trial and offered circumcision to members of the control group.

The results did not surprise many HIV prevention researchers since an inverse relationship between circumcision rates and HIV prevalence had been noted for years. An analysis of more than 30 observational studies—cross-sectional, case-control and cohort—suggested that circumcision might reduce the risk of HIV infection by 42%. The suggestion made sense, biologically. “The foreskin has HIV target cells which make it easy for HIV transmission and acquisition,” says Godfrey Kigozi, a co-principal investigator with the Rakai Health Sciences Program in southwestern Uganda, a body established in 1988 as the Rakai Project. “During sexual intercourse the foreskin is retracted, exposing a large surface area which is vulnerable to entry of HIV. Also, the foreskin is associated with genital ulcer disease (GUD), which makes entry of HIV into the body easy.”

Some researchers have likened circumcision for boys and men to a partially protective AIDS vaccine. “It is a procedure that a man undergoes once in their life; it would then provide some level of protection for the rest of their life,” says Maria Wawer of Johns Hopkins University in the US. “If circumcision is protective, its role in the fight against HIV could be really very dramatic.” An ongoing trial is investigating whether male circumcision can help prevent transmission of HIV from men to women. But even if there is no direct protective effect for women, if male circumcision can effectively lower transmission from women to men in a given population then eventually everyone will benefit—fewer transmitters mean that, overall, incidence rates will decline.

Kigozi and Wawer are two of the investigators leading an even larger randomized, controlled trial of male circumcision in progress in Rakai Province, Uganda, under the auspices of the Rakai Health Sciences Program. The US National Institutes of Health (NIH) sponsored the circumcision study because despite the considerable body of correlative research, the precise link between HIV infection and circumcision remained unclear. Public health experts have held back from recommending circumcision as an HIV preventive method because the observational studies had not established whether circumcised men were protected by circumcision

itself or by other factors. For example, in many parts of Africa circumcised men are much more likely to be Muslim, and previous research conducted by the Rakai Program showed that Muslim men in the province tended to have fewer extra-marital partners than non-Muslim men. That raised the possibility that it was not circumcision that protected them but different sexual practices. “The only way you can really find out if circumcision protects men is to take a group of men who volunteer for a study and then randomly assign them to either get the circumcision right away or to delay the procedure” says Wawer.

Putting circumcision to the test

Rakai is a province of rolling hills, red dirt roads, and simple mud and brick dwellings. It is a community on the socio-economic rise, but many inhabitants still live off subsistence farming and do not enjoy electricity or motorized transport. They share the land with cows, corn, banana trees, and a profusion of birds. They also live close to the crossroads with Tanzania. The region was the site of considerable troop movements and unrest during Uganda's civil war. In the 1980s Ugandan researchers including David Serwadda and Nelson Sewankambo of Uganda's Makerere University were drawn here by reports of the mysterious illness they called “Slim Disease.” It later became known as AIDS. The researchers began studying the population and were joined by Wawer, Ron Gray, Tom Lutalo, and Fred Wabwire Mangen and others from the Ugandan Virus Research Institute (UVRI), Johns Hopkins University, and Columbia University.

Over the years the team has conducted many studies on HIV. The circumcision study is one of their latest. On a typical morning in the spring of 2005, around 40 potential study volunteers hiked or pedaled their bikes to the Rakai village of Kyawanyana. There they gathered under a blue and white striped tent and watched a video explaining the research. HIV prevalence is high in Rakai—one in eight adults—and the men were looking for ways to protect themselves. “I came here to learn how to avoid STDs,” says one.

After the video, the men were called one by one into small pup tents for individual counseling, physical exams and testing for HIV and other sexually transmitted diseases (STDs). They were urged to use condoms and practice safe sex. A day or two later,

If circumcision is protective, its role in the fight against HIV could be really very dramatic

Maria Wawer

those who met the study criteria were invited to randomly select an envelope which informed them whether they would receive circumcision immediately or have to wait until the end of the two-year study period.

John Paul Wasa, a counselor, says that most men hope to receive immediate circumcision. "It might be STD/HIV prevention, it might be sexual prowess, it might be any other thing, but through the counseling process they get to know why we'd want them to remain in the arm in which they are randomized and the importance of that." Rakai investigators know of only three cases where volunteers in the control group went elsewhere to obtain circumcisions prior to the end of the study.

The Rakai Program performs the circumcisions in a series of new, technically-advanced operating rooms in the small town of Kalicizo. Patients undergo circumcisions under local anesthesia. As of the spring of 2005 nearly 3,000 men had been circumcised, and a roughly equal number had been randomized to serve as controls. Only about 400 more surgeries remained.

Once they are enrolled, circumcised and uncircumcised men are followed closely for two years and regularly tested for HIV infection. "We are also looking at women to see whether circumcision in the male partner might reduce transmission of HIV and STDs to the woman partner" says Wawer. This latter research is part of a separate, concurrent study funded by the Bill and Melinda Gates Foundation. Rakai is the only one of the three sites to include analysis of male circumcision's effect on HIV transmission to women.

This is just one of the reasons the Rakai Program investigators believe it is essential for their study to continue, even in light of the South African group's finding that circumcision had a powerful protective effect against female-to-male HIV transmission. "There's always a need to have more than one trial before you implement findings into policy," says Kigozi.

Officials with the Joint United Nations Programme on HIV/AIDS (UNAIDS) agree. "The two other randomized controlled trials, currently ongoing in Uganda and Kenya with a combined total of nearly 8,000 participants, remain important to clarify the relationships between male circumcision and HIV," said an agency statement. "The potential for negative or uncertain results in the other two trials cannot be ruled out at this stage."

Challenges and suspicions

Now that at least one of the randomized controlled studies has shown that circumcision might help prevent HIV infection, public health experts are considering whether the practice should be promoted widely, and how. In Uganda some experts fear that if the demand for circumcision grows, villagers seeking to avoid the typical charge of roughly 50,000 Ugandan shillings—US\$30—might turn to unqualified practitioners. If they reuse instruments between patients without proper sterilization they risk HIV infection. Every year, poorly-performed circumcisions lead to infections and disfigurement. Chief Rakai Program surgeon Dr. Stephen Watya, a consultant urologist at Makerere University's Mulago Hospital, has treated the complications of some village circumcisers. "Recently I saw one young boy about five years with a severed glans, that's the head of the penis being chopped off with the circumcision knife," he says. "Occasionally that happens."

The contrast between the Rakai Program's state of the art operating theaters and the clinics where many African men receive circumcisions is remarkable. Just a few miles away traditional Muslim circumcisers perform their operations at a spartan clinic, the Kyotera Muslim Health Unit. A single bulb dangles from the ceiling of the circumcision room, which is nearly barren except for a bed. Each circumciser brings his own tools. "This room is small and there are no special facilities here. If you compare it with the [Kalicizo] theater, this is far below required standards," says Sheik Badru Matovu who heads this clinic. Still, long-time circumciser Sheik Abudusamir Abudalazake Kakooza says that with education, many traditional and religious circumcisers in Uganda have modified their practices in order to decrease the risk of complications and contaminated equipment. Kakooza says his rate of complications is low. But no matter how advanced the facility, circumcision is never performed without risk: Rakai researchers report a 0.7% rate of serious complications, and about 1 in 20 patients overall experiences at least minor complications.

Even if circumcision is made relatively safe and affordable, how willing will men be to undergo the procedure? After all, circumcision is more than just surgery. It is a cultural and religious practice, it is wrapped up in tribal and personal identity, and many myths about it remain.



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Godfrey Kigozi

Back in the Ugandan village of Kyawanyana last spring, a group of men gathered for their post-operative check-ups. They say they've endured the disapproval of their fellow villagers. "Most people in our villages, our village men, tell us that you just want to stop us from having more children, as a form of family planning," says one. Another agrees. His friends told him "these people just bring out the program so that they can castrate you." A third shares a similar story. "People tell us in the villages there that we're just wasting our time. That AIDS, all the same, whether we get circumcised or not, AIDS is going to kill us. So all in all they tell us 'you're just wasting your time, you'll just be like us, you'll still be wiped out!'"

Father Joseph Kato, a Catholic priest with the Matala parish in Rakai Province has been privy to another concern among his parishioners: that circumcision might turn them into Muslims. "They came with that kind of fear. And I told them this has a medicinal purpose, preventing against HIV, rather than being something conversational." Other men express worries that their penis size will be reduced, or that they won't be able to resume intercourse. In the US some anti-male-circumcision activists argue that circumcision reduces sexual sensation in men and that this could lead to even lower rates of condom use.

Still, the Rakai researchers say that men have been remarkably willing to undergo circumcision, even before knowing whether it was protective. "One of our secondary endpoints was to find out whether circumcision could be acceptable in these communities," says Kigozi. "I think we have shown that circumcision can be acceptable, given the compliance we are seeing, given the overwhelming numbers that are coming to us to participate in this." The South African team also studied the acceptability of circumcision and found that 70% of

uncircumcised men expressed a willingness to undergo the procedure if it would reduce the risk of contracting HIV infection. Other acceptability research has yielded similar results, including a large Harvard AIDS Institute study in Botswana in which over 80% of uncircumcised men said they would undergo circumcision if it was performed safely and affordably.

False sense of security?

The scientists have another concern, though. Might circumcision change the men's sexual behavior? Perhaps they would feel immune from HIV and engage in more risky, unprotected sex, increasing their likelihood of acquiring—and passing—HIV infection. These questions are identical to those that would be raised by the development of a partially protective AIDS vaccine.


