

## Spotlight

### Facing a prevention crisis



#### An Interview with Zackie Achmat

*Zackie Achmat is one of the best known AIDS activists in the world. He co-founded the Treatment Action Campaign (TAC) in 1998, which is now one of South Africa's preeminent AIDS organizations as well as one of the most influential activist groups globally. Since their inception TAC has been a vocal proponent for affordable generic anti-retrovirals (ARVs) and has challenged the South African government in and out of the courtroom about their slow response to treatment access.*

*For several years Achmat refused to take ARVs to treat his own HIV infection in protest of the government's failure to provide treatment to all citizens in need. His honesty about his own struggles with the disease has helped create an open and supportive movement for the country's more than 5 million HIV-infected individuals.*

*In 2003 he was awarded the Nelson Mandela Award for Health and Human*

*Rights. Achmat remains a persistent and spirited champion for the rights of people infected with HIV, but as the epidemic in his country continues to grow—there were 500,000 newly infected individuals last year alone with a prevalence rate among adults now around 25%—he is now also turning his focus to HIV prevention efforts. TAC is organizing a prevention march for early 2006 in Cape Town and Achmat hopes it will create the same momentum as the treatment protest held at the 2000 international AIDS meeting in Durban.*

*VAX Science Writer Kristen Jill Kresge recently spoke with Achmat about the role of activism and the media in HIV prevention.*

#### **What are the key challenges you still face as a treatment activist in your country?**

Unfortunately there are still many challenges in South Africa regarding treatment. In our country about 800,000 people currently need treatment and fewer than 110,000 are receiving it. Of these, fewer than 70,000 are in the public sector. That's quite sad. There is also the need to establish second- and third-line regimens for people that fail their initial treatments and provide access to antiretroviral treatment for children.

All of these problems are worsened by some serious mixed messages from our government, including denial by some of the science of HIV infection. This political and scientific denial really reinforces very deep, personal denial for many South Africans. The government isn't utilizing the strong and open HIV-positive movement, which doesn't exist in many other countries, to create further progress and that makes all of our tasks as activists much bigger.

#### **What is the situation with HIV prevention efforts in South Africa?**

We don't simply have a crisis of treatment; we also have a critical crisis of prevention. Our country had 500,000 new HIV infections last year and it's critical that we act on that and look at why the ABC [abstinence, be faithful, use a condom] message has failed. You cannot reduce prevention of HIV to a simple slogan. We need a comprehensive prevention program that is linked to serious treatment and care issues.

I think all of us know that prevention is the key to ending the epidemic and that means we have to find new tools, like vaccines and microbicides. But there isn't a magic bullet and there's not going to be one for a long time so we have to use the array of tools that we have at the moment, whether it is barrier methods like male and female condoms or programs to prevent the mother-to-child transmission of HIV. We have some decent programs on prevention, but currently we're not doing enough to scale them up.

#### **Why haven't activists been more involved in prevention advocacy?**

For many activists their inhibition is discussing basic science. Unfortunately all of us that have worked in prevention haven't developed the scientific literacy

## In This Issue

### Spotlight

- Facing a prevention crisis
- An Interview with Zackie Achmat

### Global News

- WHO and UNAIDS release annual report that focuses on HIV prevention
- IAVI and Transgene partner on AIDS vaccine research and development
- G7 nations endorse vaccine market mechanism

### Primer

- Understanding Mucosal Immunity

that needs to go along with a serious understanding of the social problems and inequality that inhibit behavior change. There is now some understanding of how gender and economic inequality hamper prevention efforts and put people at risk, but there isn't a scientific understanding of prevention tools and how they can be used.

I remember when we were first starting to do HIV work and all we worried about was giving out condoms. We never said how the condom prevented transmission of the virus and it's a tragedy that it took politicians and the Catholic Church to make us explain exactly how these tools work and get us to think about the science of prevention in a way we didn't before.

