

# SANKALP

Vol 6 (3) June - July 2007

## IN FOCUS

### The world is waiting... for an AIDS vaccine

Shree Venkatram

May 18 is a special day. It marks the search for one of the most important things needed in the world today—an AIDS vaccine. Over the last decade, it has come to be known as the World AIDS Vaccine Day. It is a day to thank thousands of volunteers around the world who with selfless commitment have signed up for the trials, and the health professionals, researchers and scientists who persist in their efforts to find a safe and effective vaccine. In 1997, it was on this day that Bill Clinton, then President of the United States of America, made a speech calling for a vaccine for AIDS in ten years time.

A decade later, the search is still on. It is not known how long more it will take. But over the years, the search has become more urgent and intense, as commitments to funding and finding the vaccine have risen, as have the numbers of those infected with the virus.

#### Indian MPs pledge

This year, the day was observed in India, which has joined the world community in the search and the development of the vaccine, in three cities in different ways. In Delhi, a group of parliamentarians signed a declaration to strengthen existing prevention methods and support research and development of new preventive technologies including vaccines. The event, Working Together for an AIDS Vaccine, was supported by the Indian Medical Parliamentarians' Forum (IMPF), an initiative of Members of Parliament who are also medical practitioners. The forum aims at bringing the experiences,



MPs sign the Declaration

issues and concerns of the healthcare sector and of patients directly into policy and law.

The declaration highlights the growing concern of how HIV/AIDS could affect India's economic growth, and for the need to provide support to those most vulnerable to the virus.

Dr R. Senthil, Convener-Secretary of the forum, reaffirmed the urgency of looking beyond existing mechanisms and support the AIDS vaccine research. MPs from high HIV prevalence states noted the impact of the epidemic in their respective states and urged prompt action to address the challenges at the grassroots.

The former chief minister of Jammu and Kashmir, Dr Farooq Abdullah, called for awareness and sex education among the youth who are vulnerable. The Director General of the National AIDS Control Organization (NACO),

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K Sujatha Rao, gave an overview of the National AIDS Control Programme (NACP) and the role of future preventive technologies like AIDS vaccines in the country's efforts to contain the epidemic. She lauded IAVI's contribution to AIDS vaccine research in India.

### Among the community

In Chennai, where one of the two AIDS vaccine trials in the country is taking

place, NGO YRG Care had in collaboration with the Tuberculosis Research Centre and IAVI, organised meetings with the community in different places. Doctors and peer leaders reached out with information on HIV/AIDS, preventive methods and the need for a vaccine. The interest evinced by the participants who had braved the sun to come for the meetings was very encouraging.

### A thank you

In Pune, where the first phase of an AIDS vaccine trial has been completed, the National AIDS Research Institute (NARI) and IAVI thanked volunteers, scientists and medical researchers for making it successful. NARI's director Dr R.S. Paranjape gave an overview of the research at the institute, while

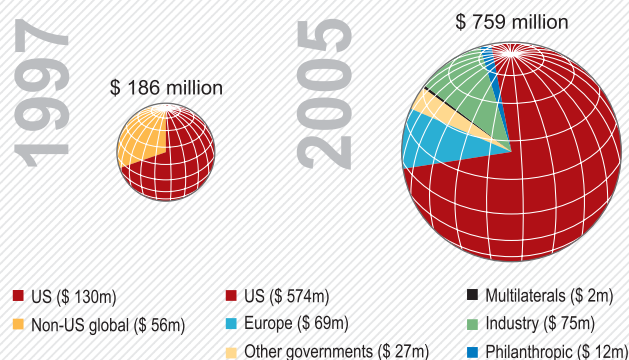
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## The momentum picks up

Can you imagine a world without vaccines for smallpox, measles, tuberculosis or polio? Today more than two dozen life-threatening diseases are prevented by vaccination. Immunization has been recognised as one of the most cost-effective means to improve health. A vaccine for AIDS is eagerly awaited.

The commitment to find the AIDS vaccine has picked up over the last decade. It saw a four-fold increase in funding. New consortia are now aggressively examining crucial scientific questions, and almost 25,000 volunteers are participating in more than 30 vaccine trials across two dozen countries worldwide. The year 2007, saw the start of Africa's first large-scale AIDS vaccine efficacy trial involving 3,000 volunteers in South Africa.