Jennifer Wagman heads up behavioral research at the Rakai Program. She is looking at how men perceive circumcision and whether circumcised men engage in practices that might put them at risk for HIV. One of those potential practices is known as "sexual cleansing." "After they're circumcised they have to go out and have sex with as many women as they can who are not necessarily their wives or main sexual partners," says Wagman. "We don't know if it's happening, so we want to find out."

Public health experts will have to take practices like this into consideration in any widespread effort to introduce circumcision. After the South African results were released, UNAIDS released a statement calling it "premature to recommend male circumcision services as part of HIV prevention programmes."

Karusa Kiragu is a behavior change scientist with the Population Council in Nairobi, Kenya. "As a public health measure, it would have to be very carefully introduced into the communities with very, very strong education and would require a

very significant paradigm shift," she says. "The paradigm of the past was that upon circumcision in many communities, the boys then go on to become sexually active. From a public health point of view the paradigm would be that yes, you're circumcised but no, it doesn't mean that you now have permission to go and have sex. So, disentangling that for communities may be difficult."

Difficult, yes, but possible, says Rakai Program principal investigator Fred Nalugoda. If circumcision is confirmed to be effective, he says, governments and other agencies should make an effort to provide the surgery to as many men as possible. "It would be unethical, once you learn something's protective, to then withhold it from the people. I think what has to be combined with the provision is the intensive health education and counseling—telling people exactly what they have to do to counter their perception that maybe because it's protective then they can do whatever they want with themselves."

So far, the men in the Rakai Program study are not reporting higher risk behavior. The potential that circumcision might provide a whole new approach to stemming the tide of HIV has many scientists feeling hopeful, including Wawer. "We have all been looking for additional tools to use against this epidemic for the last 20 years. And it has been very disappointing how difficult it has been to come up with new tools." An estimated 5 million people worldwide contracted HIV last year alone, and even a partial reduction in HIV risk could save thousands, perhaps millions, of lives. 

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.

Making a monkey out of HIV

More is becoming clear about a novel host factor that appears central to governing the species-specificity of retroviruses like HIV and could be a future antiviral target

by Philip Cohen

Popular accounts of scientific discoveries often involve a metaphorical light bulb popping up in some researcher's head. In reality, those eureka moments aren't always so illuminating. The cracking of some unsolved mysteries about HIV last year, for instance, came when cells located in Joseph Sodroski's lab at Dana-Farber Cancer Institute in Boston failed to shine.

His graduate student, Matt Stremlau, was on the hunt for an elusive factor that protects some monkey cells from HIV infection. His approach seemed simple enough: add monkey genes to human cells, stir in HIV genetically engineered to glow in the dark, and pluck out the cells that remained dim—a sign that the dose of monkey DNA had snuffed out infection of the cells by the fluorescently-marked virus. “Finding the restriction factor was an enormous effort. Many labs had tried similar approaches and had failed to find anything,” says Sodroski. “Matt succeeded on his eighth try. It's a testimony to his tremendous persistence.”

While the discovery was a technical coup, its true importance only became clear over the weeks and months that followed. Sodroski's team and other labs showed that the protein produced by this gene, TRIM5 α , was at the heart of a number of puzzles surrounding the species-specific resistance to various retroviruses. The study of TRIM5 α also promises to shed light on an important but poorly understood part of HIV biology, the uncoating of the retroviral genome following infection.

More broadly, the identification of TRIM5 α solidified an ongoing trend in HIV research—the discovery of host factors with potential antiviral activity. Only two years before, researchers identified another antiviral protein, APOBEC3G, that is now a focus of intense research (see *Guardian of the genome*, *LAVI Report* 9, 2, 2005). And it's a good bet that there are more host proteins out there that can be turned against the virus. Some attendees of a Cold Spring Harbor meeting on retroviruses in May appeared a bit stunned by the number of putative virus-fighting factors presented at the meeting, says Stephen Goff of Columbia University, whose team studies an antiviral protein in rat cells. “Someone raised their hand and asked: what's going on here, how many of these genes could there be?” says Goff. “I think the answer is that we'll keep finding new fac-



tors until we're close to scanning the real number of genes that are out there. And we don't seem to be close to saturating our screens for those genes.”


Intrinsic immunity

Researchers are clamoring to study proteins like APOBEC3G and TRIM5 α because they might offer a novel way to fight HIV—by tapping into what amounts to a previously unrecognized type of immunity, says Paul Bieniasz of the Aaron Diamond AIDS Research Center in New York City. A viral infection has long been known to trigger antibodies and immune cells specifically directed against the virus, as well as rally elements of innate immunity, including broadly-acting cellular responses like the release of interferon- α . But this new class of host restriction factors appears to be always present in the cell and they are highly specific for different viruses. “In a sense, they are even more innate than the classic innate response, because they don't need to be triggered,” he says. He prefers the term “intrinsic immunity” to describe the protection these host factors provide.


While these restriction factors are now a hot topic in HIV research, the field can be traced back at least thirty years. In the 1970s, an activity against so-called N strains of Friend murine leukemia virus (N-MLV) was discovered in some strains of mice and named the Friend virus susceptibility gene 1 (Fv1). But the field has picked up considerable steam in the last six years with the discovery of a similar anti-MLV activity, Ref1 (Resistance factor 1), in human cells and an anti-HIV-1 factor in the cells of New and Old World monkeys (Lv1, for lentivirus restriction factor 1).

In all these cases, genetic experiments demonstrated that viral replication was blocked due to some inhibitor rather than the lack of some required factor. HIV, for example, while deadly to humans, barely invades rhesus macaque cells before a molecular monkey wrench is thrown into the virus's replication cycle, freezing it before the virus can reverse transcribe its RNA genome into DNA. While these antiviral activities were discovered separately, intriguing links were found between them. Genetic studies showed that both Ref1 and Fv1 targeted amino

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When the rhesus TRIM5 α protein was knocked down in monkey cells, these cells became more susceptible to HIV-1 replication



acid residue 110 of the capsid protein of N-MLV. And Lv1 turned out to also target the HIV capsid. Viral competition experiments revealed further links. In African green monkey cells, pretreatment of a cell with any restricted virus overwhelmed the cell's ability to defend against any other, suggesting these activities shared at least one common element that could be saturated (*Embo J.* **22**, 385, 2003).

Researchers got their first peek at the molecular identity of one of these factors when Fv1 was cloned by Jonathan Stoye's group at the National Institute for Medical Research in London (*Nature* **382**, 826, 1996). The Fv1 protein proved to be very similar to a retroviral coat protein, suggesting it insinuated itself as a decoy into some stage of the viral replication cycle. However, primates don't have a similar gene, leaving what accounted for the host restriction activity in monkeys and humans unanswered.

The answer finally came from Strelau, Sodroski, and their colleagues' hunt for monkey genes that allow human cells to resist glow-in-the-dark HIV. They fingered two separate cell lines that were able to keep the viral lights low—and both proved to have the same rhesus macaque gene, *TRIM5 α* . Further characterization confirmed that they had the right factor. The monkey *TRIM5 α* strongly restricted HIV-1 but not SIV, a virus which successfully infects this species. Conversely, the human version of the protein was much less effective at halting HIV-1 replication than the monkey *TRIM5 α* . Finally, when the rhesus *TRIM5 α* protein was knocked down in monkey cells, these cells became more susceptible to HIV-1 replication (*Nature* **427**, 848, 2004).

Along with Sodroski's team, groups led by Bieniasz, Stoye, and Greg Towers of University College London rushed to show just how broad *TRIM5 α* 's antiretroviral activity is. In various species it is responsible for resisting MLV, SIV, HIV-1, HIV-2, and equine infectious anemia virus (EIAV). And when *TRIM5 α* is knocked down in human cells, their Ref1 and Lv1 activities disappeared, showing it was an essential component of those activities (*Proc. Natl. Acad. Sci. USA* **101**, 10774, 2004; *Proc. Natl. Acad. Sci. USA* **101**, 10780, 2004; *Proc. Natl. Acad. Sci. USA* **101**, 10786, 2004; *Proc. Natl. Acad. Sci. USA* **101**, 11827, 2004).

Jeremy Luban's team at Columbia University discovered that *TRIM5 α* also explains two bizarre and confusing observations about the cells of owl monkeys. These primates are unique among New World monkeys in that their cells block HIV-1 replication. And while immunosuppressive drugs called cyclosporins inhibit HIV-1 replication in human cells, cyclosporins have exactly the opposite effect in owl monkeys, strongly enhancing HIV-1 replication. Both observations turn out to stem from the unusual composition of owl monkey *TRIM5 α* , which is naturally fused to cyclophilin A, a cellular protein that both binds the HIV-1 capsid (allowing the targeting and, therefore, restriction of this virus) and interacts with cyclosporins (which compete with virus for the cyclophilin A protein, releasing HIV restriction; *Nature* **430**, 569, 2004).

All in the family

It turns out that *TRIM5 α* is part of a large and poorly characterized gene family with at least 60 members. Before *TRIM5 α* was linked to HIV restriction a number of aberrant TRIM proteins had been identified for their involvement in a wide array of hereditary diseases—for example, mutations in the TRIM family proteins PYRIN, MID1 and MUL respectively cause familial Mediterranean fever (characterized by episodes of fever and peritonitis), X-linked Opitz/GBBB syndrome (patients present with craniofacial, heart and genital abnormalities), and mulibrey nanism (involving growth delays and abnormal development of muscles, liver, brain, and eyes). And genetic breakage and fusion events that splice TRIM family genes *PML*, *RFP* and *Tif1* into other chromosomes were known to trigger the malignant transformation of cells. All these links between TRIM family genes and disease demonstrated that the proteins they encoded play important developmental and biological roles. But these data don't reveal much about the biochemistry of *TRIM5 α* or how it might fight viruses.