There are numerous prevention service organizations with people who talk about condoms or voluntary counseling and testing, but I am yet to come across someone in those programs who actually understands the science. It's just a simplistic ABC message, which is why these messages are so counterproductive because they actually stop people from thinking. Our first job as activists in South Africa was actually on the prevention of mother-to-child transmission and many of us who started TAC actually began in HIV prevention and human rights work. Now it's sort of coming full circle as we are trying to make sure that what we learned in treatment goes back into prevention.

***Presumably it's even more difficult to explain the basic science involved in the research and development of vaccines and microbicides. How can this be accomplished?***

South Africa is one of the few countries where there is a relatively good understanding of microbicides among activists and increasingly within civil society because there are some really good researchers in the country. And all of us that are activists, whether in prevention or treatment, now have a much clearer understanding of what we need to do to ensure that there is access to information about microbicide and vaccine development. It's difficult to explain the science of microbicides and vaccines, but no more difficult than treatment. HIV treatment has allowed us to become engaged in science and it's time that we became a lot more scientifically literate about HIV prevention.

We need to find a way to reach out to a broader community and find people who love to talk about basic science and then bring them into the HIV movement so that we get to the point where the conversation about HIV vaccines, microbicides, and new medicines is an informed scientific conversation. There has to be a certain level of scientific literacy within communities because otherwise they can be exploited by quacks or people who wish to misuse science for commercial or political ends.

***Recently there has also been a great deal of discussion about male circumcision to prevent HIV infection in men based on the results of a study in South Africa. How do you think the international community should react to this?***

As soon as there's a scientific consensus we need to move with rapidity. But first we have to be aware of and prepared for every single pitfall. You have to consider situations where young men will go and get circumcised in the bush with unclean implements, without having been tested for HIV.

It's really critical that there be a global and urgent summit to discuss an appropriate way to respond to this. If the reduction is valid then it will be an important intervention and it should be offered to every man who wishes to do it, along with condoms and other means of protection.

***Many African countries face problems with infrastructure and lack of medical centers or trained physicians. Is this a problem in South Africa?***

It's not South Africa's major problem but there is a problem with human resources. I was just looking at some research that said 12-16,000 of our nurses and doctors work outside South Africa. There are also 55,000 trained nurses inside the country that are working outside the healthcare system. So there's a huge potential pool of people that just need better pay, improved conditions, and minor retraining to be brought back into the system.

***You were in New York City recently to attend a Global Health Summit sponsored by TIME magazine. Do you think it is important for the international media to cover global health issues?***

I think it is a major step forward that the US media in particular is talking about global

health problems and raising it as an issue to inform Americans. Now this needs to be matched with the mobilization of civil society in the US on health, both locally and globally. It's very important to raise the issue of global public health and not just in terms of economic consequences or cost-effective strategies, but on what Helene Gayle [director of AIDS programs at the Bill & Melinda Gates Foundation] referred to as the policy of being a good neighbor and if my neighbor is sick then I should do something about it.

In that sense we still have a long way to go. We have to create a consensus that everyone has the right to life and everyone has the right to health care. And that includes understanding that the right to life is about a life with dignity.

***What role has the South African media had in covering the country's epidemic?***

The media in South Africa has played a critical role in discussing HIV. They raised awareness on the government's delay on providing treatment and on a range of other issues. There's still a lot more the media can do, but it's much better than almost anywhere else that I've seen. They've been dealing with the issues in a non-sensationalist and non-judgmental way and clearly laying out what still needs to be done.

***South Africa is now hosting a Phase II vaccine trial and a Phase III microbicide trial. Do vaccine and microbicide trials in general receive much attention in the South African media?***

Microbicides and vaccines get coverage, but the problem with the publicity has been with talking about them as magic bullets. This causes a degree of skepticism, both in the public and the activist community, about the potential for microbicides and vaccines. I think we need to eliminate this skepticism because it can paralyze us from taking action. There's no way we can proceed with an infection of this nature that continues to infect millions of people across the globe, and at least half a million people a year in our country alone, without educating ourselves.

We need to ensure that we understand the range of measures that need to be taken to end the AIDS epidemic. We can end the epidemic. But there are at least two things we have to do: find vaccines for tuberculosis (TB) and HIV.

