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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

A Cut Above the Rest

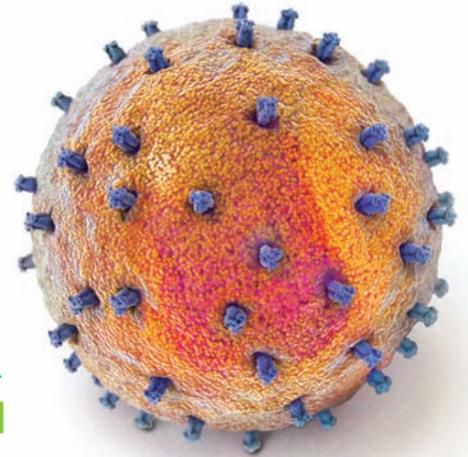
A progress report on the promotion of adult male circumcision as an HIV prevention strategy *By Jonathan Grund*

IT HAS BEEN TWO YEARS since *TIME* magazine voted male circumcision for HIV prevention the top medical breakthrough of the year. This followed results from three clinical trials in Kenya, Uganda, and South Africa, which showed that circumcised men are approximately 60% less likely to acquire HIV from heterosexual sex (see *Cutting HIV Transmission, IAVI Report*, July-Aug. 2005). Since then, this intervention has slowly started to become an integral part of HIV prevention efforts in several African countries severely affected by HIV.

In Swaziland, a tiny African kingdom known for having the highest adult HIV prevalence in the world (26.2%), male circumcision services are being scaled up in an effort to help curb the country's epidemic. Currently, the country's circumcision rate is quite low, with only 8% of adult men having already undergone the surgical procedure. Population Services International (PSI), a nonprofit organization with an office in Swaziland, recently opened a new men's clinic called Litsemba Letfu, which means "our hope" in siSwati, the local Swazi language. This men's clinic is situated between Mbabane and Manzini, the commercial center of the country, and is designed to meet some of the country's demand for circumcision services.

Several studies based on statistical modeling indicate that sustained roll-out of male circumcision could have a substantial impact on the HIV epidemic in countries, like Swaziland, that have high HIV prevalence and low circumcision prevalence. The World Health Organization has identified 13 priority countries where male circumcision could have the most significant impact in averting new HIV infections (see Table 1, page 2). Mathematical models have shown that if Swaziland could circumcise 50% of males aged 15-49 by the end of 2020, one HIV infection could be averted for every four circumcisions performed.

But the plans for Swaziland are even more ambitious. "The goal is to circumcise 80% of men and adolescent young men in Swaziland in five years," or slightly more than 100,000 males, says Jessica Greene, technical services director of PSI-Swaziland, whose work is supported by the US President's Emergency Plan for AIDS Relief (PEPFAR) and the Bill & Melinda Gates Foundation. And based on several studies among adult Swazi men, it seems that the surgical procedure should be widely accepted. "There have been a number of surveys done in Swaziland indicating that the intention to circumcise is generally 60-80%," adds Greene.



Even more ambitious than Swaziland's circumcision campaign is one that recently was initiated in Kenya. The Kenyan government, with the support of PEPFAR and the Gates Foundation, has already implemented programs that have circumcised approximately 50,000 males to date. Starting in November 2009, the country has also embarked on an aggressive campaign to circumcise 30,000 additional men in seven weeks in Nyanza Province. Nyanza has nearly half of the country's 1.2 million uncircumcised men, and its HIV prevalence is more than double the national average. With the support of the Prime Minister, this campaign is utilizing mobile clinics to provide circumcision services. At this time, there are approximately 1,200

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men undergoing male circumcision daily.

Other countries, like Botswana, have also recently begun promoting male circumcision as an HIV prevention strategy. The country plans to conduct almost 500,000 male circumcisions in the next five years, which would raise the circumcision prevalence from its current level of 11% to 80%. Public health campaigns emphasizing the benefits of circumcision have utilized soccer themes to draw on some of the excitement surrounding next year's World Cup, which is the first to take place on African soil.

