



IAVI in India

Ramlingaswami's vision becomes reality

Ashok Malik

As it commemorates its Tenth anniversary, the International AIDS Vaccine Initiative (IAVI) can look back at a packed and pulsating decade of work. Yet what is perhaps its most comprehensive country programme didn't start till roughly midway into its young life: the IAVI India project, which was officially born in December 2000, following a three-way agreement between IAVI, the Indian Council of Medical Research and the National AIDS Control Organization, both under the Ministry of Health and Family Welfare.

IAVI's partnership with the Government of India and the degree of cooperation and success it has received in the country, from partners, stakeholders, activists, the medical community and, broadly, fellow warriors in the struggle to defeat HIV, is in a sense a tribute to one man's vision. The idea of an IAVI office in India, of a role for this vast and vibrant and intellectually gifted nation in the process of finding an AIDS vaccine was patented as it were by Prof. V. Ramalingaswami, doyen of Indian medical science, former Director-General (1979-86) of the Indian Council of Medical Research (ICMR).

Prof. Ramalingaswami saw a preventive vaccine as the real solution to the AIDS epidemic



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The veteran scientist, as his wife Prabha Ramalingaswami, an academic in her own right and specialist in the social aspects of medicine, says of her late husband, was never in denial about the AIDS problem. "He didn't believe India would somehow escape AIDS," she says, "and he helped set up the first testing centres in India, despite criticism."

Prof. Ramalingaswami was also in no doubt about the fact that "infectious diseases would be back, and with a bang", particularly so after the Surat plague of 1994. As such, he was a votary of the need to develop vaccines, leveraging India's immunological and biotech skills. Remembers his wife, "He saw a preventive vaccine as the real solution to the AIDS epidemic."

It was this far-sighted man who sought out Seth Berkeley, President of IAVI, urged him to look to India, and ICMR, his old home. "Seth and Prof. Ramalingaswami," remembers an associate from those early days, "were regulars at the same conferences. They got on well, and there was mutual respect." As it happened, six months after IAVI signed its agreement with the Union government, Prof. Ramalingaswami passed away. He had lobbied for IAVI, Prabha Ramalingaswami says, virtually "from the hospital bed". By the summer of 2001, he was 80, having done his duty to medicine and mankind; by the summer of 2001, IAVI India was beginning to walk those first few steps in his path.

IAVI's approach to India was a three-pronged one. The first task was, of course, establishing credibility and winning confidence, finding the right partners, convincing policy makers, scientists and civil society groups alike of IAVI's bona fides and its credentials. The second was laying the groundwork for and actually conducting clinical trials, with protocols for informed consent, ethical 'best practices' and transparency that would become benchmarks not just in India but also worldwide. The final stage was incorporating India into IAVI's research agenda pushing it to actually develop that elusive vaccine.

"At my previous job at the Population Council," remembers Anjali Nayyar, who moved in 2005 from New Delhi to New York, from Country Director IAVI India to Vice-president, Country and Regional Programmes, "I often wondered if the AIDS vaccine search could come to India, particularly after seeing the Hepatitis B vaccine process." So when the IAVI India offer came, Nayyar was convinced India was the right choice. She was also, as she admits, a trifle over-optimistic: "I was optimistic about IAVI's potential to get the vaccine, in four or five years!"

“The support IAVI has got has been unparalleled and it says a lot for the new India and its policy maker’s forward looking attitude.”

What did worry her, and IAVI, was how various stakeholders would react to the idea of an international organisation based in the US conducting clinical trials in India. As Mark Chataway, India Country Advisor, puts it, "The key was building relationships. Early on in India, we engaged a market research organisation to interview 23 leaders of NGOs and ask them what they thought of IAVI coming to India. The universal message was: 'Be careful'."

Yet today, many of these NGOs are active partners of IAVI and instrumental in helping it widen the ambit on informed discussion on HIV/AIDS and the menu of preventive technologies needed to combat it, and within this the critical space for a vaccine.

The single most important tool that helped achieve this was, simply: transparency. The launch of **Sankalp**, the IAVI India newsletter, in 2001 was meant to establish IAVI's determined openness and nurture its bonds with other stakeholders. An

Editorial board with representation from NGOs, positive people's groups, international bodies and from NACO oversees **Sankalp**. It meets twice a year to fine-tune IAVI's principal dissemination and communication vehicle.



— AIDS awareness for the community with street theatre group Nalamdana at an IAVI meeting

Political support for IAVI has been exceptional. No less than the President of India, Dr. A.P.J. Abdul Kalam, has endorsed the need for an AIDS vaccine. In May 2002, in collaboration with ICMR and NACO, IAVI co-hosted an International Policy-Makers' Conference. Inaugurated by Atal Bihari Vajpayee, then Prime Minister of India, it was addressed by Sonia Gandhi, President of the Indian National Congress and Leader of the Opposition in the Lok Sabha.

Bipartisan support for IAVI has meant that it has benefited from the counsel and backing of health ministers through successive governments. IAVI counts C.P. Thakur, Shatrughan Sinha and Sushma Swaraj, health ministers in the previous government as well as the present incumbent, Dr. Ambumani Ramadoss, as well-wishers whose guidance has been irreplaceable.

In addition, 2002 saw the establishment of the National Advisory Board, a collective of government and public leaders, representatives of United Nations bodies, civil society activists and academics. The Board advises the IAVI India programme on information flows, social issues, gender and human rights concerns and the integrity and sensitivity of the clinical trial and research process has gone a long way in helping IAVI set standards in these areas. Says Dr. Lalit Kant, Senior Deputy Director-General, ICMR:

“The assistance of IAVI in raising political awareness and building advocacy has been extraordinarily successful.”

“The community, scientists, institutes and politicians are now sensitised to scaling up vaccine trials or taking up other AIDS vaccine studies should opportunities arise.”

It is no wonder then that today India is pivotal to IAVI's attempt to craft a global political stakeholders' constituency for an AIDS vaccine. The India-Brazil-South Africa (IBSA) framework has already committed itself to working on developing and addressing issues of access related to a preventive vaccine. The crucial support of Prime Minister Manmohan Singh must be mentioned here. IAVI's Global Political Advocacy Initiative (GPAI), the welding together of influential political voices from across the planet to boost the AIDS vaccine enterprise, will also have a markedly Indian accent.

