IAVI India Newsletter

SANKALP

Vol 6 (1) February - March 2007

SPOTLIGHT

The first AIDS vaccine trial in India breaks myths

Sonali Kochhar & Jean-Louis Excler

In early 2002, as IAVI was making preparations for India's first AIDS vaccine trial in partnership with the Government of India – acting through the Indian Council of Medical Research and the National AIDS Control Organization (NACO) – sceptics accumulated reasons why the trials would not be possible.

▲ *The NARI trial team (names on page 2)*

People and civil society had a distrust of clinical research, it was said. Community resistance due to genuine concerns had stopped – or severely delayed – much biomedical research in India in the past. There were fears of side effects due to participation in the trial, of stigma and discrimination that the volunteers might face. After all, AIDS was still a touchy subject. That aside, AIDS vaccine science was so complex that lay people would not be able to make sense of the jargon, and the whole idea of informed consent would be a non-starter.

There were also practical considerations, it was argued:

- participants would be scared of blood draws;
- volunteers may have reservations about using contraception for the short period, as required under the trial protocol;
- visits to the trial centre would inconvenience working people;
- women would not come forward to volunteer as they were not free to take their decisions;

India's first clinical trial of a preventive AIDS vaccine candidate began in February 2005 at the National AIDS Research Institute (NARI), in Pune, Maharashtra. The vaccine candidate tested for safety and immunogenicity at NARI was tgAAC09 Adeno Associated Virus (AAV). The trial centre in Pune was part of a clinical trial which also involved several centres in Belgium and Germany. The NARI researchers helped to run the whole international trial. This vaccine candidate was developed by Targeted Genetics Corp., an IAVI partner. For more details of this trial, visit **www.iavi.org.in**

A second trial with another vaccine candidate TBC-M4 (Modified Vaccinia Ankara) began in January 2006 at the Tuberculosis Research Centre in Chennai, Tamil Nadu. Further clinical studies with these vaccines and new candidates are currently under consideration.

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- participants would want money, defeating the very meaning of the word 'volunteer';
- educated sections would choose not to participate.

Such were the concerns raised by some NGOs, scientists, community activists and regulatory and ethical committee members at various stages and levels.

Reality turned out be radically different, an astonishing and happy tribute to grit, drive and the commitment of the government and HIV community groups of India. Community concerns – the root of the scepticism described above – were addressed by asking community organisations and leaders what concerns there may be and how they could be addressed well. Several NGOs and individuals eagerly contributed very large amounts of their time and expertise to make sure that all issues were considered and addressed as needed. NACO, ICMR, NARI, IAVI and their partners reached out to local, regional as well as national politicians, policy makers, media, NGOs, community-based organisations, civil society groups and medical and scientific practitioners. Those who had expressed reservations at the beginning of discussions about trials in the country were actively engaged and invited to offer feedback. These new perspectives helped IAVI do its work better.

▲ *The Immunology Lab at NARI*

To ensure volunteers received the best possible care and treatment in the course of the trial, a national-level consultation was held. The **informed consent** group helped prepare the informed consent templates for the trials, and the gender sensitisation group worked with trial site staff.

Simultaneously, the physical infrastructure was put in place. The Vaccine Trial Centre – consisting of the clinic, data management centre and laboratory – at the National AIDS Research Institute, Pune, was renovated and equipped to international standards.

There were a few bureaucratic hiccups en route, in terms of import of equipment and maintaining an uninterrupted supply of kits, reagents and back-up parts that were often unavailable in the country. All of these were overcome thanks to the commitment of partners at ICMR, NACO and NARI.

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> "IAVI has put in place systems to address gender issues in vaccine trials which didn't exist before – for example, the setting up of the gender advisory board, developing a new manual for trials, revising the informed consent form and facilitating a gender training workshop. This process sets a new standard for conducting ethical and gender-sensitive trials in India. That in itself is a tremendous achievement."
>
> Anjali Gopalan, Director,
> Naz Foundation, New Delhi

Simply put...

Informed consent is an agreement signed by prospective volunteers for a clinical research that includes their understanding of (1) why the research is being done, (2) what researchers want to accomplish, (3) what will be done during the trial and for how long, (4) what risks are involved, (5) what, if any, benefits can be expected from the trial, (6) what other interventions are available, and (7) the participant's right to leave the trial at any time.