### FINANCING THE SEARCH: THEN AND NOW

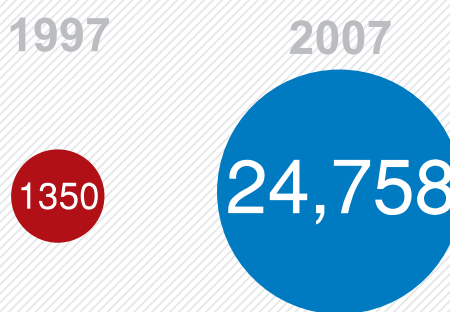


**Growing global resources:** The funding available for AIDS vaccine research has increased since Clinton's call to action. Sustained financing from many sources will be needed to continue the search for an AIDS vaccine until we are successful.

## The challenges that remain

Although there has been progress, much remains to be done to create an expedited global AIDS vaccine research effort. Currently, only a handful of private companies are engaged in vaccine research. Global spending on AIDS vaccine research still falls short of what is needed. Not only must the world's efforts to find an AIDS vaccine become substantially stronger, but they also will need to be sustained over a number of years.

### NUMBER OF VACCINE VOLUNTEERS: THEN AND NOW



**25,000 heroes:** In ten years, many AIDS vaccine candidates have moved from small safety studies to large efficacy trials. This would not be possible without the extraordinary dedication of trial volunteers.

## Growing political commitment

Between 2000 and 2005, public sector investment in AIDS vaccine research more than doubled. Last year, the Group of Eight leading industrialised countries committed to increase direct investment in AIDS vaccine research and to establish market incentives to encourage greater engagement by private industry. The 22-country Programme Coordinating Board of UNAIDS identified vaccine research as an essential component of a comprehensive global effort to prevent HIV/AIDS. Among developing countries, several have drafted their own national vaccine plans or entered into memoranda of understanding with the International AIDS Vaccine Initiative.

An AIDS vaccine offers the world's best hope of ending the epidemic. Without a vaccine, another 50 million people could become infected with HIV in the next ten years. Even a partially effective, first-generation vaccine, which reaches a fraction of those who need it, could cut the number of new AIDS infections dramatically, saving millions of lives around the world.

**SPOTLIGHT****Male circumcision for HIV protection**

Dr Nomita Chandhiok\*

In the last decade, male circumcision has become the focus of attention in international HIV prevention research. In the late 1980s, scientists observed that in some places in the developing world, levels of HIV infection were lower in places with high rates of male circumcision.

Recently, results from two randomized controlled clinical trials in Africa showed that circumcision of male adults reduced their risk of acquiring HIV by approximately 60 per cent! The closure of two clinical studies in Africa on the recommendation of their Data Safety Monitoring Board (an independent committee of experts) brings forth exciting opportunities as well as challenges. The studies were being carried out in Kisumu, Kenya and Rakai in Uganda. The results of the trials support findings from the earlier South Africa Orange Farm Study. The most important question that these three randomised controlled trials answered is that circumcision is safe when performed in sterile clinic setting by well-trained

medical professionals and it significantly reduces the risk of HIV acquisition in HIV-negative men.

Male circumcision has an advantage over other prevention options, such as condom promotion and behaviour change as it is a one-time intervention that does not have issues of adherence or sustaining change that constrain other strategies. Recent simulation models based on a 60 per cent protective effect of circumcision have projected that large scale implementation of circumcision has the potential to avert annually as many as two million new HIV infections and 300,000 deaths in sub-Saharan Africa. A similar study by Steven J Reynolds and his team at the National AIDS Research Institute, Pune, in 2004 showed the protective effect of circumcision against HIV 1 infection among males (Lancet, vol 363, 2004).

**How does circumcision prevent HIV**

The exact reason why male circumcision provides a protective benefit for men against HIV infection during vaginal sex is unknown. The male foreskin contains a concentration of HIV target cells, like Langerhans cells, which are immune cells that are targeted by HIV during the earliest stages of infection. By removing the foreskin which is not keratinised or toughened on its underside, circumcision reduces the ability of HIV to invade these cells. Research shows that circumcision lowers rates of urinary tract infections in infants and lower prevalence of genital ulcer disease (which is a risk factor for acquiring HIV). Further, removal of the penile

foreskin causes more rapid drying of the penis after sex, bathing or urination. This reduces the likelihood of bacterial or other sexual infections which flourish in damp environments.