IAVI India celebrates World AIDS Vaccine Day

Almost from day one, IAVI travelled to the interiors of India, the frontlines of the war against AIDS. Between December 2002 and August 2003, it held intensive state-level interactive meetings in Andhra Pradesh, Maharashtra, Karnataka, Tamil Nadu and the Northeast - these are among India's 'high-prevalence' states. Local partners such as the State AIDS Control Societies and the Tata Institute of Social Sciences, Mumbai, were co-hosts. Other vital confidence-building measures were the NGO Coalition conferences in Bangalore and Delhi in 2003, where IAVI worked with NGO leaders to integrate mutual concerns into an effective AIDS vaccine message. In 2003, too, state legislators' meetings were held in Guwahati and Hyderabad and strengthened the political advocacy and outreach effort.

IAVI recognised the need to explore barriers and means to facilitate participation of both men and women in clinical trials. It has worked actively with individuals and organisations working on issues of gender, women's health and rights to ensure women's participation in clinical research.

Hardware kept pace with software. While IAVI worked diligently at building its relationships in India, a more literal building process was also afoot. Preparatory to multiple Phase I clinical trials, IAVI began to augment infrastructural capacity at the National AIDS Research Institute (NARI), Pune, and the Tuberculosis Research Centre (TRC), Chennai. Both these institutions saw the creation of a vaccine trial centre and a laboratory of immunology dedicated to clinical trials. Well after the AIDS vaccine has been found, well after HIV has been felled, these laboratories will remain as the IAVI legacy in India, to help the country continue its relentless quest for a healthy, disease-free life for all its citizens.





Announcement of Phase I clinical trial of preventive AIDS vaccine at Chennai

In February 2005, India's first clinical trial for a preventive AIDS vaccine began at NARI, Pune. A year down the line, in early 2006, the second set of trials, this time for a candidate vaccine, TBC-M4, partly designed by an Indian scientist working in a government laboratory in Kolkata, began at TRC in Chennai. Recruitment for both trials was completed smoothly and expeditiously; this was a tribute to the integrity of the trial process, the informed consent and volunteer confidentiality protocols and the body of information and requisite support systems available at the trial locations. These were acknowledged as matching the best in the world.

While the results of the Phase I trials are awaited, IAVI has embarked on its third mission in India: R&D. In February 2006, IAVI met officials of the Department of Biotechnology, Ministry of Science and Technology, to discuss potential collaboration in upstream research areas. This step, says an IAVI official in

New York, "was overdue": "We should have got into research in India much earlier."

Given the progress of IAVI's three-stage evolution in India, in what way is the India programme a model for IAVI's partnerships in other developing countries? Certainly, in its clarity, glasshouse openness and proactive engagement of NGOs, civil society groups and public policy stakeholders, and promotion of ethical clinical trial protocols, the India programme is the template. Yet, as Chataway points out:

“Given its sheer size and medical and scientific talent pool, very few countries have the capabilities and the capacities to contribute to a global effort of this nature the way India does.”

One of the greatest strengths was the Indian government's interest and commitment towards scientific pursuits. "The support we got has been unparalleled and it says a lot for the new India and its policy maker's forward looking attitude," says Jayanthi Natarajan, Country Director, India Programme. In the end, in the striving to find an answer to AIDS as in a million other areas, really India needs to (and must) pull its weight. IAVI can only be the catalyst; the magic is in the chemistry of India. ■

Ashok Malik is a senior journalist

IAVI enters a new decade

As IAVI turned 10 in September 2006, the IAVI family got together to reflect on the accomplishments and look forward to the extraordinary task ahead - that of ensuring the development of a safe, effective, preventive AIDS vaccine for use throughout the world. The global meeting welcomed 230 attendees from 20 countries. Staff and partners shared the passion of IAVI's mission, strengthened existing relationships and built momentum for the challenges ahead.

"For the first time, I can see a path, or at least an avenue, towards a successful vaccine," said eminent researcher and co-discoverer of the AIDS virus, Dr. Robert Gallo during his presentation on AIDS vaccine science. Jon Cohen (author of "Shots in the Dark: The Wayward Search for an AIDS Vaccine") urged the team to "step up their game" to advance vaccine science.

What it would take to ...

Ensure a smooth rollout for an AIDS Vaccine

Shree Venkatram

The article is based on the paper "*The Introduction of New Health Technologies in India*" prepared by IEG team and IAVI New York.

As the search for the HIV/AIDS preventive vaccine, across the globe and in India, gets more intense and impassioned, a team of researchers from the Indian Institute of Economic Growth has identified what it would take to introduce the vaccine in India.

Examining past introduction of health technologies in India, they identified factors that could accelerate the adoption of this life saving tool when it becomes available. The three-member team of researchers was led by Dr Indrani Gupta, Head of the Health Policy Research Unit of the premier institute and included Mayur Trivedi and Subodh KandamuthanI. The team emphasised that though the AIDS vaccine may be some years away, now is a good time to start thinking of roles, distribution channels and training for those who would be delivering it. India has, as estimated by National AIDS Control Organization, a large number of persons living with the virus at 5.2 million (2005).

India joined the global efforts for vaccine search with the launching of the first phase of human clinical trials in Pune in 2005 and in Chennai this year of two different vaccine candidates. The researchers point out that the opportunity to plan ahead is unprecedented and should be seized so that when the vaccine becomes available it does not suffer from delays proving detrimental to prevention efforts.

The team has come up with suggestions after examining the experience of introducing the Hepatitis B Vaccine (HBV), the Universal Immunization Programme (UIP), the No Scalpel Vasectomy (NSV), the Voluntary Counselling and Testing (VCT) and the Antiretroviral Treatment (ART) in the Indian system, as these offer important lessons that can guide planners. The team relied on data and information from a variety of sources including literature reviews, national datasets, international health agency reports and discussions and interviews with field experts.

Challenges of introducing new technologies

In a paper titled, '*The Introduction of New Health Technologies in India*', the researchers note : "Even though

India has enjoyed substantial economic growth over the past two decades, more than a quarter of the population is below the national poverty line.... And while there have been improvements in life expectancy, infant mortality rates and control of infectious diseases in recent years; further improvements are needed to strengthen healthcare infrastructure, scale up resources and support public health programmes."