So researchers turned to dissecting the protein itself. The name of this protein family - TRIM, for TRIpartite Motif - refers to a trio of identifiable motifs its members typically contain: the zinc-binding motifs known as RING and B-box, plus a coiled-coil domain that is predicted to fold into a

group of α helices that wrap around each other. In addition, some family members, including TRIM5 α , contain another distinctive amino acid sequence known as a SPRY domain, a motif found in many proteins including the antibody-like molecules of the immunoglobulin superfamily.

The SPRY domain came under early scrutiny since this part of TRIM5 α can differ dramatically between primate species. By analyzing TRIM5 α sequences from 20 primates, Michael Emerman, Harmit Malik, and their colleagues at the Fred Hutchinson Cancer Center in Seattle discovered that the SPRY sequence has undergone episodes of rapid change for at least 33 million years—long before lentiviruses such as HIV evolved about a million years ago. The nature, speed, and sporadic character of these changes are consistent with the theory that new versions of TRIM5 α were fixed in each primate lineage following the emergence of new retroviruses (*Proc. Natl. Acad. Sci. USA* **102**, 2832, 2005). “The effect of a new virus on the population might not have been immediately catastrophic,” says Emerman. “It’s possible that over long periods of time, animals with particular TRIM5 α variants were protected from the virus, were healthier and produced more offspring, until the new variant took over.”

The SPRY sequence contains four variable regions that in various primate lineages are expanded, duplicated, or have changes in sequences (*J. Virol.* **79**, 3139, 2005; *J. Virol.* **79**, 6111, 2005). Researchers have been able to show directly that altering the SPRY domain of a TRIM5 α protein alters the species-specificity of the viruses it restricts. Sodroski found that changing only three amino acids gives the human protein anti-HIV-1 potency rivaling that of the monkey protein. Both Sodroski’s and Stoye’s teams have shown that altering the human protein so that the amino acid arginine at position 332 is replaced by the proline present in rhesus TRIM5 α (R332P human TRIM5 α) significantly increases the ability of this mostly human protein to restrict HIV-1 (*Curr. Biol.* **15**, 73, 2005; *J. Virol.* **79**, 3139, 2005).

Intriguingly, the R332P human TRIM5 α also has the power to restrict SIV more strongly than either of its parents, suggesting that some property of TRIM5 α ’s structure allows it to adapt to new viral threats with minor sequence variations. Sodroski speculates that this property might be the ability of TRIM5 α to bind viral capsids based on recognition of a generalized pattern in these structures that viruses cannot easily alter. “This is a different model than suggesting there is a lock and key fit between TRIM5 α and every viral target,” says Sodroski. He points out that this model is reminiscent of how Toll-like receptors recognize molecular patterns on invading microbes to trigger aspects of innate immunity. He thinks the specific sequences in the SPRY domain that target antiviral activity to specific viruses may fine tune this interaction or alter what TRIM5 α does to the viral capsid after binding.

The events that follow that binding could be the key to TRIM5 α ’s viral restriction and researchers have been busy genetically analyzing the RING, B-box and coiled-coiled domains of the protein for clues. RING is known to give some proteins the ability to attach a chemical tag called ubiquitin to other proteins, which are then quickly shuttled into the cell’s proteasomal disposal pathway. In their very first paper on TRIM5 α , Sodroski’s team proposed that the rhesus TRIM5 α may destroy HIV by

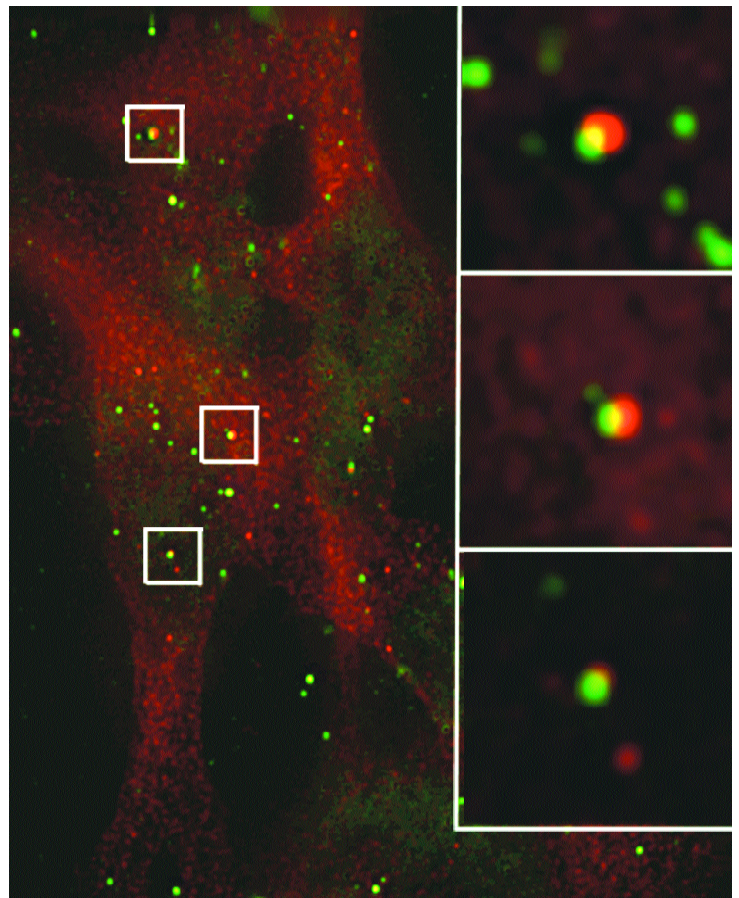



Figure 1. Shedding light on TRIM5 α ’s role. Four cells expressing rhesus TRIM5 α protein (visualized in red) were infected with HIV-1 particles (in green). TRIM5 α is dispersed throughout the cytoplasm and also clustered in roughly spherical cytoplasmic bodies. Small white squares in the left panel mark cytoplasmic bodies that appear to overlap with HIV-1 particles. The three right panels show close ups of these regions. These studies are consistent with the theory that TRIM5 α cytoplasmic bodies may restrict HIV-1 replication. Alternatively, cytoplasmic bodies may help regulate levels of active TRIM5 α or be an inactive form of the protein.

ubiquinating its capsid, but their later work argues against that simple model. When they engineered mutations into this domain they found that the antiviral activity of the protein was reduced but not completely eliminated (*J. Biol. Chem.* **280**, 26933, 2005).

In contrast, mutations in the B-Box domain completely remove the antiviral powers of TRIM5 α . What the B-box does isn’t known, although in other proteins B-boxes promote protein-protein interaction. So it’s possible the one in rhesus TRIM5 α may recruit other proteins to help it fight HIV-1. Coiled-coils are also known to foster protein-protein interactions. When TRIM5 α mutants lacking restriction activity, but containing intact coiled-coils, are expressed in the same cell as an active TRIM5 α , they suppress its activity. This argues that the coiled-coil domain helps TRIM5 α molecules associate with each other and that inactive molecules can inhibit the antiviral activity of this protein complex.

The ability of TRIM5 α to form large complexes has made moving beyond these genetic experiments to direct biochemical

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Joseph Sodroski

characterization difficult. But an important step forward was recently reported when Luban's team showed for the first time in a test tube that direct, specific binding occurs between human TRIM5 α and the capsid of N-MLV (*Retrovirology* 2, 40, 2005).

Structure is function?


The self-association of TRIM5 α molecules makes a biochemist's life difficult, but it may also be important to this protein's antiviral activity. In fact, one common property of TRIM family proteins is their formation of various structures in cells named for their appearance under the microscope: filaments, speckles, aggregates, and—in the case of TRIM5 α —cytoplasmic bodies. “An intriguing idea is that TRIM5 α forms one of these bodies around a viral core and separates it from the rest of the cell,” says Tom Hope of the University of Illinois at Chicago. His team is also exploring the possibility that these bodies serve as storage centers that regulate the concentration of free TRIM5 α . At this year's Keystone Symposia on HIV Pathogenesis and HIV Vaccines in Banff, Canada, Hope showed TRIM5 α movies his team had made using high tech “deconvolution” microscopy, a computer reconstruction of the cell's image that eliminates light distortion to create bright, detailed images. These films show cytoplasmic bodies zooming around human cells and reveal these are dynamic structures in which TRIM5 α protein is actively exchanged and not insoluble blobs as some researchers had thought. But Hope hasn't yet shown that the formation of these structures correlates with antiviral activity.

Another theory for how TRIM5 α restricts retroviruses is that it corrupts the uncoating process of the viral capsid by either accelerating or delaying disassembly of the viral capsid. Experiments suggest that for viruses like HIV to efficiently replicate, uncoating must happen at precisely the right time, although the reason for that crucial timing isn't clear. “We generally call this part of the viral life cycle a black box,” says Luban.

Understanding how TRIM5 α manages to halt virus replication could have a number of practical benefits. Bieniasz says his team and others are busy mapping the molecular interactions between rhesus TRIM5 α and HIV-1 capsid. This would be an important first step to engineering an HIV-1 strain that would evade the monkey protein and productively infect the animals. “For vaccine trials, that would allow you to test the same immunogens in monkeys that you want to test in humans,” he says.