**Limitations of male circumcision**

Male circumcision should not be seen as a 'silver bullet' in fighting HIV infection. It is important to remember that it is not 100 per cent protective and is not a substitute for other methods of HIV risk reduction. Circumcision should form a part of the range of prevention options for HIV that include counseling about the need to adopt and maintain safer sex practices, access to HIV testing, condom promotion and provision and the management of sexually transmitted infections. There is also the possibility of complications from the surgical procedure itself. Implementing circumcision is likely to increase the costs and strain in the short term on thinly-stretched health services, but in the longer-term, may prove to be cost-effective. Resumption of sexual activity before complete wound healing may increase the risk of HIV infection among recently-circumcised HIV negative men.

It has often been suggested that circumcised men will feel less inhibited about indulging in risky behaviour. All the recent trials were designed to look for such changes in risk behaviour but

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**Simply put...**

Male circumcision is the surgical removal of the foreskin of the penis. It is one of the most common surgical procedures in the world, with 25-30 per cent of men worldwide undergoing the procedure. It is performed for many reasons: hygiene, religion, tradition, or a combination of these. In many parts of the world it is considered a marker of tribal and religious identity. In some cases, male circumcision is a medical treatment for a disorder.

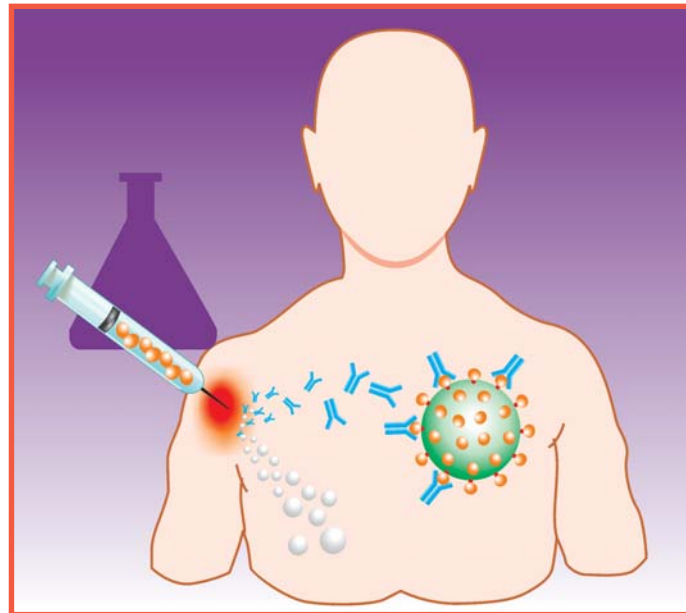
*\*Dr Nomita Chandhiok is Deputy Director General, Division of Reproductive Health and Nutrition at the Indian Council of Medical Research, New Delhi.*

### What is a vaccine?

A vaccine is a substance that is introduced into the body to prevent infection or to control disease due to a certain invader/pathogen (any disease-causing organism, such as a virus, bacteria or parasite). Without vaccines, we would still be battling polio on a global scale and living in fear of small pox across India.

### What does a vaccine do?

In normal course, an individual's immune system learns how to protect him/her against a disease only after the body is exposed to the disease or infection once. But a vaccine stimulates the immune system to recognise the disease/infection in advance, by teaching the immune cells to identify certain invaders, such as germs, that cause disease. These lessons of being able to distinguish invaders are then stored by the memory of the immune system, so that it quickly responds the next time the body is exposed to the same risk. Thus, vaccines prime the human body in advance to take charge and keep dangerous diseases at bay.