The NARI trial team in photo on page 1 :
Row 1: (from left) Dr Seema Sahay, Dr Madhuri Thakar, Dr Sanjay Mehendale, Dr Ramesh Paranajpe, Dr Aparna Shrotri, Dr Sushant Sahastrabuddhe
Row 2 : Sachin Dhondge, Prasanna Sankpal, Trupti Jadhav, Swarali Kurle, Swati Salunke, Sphurti Waghmare, Rohini Kharat, Sucheta Kadam, Shirin Shikalgare
Row 3 : Prakash Gaikar, Datta Taware, Ajit Kulkarni, Altaf Mujawar, Ashok Pawar, Prakash Patole, Rohan Deshpande

IN CONVERSATION

"A graduate curriculum should include the mechanics of drug trials..."

Lt. Gen. D Raghunath is Principal Executive, Sir Dorabji Tata Centre for Research in Tropical Diseases,Bangalore. He served as Professor and Head of Microbiology of the Armed Forces Medical College in the 1980s and later as its Dean and Commandant. In recognition of his distinguished service as Director-General, (Indian) Armed Forces Medical Services, he has been awarded the Param Vishist Seva and the Ati Vishist Seva medals.

He is currently on the Advisory Committees of many research institutes including the National Institute of Virology, National Institute of Cholera and Enteric Diseases, the National Institute of Epidemiology as well as IAVI. He also consults with the Indian Council of Medical Research. He recently spoke to Sankalp about HIV/AIDS and clinical research in India.

What are some important research issues that emerged at the '7th Sir Dorabji Tata Symposium on HIV/AIDS Research Issues' held recently at Bangalore?

The symposium focused on the technical aspects of the problem rather than the social and behavioural aspects. Several aspects ranging from epidemiology to vaccine production were discussed at length by experts. Among the key research issues that emerged from the discussions is the need to understand the phenomena of different prevalence rates in the regions of India. Low cost and easily performed laboratory tests for diagnosis and monitoring HIV infection were also identified as a priority research area.

The pros and cons of preventive and therapeutic vaccines were also discussed. The need for further research in the field and development of vaccine evaluation capability was identified as a research goal. The concept of a 'social vaccine' was introduced and further research into development of social practices that would decrease virus spread was identified as a research issue.

It was concluded that the clinical features of HIV/AIDS in India are dictated by opportunistic infections. With a steady increase in the list, it appears that the disease has protean manifestations[1]. Likewise, the pathology is modified by the secondary diseases. The HIV/TB nexus was seen as a field for priority research.

What is the significance of carrying out research on new preventive technologies – vaccines and microbicides in India?

I feel both vaccines and microbicides would play a significant role in arresting the HIV/AIDS epidemic. Vaccines can be expected to act in two ways: one type would help the HIV infected individual control the progression to AIDS while the other type would drastically reduce fresh cases. In fact, even if preventive vaccines are less that 100 per cent effective, they would have a significant impact on prevalence. Microbicides would interrupt the most important route of infection and decrease the number of fresh cases. In addition, they would also improve the status of women in society. Therefore, I consider both these modalities important and mutually supportive.

How is clinical research progressing in India?

Documentation of clinical features in HIV/AIDS is progressing fairly well. However, some serious long term studies are not being undertaken. In fact, data on clinical course, success of ARV therapy, incidence of drug resistance, optimal regimes that take into consideration economic factors are not available. There is a need for serious clinical research in the country.

Are there any specific policy implications related to clinical research that need to be introduced or made stringent in the country?

I would think that members of the medical profession require to continually educate themselves about various aspects of HIV/AIDS at the graduate and postgraduate levels. This should include training in ART and its monitoring. Over the counter sales of ARV drugs should be forbidden and only prescription-directed treatment allowed.

All patient care personnel should be well trained in universal precautions. Refusing to treat or uncontrolled HIV testing

[1] *Proteus was a Greek sea god who frequently changed his form to avoid capture. From this feature of Proteus comes the adjective protean, with the general meaning of "versatile", "mutable", "capable of assuming many forms".*

should be prohibited. Antenatal HIV testing should become mandatory even in the so called low prevalence states.

Simply put...

Schedule H drugs : As per the Drugs and Cosmetics Act 1940, prescription drugs grouped under Schedule H cannot be sold without a valid prescription of a doctor. These medicines have to be taken only when prescribed by a doctor. Self medication of these drugs could be dangerous. These drugs can be sold only under the personal/direct supervision of a pharmacist at a pharmacy / chemist and druggists / medical store having a valid retail license.

At the time of dispensing a prescription, the pharmacist should note his/her name, address and the date of dispensing above the signature of the prescriber. In dispensing **Schedule H drugs**, no substitution should be made.