India's healthcare system faces many governance, systemic and infrastructural problems that may pose particular obstacles to the introduction of new health technologies. The size of the country (geographic as well as population) is an obvious challenge, combined with limited financial resources to address significant health problems. There are significant inter- and intra-state differences in health and demographic indices, combined with substantial variation in performance of health programmes across geographic/economic lines. Poor surveillance systems make it difficult to assess true burden of disease and to monitor the impact of specific interventions. Within the public health system, there are persistent gaps in manpower and infrastructure.

The special challenges

Adopting an AIDS vaccine would have its special challenges. Continued strengthening of awareness and education

Lack of awareness and knowledge, stigma and sensitivity associated with HIV/AIDS are likely to affect not only decisions about adopting vaccines but the implementation of vaccination programmes

programmes will be required to minimise the reluctance of individuals to be vaccinated due to fear of others' perceptions. The likelihood that a first generation vaccine may have less than 100 percent efficacy is likely to complicate its implementation and adoption processes. A belief of protection due to the vaccine may lead to higher incidence of risky behaviour among people. To counter this, a combination of educational messages about continued prevention measures, especially for groups who are at higher risks will become critical.

The paper underscores the point that a "successful adoption" of a technology requires an approach that recognises that technology is much more than a simple technical tool. It comprises a complex set of factors including medicines, equipment, devices and services.

Need and affordability

For a start, defining and agreeing on the need for a vaccine seems to be the first step for its adoption. Failure to acknowledge disease incidence would generate debate and lead to confusion about how and whom to vaccinate.

The history of the Hepatitis B vaccination programme shows the need for data on disease burden, modes of transmission and cost-effective targeting of all factors relevant to the adoption of an AIDS vaccine

For a start, defining and agreeing on the need for a vaccine seems to be the first step for its adoption. Failure to acknowledge disease incidence would generate debate and lead to confusion about how and whom to vaccinate.

The experience of introducing the Hepatitis B vaccine is cited. Debate still ranges on the prevalence rates of Hepatitis B in the country and the vaccine has yet to be adopted on a national basis. The history of the Hepatitis B vaccination programme shows the need for data on disease burden, modes of transmission and cost-effective targeting of all factors relevant to the adoption of an AIDS vaccine. It also shows the limitations of the current immunisation system as an effective delivery mechanism.

The team underlines that the approval for an AIDS vaccine would depend on whether it specifically targets virus strains prevalent in the country and how different vulnerable groups respond to it. 'Affordability' would be a crucial issue. Therefore, the team recommends that public health researchers undertake cost effective analysis of the vaccine as early as possible and plan for adequate financing in the form of government subsidies and donor funding in advance.

Donors can influence the course and pace of introduction of technologies, by simply making the relevant funds available. This is especially true in the case of countries that rely heavily on bilateral and multilateral donors.

The researchers give the example of the '3 by 5' initiative launched by WHO and UNAIDS in 2003. This initiative helped countries acknowledge that treatment is essential and facilitated access to antiretroviral therapy (ART). Although India was not included in the initiative's target group of countries, domestic and international pressure to respond to the increasing need for HIV treatment made the Indian government announce free distribution of ARVs in selected states. The team has identified the endorsements of political leaders, professional societies and medical associations as crucial to the adoption of a new health technology. The existence of technical data, availability of funding, regulatory guidance from trusted sources contributes greatly to their willingness to support a policy and promote its use.

Infrastructure and human resources

There are lessons to be learnt from the vast system of procurement and distribution for immunisation programmes, including both its successes and failures. While AIDS vaccine delivery is unlikely to be able to take advantage of the established childhood immunisation system, it could perhaps be integrated with the extensive network of VCT and ART centres. These centres could be a one-stop shop for all.

Individuals could enter the "system" through VCT services; those testing positive could take advantage of ART services, whereas those testing negative could be counselled and vaccinated, if appropriate

Adequate training is a must in technologies that require high human-resource such as VCTs. Shortage of trained manpower, or if health facility personnel are already overwhelmed with providing for other services, the introduction of a new technology would not be smooth. In fact, shortage of trained staff continues to plague vaccine service delivery. Many districts lack Immunisation Officers altogether and the Auxiliary Nurse Midwives (ANMs), responsible for vaccine service delivery, have seen a steady rise in the number of villages and target populations they are yet to reach.

Bigger Role for NGOs

Among the recommendations the researchers make, is that the vast experience of the NGO sector should be put into use for formulating and disseminating informative and educative materials on AIDS vaccines to the communities.

The paper cites the significant role played by NGOs in HIV interventions. In 1996, in a first-of-its-kind partnership, six Delhi-based NGOs partnered with UNAIDS and NACO to start a Model Counselling Centre (MCC). The aim was to provide pre, post-test, follow-up, general and family counselling to the public coming to the hospital. By providing support and after-care services for HIV positive clients and disseminating information regarding STD, HIV/AIDS, the Centre helped facilitate behaviour and attitudinal change in people practicing high risk behaviour. The partnership helped NACO design its VCT model.

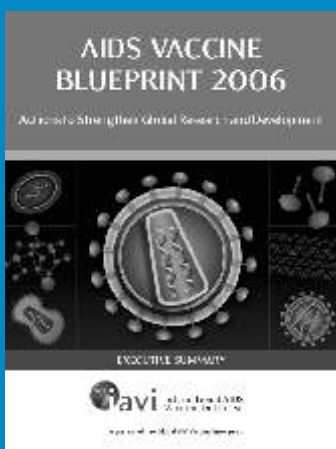
This also encouraged clients, especially from marginalised groups, to access the services at the Centres, which seemed friendlier than government-sponsored ones. A network of NGOs also positively influenced the introduction of free antiretrovirals and successfully promoted the government-sponsored ART programme by addressing sensitivities around HIV services,

increasing public awareness and encouraging counselling with treatment. As a result, there is overwhelming demand for ART services that cannot actually be met at this time.

The government started free ART in April 2004. But due to the sudden launch of the programme, systems could not be put in place to ensure smooth functioning of the ART sites. However, it is an example of a rapidly scaled-up extensive programme, which improved due to the willingness to learn-and-correct, the team notes, calling it “one of the more successful adoptions” in recent history.

