CONTROVERSY

AIDS vaccine trials for India: getting the facts right

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In the last several months, there have been discussions in the media, including in this journal (1), about issues related to how AIDS vaccine trials are conducted in India. The International AIDS Vaccine Initiative (IAVI) has partnered with the ministry of health and family welfare in India through the National AIDS Control Organisation (NACO) and the Indian Council of Medical Research (ICMR) since 2002 to implement the AIDS vaccine research and development programme. With our partners, we strongly support transparency and the highest ethical standards in our joint efforts to find and deliver an AIDS vaccine that the world so desperately needs. In fact, IAVI's intellectual property agreements are also used as a mechanism to avoid any delay in the introduction of vaccines to developing countries (delays of more than 10 years or so in the past) by insisting that any vaccine will be made simultaneously available in developed and developing countries (2).

The government's AIDS vaccine programme in India follows these guiding principles: 1) moving the most promising vaccine candidates to trials; 2) testing multiple vaccine candidates simultaneously; 3) establishing centres of excellence to conduct research at par with international standards 4) contributing to in-country capacity-building for AIDS vaccine clinical trials by providing training of international standards on good clinical practices, good clinical laboratory practices, gender specificities, laboratory and standard operating procedures for clinical trials; 5) disseminating scientific information generated by international and national AIDS vaccine research.

The multi-pronged strategy of testing vaccines in parallel rather than sequentially and in different populations with diverse genetic profiles is well-recognised and standard scientific practice all over the world. The Indian programme has prioritised vaccines designed to prevent clade C infections since this was the predominant subtype of HIV circulating in India (3, 4, 5, 6). High-level science review meetings of national and international experts were held by ICMR in May 2003, February 2004, and October 2004 to evaluate and review possible AIDS vaccines suitable for India. Representatives of institutions such as ICMR, Tuberculosis Research Centre, National AIDS Research Institute (NARI), YRG Care, National Institute of Cholera and Enteric Diseases, National Institute of Immunology, Centre for DNA Fingerprinting and Diagnostics, Centre for Cellular and Molecular Biology, Sir Dorabji Centre for Research in Tropical Diseases, Christian Medical College, Vellore, Targeted Genetics Corporation (TGC) as well as other Indian experts were also present. Several candidates were prioritised for testing (7), including a recombinant Adeno-associated Virus (AAV) vaccine and a recombinant Modified Vaccine Ankara (MVA) vaccine candidate. In February 2004, the panel recommended that India should participate in the multi-country Phase I AAV-based AIDS vaccine clinical trial. A joint meeting of the ICMR and the department of biotechnology (DBT) was held in October 2004 to review the research and development activities being undertaken in India for the development of AIDS vaccines. The committee endorsed ICMR's plan to pursue the AAV and MVA vaccine Phase I trials.

The AAV study marked India's first ever AIDS vaccine trial and was part of a joint international protocol designed to generate reliable data on this vaccine candidate in different populations. This vaccine was designed by Targeted Genetics Corporation, a Seattle-based, public-listed biotechnology company, and Columbus Children's Research Institute. The partners initiated the trial in India in 2005 at NARI after a two-year preparatory process, which included participatory processes with stakeholders, extensive community outreach, the review of an expert committee convened by the government, and after receiving all required scientific, regulatory, and ethical clearances. In India, approvals were obtained from the NARI scientific committee, NARI ethics committee, the Drugs Controller General of India, the central ethics committee, the Genetic Engineering Approval Committee, and the health ministry's screening committee.

Soon after the NARI trials were initiated, the preliminary results from the European trials showed that the vaccine was safe and well tolerated amongst the European population. Immunogenicity results of the trial in European volunteers also indicated that while the vaccine candidate was not disappointing, the European results had fewer responses than expected. Several press reports have suggested IAVI failed to share these results with its Indian collaborators. In fact, IAVI provided the data to all its Indian partners, and the decision to go ahead with the NARI trial was taken after all aspects were considered, and safety, ethical, scientific, and regulatory issues were fully addressed. These results were also shared with the NARI ethics committee and information was provided to the India trial volunteers through the trial's informed consent documents.

IAVI and its partners, including the manufacturer, TGC, concluded that the trial met its primary endpoints: it proved

AAV was safe and well tolerated. Early data from the Belgium and Germany volunteers showed that these endpoints were met and hence the availability of that early data did not mandate the need to alter the protocol in India as it had no implications on the trial design. It was critical to document the safety and immunogenicity of the product in Indian volunteers based on the same design used in Europe before proceeding to further development.

The vaccine trials at NARI were completed in December 2006. All 30 healthy volunteers enrolled were followed up on for 12 months post-vaccination. The conduct of the vaccine trial went smoothly, no safety concerns were identified, and the vaccine was well tolerated. In addition, a single administration of the vaccine at the doses evaluated in this initial study elicited modest immune responses in some volunteers. The trial was monitored by an independent monitoring agency, and a safety review board consisting of both national and international experts reviewed the data at every stage. Two independent monitors appointed by the central ethics committee also monitored the trials. The monitors concluded that the trial was ethically conducted to the highest international standards. This was also confirmed by an independent audit preformed by an international auditing firm.

The decision to go ahead with the NARI trial was also wise and prudent from a scientific point of view. The Indian authorities and IAVI believed that it was important to have safety and immunogenicity data from India, as the vaccine candidate was specifically designed for the type of HIV circulating in Asia and Africa.

While the trial in India was ongoing, IAVI initiated another clinical trial in Africa to determine if a higher dose and two injections of the same vaccine would be safe and enhance the immune responses. As in India, African researchers were fully involved in the trial designs. Participants, all HIV-negative healthy volunteers, were fully briefed about the trial through the highest standards of informed consent procedures. The Africa trial is ongoing, and will also contribute to the global understanding of vaccine science and the development of a suitable candidate for the African region.

Clearly, AIDS is outpacing our response in India with a steady increase in the number of new HIV infections annually. While the government of India has implemented a number of prevention and treatment strategies, which have shown very positive results, the facts suggest that a great deal still remains to be done. A recent study by the National Council of Applied Economic Research has suggested that the epidemic could dent India's growth by as much as one percent in GDP terms and impede India's developmental goals (8).

The AIDS epidemic thus requires a bold research and development strategy that includes the acceleration of early, Phase I safety and tolerability testing of several technologies simultaneously. To answer key scientific questions and move the field forward, we also must study the same technology at different sites among different populations without waiting for data from one technology or site to begin at another. At the same time, IAVI is committed to working with its partners, ICMR and DBT, to maintaining the highest standards of transparency and ethics in the conduct of vaccine trials. In this regard, we appreciate the many reports citing our "ethical benchmarks," our informed consent procedure which "documents disclosed all known risks and clearly stated the right to withdraw at any stage" and the standards of care in the trial. Indeed, the volunteers in all our AIDS vaccine trials are our paramount concern.

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