In your capacity as member of the Central Ethics Committee, what are the changes that you would suggest to expedite the regulatory and ethical review processes in the country?

The ethical review process at the level of the Central Ethics Committee (CEC) is functioning well. Ethical reviews are performed at various levels and finally considered at the CEC. The weak link is at the institutional level. Many of these committees are not adequately broad-based nor do they have the comprehension of ethical issues so necessary for them to function. Medical ethics is still in its infancy in the country. It would be possible to hasten clearances when the quality of ethical scrutiny improves at the grassroots level.

Have the clinical trials being conducted in partnership with IAVI had an impact on the clinical research scenario in India?

Not yet. The clinical research scenario particularly drug trials are strongly oriented to drug company initiatives. Clinical research organisations in the country are not well supervised. The two IAVI trials on vaccines have not been adequately publicised. As a member of the Central Ethics Committee overseeing the functioning of the clinical trial, the conduct of these trials was an eye opener. The trials have been conducted in a very transparent manner unlike some others in the country. Hopefully, when the details become known to interested parties, some impact will be perceived. I recommend that the mechanics of drug trials should be introduced at the graduate level in the pharmacology curriculum. ■

◄ Spotlight

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Next, staff responsible for clinical, laboratory, community and data management received training in India and, in some cases, abroad. Simultaneously, the process of navigating the clearances necessary for India's first AIDS vaccine trial was gone through. Since this trial was going to set many precedents, the relevant committees were particularly scrupulous in making sure that all procedures were followed correctly. The approval process was efficient and extremely thorough.

In the end, these efforts paid off. The trials were conducted smoothly and held up as a model in terms of ethical practice. This won ICMR, NACO, NARI, IAVI and their partners' appreciation among the community, policy-makers and the media.

Though the initial enrollment of volunteers was slow, it picked up significantly as the trial proceeded. There was almost equal participation of males and females, unlike in Europe, where there was only 30 per cent female participation. Trial participants came from all socio-economic and educational sections.

The vaccine has been found to be safe among both European and Indian volunteers. Several laboratory audits and an international, independent audit rated the NARI trial ethically exemplary and scientifically sound.

Eventually, India's first AIDS vaccine trial was important not just for furthering the quest to defeat HIV or for contributing to infrastructure and skills augmentation and capacity building or for setting the template for future trials. Its biggest achievement, perhaps, was that it was carried out so seamlessly. This debunked many myths about India, and validated its position as a scientific leader. ■

Dr Sonali Kochhar is Medical Director, IAVI India.
Dr Jean Louis Excler is Senior Medical Director, IAVI India.

IN FOCUS

Chocolates, chips and condoms

K Sudarshan

With an estimate of over five million Indians carrying HIV, the Union health ministry has been projecting condoms as a major preventive priority given that 86 per cent of India's HIV cases are sexually transmitted.

The ministry installed 10,000 vending machines across the country to improve accessibility of condoms and provide the necessary anonymity in their purchase because people still hesitate to buy condoms across the counter.

In Delhi, over a hundred condom vending machines have been installed in the last 20 months at airports, hospitals, universities and government offices. "Although condoms have been available at health centres and at chemist shops, it was not possible to access them, for instance, late at night, resulting in unprotected sex," says Dr J P Kapur, Director, Delhi State AIDS Control Society (DSACS), which is coordinating the installation of condom vending machines, in the capital. The vending machines ensure that people can avail of condoms round-the-clock without having to buy them in full public glare, he explains.

▲ *The Health Centre at Jawaharlal Nehru University, Delhi*

DSACS has also set up nine 'health dispensers' that sell chocolates, chips and cakes along with condoms at the drop of a coin. The dispensers were introduced when it was found that people were still shy of approaching machines selling only condoms. The health dispensers, have been installed at the international airport, Lady Hardinge Medical College and on the Jawaharlal Nehru University (JNU) and Delhi University campuses.


▲ *The condom vending machine at JNU*

In its ongoing efforts to expand coverage and reach out to more people, DSACS is also providing free condoms through dispensers in both ladies and gents toilets in Delhi Secretariat offices. Bipin Joshi, assistant director (condom promotion), DSACS, says over 9.33 lakh condoms were sold through the vending machines and picked up from dispensers in the toilets in 2006.

Dr Kapur is particularly happy with the way JNU has responded. At least 80 condoms are sold on the JNU campus everyday. "The uptake of condoms is very good. Recently when the machine broke down, we were besieged with telephone calls seeking its early repair," he recalls.

It also helps that the dispenser is located at the JNU health centre, which is near the now-legendary *Ganga Dhaba*, a regular hang-out place for the students that is constantly abuzz with activity.