While many of the factors that have influenced other health technologies are not new and unexpected, they do underline the fact that significant efforts must be made now to begin preparing for an AIDS vaccine, even though its appearance may be years away. ■

Given the magnitude of the epidemic in India (and indeed, across the globe), it is critical that all possible steps be taken to ensure that an AIDS vaccine, our best hope for ending the epidemic, can be adopted and implemented as quickly and successfully as possible



IAVI launched its biennial flagship publication, *AIDS Vaccine Blueprint 2006: Actions to Strengthen Global Research and Development* at the XVI International AIDS Conference, Toronto. The blueprint includes an assessment of vaccine candidates in the pipeline and highlights key scientific obstacles to the discovery and development of a vaccine. It also pinpoints some of the critical operational and resource issues that need to be addressed and the importance of building capacity in developing countries for AIDS vaccine research and clinical trials. Perhaps most importantly, the Blueprint puts forth new initiatives for overcoming these challenges, including a new vaccine development model to move more novel candidates targeting different immune responses into the pipeline and to speed feedback on their immunogenicity. To access the Blueprint visit www.iavi.org.in

Volunteerism in AIDS Vaccine Trials

“Never had a chance to do something noble, here is the chance”

Jaya Shreedhar



 Counselling at the Tuberculosis Research Centre, Chennai

Call it informed humanitarianism, commonsensical community spirit or quality citizenship: 67 members of the public volunteered to participate in the Phase 1 trial of the TBC-M4 Modified Vaccinia Ankara (MVA) vaccine for HIV in Chennai and 32 have been enrolled. 16 of them were enrolled for the second part of the trial in a brief span of seven days - a record time for enrollment across IAVI trial sites worldwide. “Over 300 people have made inquiries about the trial since December last. The media did a great job of informing the public about the importance of civil society support for the trial and gave helpful information about how to volunteer,” said Dr. P. R. Narayanan, Director of the Tuberculosis Research Centre which presently hosts this IAVI sponsored vaccine trial. “We were gratified at the response; volunteerism is alive and well in India.”

Most volunteers at the Chennai trial are in their 30s and all are fit, able and productive members of society. “A desire to help is the single common characteristic that distinguishes those who drop in saying they'd like to participate,” said Dr. V.D.Ramanathan, Principal Investigator of the trial. “One volunteer who ultimately could not join the trial said, “I have always wanted to help society and I was not sure how to go about it. Volunteering for the trial was a good opportunity to help fellow human beings.”

“Their altruism is inspiring for us researchers”, said Dr. Jayashri

Mahalingam, project team member working on the TBC M4 MVA trial. One told us: “I heard that Bill Gates is giving millions from his personal wealth to the cause of AIDS I can't dream of a contribution on that scale in ten lifetimes, leave alone one! Volunteering for this trial is my way of making a worthwhile contribution”. Some made the decision to volunteer in the trials after losing loved ones to AIDS. “I did not want anyone to undergo the kind of pain and loss that I experienced when a family member died of AIDS. I wanted to help the doctors find a vaccine as soon as possible so that they can save society from this disease.” Some volunteers refuse to accept the few rupees offered to cover the costs of their transportation to and from the trial site. One volunteer of very modest means to whom the local transport reimbursement could have made a difference, nonetheless refused to accept it.

Who can participate in AIDS Vaccine Trials ?

Individuals can participate in a Phase I clinical trial if they are...

- men or women between 18-50 years of age;
- in good health;
- HIV-uninfected;
- Persons who stands a very low chance of contracting HIV;
- residents of India and are planning to live close to the trial site for the entire duration of the Phase I trial;
- able to understand the process of the trial and give their signed informed consent to participate
- willing to come for all scheduled visits for clinical examination and blood draws. These visits are designed to intensively monitor the effects of the vaccine.

Women who are pregnant, lactating or planning to become pregnant within four months after the vaccination do not qualify to participate in a Phase I clinical trial.

Source - IAVI

At the present time, there are two preventive AIDS vaccine candidates in Phase I clinical trials in the country. The first, named tgAAC09, an Adeno-associate virus based vaccine, began trial in early 2005 at the National AIDS Research Institute (NARI) in Pune. The second candidate -- TBC-M4 (MVA) began trial in early 2006 at the Tuberculosis Research Centre (TRC) in Chennai. The trials are a joint effort of the Ministry of Health and Family Welfare through the National AIDS Control Organization (NACO), the Indian Council of Medical Research (ICMR) and the International AIDS Vaccine Initiative (IAVI).

The trials were approved by all the required government appointed Ethics Committees and regulatory authorities including the Drug Controller General of India, once it was clear that the trial protocols were in accordance with the highest international standards and ethical guidelines for the conduct of clinical trials. Vaccine trial protocols provide detailed information on who can participate, how the vaccine will be given, the schedule for clinical examination and blood tests, how long the study will last, how results will be assessed and so on. Most importantly, this information is accessible to the public to ensure openness and equal partnership with civil society. "Some volunteer out of healthy academic curiosity," says Dr. Seema Sahay, Senior Research Officer at NARI. "Others want recognition; they ask why am I not in the newspapers?" The warmth and support that the two trials receive from the local communities, and the willingness of many to volunteer their participation are the result of months of efforts by the teams at the trial sites to make the trials an inclusive, joint endeavour of the community as a whole.

“A desire to help is the single common characteristic that distinguishes those who drop in saying they’d like to participate.”

The Pune and Chennai vaccine teams met with NGOs, doctors, lawyers, students, teachers, working women and industrial workers to raise public understanding about HIV/AIDS and the need for an AIDS vaccine. "We spoke in 73 places including community colleges, corporate offices, banks and factories, explaining basic terms such as 'target population', 'preventive vaccines,' and so on. There is tremendous interest and curiosity; even the timid ones will come up after the talk to clarify their doubts and share their opinions," said Dr. Ramanathan in

What happens in clinical trials?

The many vaccines in popular use today such as vaccines for polio, cholera or Hepatitis B took decades of research and development to progress from laboratory to pre-clinical or animal testing and then to three phases of trials on human volunteers - known as Phase I, II and III clinical trials - before they reached the people. AIDS vaccine development embarked on a similar journey in the mid 80s. Over a 100 clinical trials of AIDS vaccines on healthy human volunteers have been carried out since the late 1980s and about 15,000 volunteers have participated in these trials in about 40 countries.