The ability of primate TRIM5 α to restrict HIV-1 also suggests a number of theoretical strategies for antiviral therapy. The most direct would be to engineer a human protein that potently restricts HIV-1 and use gene therapy to introduce this gene into the immune cells of HIV-infected individuals, making them HIV-1 resistant. Presumably the molecules that enhance the ability of the human protein to target the HIV-1 capsid would also give it the power to stop the virus. But designing such drugs will be difficult until the biochemical basis of this recognition is better understood.

Indeed as quickly as research on TRIM5 α is moving, it is still at a very preliminary stage. And the potential for TRIM5 α as an HIV therapy will largely depend on how it is acting, what other proteins are involved in its activity, and how easy it is to target drugs to this pathway, says Sodroski. “Part of what makes this exciting is that TRIM5 α acts at an early stage in the viral life cycle where there are many unknown elements, and potentially many opportunities to understand new steps and interrupt them.”

Luban agrees that the biggest payoff from TRIM5 α may be what it reveals about HIV. The better researchers know their adversary, the better they are equipped to fight it, he says. “If you want to bring down a tiger, the more you find out about its behavior, what it needs, what it wants, the more chance you have to catch it and not get hurt in the process.” 

If you build it, they will pay

A novel incentive called an Advance Market Commitment could help spur private sector investment in AIDS vaccine research and development

by **Catherine Zandonella**

What if you could order your dream house, the perfect abode that would take years to design and build to perfection, but only have to pay for it on the day you are ready to move in? Global public health experts are exploring just such a concept, only the "house" is a vaccine for a disease such as AIDS and the people buying it are international foundations and governments that want to provide the vaccine to the poorest nations on the planet. The important part is these donors only have to pay for the vaccine once biopharmaceutical companies create it.

This "build now, pay later" approach is designed to provide a binding promise to vaccine manufacturers that if they develop a vaccine, there will indeed be an adequate market waiting, providing financial returns comparable to those they could expect from spending their resources developing a successful drug for the Western market. Given the opportunity to make a profit on such drugs and the large scientific and commercial risks associated with an AIDS vaccine, companies today have little incentive to spend the massive sums required to develop and produce such a vaccine. Indeed most companies have stayed on the sidelines or have invested only modestly in AIDS vaccine R&D.

This novel incentive mechanism is called an advance market (or purchase) commitment (AMC), and could provide the motivation that industry needs to substantially increase investment in vaccine development. These market-based mechanisms are attracting attention from private foundations, governments, and the global health community as a way to encourage companies to proceed with vaccine research and development to target diseases like AIDS, malaria, and tuberculosis that primarily afflict developing countries.

Under an AMC, donors would pledge to purchase a new vaccine for one of these developing-country diseases at a price that would generate revenues that match other health products in a global competitive marketplace. The donors would commit to pay a set price for a certain number of people immunized, after which the vaccine company would be obligated to sell to eligible countries at an agreed-upon lower price that is affordable in the developing world.

"The goal is to create a market of sufficient size to encourage industry to invest in vaccine development," says Robert Hecht, senior vice president for public policy at IAVI, one of several organiza-

tions exploring the concept.

IAVI envisions AMCs as part of a comprehensive strategy. The commitment would "pull" on industry to engage in vaccine research and would complement existing "push" mechanisms such as funded research in academic labs and biotechnology companies. To make the concept successful, the global health community must also work on removing barriers to vaccine research across a range of issues, including clinical trials, intellectual property, and liability. "Advance market commitments are part of a menu of things that are necessary, none of which alone is sufficient," says Seth Berkley, president and CEO of IAVI.

A sound idea

The concept of the AMC has found widespread favor among donors such as the Bill & Melinda Gates Foundation, public-private partnerships, the World Bank, the G8 Finance Ministers, and biopharmaceutical industry representatives. Although the concept has been around for some time, AMCs started coming into focus in the late 1990's through the writings of Harvard University economist Michael Kremer and Rachel Glennerster, director of Poverty Action Lab at the Massachusetts Institute of Technology (Kremer, M, Glennerster, R, *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases* Princeton University Press, 2004). In 2003 the Center for Global Development (CGD), an independent think tank working to reduce global poverty, assembled a working group of economists, public health professionals, lawyers, and pharmaceutical and biotech experts to transform a "sounds-good" idea into a concrete proposal. Their report (www.cgdev.org/section/initiatives/_active/vaccinedevelopment), issued in May of this year, examines the major issues and provides a basis for IAVI's draft proposals.

In late 2004 the UK government expressed support for AMCs as part of a larger package of new mechanisms to expand financing for international development and the achievement of the Millennium Development Goals. The UK and the other G8 countries asked the World Bank in May to coordinate a process of consultation with industry on the feasibility of establishing an AMC to support development of vaccines against AIDS, malaria, and other diseases. At



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Robert Hecht

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An Interview with Stephen Lewis



Waiting for a breakthrough

Stephen Lewis is the Special Envoy to the United Nations (UN) for HIV/AIDS in Africa. He has served in this capacity for four years and has become an unwavering voice in the battle for the development of new prevention technologies like AIDS vaccines and microbicides that could help to slow or end the pandemic, as well as for the rights of women. Lewis was born in Canada and resides in Toronto, but the majority of his time is spent on the road or in a plane. Whether visiting with affected communities in Africa or at the UN headquarters in New York City, Lewis always commands attention.

Prior to his role as envoy, Lewis served as the deputy executive director of the UN Children's Fund (UNICEF) and also as the Canadian Ambassador to the UN. He spent the early part of his career entrenched in national politics and was once leader of the New Democratic Party in Ontario, Canada. His humanitarian efforts and outstanding oratory skills have earned him numerous honors, including more than 20 honorary degrees. Earlier this year Lewis was named one of the world's one hundred most influential people by US-based TIME magazine. And at 67, Lewis shows no signs of slowing.

Lewis recently gave a rousing speech at the opening ceremony of the HIV Pathogenesis and Treatment meeting held by the International AIDS Society in Rio de Janeiro, Brazil. He used the speech to criticize the recent meeting of the G8 nations for "getting caught up in celebrity." He leveled an abundant amount of praise on the '3 by 5' initiative of the World Health Organization, the progress of The Global Fund to Fight AIDS, Tuberculosis, and Malaria, and the continued dedication of UNAIDS, saying these efforts have made all the difference in the world. Lewis also emphasized the pressing importance of vaccine research.

VAX and IAVI Report Science Writer Kristen Jill Kresge recently spoke with Lewis about progress in battling AIDS in Africa and what new initiatives he thinks may help halt the epidemic's unchecked spread there.

As envoy for HIV/AIDS in Africa, you are reporting directly to the Secretary General on an entire continent's epidemic. How do you accomplish this and what do you see as your main activities as UN envoy?

The primary activities of my job are to visit African countries, meet with the political leadership, meet with groups of people living with AIDS, and spend time seeing projects in the field. I've always seen these last two activities as critical so that I can see how the diplomatic community can be of greater use. When I come back to New York I hold a media briefing so that the international media has a sense of what I have found. Then I meet with the Secretary General and discuss with him what I've seen and together we discuss how that might influence the way in which he, and the UN more generally, responds.

In the process I have come to understand that advocacy is also a very important component of the envoy role. I've therefore spent a great deal of time speaking around the world at conferences and meetings in order to convey what is happening in Africa and why it is so desperately important for the world to respond.

How has the response to the HIV epidemic in Africa changed in your four years as envoy?

That's a difficult question. The envoy role has clearly evolved since the early days when I or anyone at the UN didn't have a substantial sense of what it would be. The sense of hope right now is more alive than at any time during the previous four years. The tremendous efforts by the World Health Organization to put millions of people on treatment and the evidence, although very slight, of increased resources has made people feel glimmers of hope in the midst of pervasive anguish. This pandemic has been going on for over 20 years and we are only now, literally at this moment in time, beginning to come to grips with it. So the job has changed in the sense that I feel now more keenly than ever before that we must do something to subdue the pandemic. Unfortunately, on the ground things are as painful as they've always been because people are dying in such vast numbers.

How has your attitude changed during your tenure as envoy? Do you find it difficult not to get discouraged?

When I started as envoy I was swamped with despair. Now I live in a perpetual rage. I feel an even greater sense of urgency four years into it. At first I heard all these numbers about the situation in Africa and I was lost in the data. Now when I travel I just want to save individual lives. You reach a point where every single human life becomes a matter of obsession. Instead of getting discouraged I get angry because when you are surrounded by death you can't get over it.

One example is the situation with orphans. Everyone understands that one of the single most important things for orphans is to eliminate all school fees so that these kids can get into school, have peers to play with, and gain some self-worth. And even though everyone knows that we should abolish school fees, nothing changes year after year. I'll never forgive those who have been indifferent, insensitive, and just paralyzed over such long periods of time. But there's no point in being discouraged because futility leads nowhere. Instead, I get neurotic.

I'm just one person out of thousands who are responding to this from within the UN family and when I think of all the people who are in the field, I don't know how they hold their emotional fabric together. It's so incredibly painful on a daily basis and I'm in a rage about it.

AIDS is now disproportionately affecting women. What is the situation like in Africa?

I feel more deeply now than I ever did before that the vulnerability of women is possibly the most terrifying component of the pandemic and about which the world is doing almost nothing. This is true in Africa, as well as in other regions of the world. The women are the core of the society—they do the farming, they carry the burden of care—yet they are really under siege. The disproportionate number of infections is huge and women are suffering so extensively. Women are fighting more and more for their voices to be heard because they themselves are so appalled at the carnage.