**It is important to note, no vaccine is 100% effective. In fact, most vaccines are between 70% - 95% effective.**

### How do preventive vaccines work?

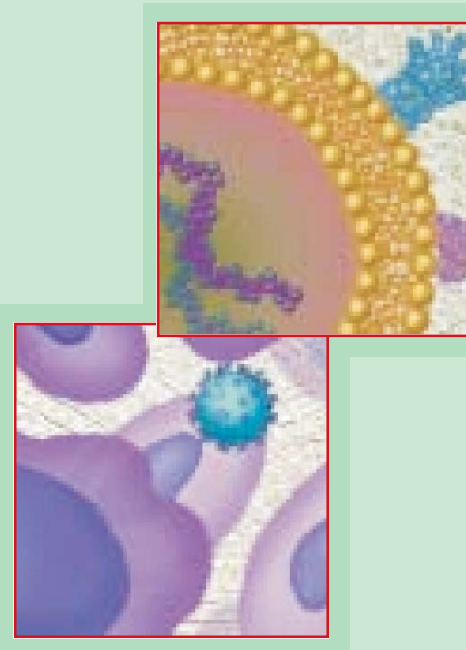
1. The vaccine introduces a small piece or a non-harmful form of the pathogen into the body. This is called the foreign antigen ('foreign' indicates that it is not from the person's own body).
2. The immune system in the body produces an immune response to the pathogen by making antibodies, killer cells or both.
3. The immune system has memory B cells (producing antibodies) and memory T cells (helping the production of antibodies or killer T cells). The next time the real pathogen is encountered, the immune system remembers it and mounts a much larger and quicker response than it would have if the person had never received the vaccine. This is called 'immune memory'.
4. This larger and quicker immune response can act in several ways to fight infection and/or disease:
  - ❖ By stopping replication of the pathogen, so it cannot infect more cells
  - ❖ By producing antibodies that attach to the pathogen, rendering it harmless (antibody response)
  - ❖ By producing immune cells that attack and kill other cells that have been infected with the pathogen (killer cell response).

**Vaccines can be introduced in different ways, such as injection into the muscle (intramuscular) or into or under the skin (intradermal or subcutaneous); by application to the skin (transdermal); by application to the inside of the nose (nasal); or by being swallowed (oral).**

### Vaccine-Preventable Infectious Diseases

Anthrax	<b>Mumps*</b>
Bacterial Meningitis	<b>Pertussis*</b>
Chickenpox	Pneumococcal Pneumonia
Cholera	<b>Polio*</b>
<b>Diphtheria*</b>	Rabies
Haemophilus Influenzae Type B	Rotavirus
Hepatitis A	<b>Rubella*</b>
<b>Hepatitis B*</b>	<b>Tetanus*</b>
Human Papilloma Virus	<b>Tuberculosis*</b>
<b>Influenza*</b>	<b>Typhoid*</b>
Japanese Encephalitis	Yellow Fever
<b>Measles*</b>	

\* These are part of the Expanded Programme of Immunisation as recommended by WHO



**There are many steps involved in the development of any vaccine before it can be licensed and used in humans. After a vaccine is designed or developed in the laboratory, it is tested in animals for safety, immune response and toxicity. Then it must go through a series of clinical trials in humans. Many of the modern, licensed vaccines that are used today have taken several years before they cleared the many complex stages of their development.**

### Check out the R&D development timelines of some common vaccines...

Vaccine	Discovery of Cause of Disease	Number of Efficacy Trials	Vaccine Licensed in US	Years Elapsed in Development Process
Typhoid	1884	7	1989	105
Haemophilus Influenzae	1889	2/9	1981	101
Pertussis	1906	2/9	1995	89
Polio	1908	2	1955	47
Measles	1953	1	1995	42
Hepatitis B	1965	2	1981	16
HIV	1983	2	???	As of 2007, 24 years

Adapted from: Heyward W et al. AIDS Research & Human Retroviruses December 20, 1998; Vol 14.

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researchers saw very little evidence of any increased risk-taking in the South African trial and none at all in the trials in East Africa.

**Circumcision in India**

India is largely a non-circumcising nation, with the practice confined to India's small Jewish community and to Muslims who constitute around 13 per cent of the population. Usually neonatal circumcision along with the blessing ceremony is done in this community. It is traditionally done by the 'barber' and herbal and ayurvedic medicines are applied to promote healing. Among an urban minority of Muslim populations, male circumcision is now performed by medical personnel with aseptic precautions. Male circumcision is considered a marker of religious identity and proof of belonging to a religion. It has the risk of converting a hitherto neutral public health issue into a religious and political issue.