A Phase I trial determines how safe the vaccine candidate is and ascertains whether the human immune system responds to it. Phase I trials usually take about one to two years to complete. They involve small numbers of volunteers, say anywhere between 20-100 healthy adults who are HIV-uninfected and who practice low-risk behaviour and are thus unlikely to be exposed to HIV in their routine lives

A Phase II trial focuses mainly on determining the extent of the immune response to the vaccine candidate, while continuing to test the vaccine for safety. Phase II trials may take up to two years and involve some hundreds of healthy HIV -uninfected adults.

A Phase III trial represents a critical stage in vaccine development and is the ultimate test of efficacy and safety of the vaccine in affording protection against HIV infection or even preventing progression from infection to disease. Phase III trials may last from three to several years and enlist between 2500 and 20,000 adult volunteers who are HIV-uninfected but whose behaviors may put them at risk of exposure to HIV.

Globally, more than 30 AIDS vaccine trials are underway. Only two vaccine candidates for HIV have ever progressed to Phase III clinical trials and neither was found successful.

The conduct of Phase I trials in a community sometimes raises expectations that an AIDS vaccine may be available soon after the trial is over. Even after a vaccine candidate has cleared all three phases of clinical trials, a process lasting many years, regulatory approvals would be required before the vaccine can be licensed.

Chennai. "Sharing our understanding about HIV/AIDS and AIDS vaccine research in a respectful and transparent manner helped allay fears and addressed concerns about the vaccine trial. It inspired community support and also pegged the expectations of the community members at a realistic level," said Dr. Sanjay Mehendale, Principal Investigator of the tgAAC09 trial at NARI.

AIDS vaccine trials today embody many of the finest lessons learnt in public health research in the last decade. Perhaps the central one is to respect human rights and dignity while planning and delivering health research and services. Enabling communities to access health information and services, question health providers and make independent, informed decisions have been the philosophical and ethical basis underlying AIDS vaccine trials.

"And this usually begins with first training the clinical trial staff at the vaccine trial sites in ethics-sensitive good clinical and laboratory practices that are especially responsive to gender related issues," says Sahay. Indeed, some health care professionals are themselves volunteers in the AIDS vaccine trials saying, "I'd like to set an example for my patients."

The transparent communication and equal partnership between the trial volunteers and the researchers continues as the trial unfolds. "When volunteers want correct and adequate information about risks, benefits and confidentiality associated with the trial and to understand trial related procedures better,

they talk to us. Those who are literate also get a study info-kit and volunteer's brochure and many access information from our website."

Sometimes volunteers tend to worry about side effects or about the options available for care, support and long-term follow-up. "Outpatient and inpatient care is available at local hospitals through 24-hours contact system, in addition to NARI's commitment to provide post-trial care," said Dr. Paranjpe at NARI.

Community ownership of the vaccine trials has raised overall awareness about human behaviour and civic responsibility. In Pune, an HIV hotspot, the NARI vaccine team found many with high risk of exposure to HIV "were willing to participate in future AIDS Phase II and III vaccine trials, and showed willingness to accept a safe and efficacious vaccine in future."

The search for a vaccine that will protect human beings from HIV infection would flounder without volunteerism. As Jayanthi Natarjan, Country Director of IAVI puts it, "The most critical ingredient in AIDS vaccine development is not just good science and adequate funding. It is the cry of the community from within itself for a vaccine and its spontaneous participation to fulfill its needs by taking ownership and leading the way." ■

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Enabling communities to access health information and services, question health providers and make independent, informed decisions have been the philosophical and ethical basis underlying AIDS vaccine trials



Putting it together :

AIDS and the Millennium Development Goals

...Making the right to development a reality for everyone and freeing the entire human race from want.

United Nations Millennium Declaration



“How we fare in the fight against AIDS is crucial. Halting the spread is not only a Millennium Development Goal in itself; it is a prerequisite for reaching most of the others. Only if we meet this challenge can we succeed in our other efforts to build a humane, healthy and equitable world. Let us ensure we are equal to it.”

Kofi Annan, Secretary General, United Nations

In September 2000, 189 governments from around the world signed the Millennium Declaration and committed to achieving sustainable reductions in all dimensions of extreme poverty. To track progress against this visionary global compact, the Millennium Development Goals (MDGs) were established as eight quantifiable and shared priorities to be achieved by 2015. Although each MDG is tracked separately, the reality is that they are strongly interlinked.

A key factor in determining whether countries can attain the MDGs is their response to HIV/AIDS. This is because HIV/AIDS not only has severe health repercussions - hence one of the MDG targets is to halt and reverse the epidemic - but because AIDS is a major threat to other development goals. The pandemic's scale will make it difficult for many countries to achieve their targets to lower poverty rates, ensure that all children complete primary education, reduce child mortality, improve maternal health, and curb the global tuberculosis epidemic.

Millennium Development Goals

- Goal 1: Eradicate extreme poverty and hunger
- Goal 2: Achieve universal primary education
- Goal 3: Promote gender equality and empower women
- Goal 4: Reduce child mortality
- Goal 5: Improve maternal health
- Goal 6: Combat HIV/AIDS, malaria and other diseases
- Goal 7: Ensure environmental sustainability
- Goal 8: Develop a global partnership for development

HIV at a glance

- Between 34.6-42.3 million are living with HIV. More than 20 million have died of AIDS in the past 3 decades
- Each day, 15,000 people are infected with HIV, and 4,000 people die of AIDS
- 95% of new infections occur in the developing world
- Sub-Saharan Africa, home to 10% of the world's population, has 60% of those infected with HIV
- 90% of those infected do not know it

Goal: Eradicate extreme poverty and hunger

Target: Halve, between 1990 and 2015, the proportion of people whose income is less than one dollar a day

HIV/AIDS increases poverty

Nations suffer at the macroeconomic level

A range of studies suggest that AIDS can lower GDP growth by up to 1.5% per year. In a "typical" African country with 20% HIV prevalence, the rate of GDP growth could be 2.6% lower each year than it would have been in the absence of AIDS, due to a reduction in growth per capita and a slower rise in population. At the end of a 20-year period, GDP would be 67% lower than it would have been without AIDS.