"There have been no objections to this initiative," says Manoj, a student at the School of Social Sciences. "It has generally been welcomed. It is well known that students are sexually active. In such a situation, it is better that

they are properly equipped so that they practice safe sex."

Unlike JNU where the dispenser is at a prime location, the machine in Delhi University is tucked away at an invisible corner behind the Utility Centre. There are virtually no sales at Delhi University (DU). The contrasting experience of JNU and Delhi University has shown that the location of the vending machine is critical to condom sales.

Women employees at the Delhi Secretariat office say access to condoms in the toilet is a new experience for them and has empowered them immensely. But they are still reluctant to be seen discussing condoms and were not willing to be quoted on the issue.

"Contraception is generally looked upon as the sole responsibility of women. But the availability of condoms has helped us push the men into taking equal responsibility," says Rachna Sharma (name changed), a section officer. She felt comfortable giving her opinion only when she was told that her real name would not be used in the article.

DSACS has approached the Delhi Metro authorities and many banks with ATMs to help take this initiative forward. But, DSACS officials say the response has not been encouraging. They have also requested for the shifting of the health dispenser in Delhi University to another location. But, Dr Kapur laments of an underlying resistance to the availability of condoms on campuses.■

TEXTBOOK

AIDS vaccine trials - Leaving communities better off

An AIDS vaccine candidate must be tested in the populations that are most affected by the disease to determine whether it is effective. Therefore, clinical trials have to take place in communities where there is a high enough incidence of HIV infection for researchers to determine positive benefits from the vaccine. This often requires running trials in developing countries, where there is the highest HIV/AIDS burden. It is also essential that vaccines be evaluated in communities that need them the most and where they will be used, since there may be unanticipated issues with vaccines tested only in developed countries.

Building infrastructure

Successful trials require the active support of the communities where they take place and of the governments that review and supervise the conduct of the trials. Establishing this support is the first step when developing a clinical trials site.

The next step involves constructing the actual buildings that will serve as clinics and laboratories or modifying those that already exist. These facilities are then equipped with the instruments necessary to process laboratory samples obtained from volunteers during the trial and preparing these specimens for storage or shipment. Some sites may even develop sophisticated HIV immunology and virology laboratories that can analyse samples and process the data from the trial in the country where it takes place.

The sites must also be prepared to offer the best prevention interventions available and must establish facilities through which these can be offered. Provision must also be made to link to voluntary counselling and testing facilities. Treatment may be needed for people who are infected in the trial through risk behaviour, and not from the vaccine candidate being tested. Trial sites may provide referrals to existing treatment programmes provided either by the national governments or by outside organisations to ensure that volunteers have access to treatment.

Developing these sites also benefits the community by providing career opportunities for healthcare workers that can serve the community long after the trial ends or by attracting other medical services to the area, such as HIV treatment programmes.

Training medical professionals

It is also important to build human capacity at AIDS vaccine trial sites. Sponsor organisations spend significant amounts of time hiring and training medical professionals with the correct skills to handle the activities associated with the trial and to uphold the highest ethical standards.

Workshops are an important part of training these individuals and they cover all aspects of the clinical trial process, from screening and enrolling volunteers

India recently started an AIDS vaccine trial sponsored by IAVI in partnership with the Indian Council of Medical Research and the National AIDS Control Organization at the Tuberculosis Research Centre (TRC) in Chennai. The TRC, a newly-established centre of excellence for the clinical evaluation of vaccines in the country, features a safety and immunology laboratory where all laboratory tests will be run.

A similar centre was set up at National AIDS Research Centre at Pune in 2005 for the first clinical trial of a preventive AIDS vaccine in the country. The centre includes a data management unit, a laboratory of immunology and a community centre entirely dedicated to clinical trial activities.

▲ *The National AIDS Research Institute, Pune*

to collecting and analysing data, and are based on a set of work practices developed specifically for each site. All trials are certified according to a set of international guidelines, known as Good Clinical Practice (GCP). Compliance with GCP guidelines ensures that the trial is run properly, that the rights and needs of the volunteers are protected, and that the data collected during the trial is of high quality. Counsellors and nurses are trained to work with potential volunteers and to administer the informed consent process. These individuals may also receive specialised training on enrolling women in AIDS vaccine trials and other gender-related issues.

