

# Preparedness for AIDS vaccine trials in India

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**India bears a heavy disease burden of HIV/AIDS infected and affected people. A safe, effective and accessible preventive AIDS vaccine, used along with other preventive interventions, is urgently needed to stem the epidemic. This review highlights the extensive preparedness activities undertaken from 2002 by the International AIDS Vaccine Initiative (IAVI), its Indian government and non government partners with the Indian scientific, political, media and community stakeholders and the capacity building process, before the conduct of the first ever AIDS vaccine trials in India in early 2005. Issues addressed included mistrust of clinical research due to past history of some unethical trials, transparency, community involvement, stigma and discrimination, provision for care and treatment of participants, informed consent, gender considerations, approval process, and operational aspects. The strong political support along with preparedness activities led to the successful conduct of AIDS vaccine trials enrolling equitably healthy women and men from all sections of society. This has paved the way for future vaccine trials in the country.**

**Key words** AIDS vaccine - clinical trials - HIV - India - preparedness

At the end of 2007, the WHO and UNAIDS global estimate was 33.2 million people living with HIV. In Asia, the estimate was 4.9 million HIV-infected people<sup>1</sup>. The National AIDS Control Organisation (NACO) has estimated that 2.5 million people were living with HIV/AIDS in India, present in all the states. A majority of HIV infections are due to heterosexual transmission, followed by intravenous drug use and mother-to-child transmission<sup>2</sup>. The HIV epidemic has been spreading from high risk to low risk populations and from urban to rural areas during the last 12-13 yr<sup>3-6</sup>. Although the overall prevalence of HIV infection remains low at country level, India shares the

highest disease burden in terms of absolute number of HIV infections and AIDS cases in Asia<sup>1</sup>.

Some of the scientists thought that only a preventive AIDS vaccine, as a critical segment of a matrix of preventive technologies along with care and treatment programmes, can stem and ultimately end the HIV/AIDS epidemic<sup>7-9</sup>. The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit, public-private partnership, created in 1996 with the goal of accelerating the development of a safe, effective and accessible preventive AIDS vaccine for the world, especially for resource-poor nations. IAVI supports a comprehensive approach to fight the HIV/AIDS

epidemic that balances the expansion and strengthening of existing HIV prevention and treatment programmes with targeted investments in new AIDS prevention technologies<sup>10</sup>.

With its large pool of skilled scientists and doctors and thriving pharmaceutical and biotechnology industry, India can play a lead role in AIDS vaccine research<sup>11</sup>. To respond to this need and opportunity, in December 2000, NACO, under the Ministry of Health and Family Welfare, and the Indian Council of Medical Research (ICMR) signed a memorandum of understanding with IAVI to accelerate the development of an AIDS vaccine for India.

Without minimizing the challenges, the IAVI clinical trial experience in India has come to represent a credible template for the conduct of such trials and holds lessons. We discuss here the key elements and processes leading to IAVI's and its partners' success in implementing AIDS vaccine trials.

### **Political advocacy and policy**

The IAVI programme was initiated with a large eight-nation Conference of International Policy Makers in May 2002 organized with the two India programme partners, ICMR and NACO, inaugurated by the then Prime Minister, and addressed by, among others, the President of the Indian National Congress, the Union Health Minister, the Chief Ministers of three high-prevalence States, Maharashtra, Andhra Pradesh and Karnataka, and the United Nations representative. In addition, the presence of a representative from the Positive Women's Network in India with political leaders sent a strong message against the stigma and discrimination prevalent in the country.

In the absence of a National AIDS Vaccine Plan, this Policy Makers Conference was a milestone in forging broad support across the political spectrum on broad HIV/AIDS issues. This led to the creation of an informal core group of parliamentarians and policy makers who are kept updated on the advancement of the AIDS vaccine programme. Testimony to IAVI's credentials was the subsequent vocal and sustained support its mission received from senior politicians and policy makers. IAVI worked closely with the then President of India's Office to provide input to his various comments on HIV/AIDS and vaccines. The President of India, Dr A.P.J. Abdul Kalam, stressed the need to prioritise AIDS vaccine research and development in India, in several addresses to the Nation and the parliament on January 26, 2005.

At the State and local levels, IAVI held meetings with State and municipal elected representatives to sensitize them on key issues related to HIV/AIDS and preventive AIDS vaccines. These interactions helped identify local political leaders committed to supporting the programme.