Households face revenue losses and heavy costs

Because of the high medical and other costs of HIV-related illness and death, and because AIDS often kills working-age adults, the epidemic can have a significant household-level impact. Studies from Thailand and South Africa demonstrate that poverty is higher among AIDS-afflicted households than among families without HIV-infected members. In rural areas of five high-prevalence countries, there is a correlation between AIDS deaths and declining household wealth. Adult AIDS deaths in Kenya, for instance, have a significant impact on both crop income and value of household assets. A study from Botswana suggests that average income per capita could fall by 10% over the next ten years due to HIV/AIDS. It also predicts a 6% rise in households below the poverty line, with income loss twice

as large among the poorest households as for the population as a whole.

These effects will escalate over time

The long-term impact of AIDS, both at a macroeconomic level and for individual households, can be expected to accelerate. Scarce household resources and family income reductions during severe illness force parents to choose immediate consumption over long-term investments in the next generation's human capital (e.g. school fees). As a result, children orphaned by AIDS who reach working age earn reduced incomes and possess less capital to invest in the future of their own children. The increasing number of children who become orphans due to AIDS (Figure 1) can also be expected to raise poverty levels over time since orphans add to the economic burden of their adoptive families and communities.

Orphans - statistics and predictions

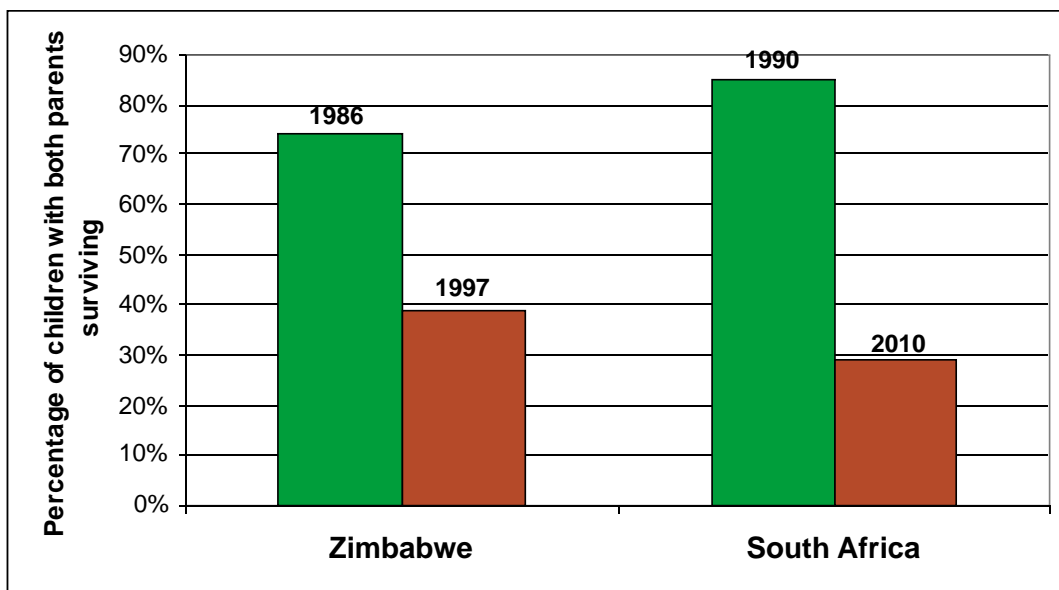
15 million children have been orphaned by AIDS worldwide

8 in 10 live in sub-Saharan Africa

The proportion of orphans under 15 years of age is as high as 17% of all children in some countries

By 2010, there may be as many as 18 million children orphaned by AIDS in sub-Saharan Africa alone

Figure 1. Probabilities of two parents surviving over time



Goal: Eradicate extreme poverty and hunger

Target: Halve, between 1990 and 2015, the proportion of people who suffer from hunger

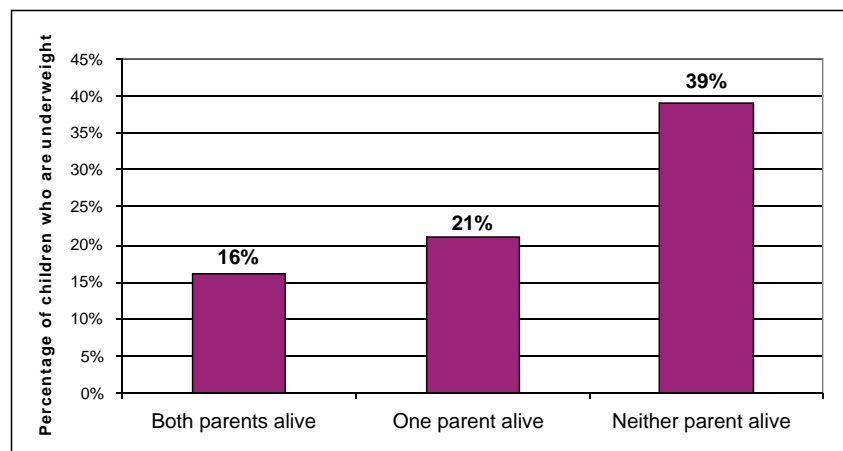
HIV/AIDS worsens the nutritional status of children

There is growing evidence of an important link between child nutrition, food security and HIV/AIDS. HIV prevalence is strongly negatively correlated with increasing calorie and protein consumption in 44 sub-Saharan countries. Evidence suggests that child nutrition rapidly deteriorated in the presence of high HIV prevalence during a 2002 drought in southern Africa. Changes were much smaller during non-drought periods and in areas with lower HIV prevalence.

Orphaned children are more likely to live in poverty conditions

and receive inadequate nutrition than non-orphans. For example, a study from Kenya shows that the weight-for-height scores were almost 0.3 standard deviations lower for orphans than for non-orphans. In Zimbabwe, orphans were significantly more likely to be underweight than children whose parents were both alive. And in Lesotho, almost 40% of children under four who had lost both parents were underweight, compared to approximately 16% of non-orphans (Figure 2).