As countries begin promoting adult male circumcision more aggressively, they have also had to respond to the paucity of trained healthcare professionals capable of performing the surgical procedure. In Orange Farm, South Africa—the township outside of Johannesburg where one of the clinical trials

of adult male circumcision for HIV prevention took place—healthcare providers are trying to increase their capacity to conduct adult male circumcision through highly coordinated sharing of clinical responsibilities among healthcare provider teams. This model “improves efficiency while taking advantage of the key skills of each provider to provide safe circumcisions,” according to Catherine Hankins, chief scientific adviser at the Joint United Nations Programme on HIV/AIDS (UNAIDS). Other approaches to improve the efficiency of male circumcision have also been explored, including having nurses and other clinical officers perform the procedure.

Meanwhile, research on adult male circumcision is still ongoing. Researchers are currently exploring the potential HIV prevention benefits circumcision may afford in men who have sex with men, as well as innovative surgical techniques that improve the efficiency of the procedure, lower complication rates, and reduce post-operative healing time. Hankins describes the overall global progress as “slow but steady,” though she says the progress is “never as fast as you'd want it to be.” ■

Jonathan Grund is a contributing writer based in Atlanta, Georgia.

TABLE 1

HIV and Male Circumcision Prevalence in Priority Countries*

Country	HIV Prevalence	MC Prevalence
Botswana	17.6%	11.2%
Kenya	7% nationally; 15.3% Nyanza Province	84% nationally; 40% Nyanza Province**
Lesotho	23.2%	48%
Malawi	12%	21%
Mozambique	12.5%	60%
Namibia	18%	21%
Rwanda	2.8%	15%
South Africa	18.1%	35%
Swaziland	26%	8%
Tanzania	5.7%	70%
Uganda	6.4%	25%
Zambia	14.3%	13.1%
Zimbabwe	15.6%	10%

*Data from: Progress in Male Circumcision (MC) Scale-up Country Implementation Update, July 2009; www.malecircumcision.org/documents/Country_Update_July09.pdf

**Ministry of Health. Policy on Male Circumcision in Kenya; September 2007.

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IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 25 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it. For more information, go to www.iavi.org.

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GLOBAL NEWS

New Home, New Expectations For African AIDS Vaccine Programme

NEARLY 250 POLICYMAKERS, SCIENTISTS, and HIV prevention advocates gathered from December 13–15, 2009 for the 5th Forum of the African AIDS Vaccine Programme (AAVP), which was held in Kampala, Uganda, the new home of the Programme's secretariat. At the forum, Marie-Paule Kieny, director of the Initiative for Vaccine Research at the World Health Organization (WHO), announced that the Uganda Virus Research Institute (UVRI) had won a competitive bid to host AAVP's secretariat for the next five years. “Thank you for recognizing the important role that this country can play in the work of finding an AIDS vaccine,” said David Kihumuro Apuuli, co-chair of the 5th AAVP Forum and director general of the Uganda AIDS Commission.

AAVP is a network of organizations involved in AIDS vaccine research that was formed in 2000 to support the development of and future access to an HIV vaccine that is suitable for use in Africa. Since its inception, AAVP has been supported by the WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) and its secretariat housed in Geneva, Switzerland. Kieny said her organization would work with UVRI to finalize a hosting agreement within six months. The agreement will convert AAVP into a legal entity with its own governance structure and systems, allowing it to

fundraise independently for its activities.

There was consensus among those who attended the Forum that better HIV prevention strategies are urgently needed in sub-Saharan Africa, and that research into new prevention technologies, including an AIDS vaccine, should be continued and strengthened in the region, which is home to 22 million of the world's 33 million people living with HIV/AIDS. Participants at the forum were brought up to speed on the results of recently completed HIV prevention trials, the largest among these being the 16,000-person AIDS vaccine efficacy trial conducted in Thailand, which provided the first evidence that an AIDS vaccine could prevent HIV infection in humans.

"The costs of treating an ever-increasing number of people are not sustainable," Ugandan Health Minister Stephen Mallinga said at the Forum's opening. He added that the revised treatment guidelines issued by the WHO in December, which suggest antiretroviral therapy (ART) be initiated earlier, would "pose problems for Uganda." Based on the previous guidelines, ART reaches fewer than half of those who need it in most African countries, and 1.4 of the estimated two million AIDS deaths in 2008 occurred on the continent.