What is being done on the ground to address the vulnerability of women?

I see very little change on the ground. There is little progress in building a legal infrastructure and getting laws in place to protect the property and inheritance rights of women. It

moves from inertia to paralysis. We need the toughest laws imaginable against sexual violence and marital rape, and we need ways to enforce them. We need to encourage the social empowerment of women, whether it's putting girls in school or starting income-generating projects. But I just can't get over how slowly this is happening. What we have is an absolute vindication of the feminist analysis: when you're dealing with the inability of men to relinquish power and authority, then you are in real trouble.

So what do you think can be done to alter the course of the epidemic in women?

I've come to the conclusion that we must have an international women's agency rooted in the UN. There is a United Nations Fund for Women (UNIFEM) and it has a budget of around US\$20 million a year for the whole world. In comparison, UNICEF has a budget of over \$1 billion and the United Nations Development Program (UNDP) nearly \$2 billion. So more than half of the world's population gets a pittance of support from within the UN system. This is not the fault of the UN; it's the fault of the member states. And maybe you could get away with that until the dramatic expansion of the pandemic in women, but now there must be an international agency for women. This is the single most important reform that could happen within the UN as far as I'm concerned. It dwarfs all other development issues.

UNAIDS (the Joint United Nations Programme on HIV/AIDS) must also take on AIDS as a women's issue as though there were no tomorrow, because for the women of Africa there is no tomorrow.


The UK government recently released a report from their Commission on Africa. Did this commission's report confront the situation facing women?

The one major flaw in the Blair Commission report, an excellent report in all other respects, was that it is lousy on women. I just ask the question, how is it possible that they had 17 commissioners and only 3 were women? How do you strike a commission, where you can appoint anyone in the world, and only find three women? What does that immediately say about what you think is important?


If we had a Commission on Africa with 14 women and 3 men, we would get a much more valid and significant view of the continent.



There must be an international agency for women. This is the single most important reform that could happen within the UN



A vaccine is the ultimate answer. It's really strange that we don't integrate that into absolutely everything we say and do



Research into new preventive technologies like AIDS vaccines and microbicides is seen as a critical way for women to become empowered and be able to protect themselves from HIV infection. Do you think there is enough political action into the search for an AIDS vaccine?

I remember the first time I met Seth Berkley of IAVI and he said to me the most obvious thing in the world—a vaccine is the ultimate answer. It's really strange that we don't integrate that into absolutely everything we say and do because it is the ultimate answer for women, and for everyone. But this urgency has not gripped everyone yet, and we're still not putting enough money, or energy, into it.

I think the excitement that has been growing around a microbicide is pretty legitimate. It looks as though there may be something not that far down the road and, even with all the limitations, over time millions of lives could be saved. But I love the sense that a vaccine and a microbicide are marching together and that these aren't separate initiatives as they have tended to be seen. You have to fight like hell on both fronts simultaneously. The traditional prevention vehicles, indispensable though they are, need a tremendous shot in the arm, and a vaccine or microbicide may be just that.

How important a role does debt relief play in reversing the trend of poverty on the African continent?

The cancellation of debt in the poorest developing countries is absolutely an obligation that the Western world should fulfill. If we were able to cancel over \$30 billion of Iraqi debt overnight just because the US wanted us to, then surely the world can come together on the cancellation of African debt. That would free a good deal of money, otherwise used for servicing debt, to invest in social sectors where the needs are great.

I think, however, that doubling the official development assistance to reach the famous target of 0.7% GNP [gross national product] is probably the single most important immediate response. And there we're in trouble because the US refuses to embrace the objective. We're surprisingly also in trouble because Canada refuses to set a timetable for that objective. The development assistance is so important because if the disease burden of a country is as high as it is in the case of these AIDS-afflicted countries, then you never get economic growth until you deal with the disease burden, and that requires resources. This

is the argument that Jeffrey Sachs makes—once you've dealt with the disease burden you can start talking more vigorously about economic growth.

However even with debt cancellation and foreign aid, you don't build economies until you have fair international trading laws. There is not yet any substantive movement to give the producers in Africa a chance to compete fairly in the world, which would be the strongest way to repair the economies.

The UN general assembly recently held its special session on HIV/AIDS (UNGASS) in New York City. Were AIDS vaccines or microbicides high on the agenda? Was there discussion on the pressing needs of women?

I sat in on the “so-called” session on gender and AIDS and there was no meaning to that meeting, and I don't care who is offended by that. I would say it ranged from fatuous to nondescript. There was nothing in that meeting that would galvanize a response by governments to what is happening to women. There was a lot of rhetoric, which is symptomatic of what's happening—we're not responding. The Secretary General opened UNGASS by saying that although we have made some progress, most countries have failed to meet their promises. This isn't just Stephen Lewis being Cassandra; I'm just mirroring what others are saying.

In the materials on prevention produced for the meeting there was absolutely no mention about AIDS vaccines or microbicides. How is it humanly possible that the people who are responsible for setting out the details on prevention forget these important technologies? It just isn't rooted in the minds of those who have to respond.

You have become such a strong voice for women's rights that I wonder how your wife has influenced your work.

My wife, Michele Landsberg, has been one of the strongest feminist voices in print in Canada for a quarter of a century, and the feminist analysis has very much become part of my own ideology because of her influence. She's been an absolutely extraordinary and uncompromising voice and the power and force of her ideas has been unquestionably the greatest influence on my life.

We have been married for 42 years and Michele always says that it took her 20 years to turn me into a human being, and then the next 20 years were tolerable. I think that's probably accurate. I also inherited a lot from family, of

course, and was deeply engaged in politics for a while, but in terms of what I think is and isn't important in this world, the benchmark for me has been my wife.

How important was your work in politics and how has it shaped your current position?

I love politics and I regarded it as a principled and useful profession. I served in parliament for more than 15 years and I am very sad that politics has now descended into such personal animus and vitriol in the US and in Canada. It's very different from the days when I was in politics, or when my father was in politics in the 60s and 70s. But I was very lucky, I got into politics when I was 25 and out when I was 40. My political experience has helped me most in the advocacy around AIDS.

What are the most critical steps the international community can take in advocating for a suitable response to AIDS?


Let me say something that is a trifle provocative. The world is now assessing questions of how the UN and the international community are responding to critical issues like Darfur, the way it responded to Rwanda, and the way in which it is failing to respond in Northern Uganda. And national governments have every right to disagree with the interpretation of the international community and say go to hell, but I think that with this pandemic everything changes. We can't allow ourselves the diplomatic privilege of always working behind the scenes and being silent.


If you think that treatment is rolling out

too slowly in South Africa, the country with the highest absolute number of infections in the world, then something has to be said about that. If in a country like Zimbabwe you see the pandemic eviscerating the population, there has to be a desperate effort made to confront the turbulent political situation. It just seems to me that the UN cannot be seen as complicit in the passivity and slowness that characterizes some of the responses, because people's lives are at stake. We have a responsibility, in a thoughtful way, to say to recalcitrant countries that this isn't good enough and we expect more because we're fighting for every life.


How do you get the world to realize the consequences of this pandemic?

You have to keep at it relentlessly by driving home your arguments, trying to persuade people, and never allowing your voice to be silenced. You have to be tenacious and indefatigable. We know that we can save lives because we have generic antiretroviral drugs at a low enough cost that they should be available to everyone. But even though treatment is now being rolled out it's happening too slow, too late, and too incrementally. That drives me crazy.

The criminal negligence on the part of the Western world has lasted for so long that we'll never be able to compensate for the deaths that have occurred. But you have to continue fighting, and one day, unexpectedly, you break through. That's what I'm waiting for. 



With this pandemic everything changes. We can't allow ourselves the diplomatic privilege of always working behind the scenes and being silent



their July summit in Scotland, G8 heads of state reaffirmed support for advance market incentives and asked the Italian government to lead the development of a concrete proposal by the end of this year.

Lack of incentive

These global leaders hope that market incentives will draw more private sector investment to vaccine R&D. Even though the total investment in AIDS vaccine research has climbed from US\$160 million in 1996 to an estimated \$690 million in 2004, annual spending on AIDS vaccine R&D from all sources still represents less than one percent of expenditures on all health R&D. And whereas about 48% of investment in health R&D across the world comes from the pharmaceutical industry, the private sector accounts for just 10% of all AIDS vaccine R&D funding.

Private sector investments are needed because vaccine development requires expertise not found anywhere else. While the key scientific breakthrough that leads to a successful vaccine may well come from a university laboratory or small biotechnology company, the biopharmaceutical industry is best equipped to translate this research into a successful product. These companies have the experience and infrastructure to devote to the costly later stages of vaccine development—clinical testing, regulatory approval, and production. "Pharmaceutical companies look to biotech companies for new product candidates, so a market commitment that stimulates Big Pharma investment will benefit large and small companies alike," says Berkley.

But companies won't put forth resources if they can't foresee how to recoup their research, development, and production costs. Even a company that has a strong social commitment must answer to shareholders. "The main thing that causes companies to enter a field is the prospect of a market," says Stanley Plotkin, emeritus professor of pediatrics at the University of Pennsylvania and executive adviser to the chief executive officer of Sanofi Pasteur, the vaccine business of Sanofi-Aventis.

Consolidation among pharmaceutical companies and vaccine companies has left just five major vaccine manufacturers; GlaxoSmithKline, Sanofi-Aventis, Merck, Wyeth, and Chiron. Vaccine candidates now compete in a company's portfolio against potential drug blockbusters to lower chole-

sterol, improve erectile function, or restore hair loss. In terms of revenues, vaccines are sure to lose out against drugs since a vaccine may be used only a few times in a lifetime while drugs are often used every day. Whereas the market for a single drug can reach billions of dollars, the total market size for vaccines in developing countries is about \$500 million a year.