Figure 2. Prevalence of being underweight among children under four, Lesotho



Goal: Achieve universal primary education

Target: Ensure that, by 2015, children everywhere, boys and girls alike, will be able to complete a full course of primary schooling

AIDS compromises efforts to reach universal primary education

AIDS reduces the demand for schooling

Children affected by AIDS may drop out of school because they can no longer afford fees or because their families rely on them to contribute economically to the household or provide care for ill family members. A study from Tanzania shows that schooling was delayed for young children (7-10 years) who had lost their mothers. In Zimbabwe, 65% of all children aged 13-15 years had completed primary school, but the completion rate for maternal orphans was only 53%.

Data from Indonesia show that 14% of children who had recently lost a parent dropped out of school between ages 6 and 10, whereas only 7% of non-bereaved children did. In Mexico, maternal death caused a statistically significant 2.3% increase in dropout rates in the first six months following a mother's death; higher levels of household consumption did not reduce this effect.

AIDS hampers countries' ability to supply education

Absenteeism and mortality of teachers and other staff are growing problems in AIDS-affected areas. Data from a comprehensive study of South Africa's public school system show that the total number of in-service deaths grew by 30% between 1997 and 2004, and a quarter of all teacher attrition during this period was due to death and illness.

Losing teachers can lower the quality of learning and prevent children from obtaining a basic education. In poor countries, administrators face substantial challenges in finding qualified teachers to replace those who died. Even when replacement teachers are readily available, the death of a teacher imposes costs (for temporary and permanent replacement, as well as for training) on education systems that are already fiscally burdened.

Goal: Reduce child mortality

Target: Reduce by two-thirds, between 1990 and 2015, the under-five mortality rate

AIDS has a negative impact on child mortality

AIDS is a growing contributor to childhood deaths

The challenge of achieving the child mortality MDG in the presence of HIV is illustrated in the nine highest HIV prevalence countries in Africa, all of which are "off track" for reaching the MDG, and in five of which under-five mortality actually increased between 1990 and 2003 (Figure 3). One study estimates that by 2015, up to 90% of under-five deaths in Botswana will be directly or indirectly caused by HIV/AIDS.

studies show that children born to HIV-infected mothers are approximately three times more likely to die than children born to uninfected mothers. This effect lasts throughout the childhood years, but the risk of dying is highest during the years immediately before and after a mother's death, suggesting that the mother's illness and demise has a strong effect on the child's well-being.

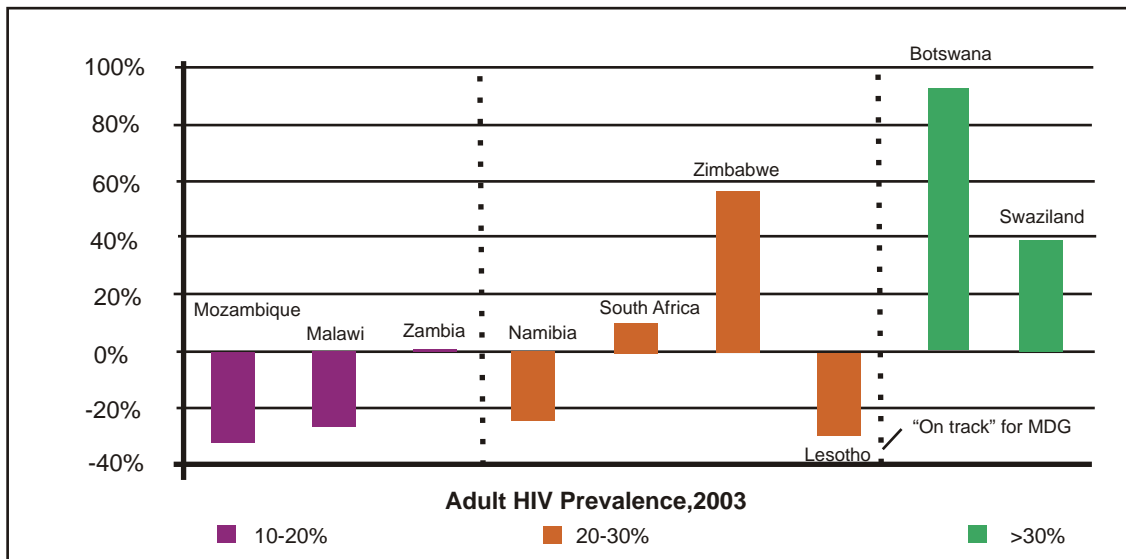
AIDS increases child mortality directly and indirectly

HIV, nearly always acquired through perinatal transmission, accounted for about 570,000 child deaths in 2005. Sixty percent of infected children die before their fifth birthday. Child mortality can be attributed to AIDS even for uninfected children, since families and communities weakened by AIDS render children more susceptible to illness and death from other causes. Several

The effect of AIDS on child mortality is increasing

An analysis of the HIV-related risk of dying before age five in 42 countries in sub-Saharan Africa estimates that in 1999, HIV accounted for 7.7% of under-five mortality, up from 2% in 1990. A more recent analysis estimates that in 2002 nearly 10% of all under five deaths in sub-Saharan Africa could be attributed to HIV/AIDS.

Figure 3. Change in under-five mortality rate in select countries with high HIV prevalence, 1990-2003



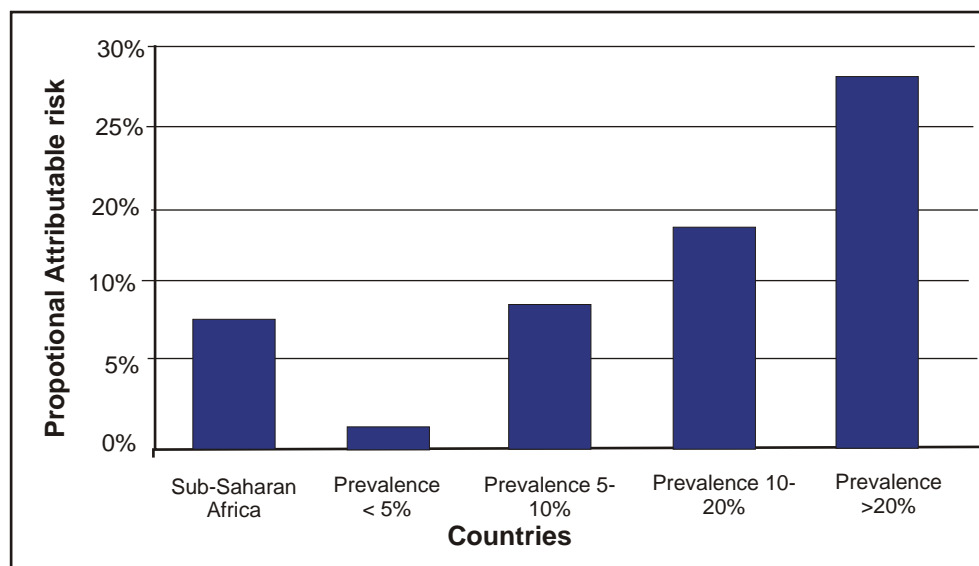
Note: To be "on track," a country would have to have experienced at least a 33.3% decline in child mortality during the period 1990-2002. Only Lesotho and Mozambique approach this result.