A policy consultation was conducted in 2006 to assess the preferences and perceptions of Indian policymakers and policy influencers which could affect demand for a first-generation preventive HIV vaccine in India. Vaccine efficacy of at least 50 per cent would be necessary to persuade the public sector to mount a vaccination programme for groups at higher risk of exposure to HIV. Consultations suggested that an HIV vaccine with an efficacy threshold as low as 30 per cent efficacy could nevertheless be seen as acceptable and be taken up by paying individuals in the private market<sup>12</sup>.

At the global level, IAVI India has contributed to the Global Political Advocacy Initiative – a project to ensure sustained interactions between political leaders of the north and south. This aims to ensure that AIDS vaccines are accepted as an integral component of the development agenda, in particular, efforts to meet the Millennium Development Goals in international fora. An example of IAVI's attempt at fostering international south-south co-operation is the declaration announced at the India-Brazil-South Africa heads of government summit in Brasilia in September 2006, to collaborate on an AIDS vaccine<sup>13</sup>.

### **Consulting and involving communities**

The Government of India has always stressed that successful and ethical clinical trials require the informed and active participation of local communities and support from within those communities. Concerns were expressed that the mistrust generated by some previous unethical clinical trials in India<sup>14,15</sup> and ignorance, stigma and discrimination about HIV/AIDS might make it more difficult to set up trials and to recruit volunteers. Qualitative research was conducted in 2002 to understand the concerns of stakeholders. Extensive community preparedness work was undertaken in the country over a three-year period to address these concerns before the initiation of the clinical trial process. A critical role was played by Community Advisory Board members to ensure participation and representation of the community.

In this spirit, IAVI and its partners organized numerous meetings with community representatives in 2003 including large open-house meetings with civil

society in the high prevalence States to address questions by the community. These measures pre-empted potential misunderstandings, demonstrated IAVI's intentions to be transparent, accountable, and enabled a smooth, ethical and culture-sensitive conduct of clinical trials with the participation of well-informed communities and trial volunteers from all sections of society. This helped in building trust and confidence with communities and a whole range of influential and disinterested advocates.

*National Advisory Board:* In recognition of the complexity of the programme, a National Advisory Board was set up in March 2002 and is chaired by NACO and co-chaired by ICMR to provide strategic direction and advice to the programme. The Board comprises distinguished senior members of the government, United Nations organizations, human rights activists, ethicists, lawyers, health and gender experts, media representatives and members of national and international non governmental organizations (NGOs) split in four subgroups addressing science, access, communication and social issues.

*Website and Newsletter:* Information on the AIDS vaccine programme and prevention technologies is disseminated through 'Sankalp', the IAVI India newsletter, and the IAVI India website<sup>16</sup> that are available in English as well as in two regional languages.

*Gender Advisory Board:* With individuals and organizations working on gender issues and women's health and rights, a Gender Advisory Board of independent experts was constituted in 2003 to guide IAVI in developing a gender training module for clinical trial staff and ensuring that informed consent forms incorporate a gender-sensitive perspective<sup>17,18</sup>. Prior to the two Phase I clinical trials, IAVI facilitated a gender-sensitization training of trial staff<sup>19</sup>. Gender issues covered included the limited autonomy in decision-making of women; the potential consequences for women following breaches of confidentiality regarding trial participation, including stigma, blame and loss of economic support and ways to overcome or mitigate these barriers.

*NGO Working Group:* IAVI and its partners actively engaged with NGOs and community-based organizations (CBOs) working on HIV/AIDS and sexual and reproductive health, by explaining the complexities of AIDS vaccine trials, understanding their concerns and seeking their advice. In 2003, an NGO working group was constituted with six nationally networked

NGOs, including the Indian Network of Positive People. This group acting as a community interface to health care programmes and in co-ordination with IAVI ensures informed community participation by disseminating information at grass root levels. In 2006, they registered themselves as the National Coalition on Health Initiatives.

*Informed Consent Consultation:* As an ethical imperative, the informed consent documents of AIDS vaccine trials should not only provide the requisite scientific and technical information, a full understanding of risks and benefits of trial participation, rights of participants and the potential use of all clinical trial samples but must also be concise, intelligible and culture-sensitive<sup>20-22</sup>. In order to make the informed consent locally relevant, a committee of 15 experts – scientists, clinicians, ethicists, lawyers, gender experts, activists and NGO members – met to develop a template for the informed consent documents (screening and enrolment forms, volunteers' information brochure and test of understanding) to be used in the Phase I AIDS vaccine trials. One of the recommendations was to set up of a unique local arbitration board composed of three legal, social and medical experts to address possible dispute and volunteer's grievances during the course of the trial.