Pennies a dose

One factor keeping the market size small is the negotiating power of international agencies like UNICEF. In the late 1990s several companies either reduced or dropped altogether production of the vaccines routinely purchased by UNICEF. While the low prices have helped ensure the expansion of immunization programs around the world, writes World Bank senior health specialist Amie Batson, "They have also created expectations that all vaccines should cost pennies per dose forever." (*Health Affairs* 24, 693, 2005)

The urgent social concern for these vaccines may put enormous pressure on the vaccine maker to sell the vaccine at a greatly discounted price or even give it away for free. More worrisome than bad publicity is the prospect that the vaccine could be "confiscated" through compulsory licensing in response to a public health crisis, says Wendy Taylor, executive director of BIO Ventures for Global Health, an organization formed to address the development and distribution of biotechnology products for developing-country diseases. When anthrax was deemed to be a threat, the US government appeared to threaten such a move on the antibiotic ciprofloxacin (Cipro).

An AMC could go a long way toward persuading biopharmaceutical companies that vaccines for diseases like AIDS or malaria are a viable investment. Such a fixed-price commitment would only apply to low-income countries, leaving companies free to sell the vaccine at market prices in higher-income countries.

To assure vaccine developers that they will indeed receive the money promised to them, the AMC would be legally binding. As long as the new vaccine meets efficacy and other standards put forth in the AMC contract and eligible countries want to use the vaccine, the developer will receive the guaranteed price per vaccinated individual. An independent adjudication committee composed of experts from both the biopharmaceutical industry and the global public health community would

Pharmaceutical companies look to biotech companies for new product candidates, so a market commitment that stimulates Big Pharma investment will benefit large and small companies alike

Seth Berkley

decide if the product has met the qualifying criteria, and could grant waivers if a vaccine does not meet the original standards but is still judged to be of significant public health value.

For an AIDS vaccine, IAVI has proposed a draft market commitment that would require the vaccine to be at least 50% effective at preventing the transmission of HIV subtypes A and C, the subtypes circulating in the poorest nations (Figure 1). Eligible countries would contribute a small "co-payment", and the donor would make up the rest.

Donors might be government entities or private foundations. The UK government, for example, through the Department for International Development (DFID), would be able to commit to an AMC within its existing budget mechanisms. The US government, however, would face procedural obstacles because Congress does not normally make multi-year financial commitments. The World Bank is another possible sponsor but under current rules it cannot commit to programs beyond five years. Private foundations would face the fewest obstacles.

Win-win

The proposal has numerous benefits for both vaccine developers and donors. For developers, the commitment reduces the risk that an urgently-needed vaccine would be subject to compulsory licensing while preserving the company's intellectual property rights. Companies will be able to assure investors that there is indeed a market for this vaccine. And AMCs could help deflect criticisms that Big Pharma doesn't do enough for the poor.

For donors, the AMC would ensure that an AIDS vaccine is made available in the low-income countries in Africa and Asia that bear the biggest disease burden. It would also stimulate competition among manufacturers to produce the vaccine as quickly as possible and thus claim the guaranteed price. If a second company or "second-entrant" to the market develops a better vaccine, it too will be eligible to sell its second-generation vaccine at the guaranteed price.

Importantly, donors would only pay when a vaccine is developed, leaving them free to spend their current funds on push mechanisms and vaccine-promoting efforts. If a vaccine is developed and it is met with little or no demand then the donors' financial outlays will be limited.


AMCs might help vaccines reach developing countries sooner, avoiding millions of needless deaths that can occur when a vaccine is too expensive for developing countries. A vaccine against *Haemophilus influenzae* serotype b (Hib) developed in the mid-1990's is still too expensive for use in many low-income countries and an estimated 4.5 million unvaccinated children have died from Hib-related disease over the last decade.

Even if the vaccine can be made affordable, infrastructure problems can derail the delivery of vaccines. Every year about 3 million people die of diseases such as measles, hepatitis B, and tetanus that can be prevented with existing affordable vaccines. These issues are being addressed by the Global Alliance for Vaccines Initiative and its partner, the Vaccine Fund, both of which are supportive of AMCs. "We very much welcome the conversation surrounding advanced market commitments," says Alice P. Albright, the Vaccine Fund's chief financial officer.


How big?

One of the toughest challenges in developing an AMC is determining the market size needed to stimulate vaccine R&D. Rather than use estimates of actual R&D costs, which could be far off the mark, economists calculate the market size based on sales revenues of existing commercial products, reasoning that comparable revenue levels will be attractive enough markets for vaccines. IAVI, working with a model developed by the Center for Global Development, estimates that an AIDS vaccine AMC would require total lifetime sales revenues of about \$4 billion. After subtracting out \$0.7 billion in revenue that a company would likely recoup from sales in developed countries, the AMC market would be \$3.3 billion. In one of the illustrative scenarios developed by IAVI this would be achieved by guaranteeing a price of \$15 per course for 250 million people (Figure 1). Since it will likely take a number of years to get the vaccine to everyone who would benefit from it, IAVI's proposal is based on the expectation that the commitment would last about ten years.

An important feature of AMCs is two-stage pricing. In IAVI's proposed AMC, after the first 250 million people are vaccinated the developer would be required to drop the price to a level that allows the company to cover its production costs but keeps the vaccine affordable for eligible countries. Under the



***Donors
would only
pay when a
vaccine is
developed,
leaving them
free to spend
their current
funds on push
mechanisms
and vaccine-
promoting
efforts***



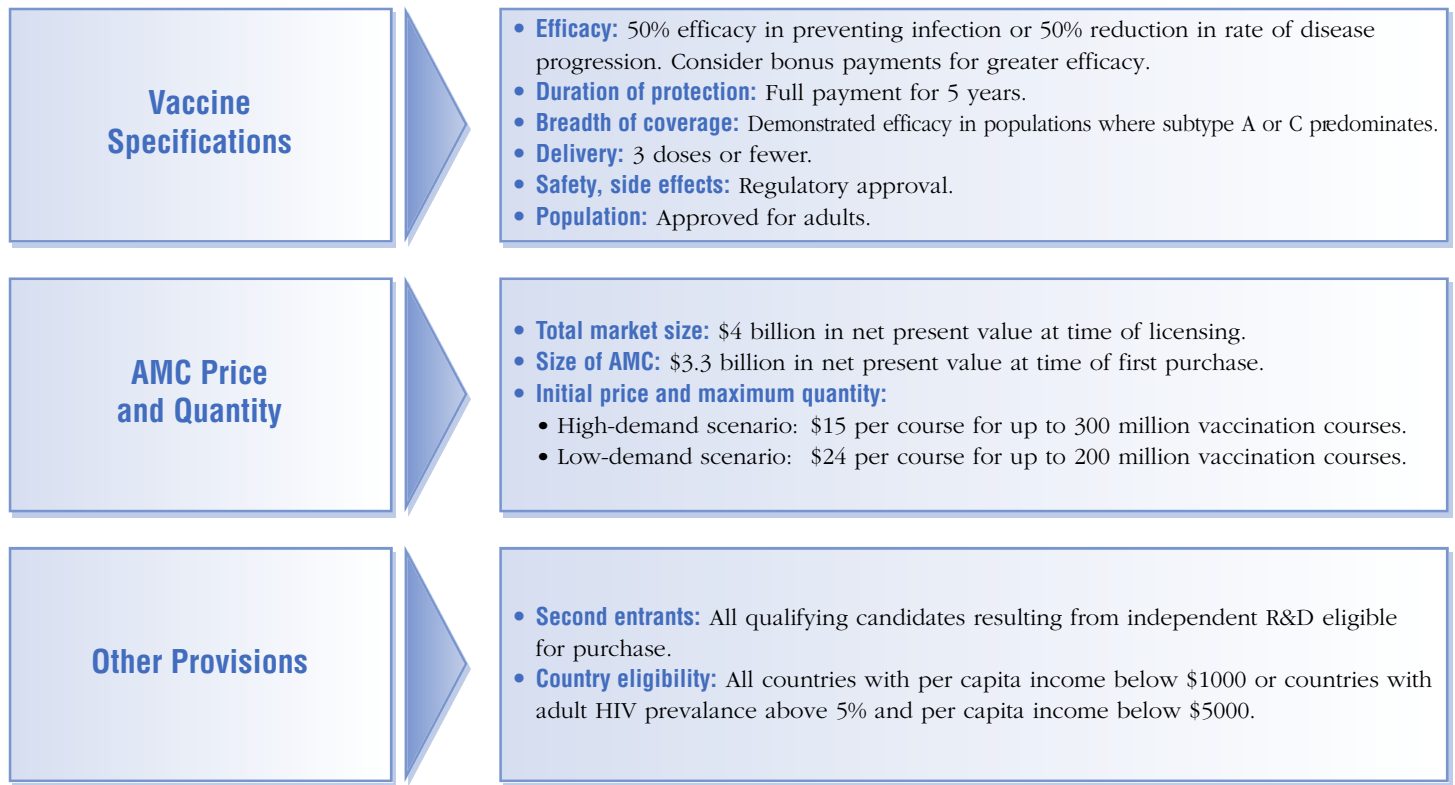


Figure 1. Overview of IAVI's draft proposal for an AMC for an AIDS vaccine.

current proposal the developer would retain the intellectual property rights and existing patent laws would apply. "The two-tiered pricing system ensures that the vaccine developer will continue to sell the vaccine if sufficient demand exists after the initial price and quantity provisions are fulfilled," says John Hurvitz, a Washington DC-based lawyer who worked on the IAVI AMC proposal. "We don't want the product to disappear from the developing world when the purchase contract goes away."