These figures, furthermore, average the rates across many countries. When the analysis broke down HIV-related proportional attributable child mortality for individual countries for 1999, countries with high prevalence showed the effect of HIV even more strongly (Figure 4). For instance, in Botswana and Zimbabwe, both of which have seen increases in all-cause child mortality since 1990, the percentage of under-five deaths attributable to HIV/AIDS was estimated at 42.4% and 35.1% respectively. In Namibia, where all-cause child mortality has decreased, HIV/AIDS contributes substantially to the under-five

mortality rate, accounting for approximately 26.8% of under-five deaths.

A study on the long-term impact of HIV and orphanhood on child mortality in rural Malawi, where approximately 10% of pregnant women were HIV-positive at the time of the study, estimated that 18% of under-five deaths in this population were attributable to HIV. On the basis of pooled data from community-based studies in Uganda, Tanzania and Malawi, another study estimates that, in a population with adult HIV prevalence of 11%, the fraction of child mortality attributable to maternal HIV infection was 15.7%.

Figure 4. HIV-related population proportional attributable risk of dying before age five, sub-Saharan Africa, 1999



Goal: Improve maternal health

Target: Reduce by three-quarters, between 1990 and 2015, the maternal mortality ratio

HIV/AIDS worsens maternal health

Due to the additional risks that HIV-positive mothers face, the HIV epidemic could further limit progress toward achieving the MDG target to reduce maternal mortality, particularly in sub-Saharan Africa and Southern Asia, where more than 80% of maternal deaths occur.

Pregnant women who are infected with HIV are at higher risk for prenatal and childbirth complications because of suppressed immunity. These complications include miscarriage, anemia, postpartum hemorrhage, and puerperal sepsis, in addition to indirect causes during and after pregnancy, such as malaria or pneumonia.

Thus, maternal mortality ratios for women infected with HIV can be substantially higher than for uninfected women. For example, the maternal mortality rate for HIV-positive mothers in Durban, South Africa between 1996 and 1998 was more than twice the rate for uninfected mothers. Similarly, another study shows the rate of maternal deaths among HIV-positive women to be three times higher than the rate among uninfected women in Rakai, Uganda. In South Africa, the proportion of maternal deaths due to indirect infections (including AIDS) increased from 23% to 31% over the period 1998-2001, making these from 23% to 31% over the period 1998-2001, making these infections the leading cause of maternal mortality.

Goal: Combat infectious diseases

Target: Have halted by 2015 and begun to reverse the incidence of major diseases

HIV/AIDS undermines global efforts to control tuberculosis

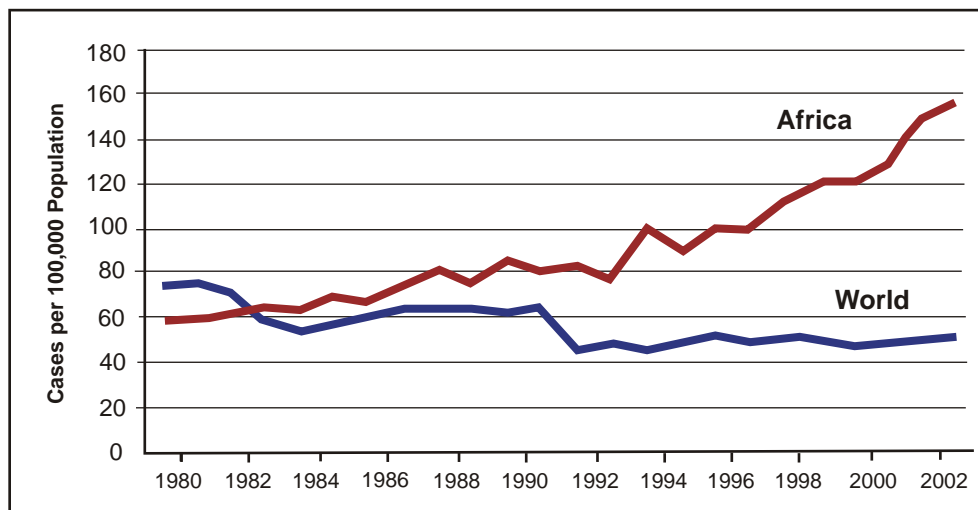
The epidemics of HIV and tuberculosis (TB) are closely intertwined. Of the 40 million people currently living with HIV/AIDS worldwide, it is estimated that nearly one-third are also infected with TB. Because of HIV-related immune suppression, HIV-positive individuals who carry the TB bacillus are more susceptible to active TB than HIV-negative people who carry TB.

The risk of acquiring TB doubles soon after infection with HIV and continues to increase during subsequent years. One study estimated that 9% of the estimated 8.3 million new adult TB cases worldwide in 2000 were directly attributable to HIV. In

addition, HIV infection makes it harder to treat active TB successfully. Thus TB rates are actually increasing in high-HIV prevalence areas of sub-Saharan Africa (Figure 5), and the spread of HIV in sub-Saharan Africa is primarily responsible for driving the number of active TB cases upwards by 6% per year.

A recent review on progress toward the MDGs argues that the AIDS epidemic represents the greatest emerging threat to TB control. One analysis finds that if sub-Saharan Africa and Eastern Europe were excluded from global statistics, under current trends the TB prevalence rate could be cut in half between 1990 and 2015.

Figure 5. Tuberculosis case notification rates, 1980-2003



Long term control of the HIV pandemic requires a truly comprehensive approach, including investing in better preventive technologies

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IAVI is a scientific organisation 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 AIDS vaccine development.

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