*Consultation on Care and Treatment for Trial Participants:* Phase I trials classically involve individuals at lower risk for HIV infection while Phase IIB test of concept trials and efficacy trials recruit people at higher risk<sup>23</sup>. Despite repeated risk reduction counselling offered during the course of clinical trials, some volunteers might become HIV-infected due to their risk-prone behaviour (none of the vaccines in development could cause HIV infection). The provision of appropriate HIV care and treatment to trial participants is therefore a significant part of an AIDS vaccine clinical development<sup>24-27</sup>. The IAVI policy is to provide free of charge HIV care and treatment including anti-retroviral drugs, to volunteers who would become HIV-infected during the course of the trial and for a period of five years from treatment eligibility.

A national consultation was held in 2004 in collaboration with IAVI, NACO and ICMR to delineate the responsibilities of research sponsors, investigators and government, and the technical guidelines and provision for HIV care and treatment for trial participants and host communities within the framework of national policy guidelines. These recommendations have been followed for the IAVI-sponsored Phase I trials

conducted in India<sup>28</sup>. Soon after this consultation, the Ministry of Health & Family Welfare issued its national policy of access to anti-retroviral drugs for HIV-infected people in the public health sector<sup>29</sup>.

### The research and development thrust

*Guiding principles:* Although India has been a global leader in paediatric vaccine production, its involvement in AIDS vaccine research and development (R&D) has been limited, particularly in the private sector. While several market and policy challenges have deterred both private and public sectors from greater engagement, there are opportunities to improve the policy and business environment for AIDS vaccine R&D in India<sup>30</sup>. The IAVI AIDS vaccine R&D programme in India follows the guiding principles of accelerating the development of a safe, effective and accessible vaccine: (i) Bring the best vaccine candidates in the IAVI portfolio and most relevant to the country epidemic; (ii) Test multiple vaccine candidates simultaneously; (iii) Conduct scientifically sound and ethical clinical trials; (iv) Set up centres of excellence for vaccine trials; (v) Contribute to in-country capacity building; (vi) Conduct as quickly as possible ethical clinical trials; and (vii) Disseminate scientific information generated<sup>31</sup>. The multi-prong AIDS vaccine candidate strategy testing vaccines in parallel rather than sequentially was endorsed by the President of India<sup>32</sup>. The Indian programme has prioritised vaccines designed to prevent HIV-1 subtype C (the most prevalent subtype of HIV in India) infections<sup>33-36</sup>. High-level review meetings of national and international scientific experts were held by the ICMR to evaluate possible AIDS vaccines suitable for India. The scientific experts prioritised several vaccine candidates for testing including various replication-incompetent vectors such as Adeno-associated virus (AAV), adenovirus, modified vaccinia Ankara (MVA) and DNA vaccines<sup>37</sup>.

To allow for the testing of several selected vaccine candidates in India, two centres of excellence for AIDS vaccine clinical evaluation were set up at ICMR-affiliated institutes, the National AIDS Research Institute (NARI), Pune and the Tuberculosis Research Centre (TRC), Chennai. Both sites are located in high HIV prevalence States. The Vaccine Trial Centre (VTC) at NARI opened in 2004, consists of a clinic, data management centre and a laboratory of immunology dedicated to the clinical trial. A Community Centre was also set up to facilitate the recruitment of volunteers. Similarly, the VTC at TRC was opened in 2005. IAVI-sponsored clinical and laboratory centres in developed

and developing countries have standardized equipment and reagents to ensure comparability of results<sup>38-40</sup>.

VTC staff training to international standards included good clinical practices, good clinical laboratory practices and laboratory techniques and standard operating procedures (SOPs) with the IAVI Core Laboratory, London, and Contract Laboratory Services, South Africa, gender sensitization, data management, and protocol SOPs.

The laboratories are quality controlled, the tests performed part of international accreditation schemes and both laboratories and trials are regularly audited by international teams<sup>41</sup> ensuring the clinical trials are conducted according to international standards.

### Regulatory and ethical approval process

ICMR ethical guidelines<sup>42</sup> along with preliminary exploration of ethical issues in AIDS vaccine trials<sup>43</sup> were instrumental for smooth clearance of protocols. The documents of the AAV and MVA-based vaccine Phase I trials were approved by the Institutional Ethics Committees, Institutional Scientific Committees, Drug Controller General of India, Central Ethics Committee, Genetic Engineering Approval Committee and the Health Ministry's Screening Committee. The approval process framework and lessons learned have been shared with other organizations interested in conducting vaccine clinical research in India. IAVI and other vaccine developers have held discussions with the regulatory and ethical bodies to discuss how the approval process could be streamlined and timelines shortened while maintaining its stringency<sup>44, 45</sup>.