Not just ivory tower

IAVI has held consultations with industry to gauge the interest in the proposed AMC. "We haven't just sat back in an ivory tower," says Hecht, "We've taken the idea on the road." In general the response from executives has been positive, although most agree that details remain to be worked out. One concern from industry is that if an AMC is structured to provide a market of \$3 billion and three vaccine-makers hit the mark, each will receive only \$1 billion each. "That may not be enough to recoup a company's investment," says Rudi Daems, executive director of policy and corporate affairs at Chiron Vaccines, who thinks AMCs are a very promising concept once the details get worked out. "If you don't put significant resources into a vaccine commitment then you will fail, and we will all be waiting 30 years from now for an HIV vaccine."

Some industry representatives find problematic the lack of a guaranteed purchase if demand dries up. That is unlikely to happen, however, because companies and public health officials will forecast demand and remove barriers to adaptation, says Saul Walker, a policy analyst at DFID. "In the end, it is in everybody's

interests to develop a product that will actually get used."

Companies don't have guaranteed markets for any vaccine or drug they develop, even those marked for sale in developed countries, points out Owen Barder of the CGD and one of the lead authors of the organization's AMC report. "Companies should have an incentive to develop the best possible product, one that people will want to buy".

Venture capitalists have expressed support for the concept, although it is too soon to tell how widely their enthusiasm is spread. "It will be viewed as a curiosity at first," says J. Leighton Read of Alloy Ventures, an early-stage venture capital firm, "but once a company with a credible vaccine plan signs such a commitment, the signing could generate a lot of interest."

Untried but true

Not everyone favors AMCs as a way to motivate the discovery of an early-stage vaccine against AIDS or malaria. The concept has sparked criticism from a handful of scholars, including some members of the CGD working group.

One concern is that the scientific hurdles involved in creating vaccines for AIDS, malaria, and TB are so high that an AMC will prove to be an ineffective tool for these diseases. A further risk is that vaccine firms and AMC donors will fight over whether a vaccine meets the requirements, which were set out years in advance. An AMC runs the risk of either costing too much, yielding nothing, or, most disastrously, disintegrating amid acrimonious litigation, says Andrew Farlow, an economist at the University of Oxford. "We have no proof at all that this mechanism will pull a major vaccine

through," says Farlow. "It has never been used for anything." Not so, says Barder. "The AMC replicates the incentives that produced almost all the drugs on the shelves in one's local pharmacy."


Other critics charge that the advance markets are structured to unfairly reward large biopharmaceutical companies and that the \$3 billion per disease price tag is far too high, especially when many of these companies already receive significant amounts of "push" funding. "The most cost effective and fastest way to discover new vaccines is to fund research directly," says Donald Light, professor of comparative health care systems at the University of Medicine and Dentistry of New Jersey and a member of the CGD's working group who decided not to sign the final report (*PLoS Medicine* 2, e271, 2005). However, Hecht replies that public funding alone will not bring in the full resources of the private sector.

These critics say the solution is to first test AMCs on 'late-stage' vaccines against rotavirus or pneumococcus, where the biology has been worked out and the goal is to get the vaccine produced and deployed in developing nations. However, a successful AMC for a late-stage vaccine will do little to actually prove that the commitment can motivate R&D for early-stage vaccines for AIDS and malaria, says Adrian Towse, director of the Office of Health Economics, an independent research, advisory and consultancy service in London. "The right design for an AMC might be determined only through the action of setting one up."


Many global health experts would agree that AMCs are not a panacea for the problems that bedevil vaccine development and delivery. Market incentives alone will not deliver an AIDS vaccine. As the research efforts progress so must capacity building for testing, distribution, delivery and training.

If AMCs can pull research and accelerate development of a vaccine they will prove their worth. Over the next ten years, the \$3 billion price tag for stimulating the AIDS vaccine market will look like a bargain in comparison to the cost of providing anti-retroviral (ARV) therapy to infected persons in developing countries; UNAIDS estimates the cost of ARV programs at \$3-9 billion in 2007 and \$8-\$20 billion in 2015.


IAVI calculates the cost-effectiveness of an AMC to be between \$21 and \$67 per saved disability-adjusted life year (DALY), a measurement that reflects the loss of healthy life due to AIDS-related illness and premature death. At this rate, investing in a vaccine would be more cost-effective than spending on most other means to fight AIDS or to otherwise improve the health of people in poor countries of Africa, Asia, and Latin America. The actual cost-effectiveness will depend on vaccine characteristics such as efficacy against HIV transmission and how long protection lasts, and on how long it takes for the majority of people to get vaccinated.

Vaccines are the best way to protect the most vulnerable victims of the AIDS pandemic, such as women and children, says Kate Taylor, IAVI's senior director of policy and advocacy. "It is critical to continue care today but also to develop the next generation of preventive technologies because the tools we have today are not sufficient," she says. "Developing a vaccine against HIV is one of the greatest scientific challenges of all time. The science is really hard. Advance market mechanisms provide incentive for the required long-term commitment and significant investment." 

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



The AMC replicates the incentives that produced almost all the drugs on the shelves in one's local pharmacy



Owen Barder

The latest twist on microbicides

Microbicide gels and creams which contain chemicals or biological molecules that reduce the transmission of HIV are already being tested in clinical trials. Microbicides are generally applied topically to the vagina or rectum to create a protective film which may reduce the transmission of HIV during sexual intercourse and are sometimes referred to as “chemical condoms.”

But researchers have recently begun experimenting in test tubes and on animals with what could be called a “living condom.” In these microbicides, the antiviral agents are delivered by genetically-engineered bacteria that mix with the microbial flora populating the mucosal tissue.

A team led by Dean Hamer demonstrates the state of the art for living microbicides in a new report (*Proc. Natl. Acad. Sci. USA* **102**, 11993, 2005). Their choice of antiviral agent was a 52 amino acid peptide that inhibits HIV fusion by binding to a structure in gp41 that forms transiently after HIV engages target cell receptors. This class of small antiviral peptides is attractive to microbicide designers because they are relatively resistant to degradation and inactivation and are immediately active without modification. And the *in vivo* efficacy of related molecules has already been demonstrated. A drug in the same class is Fuzeon or T20 which is currently used as a last resort treatment for drug resistant HIV.

For their bacterium, the researchers selected the *Escherichia coli* strain Nissle 1917 which has a long history as an oral probiotic treatment for inflammatory bowel diseases. The antiviral peptide gene was fused with part of the bacterial protein hemolysin. This construct and hemolysin transporters—to drive secretion of the antiviral protein—were engineered into the cells on antibiotic-selectable plasmids.

To test the ability of bacteria to colonize mucosal surfaces, the researchers fed the bacteria to mice or administered them rectally. Animals treated with antibiotics for 50 days to eliminate endogenous microbial flora maintained the engineered bacteria at high levels (one million per gram feces) for 50 days after antibiotics were stopped. The highest levels of colonization by bacteria delivered by either route were in the colon and cecum. Orally administered bacteria were found at lower levels in the duodenum, jejunum and ileum, while those rectally delivered were also detected in the rectum and vagina. In addition, the researchers showed that nanomolar amounts of the anti-fusion peptide secreted by bacterial cultures were potent inhibitors of HIV infection.

The authors note several potential advantages of this approach for blocking HIV infection, including the long lasting nature of the protection, the simplicity of manufacturing and storing Nissle 1917 (it is sold as dried tablets that can be stored at room temperature indefinitely) and the potential to engineer many different antiviral peptides, designed to attack different strains of HIV. They also propose that the thin, germ line of defense provided by a microbial microbicide may be of therapeutic as well as preventive value by targeting antiviral compounds to the gut-associated lymphoid tissue which is a crucial compartment in HIV replication and pathogenesis.

In an accompanying commentary (*Proc. Natl. Acad. Sci. USA* **102**, 12295, 2005), NIH researchers Laurel Lagenaur and Edward Berger say this noteworthy proof-of-concept study faces some challenges moving forward to the clinic, including efficacy studies in a monkey/SIV model, the development of strains that don't depend on antibiotics for colonization, and demonstration that long term exposure of the gut to these antiviral peptide won't result in an inflammatory response which may recruit target cells for HIV. —PC

HIV's fusion peptide inhibits T-cell activation

It seems that HIV may have yet another weapon in its immune evasion arsenal. From its ability to go silent and establish latency to its capacity to decorate itself with an ever-changing shield of sugar residues, HIV is a master at making itself an impossible target to pin down. Now evidence is mounting that an HIV protein may also directly interfere with antigen-specific T cell activation and account for part of the immune suppression that characterizes infection.

The hydrophobic fusion peptide (FP) at the N terminus of HIV's gp41 protein is integral to the membrane fusion process that brings the virus membrane into contact with the target cell membrane and enables entry. Yechiel Shai and colleagues previously reported that FP localizes to ordered microdomains on T cell membranes, leading them to test the hypothesis in their latest study (*J. Clin. Invest.* **115**, 2149, 2005) that if these microdomains also contained the cells' CD4 and TCR (T-cell receptor) complexes then FP might directly inhibit T cell activation.