## What advice would you give to the activist community?

We must continue to educate ourselves, spread the message, and ensure that there's money available. But then also start looking 3, 5, even 10 years ahead.

## Global News

### WHO and UNAIDS release annual report that focuses on HIV prevention

The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) recently released their annual report on the global AIDS epidemic. It highlights the progress made by some countries in lowering HIV infection rates despite a continued increase in the total number of people infected with HIV throughout the world. The report, *AIDS Epidemic Update 2005*, was released in advance of World AIDS Day on December 1st and focuses on the importance of HIV prevention efforts and the need to increase and improve these efforts throughout the world.

Kenya and Zimbabwe are two countries where an increase in the uptake of voluntary counseling and testing (VCT) and a delay in the initiation of sexual contact are linked with a decline in HIV prevalence over the past few years. Burkina Faso also had an overall decline in infection rates among adults.

But there were still 4.9 million new infections in 2005, taking the total number of HIV-infected individuals worldwide to over 40 million. Sub-Saharan Africa was the hardest hit region globally, accounting for 64% of all new infections or more than 3 million newly HIV-infected people. The sharpest rise in infection rates was seen in Eastern Europe and Central Asia where the epidemic is now being fueled by both injection drug users (IDUs) and heterosexual transmission. Pakistan and Indonesia are two countries facing explosive epidemics among both IDUs and sex workers.

"We really are failing to prevent this epidemic in most parts of the world," says Jim Kim, director of WHO's HIV/AIDS program. "And we have real opportunities to scale up prevention." He said one of those opportunities is ensuring that some of the momentum created around starting HIV treatment programs in developing countries is extended to HIV pre-

vention efforts, such as massively scaling up VCT programs and focusing on preventing mother-to-child transmission. Kim also suggested that the increase in available funding for HIV treatment could be used to help countries start comprehensive prevention programs.

### IAVI and Transgene partner on AIDS vaccine research and development

IAVI is partnering with Transgene, a French biopharmaceutical company, on the development and production of an AIDS vaccine candidate that uses an adenovirus serotype 35 (Ad35) vector to deliver HIV antigens into the body. The naturally-circulating form of adenovirus causes the common cold in humans and two ongoing AIDS vaccine trials are evaluating adenovirus serotype 5 (Ad5) as a vector, including a Phase IIb "test of concept" trial with a candidate developed by Merck.

The development of a novel candidate based on the Ad35 vector may have advantages over the Ad5 vector because fewer people worldwide have been previously infected by this serotype and therefore are less likely to have pre-existing immunity to the viral vector, which could limit the vaccine's efficacy (see February *Primer on Understanding Pre-Existing Immunity*).

IAVI has worked with Transgene on past studies and on the production processes for other AIDS vaccine candidates that the organization has tested in clinical trials.

### G7 nations endorse vaccine market mechanism

At a meeting of the G7 countries in London earlier this month, finance ministers approved a pilot project to spend approximately US\$1 billion that will ultimately aid the development of vaccines for the world's biggest killers: AIDS, malaria, and tuberculosis. The vaccine proposal was developed by the Italian minister, Giulio Tremonti, and will ultimately emphasize the use of Advance Market Commitments (AMCs) to give pharmaceutical companies more incentive to invest in vaccines that they can

issues with intellectual property and how we can ensure the widest possible access everywhere. Every person has the right to decent health care whether it's in the US, China, India, or South Africa.

then sell for a guaranteed price (see September *Spotlight, An industrial incentive*).

Several organizations involved in vaccine development and advocacy, including Aeras Global TB Vaccine Foundation, PATH Malaria Vaccine Initiative, and IAVI, expressed their support for AMCs as a way to combine the expertise of private industry with the urgent need to develop vaccines for the world's most neglected diseases.



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IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 23 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it.

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## How could the need to assess mucosal immunity affect AIDS vaccine trials?

The most common way that HIV can be transmitted from person to person is through sexual contact with an HIV-infected partner. Researchers estimate that about 85% of HIV infections are caused by sexual transmission of the virus. HIV can enter the body during vaginal or anal sex, and also very rarely during oral sex, through the surface tissues (mucosae) of the genitals.