**Challenges in introducing male circumcision in India**

Given the compelling evidence the question that arises is: should male circumcision be introduced as an HIV prevention option in India? The WHO/UNAIDS convened a global consultation in March 2007 to discuss the policy and programme issues in the light of the evidence generated through the clinical trials. A single standard global position regarding male circumcision was thought to be inappropriate as the level of epidemic differs between countries. The WHO/UNAIDS recommendation for countries like India, where HIV is largely concentrated in specific population groups, is that there would be a

**Points to remember**

- There is a risk that introducing male circumcision as an HIV prevention intervention may position it as an alternative to condoms. This will have serious implications for women's ability to negotiate for condom use.
- Current evidence does not support male circumcision in HIV positive men as an intervention to reduce HIV transmission to women.
- There is insufficient evidence that male circumcision has any benefit in men who have sex with men.
- Female genital mutilation (sometimes erroneously called "female circumcision") has no health benefits of any kind and, in fact, poses multiple, serious health risks for the woman. It is highly likely that it increases a woman's lifetime risk of becoming infected by HIV. This practice is, fortunately, rare in India.

limited public health benefit of promoting male circumcision in the general population.

Nonetheless, men practicing risky sexual behaviour who are at higher risk for acquiring infection, especially those living in areas reporting a high HIV epidemic, would benefit from it. There is a need to provide them with correct and context-specific information, that includes the risks and benefits of male circumcision.

For this, non-governmental organisations, community-based organisations, professional organisations and health ministries could be involved in developing and disseminating communication messages to increase awareness. Initially, this information could be given to those with multiple sexual partners and STI clinic attendees, so that a voluntary demand for the procedure is generated. Communities should be informed about the potential benefit of male circumcision for HIV risk reduction separate from its use as a marker of religious affiliation. Based on this experience, information dissemination can be widened to other groups and communities.

**Cultural sensitivity**

Considering the cultural and religious sensitivity and corresponding issues of acceptability, it would be difficult to hypothesise how big would be the voluntary demand for male circumcision. Nevertheless, the provision of quality counselling and surgical services that are safe, available, acceptable, accessible, and of the highest possible quality are mandatory if it is to be introduced in addition to other risk reduction measures against HIV/AIDS. The Indian public health delivery system will need to be sensitised to this new indication for circumcision and capabilities strengthened through appropriate training and upgradation of facilities. Without proper training for medical/non medical practitioners and stringent systems for monitoring quality of care, safety and complications, male circumcision will not be safe and its efficacy will be severely compromised.

Provision of safe male circumcision services in primary health care would also

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enhance access to quality services for the circumcising Muslim community and can easily be made available up to the first referral unit level, which covers a population of 100,000. As 80 per cent of the health care needs of the population are accessed from the private health sector, systems would need to be developed and put in place for monitoring quality of care, safety and complications, in both the public and private health sectors. Rollout of male circumcision therefore requires strengthening in many quarters: human resources, infrastructure, communications, training and technical assistance from governments and health ministries.

### More research needed

In India there is a dearth of research related to circumcision. There is no data available on current practices, facilities available or complications of the procedure. Most of what is known about circumcision practices is through hearsay. In the first instance, there is a need to mount multi-site studies to get a clearer understanding of what is happening on the ground. Attitudes and perceptions, cultural and religious beliefs towards male circumcision will have a major impact on its acceptability in India. Studies to understand these as well as, norms and practices need to be carried out. Qualitative data on barriers to accep-

tance would guide development of communication messages and help in sensitising communities.

Male circumcision is a one-time biomedical intervention that should be included in the comprehensive HIV prevention strategy. However, due to its social, cultural, religious and gender perspectives, it would present many challenges in its promotion, acceptance and programme implementation. Urgent, coordinated, well informed action will be needed to translate these plans into the real world where shortages of human resources and medical facilities present significant challenges. ■

### ◀ In Focus

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its assistant director, Dr Seema Sahay, presented the strategies and the information dissemination process adopted for the successful recruitment and retention of participants for the trial.

The principal investigator of the Phase I AIDS Vaccine Trial, Dr Sanjay Mehendale, summarised the regulatory approval process and presented the results of the safety and immunogenicity study of tgAAC09, the trial vaccine at Pune. Senior clinical research coordinator, IAVI, Dr Aparna Shrotri, briefed

the audience about IAVI India's role in trial preparations.