The researchers demonstrated through confocal fluorescence microscopy that FP colocalizes with CD4 and TCR on rat and human T cells, and confirmed this colocalization with fluorescence energy transfer (FRET). They also showed that FP immunoprecipitated with TCR molecules, suggesting a direct physical interaction between the two.

They then demonstrated functional consequences of the presence of FP to T cell activation, first in a reduced T-cell proliferation to a recall antigen in culture and also a dose-dependent inhibition of interferon (IFN) γ and interleukin 10 secretion. FP did not inhibit T-cell activation by mitogens, suggesting that the inhibition acts through the MHC-peptide recognition pathway, most likely by interfering with TCR/CD3 crosstalk.

They then looked to see if this FP-induced T-cell inhibition could have consequences in a T-cell mediated disease model. In an adjuvant arthritis model in rats, FP inoculated simultaneously with the triggering antigen led to a significantly milder arthritis, reflecting a reduced T-cell response as measured by IFN- γ secretion.

The extent to which this FP-specific immune suppression mechanism might act in HIV-infected humans is not at all clear, but the authors speculate that FP in virions carried externally on dendritic cells (DCs) to HIV-specific T cells might act in two ways—to mediate viral entry and to inhibit T cell activation—and that the immunosuppression might increase DC survival and allow further interaction with and infection of other T cells.

Defining the precise mechanisms that HIV employs to downregulate the CD4⁺ T cell response will help researchers more fully understand just how AIDS develops following infection and give insight into vaccine design and therapeutic targets. The authors also speculate that an immunomodulatory protein like FP could find utility in other disease settings, such as autoimmune conditions. —SN

CHAVI grant awarded by NIH

The National Institute of Allergy and Infectious Diseases (NIAID) recently awarded a large grant to a consortium of research institutes and medical centers known as the Center for HIV/AIDS Vaccine Immunology (CHAVI). This center was established by NIAID, a department of the US National Institutes of Health, in response to the goals set out by the Global HIV/AIDS Vaccine Enterprise, an alliance of independent groups that has called for a near doubling of the funding for AIDS vaccine research. Barton Haynes of Duke University Medical Center will lead the CHAVI team of immunologists and researchers, which was announced on July 14th. Haynes' team will receive US\$15 million for the first year and as much as \$300 million over 7 years for AIDS vaccine research.

The senior scientific leaders that will be working with Haynes include Joseph Sodroski and Norman Letvin of Harvard Medical School, George Shaw of the University of Alabama, and Andrew McMichael of Oxford University. This team will use the grant to address the major barriers to AIDS vaccine development, as well as to design novel AIDS vaccine candidates for clinical trial. The group of researchers will also use the grant to form new partnerships with other scientists and institutions.

The CHAVI researchers are particularly interested in studying the earliest viral and immunological events and host genetic factors associated with HIV transmission and establishment of infection, including the partial containment of virus replication evident in some people. Another priority will be studying the immune responses in the macaque model of SIV infection to try to define the long-sought 'correlates of protection'. This is intended to enable the development of novel immunogens and adjuvants that can induce persistent mucosal and/or systemic immune responses.

The initial plan for CHAVI includes investing in 5 core disciplines: host genomics and viral genetics, clinical sites for the study of HIV transmission, vac-

cine vector development, structural biology, and clinical trials of vaccine candidates. Teams of researchers have already been selected by Haynes and his colleagues to lead each of these sections.

"CHAVI is not a Manhattan project," said Haynes in a presentation at the AIDS Vaccine 2005 conference in Montreal. "We don't have the enabling technology to make an AIDS vaccine today." Haynes compared the center to the Human Genome Project since it will be sharing research discoveries as they occur. It is hoped this will help advance the research of others in the field.

The initial CHAVI meetings were held in August and included 166 attendees who are involved in the work of the center, including researchers, managers, and administrators. At this meeting a timeline was established for the first year of the grant, which will mostly focus on the discovery phase. In mid-September, this virtual consortium of researchers scattered across several continents will submit their clinical protocol to the US National Institutes of Health for approval. The development of cohorts to study very early events in acute HIV infection is planned to begin by mid-January 2006, and will variously include acutely-infected patients who have yet to seroconvert, exposed but uninfected subjects, and chronically-infected patients. The head researchers can decide to include new discovery teams after the first year. A website dedicated to the plans and advancements of CHAVI will soon be available to the public at www.chavi.org.

Haynes emphasized at the AIDS Vaccine 2005 meeting that the most important attributes of CHAVI would be its ability to afford researchers with the freedom to do "risky" research and enable them to avoid redundancy so that the pace of AIDS vaccine research is accelerated. "The field has grown frustrated with the tempo of the work," said Haynes. "A measure of our success will be the number of failures we have and the tempo of these failures. There's no point in doing this if we only do what's been done before."

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

IAVI (www.iavi.org) is a global not-for-profit organization working to accelerate the development of a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 23 countries, IAVI and its network of collaborators research and develop vaccine candidates. IAVI also works to assure that a vaccine will be accessible to everyone who needs it. IAVI's major financial supporters include the Bill & Melinda Gates Foundation; the Rockefeller, Sloan and Starr foundations; the World Bank; BD (Becton, Dickinson & Co.); the European Union; and the governments of Canada, Denmark, Ireland, the Netherlands, Norway, Sweden, the United Kingdom and the United States.

GSK and IAVI collaborate to develop new AIDS vaccine vectors

GlaxoSmithKline Biologicals (GSK Biologicals) is collaborating with IAVI to conduct pre-clinical development of viral vectors based on non-human primate adenoviruses as AIDS vaccine candidates. Vaccine candidates using a human adenovirus vector, mostly serotype 5 (Ad5), have already been tested in several clinical trials, including the ongoing Phase IIb proof of concept trial of Merck's lead candidate, MRKAd5.

While many eagerly await the results of the Merck trial, the prevalence of pre-existing antibody immunity to human adenoviruses (especially Ad5) in many parts of the world may affect the efficacy of this vaccine. The prevalence of Ad5 pre-existing immunity is highest in Thailand and is around 60% in some parts of Africa. The level of pre-existing immunity in these populations could hinder the response to the MRKAd5 vaccine, though data from the Phase IIb trial in people with high Ad5 neutralizing antibody titers (>1:200) is

still unavailable.

Researchers are hopeful that chimpanzee adenoviruses will be as immunogenic as Ad5 and will be able to successfully sidestep the issue of pre-existing immunity. Other strategies to overcome this obstacle include using prime-boost combinations of different human adenovirus serotypes.

Emphasis has recently been placed on public-private partnerships to speed the development of new prevention technologies to halt the spread of AIDS. The collaboration between Europe's largest pharmaceutical company and a non-profit international health organization is the first of its kinds in the AIDS vaccine field. Similar public-private partnerships are already in place for other diseases like tuberculosis.

Scientists at IAVI and GSK will form a joint team to advance the research and development of the vectors. Both are committed to making an effective AIDS vaccine available in developing countries at an affordable price.

Italian AIDS vaccine candidate advances into Phase II trials

Italian researchers are planning both preventive and therapeutic Phase II trials with an AIDS vaccine candidate at several sites in Africa and Italy. The candidate, which contains the HIV Tat protein and was administered with an alum adjuvant, was tested in both preventive and therapeutic Phase I trials at four clinical sites in Italy. The results of these trials in 20 HIV uninfected and 27 infected volunteers indicated that the vaccine was safe, well tolerated, and immunogenic.

In the preventive trial the vaccine candidate elicited anti-Tat antibodies in all vaccinated volunteers and anti-Tat specific cellular responses in 93% of them. In the therapeutic trial, an anti-Tat antibody response was observed in all vaccinated volunteers and 83% also had a cellular response, according to Barbara Ensoli of the

AIDS Center at the Instituto Superiore Di Sanita (ISS) in Rome. Ensoli is leading the studies and is currently seeking funding to run the Phase II trials in both Africa and Italy.

Tat is a key regulatory protein produced soon after infection and is essential for viral gene expression, cell-to-cell viral transmission, and disease progression. Previous studies have alluded to the role of anti-Tat immune responses in preventing disease progression in HIV-infected individuals, including long-term non-progressors.

The preventive and therapeutic Phase II studies with the Tat vaccine candidate will take place simultaneously and are expected to start early next year. The preventive trial is an open-label study that will enroll individuals at high risk for HIV infection in order to evaluate a prime-boost regimen. The therapeutic study is a randomized, placebo-controlled, double-blinded study in HIV-infected volunteers, some of whom will be on antiretroviral therapy. The Phase II trials are expected to cost approximately US\$60 million.

Russian AIDS vaccine candidate approved for human testing

The first Russian AIDS vaccine candidate was approved by the National Regulatory Authority of the Russian Federation Ministry of Health for Phase I trials. The candidate, known as VICHREPOL, is a recombinant protein vaccine containing both Gag and Env proteins from HIV that are conjugated with a novel adjuvant called polyoxidonium, an immunomodulator approved for use in humans. The Ivanovsky Institute of Virology and the Institute of Immunology in Moscow are developing the vaccine.

The candidate has been evaluated in pre-clinical studies in mice

and the results were presented in a poster at the recent 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment in Rio de Janeiro. Mice received 3 immunizations with VICHREPOL at doses ranging from 2.5 to 100 µg. Potent immune responses were observed in the vaccinated animals and the adjuvant increased the neutralizing antibody response induced by vaccination.

The Russian Federation remains a hotbed for the spread of HIV in Eastern Europe and is home to a growing epidemic among injection drug users (see *Brazil's model approach*, page 1). This population will likely serve as the cohort for studying the safety of the vaccine candidate.