The human immune system can be divided into several parts. One of these, referred to as the mucosal immune system, relies on immune cells and a specific class of antibody to prevent pathogens such as viruses or bacteria from penetrating and then replicating at mucosal surfaces—including those of the genital, intestinal, and respiratory tracts.

For sexually-transmitted viruses like HIV that enter the body through the genital mucosae, the mucosal immune responses are the first line of defense and play an important role in fending off a possible infection. Since an effective preventive AIDS vaccine will primarily have to protect an individual from sexual transmission of HIV, researchers think it will probably be important for a vaccine candidate to induce strong mucosal immune responses.

So in recent years there has been an increased interest among researchers in developing vaccines that stimulate mucosal immunity. But there is still relatively little known about the events leading up to the sexual transmission of HIV or the immune responses necessary to prevent infection. Researchers are now beginning to study the mucosal immune responses induced by AIDS vaccine candidates in animal models and are also looking at ways to improve and optimize these responses.

### Vaccines to induce mucosal immunity

One factor that affects the level of immune responses at the mucosal tissues is the route of vaccine administra-

tion. Most of the AIDS vaccine candidates that are currently in clinical trials around the world are delivered by intramuscular or intradermal injection. This route of administration can produce antibodies and cell-based immune responses in the blood (systemic immunity), but does not guarantee a robust immune response at the mucosal surfaces. Scientists think that mucosally-administered vaccines, including those by oral or nasal administration, will be more effective at producing responses in these tissues.

But the immune responses generated by mucosally-administered vaccines may vary greatly between the different mucosal surfaces in the body. Vaccines that are taken orally tend to produce the greatest immune responses at the mucosae of the intestinal tract, but are not very efficient at producing a specific class of antibody known as immunoglobulin A (IgA) at the vaginal mucosae, which could be necessary for protection against infections that can be sexually transmitted. Oral vaccines however are effective at preventing infections that primarily target intestinal tissues. There are a few licensed vaccines that are administered orally, including one for polio and two for cholera, which is a diarrheal disease caused by bacteria that mainly infect the intestine.

Recent research suggests that vaccines that are administered to humans as sprays into the nasal passages can give rise to substantial IgA production in the mucosal tissues of the vagina, making this type of immunization appealing to AIDS vaccine researchers. However there are also possible safety issues with nasal immunization that will need to be fully explored before they are evaluated in human clinical trials.

Another way that mucosal immune responses can be optimized is by the choice of delivery system for the vaccine components. Several bacterial and viral vaccine vectors are currently being developed as AIDS vaccine candidates and some of these are known to generate strong mucosal immune responses, depending on how they are adminis-

tered. Researchers are also studying how some factors, such as cholera toxin, which are known to be potent inducers of mucosal immunity, can be altered to make them safe for human administration.

Scientists are also looking at how substances called adjuvants delivered along with the vaccine candidate can be used to improve the mucosal immune responses induced. Adjuvants are already used with several licensed vaccines for other diseases to boost the level of immune responses and their duration. Now several research groups are looking at novel substances that can specifically increase the production of antibodies and immune cells at mucosal surfaces.

### Measuring mucosal immune responses

Researchers are studying how AIDS vaccine candidates induce mucosal immunity in animals, but they are not sure how these responses will differ in humans who receive the vaccine candidate in clinical trials. In the future they may need to actually measure in people the level of antibody or cellular immune responses at the mucosae during an AIDS vaccine trial. While systemic immunity can be measured by a simple blood test, measuring mucosal immunity will involve more invasive procedures that would need to be done repeatedly throughout the course of the trial.

This could make AIDS vaccine trials more complex because it will involve fully and clearly explaining these procedures to all potential trial volunteers as part of the informed consent process. It would also require training the site staff on how to take mucosal samples and providing the trial sites with the equipment required to assess the level of mucosal immunity from the small quantity of cells obtained through such sampling.

It will be important that mucosal immune responses are measured in diverse populations of people during clinical trials because differences in nutrition, intestinal environment, and previous infections have been shown to affect the efficacy of mucosal vaccines.