Uganda's First Lady H.E. Hon. Janet Museveni, the chief guest at the Forum's opening, expressed full support for AAVP's mission and vision, and said Uganda had been a trailblazer in AIDS vaccine research—the first AIDS vaccine trial to ever be conducted in Africa was done at UVRI in 1999. "By conducting HIV research, Africa is gaining the capacity to manage any other medical catastrophe that is waiting to pounce on us in the future," she said. "That may be the silver lining on the cloud that is AIDS." Mrs. Museveni envisions an expanded role for AAVP, incorporating tuberculosis, malaria, and other diseases with a disproportionately high burden in Africa.

Representatives from development agencies and organizations involved in conducting clinical trials expressed their hope that a re-invigorated AAVP, with a fully staffed secretariat based in Africa, would be better able to support HIV vaccine research and development on the continent. They said they were willing to work with AAVP to secure political and financial commitments from African governments, and to leverage the regional and international collaborations needed to accelerate progress in the quest for an AIDS vaccine. —*Daisy Ouya, Program Manager, Information, Education, and Communication at IAVI in Nairobi, Kenya*

PrEP Trial Unable to Meet Efficacy Endpoints

A PHASE III TRIAL ORIGINALLY DESIGNED to test the safety and efficacy of Truvada—a combination of the antiretroviral (ARV) drugs tenofovir and emtricitabine—in reducing the risk of HIV infection among 1,200 HIV-uninfected heterosexual men and women in Botswana will not be able to determine the efficacy of this drug combination because the HIV incidence rate among volunteers was lower than anticipated. To meet the pre-specified efficacy endpoint for this trial, investigators would have had to double enrollment. However, the clinical research centers participating in the trial had also encountered unanticipated problems in retaining volunteers, so instead trial investigators have decided to modify the protocol and collect only safety and behavioral data.

The study, known as TDF2, is among several large clinical trials investigating whether the delivery of ARVs prior to HIV exposure, an idea known as pre-exposure prophylaxis (PrEP), can prevent HIV transmission among individuals at risk of HIV infection. The trial began in 2005, testing tenofovir alone, but then switched to testing Truvada in early 2007. TDF2 is being conducted by BOTUSA, a partnership between the Botswana Ministry of Health and the US Centers for Disease Control and Prevention (CDC) in Atlanta. The amended trial protocol will be submitted for approval to the scientific and ethical review boards in Botswana and the US in January.

Lynn Paxton, team leader for the PrEP and Microbicides Team for the CDC's Division of HIV/AIDS Preven-

tion, says the incidence data for men and women ages 18-29 in Botswana was initially estimated at around 10%. "We were conservative and halved that number but we subsequently found, over the course of the study, that the incidence was likely much lower than that." Paxton said researchers are still analyzing data collected from the trial and are unable to say what the observed HIV incidence rate was during the three-year study.

Paxton attributes the lower-than-anticipated HIV incidence to a number of factors, including government-sponsored education and prevention programs that target younger men and women. She says the availability of ARVs among HIV-infected people in Botswana may also play a role in driving down HIV incidence rates in the country.

The low retention rates in TDF2 were also due to many factors. Some enrollees moved out of the area or became pregnant, which made them ineligible to continue in the trial, while others found the time requirements for participation too great. Paxton says BOTUSA took steps to overcome these challenges, including expanding weekend clinic hours, increasing participant reimbursements, and strengthening participant education and retention procedures. While these improvements have made a difference, the trial organizers still weren't sure a valid efficacy endpoint could be determined.

Proposed plans are being discussed and finalized with the Botswana Ministry of Health, as well as with the trial's community advisory boards. —*Regina McEnergy*

Understanding Antibody Functions: Beyond Neutralization

What other antibody functions are being explored to explain the RV144 results? *By Andreas von Bubnoff and Kristen Jill Kresge*

ALL VIRUSES, INCLUDING HIV, must infect cells to survive. Once a virus infects a cell, it uses the cell to reproduce more virus, which is then released and goes on to infect other cells, setting off a vicious cycle of cell infection and destruction.