Once established, the sites can continue to function well beyond the end of the current trial. The staff's expertise could make the site suitable for other types of HIV prevention trials, including microbicides, or for clinical research studies that contribute to the understanding of the HIV/AIDS epidemic in the country. These sites may also attract HIV treatment programmes or other healthcare services that can continue adding benefit to the community. Keeping these sites active is also of great interest to organisations sponsoring AIDS vaccine trials, since many vaccine candidates will need to be evaluated in the future and these trials will require experienced sites and surrounding communities that have successfully conducted past trials. ■

Adapted from an article by Kristen Jill Kresge in the March 2006 edition of VAX, a monthly AIDS Vaccine bulletin.

Microbicide trials halted in Africa and India

Phase III trials of the candidate microbicide, cellulose sulfate (CS) to prevent HIV transmission in women have been stopped prematurely. A microbicide is a substance that has the ability to prevent the sexual transmission of HIV and other sexually transmitted diseases (STD) pathogens when applied topically either in the vagina or rectum. A microbicide could be produced in the form of gels, creams, suppositories, sponge or a vaginal ring that slowly releases the active ingredient. No microbicide is currently available on the market. About 18 microbicide candidates have proven safe and effective in animals and are now being tested in humans.

An independent scientific committee found an increased risk of HIV transmission among women who used CS compared with women who used a placebo gel at one of the sites. The negative results of the Phase III trials of the CS microbicide are unfortunate. The reason behind the failure of this particular microbicide is unclear and needs to be determined.

CONRAD, a reproductive health research organisation, was conducting Phase III trials to assess its effectiveness in Benin, India, South Africa, and Uganda. Another Phase III trial of CS sponsored by Family Health International was underway in Nigeria.

Adding his perspective, Director of the AIDS Vaccine Advocacy Coalition (AVAC) Mitchell Warren observed: "Getting a negative result for one product certainly doesn't signal failure for the microbicide field or broader biomedical HIV prevention research effort as a whole. The nature of research is that the information gathered is cumulative. Each trial result is a puzzle piece and, together, they make up the complex picture that will show us how to develop successful new HIV prevention tools."

There are significant differences in the mechanism of action of microbicides and vaccines. A microbicide is a chemical which acts locally at the level of the vagina or rectal mucosa to kill, repell or immobilise the HIV and STD pathogens or block infection by creating a barrier between the pathogen and the cells. The chemical would need to be able to kill the pathogen but be gentle enough to spare the female genital tract from corrosive chemical effects that have the effect of favouring infection.

Vaccines on the other hand stimulate the body's immune responses to protect against HIV infection or to protect against progression to disease. They do not have the local side effects associated with microbicides. Hence, it is necessary to distinguish between the two preventive technologies and understand that the results from the microbicide trial cannot be translated to AIDS vaccine trials.

ASK to get ANSWERS...

Your question: How is an AIDS vaccine developed? Can this experimental vaccine cause HIV infection or AIDS?

An AIDS vaccine is tested in various stages over several years, as with most other vaccines. Initial laboratory work is followed by animal studies and then human clinical trials. Many of the modern, licensed vaccines that are used today have taken several decades before they cleared the many complicated stages of their development. Experts believe a safe and effective AIDS vaccine may be found within the decade, but there are others who feel it may take much longer than that.

There is no risk at all of getting infected with HIV due to this vaccine because the HIV virus is never used in its natural, active and infectious form to make the vaccine. Scientists create synthetic copies of a small part of HIV's genetic material in the lab and use them for the vaccine. It is impossible for the experimental vaccine to cause HIV infection or AIDS.

If you have a question on any issue pertaining to HIV/AIDS or AIDS vaccines, write to us at:

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Our experts will give the answer. The question and the answer will be published in the next issue of Sankalp.

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

Alfred P. Sloan Foundation · Basque Autonomous Government · Becton, Dickinson and Company (BD) · Bill & Melinda Gates Foundation · Broadway Cares/Equity Fights AIDS · Canadian International Development Agency · Continental Airlines · Crusaid · Deutsche AIDS-Stiftung · European Union · Google Inc. · The Haas Trusts · Irish Aid · The John D. Evans Foundation · Merck & Co., Inc. · The Netherlands Ministry of Foreign Affairs · The New York Community Trust · Norwegian Royal Ministry of Foreign Affairs · Pfizer Inc · The Rockefeller Foundation · Royal Danish Ministry of Foreign Affairs · The Starr Foundation · Swedish International Development Agency · Swedish Ministry of Foreign Affairs · U.S. Department for International Development · Until There's a Cure Foundation · The U.S. President's Emergency Plan for AIDS Relief through the U.S. Agency for International Development · The World Bank/Global Forum for Health Research

And many generous individuals from around the world.

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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