While the morning session had scientists and medical researchers, the afternoon session was attended mainly by members of the community, social scientists and NGO representatives. At both sessions, the audience participated by asking questions related to the trial.

### The reality

Each day, almost 12,000 persons are infected with HIV, 95 per cent of them in developing countries. Last year alone, AIDS claimed 2.9 million lives. So far, AIDS has killed more than 25 million people worldwide and poses a serious threat to the economic and political stability of the countries hardest hit by the pandemic.

Only 28 per cent of HIV-infected individuals in the developing world have access to ARVs, and the cost of treatment and care is escalating each year. UNAIDS conservatively estimates that US\$12.5 billion will be required over the next two years to fund AIDS treatment and care in the developing world alone.

### Close to 30 vaccine candidates are today in clinical trials in countries on every continent:

- ❖ Africa: Botswana, Kenya, Rwanda, South Africa, Uganda, Zambia
- ❖ Asia: India, Thailand, China
- ❖ Australia
- ❖ Europe: Belgium, Finland, France, Germany, Italy, Switzerland, United Kingdom
- ❖ North America: United States
- ❖ South America and the Caribbean: Brazil, Dominican Republic, Peru, Puerto Rico



At a community meeting in Chennai

"Ten years ago the AIDS vaccine effort was languishing," states Seth Berkley, President and CEO, IAVI. "Today, new players, vigour and commitment have enabled IAVI and the field to effectively overcome huge barriers. We still have a distance to travel before we can realise President Clinton's objective, but I am confident that we will get there, if our best scientific minds work together on this enormous problem, and world leaders and their communities back our important efforts." ■

## The Indian Government and IAVI come together for a new Indian Medicinal Chemistry Programme

The Department of Biotechnology, Ministry of Science & Technology, Government of India and the International AIDS Vaccine Initiative signed an agreement on May 2 2007 to address a major obstacle in AIDS vaccine development: the design of candidate vaccines to elicit neutralising antibodies against HIV. A new Indian Medicinal Chemistry Programme, co-sponsored and co-funded by IAVI and the Department of Biotechnology, will comprise top Indian and U.S. scientists tasked with accelerating the pace of AIDS vaccine discovery and developing creative concepts for the next generation of AIDS vaccines.

The Indian programme will complement the work of IAVI's Neutralising Antibody Consortium (NAC), a team of internationally recognised scientists working on the neutralising antibody challenge. Researchers believe an ideal AIDS vaccine

must evoke an antibody response that can block HIV from entering healthy cells, as well as reduce the amount of viral dissemination through a cell-mediated immune response to HIV-infected cells. Yet today, virtually all current vaccine candidates in the pipeline are based on cell-mediated immune responses alone, failing to target the second critical arm of the human immune system.

The first component of the DBT-IAVI programme will consist of a collaboration of principal investigators from different academic research laboratories to design novel HIV antigens. The investigators include Professor Virander S. Chauhan of the International Centre for Genetic Engineering and Biotechnology, New Delhi; Professor Raghavan Varadarajan of the Indian Institute of Science, Bangalore; Dr Stephen Kaminsky of IAVI's AIDS Vac-

cine Development Laboratory, New York; and Dr Philip Dawson of The Scripps Research Institute, California. IAVI and DBT may select additional principal investigators, contract researchers, or partners in India to participate in the programme, and will discuss ways to build infrastructure for subsequent HIV/AIDS vaccine candidate evaluation. At a later stage, based on their initial research and vaccine design concepts, both partners expect to work with an Indian manufacturer to assist with high throughput synthesis, antigen chemical characterisation and potency evaluation of proposed AIDS vaccine candidates.

"This is a most welcome and truly collaborative effort," stated Seth Berkley, CEO and President of IAVI. "Public, private and non-profit entities are increasingly working together to come up with innovative biotechnology solutions to end the AIDS crisis." ■

IAVI gratefully acknowledges the generous support provided by the following major donors.\*



Provided with the support of the European Union



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\*As of 11/06



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IAVI is a scientific organisation founded in 1996 whose mission is to ensure the development of safe, effective, accessible, preventive AIDS 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 AIDS vaccine development.

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