Most, if not all, vaccines that exist today are thought to work because they train the immune system to produce Y-shaped proteins known as antibodies. Following vaccination, some of the cells that produce these antibodies are stored away in the body. When a vaccinated individual is exposed to that same virus in the future, these cells are activated and begin rapidly producing antibodies. One job of these antibodies is to latch onto viruses and block them from ever infecting cells. This process is referred to as neutralization (see VAX February 2007 *Primer on Understanding Neutralizing Antibodies*). By neutralizing the invading virus, antibodies are able to stop an infection from occurring. Although vaccines likely induce other types of immune responses in addition to antibodies that may also play a role in protection, in most cases antibodies are required for the vaccine to be effective.

Researchers are working on developing HIV vaccine candidates that are capable of inducing neutralizing antibodies that can inactivate a large proportion of the HIV variants that are in circulation. None of the AIDS vaccine candidates that have been tested so far have been successful at inducing so-called broadly neutralizing antibody responses against HIV. But recently, the results from a 16,000-person efficacy trial

in Thailand, known as RV144, showed that two vaccine candidates administered sequentially in what is called a prime-boost regimen reduced the risk of HIV infection by about 30% as

compared to an inactive placebo. This was the first evidence of efficacy for any AIDS vaccine candidate (see VAX October 2009 *Spotlight* article, *Vaccine Research Gains Momentum*).

The explanation for this protection is still unclear, but many researchers speculate that it is likely due to antibodies. However, in previous trials this combination of vaccine candidates did not generate a potent or broad neutralizing antibody response, so researchers think this is an unlikely explanation. As researchers try to understand just what immune responses may be responsible for the modest protective effect seen in RV144, they are focusing on antibody functions other than neutralization.

One of the mechanisms being investigated is known as antibody-dependent cellular cytotoxicity (ADCC). In addition to binding directly to the virus, antibodies can also bind to cells that have already been infected with HIV. The general principle of ADCC is that antibodies that bind to cells infected with HIV can facilitate the killing of these cells by other immune cells. Some researchers speculate that processes like ADCC could explain how the vaccine candidates tested in RV144 were able to protect some volunteers from HIV infection even in the absence of broadly neutralizing antibodies.

To see if ADCC is responsible for the RV144 results, researchers are planning to measure antibody responses that are involved in ADCC in samples from some RV144 participants (see VAX November 2009 *Primer on Understanding the Hunt for Immune Correlates of Protection from RV144*). There are several different laboratory tests or assays that can be used to measure ADCC.

The mechanism

For ADCC to occur, an antibody acts as the bridge between an HIV-infected cell and other immune cells that can destroy it. The mechanism of ADCC requires that the tips of a Y-shaped antibody bind to an HIV-

infected cell. The other end of the antibody must then bind to proteins on the surface of other immune cells, which can then kill the HIV-infected cells and stop it from pumping out more HIV.

Although it is possible that ADCC contributes to the protection afforded by some vaccines that are used today, this mechanism has not been shown to be the sole mechanism of protection for any vaccine so far. In cancer research, ADCC has been shown to play an important role in the activity of therapeutic antibodies given to treat cancer.

There is also some evidence to suggest that ADCC may play a role in the control of HIV in infected individuals. Researchers have found that the levels of ADCC activity are higher in so-called elite controllers—individuals who are infected with HIV but are able to control the virus without the use of antiretroviral therapy. Scientists are now studying the antibodies in elite controllers to see how they might differ from those in other HIV-infected people who cannot control HIV. Eventually, such studies might result in the identification of specific markers on antibodies that could help researchers identify the types of antibodies that would facilitate ADCC. This information could then be used to develop vaccine candidates capable of inducing such antibodies.

Beyond neutralization

In the case of RV144, researchers think that the antibodies generated by the vaccine candidates may have facilitated ADCC without being able to directly neutralize the virus. This, however, does not mean that neutralizing antibodies cannot also facilitate ADCC. Research conducted in non-human primates suggests that blocking the ADCC function of broadly neutralizing antibodies reduces their protective effect. This suggests that a vaccine candidate that could induce broadly neutralizing antibodies may be able to attack the virus through both mechanisms. ■