### AIDS vaccine trials in India

The first ever Phase I trial in India of a preventive AIDS vaccine assessed the safety and immunogenicity of an adeno-associated virus (AAV)-based vaccine (tgAAC09) expressing *gag*, *protease*, *delta-RT* HIV-1 subtype C genes, administered intramuscularly to 30 healthy, HIV-uninfected male and female adult volunteers. The vaccine has been developed by Targeted Genetics Corporation, Seattle. It was initiated in February 2005 at NARI, Pune, as part of a joint trial with centres in Germany and Belgium. The trial was completed successfully in December 2006. The vaccine was found to be generally safe, well-tolerated and modestly immunogenic<sup>46,47</sup>.

The second Phase I trial was initiated in January 2006 at TRC, Chennai, assessed the safety and immunogenicity of a multigenic Modified Vaccinia

Ankara (MVA)-based vaccine (TBC-M4), an attenuated form of the vaccinia virus expressing *env*, *gag*, *tat-rev*, and *nef-RT* HIV-1 subtype C genes identified from recent seroconverters in India<sup>48</sup>, and administered intramuscularly to 32 healthy, HIV-uninfected male and female adult volunteers. The vaccine was designed and manufactured by Therion Biologic Corporation, Cambridge, MA with the participation of a scientist from the National Institute of Cholera and Enteric Diseases, Kolkata<sup>49</sup>. TBC-M4 is currently in Phase I trial at TRC. Preliminary results suggest that the vaccine is generally safe and well-tolerated and very immunogenic with 100 per cent responders (as measured by IFN $\gamma$  ELISPOT) after three injections of the high dose<sup>50</sup>. Collaboration between TRC and YRG CARE, a leading NGO<sup>51</sup> in the field of HIV/AIDS in Chennai, was established for the advocacy and recruitment of volunteers along with the TRC team. This is an exemplary illustration of a successful public-private partnership at a micro level. The trial will be completed in February 2008.

A research study at NARI assessed the willingness and perception of risks and benefits of potential volunteers for the Phase I AIDS vaccine trial. Among 349 patients attending three sexually transmitted infections clinics and one reproductive tract infections clinic, the overall willingness to volunteer for HIV vaccine trials was 48 per cent. Women and men at risk of HIV infection were willing to participate in the HIV vaccine trials. Factors associated with increased willingness to participate in these trials were awareness of current HIV vaccine efforts, realization of importance of vaccine for self, concern about adverse events and altruism<sup>52</sup>. These findings and several advocacy meetings helped NARI and IAVI to prepare effective communication and advocacy material for volunteers, including information kits (on HIV/AIDS, AIDS vaccines, trial organizers, and a motivational brochure), volunteers' information brochures, pamphlets and frequently asked questions. These were developed and distributed to the community in Pune and, following a further process of adaptation, by TRC in Chennai.

Vaccine efficacy trials, particularly those for AIDS vaccines, represent a tremendous scientific, ethical and organizational challenge that must be anticipated years in advance<sup>53,54</sup>. To assess the feasibility of such trials in India, an international team visited selected scientific institutions and NGOs in southern, western and northeastern India, assessing infrastructure and organizations working with different communities and reviewed the local

epidemiological data. Given the pattern of the epidemic in India<sup>55,56</sup>, the team recommended that HIV prevalence and incidence epidemiological studies be conducted in high risk groups for HIV infection including sex workers (SW), men having sex with men (MSM), transgender groups (TG), injecting drug users, and sexually-transmitted infection clinic attendees<sup>57</sup>. Meetings were then held with health-care providers and members of the MSM and TG communities to explore the possibilities of conducting such studies. Medical facilities offering antiretroviral therapy (ART), care and treatment for medical conditions and opportunistic infections and VCT (Voluntary Counselling and Testing) to the MSM and TG communities were also visited. More recently a consultation with MSM and TG communities was held to address their specific concerns and requirements for VCT. It was recommended that specific VCT training sessions be conducted with doctors, counsellors, health workers, NGOs and CBOs to address the needs of more vulnerable and stigmatized groups like MSM and TG communities. A formative research is being conducted to explore barriers to and opportunities for involving MSM and TG communities in HIV vaccine feasibility studies.

### Future steps

The first AIDS vaccine trials in India have led IAVI and its Indian partners to plan further trials in India. These trials would possibly test the current vaccine candidates in sequential administration (prime-boost) and new vaccine candidates.

Development of new generation of vaccines capable of inducing broadly neutralizing antibodies against HIV-1 primary isolates has triggered a worldwide scientific effort<sup>58,59</sup>. IAVI in collaboration with the Department of Biotechnology, Ministry of Science and Technology, has initiated partnerships with leading private and public institutions for the initiation of a vaccine immunogen design programme (Fig.).

### Lessons learnt

The conduct of AIDS vaccine trials in developing countries like India, where HIV infection and AIDS are still a highly stigmatized condition, requires extensive preparatory activities with all levels of society and different stakeholders. These include politicians, policymakers, regional and national media, scientific community, NGO's, CBOs, community

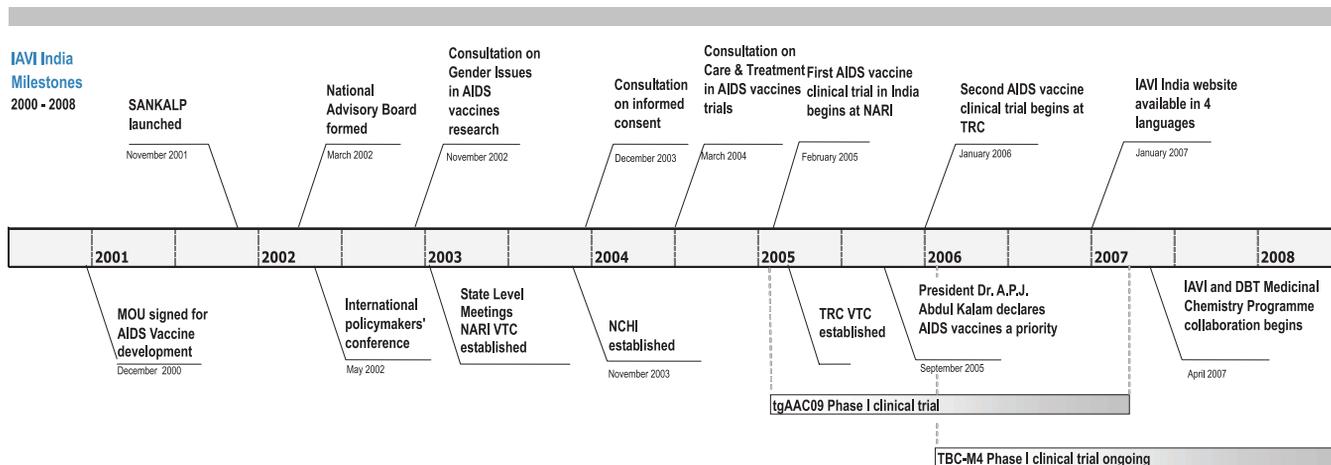


Fig. Timelinan of preparedness activities.

advisory boards, community members, HIV-infected and affected populations along with regulatory and ethics authorities. Participation of Indian scientists in the vaccine design and protocols fostered a sense of ownership which resulted in smooth trial acceptance, conduct and follow up. This holistic and comprehensive approach and transparent process led to the conduct of ethical trials, following all internationally accepted practices and scientific standards, avoiding controversy. IAVI-sponsored AIDS vaccine trials in India received extensive support from the media, community and politicians thereby enabling the recruitment of volunteers from all socio-economic and educational segments of the society. An almost equal number of men and women were enrolled in these trials. This helped to dispel the myths of Indian women not coming forward to participate in clinical trials due to social pressure or people from the higher socio-economic class not being willing to participate in clinical trials. Advocacy activities in the community, while helpful in raising trial awareness, were not successful in volunteer recruitment. Conversely, targeted efforts conducted with teams experienced in community advocacy and volunteer recruitment proved to be very successful.

Specific training sessions for the trial team members were key to success. These first AIDS vaccine trials in India have also contributed to capacity building of research staff and infrastructure to international standards, helped to streamline preparedness and implementation processes. The approval pathway for vaccine trials led to the creation of documents and templates that can be used for other trials, dispelled

myths about conducting AIDS vaccine trials in India and paved the way for future AIDS vaccine development in the country. The concept and conduct of AIDS vaccine trials in India is now benefit of a large acceptance in the civil society.

Phase IIB Test-of-Concept and III trials will require larger number of volunteers (several thousands) from communities highly exposed to HIV infection. Their implementation in India will represent a significant challenge requiring a significant expansion of the clinical trial, laboratory and referral infrastructures. Epidemiological studies to determine incidence of HIV infection and retention rate in the community and a specific preparedness programme will require a significant efforts of all partners and stakeholders<sup>55</sup>.

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