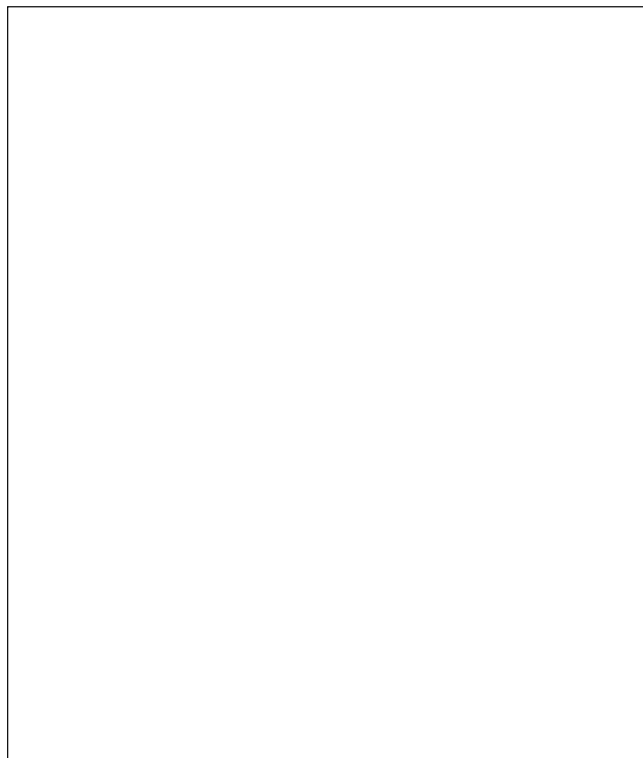


Since the first cases of AIDS were identified in 1981, almost 50 million men, women, and children have become infected with the human immunodeficiency virus (HIV) and some 14 million have already died of AIDS. Today, more than 33 million people are living with HIV/AIDS in the world, more than 95% of them in developing countries. In 1998 alone, approximately 2.5 million people died of AIDS, which is now the leading cause of death in Africa, and the fourth worldwide.

Moreover, despite the intense international response to the HIV/AIDS pandemic, HIV continues to spread, causing more than 16,000 new infections every day. As is the case with other infectious diseases, a safe, effective and available vaccine may be ultimately required to control the HIV/AIDS pandemic, especially in developing countries. The development of such vaccine(s), however, will depend on the success of the international community to address and solve the multiple scientific, logistical, and ethical challenges that arise in the process.

#### SCIENTIFIC ISSUES RELATED TO HIV VACCINE DEVELOPMENT

We still have a number of important scientific questions that remain to be answered in relation to HIV vaccine development. For instance, AIDS may be different from other vaccine preventable diseases in that HIV infection may persist, or AIDS may develop, despite the development of strong anti-HIV immune responses from the host. The hope is that pre-existing immune responses induced by a vaccine would be sufficient to tilt the balance in favour of the host, preventing the establishment of chronic infection after exposure to HIV. The efficacy of that "barrier to HIV infection" may depend on the induction of humoral and/or cell mediated immune responses by the candidate vaccine. In fact, primate protection experiments using the chimpanzee/HIV-1 model, or infection of macaque



HIV/AIDS has raised a number of important scientific questions with regard to clinical trials carried out in developing countries. A broad consultation process was carried out by UNAIDS aimed at the development of local capacity and international guidance for HIV vaccine trials. This consultation process has been launched in advance of the major thrust in clinical trials in this area in order to assist researchers and communities in addressing the basic questions of international collaborative research.

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## *Establishing standards for HIV vaccine trials: a process of international dialogue*

*José Esparza, Claire Pattou, and Saladin Osmanov  
report on the UNAIDS initiative to develop scientific  
and ethical capacity for HIV vaccine trials at an  
international level.*

monkeys with SIV (simian immunodeficiency virus) or SHIV (chimeric SIV/HIV viruses) have shown that a vaccine against HIV is possible. A complicating factor is that different candidate vaccines show different levels of efficacy in these animal models, and their relevance to vaccine-induced protection in humans remains to be established by clinical trials.

The other important scientific unknown is related to the genetic variability of HIV. Nucleotide sequencing of the gene coding for

the envelope protein of HIV-1 (gp120) has been used to classify HIV-1 strains into ten genetic subtypes (subtypes A through J). These genetic subtypes are unequally distributed in different parts of the world. Subtype B is the prevalent virus in Europe and the Americas. The most abundant subtype, however, is subtype C, causing almost half of all HIV infections in the world, and especially prevalent in southern Africa and India. Almost every subtype exists in Africa, with subtypes A

***We still have a number of important scientific questions that remain to be answered in relation to HIV vaccine development.***

and D being the most prevalent in East, Central, and West Africa.

Most candidate vaccines to date have been based on subtype B strains, but the high prevalence of non-B subtypes in developing countries is stimulating the development of vaccines based on other subtypes, especially E, C, A, and D. These efforts are important, although we do not know the relevance of the HIV-1 genetic variability in terms of potential vaccine-induced protection. Cross-neutralisation between different virus subtypes has been demonstrated, but the neutralisation patterns have been complex, not allowing for clear identification of virus immunotypes. Likewise, people infected with HIV, or immunised with certain candidate vaccines, have shown to develop cross-reactive cell mediated immunity, although it is not clear how cross-protective the vaccines would be.

**CLINICAL TRIALS OF HIV VACCINES**

Despite these scientific uncertainties, clinical trials of HIV candidate vaccines are being implemented. In fact, the first Phase I trial of an HIV candidate vaccine was conducted in 1987 in the United States and, since then, approximately 25 HIV-1 candidate vaccines have been tested in Phase I/II safety/immunogenicity trials, involving over 4000 healthy HIV-negative volunteers. Most of these trials have been conducted in the United States and Europe, but some have also been implemented in developing countries.

The first candidate vaccine to enter Phase III efficacy trials is a mammalian-cell derived recombinant gp120 monomeric glycoprotein produced by VaxGen (Brisbane, California, United States). A bivalente product composed of proteins derived from two subtype B viruses entered

Phase III trial in the United States in 1998, and will enroll a total of 5000 volunteers, mostly men-who-have-sex with men. A second Phase III trial started in March 1999 in Thailand, with an equivalent candidate vaccine containing gp120 derived from a B and an E strain (the prevalent subtype in Thailand), and will enroll a total 2500 volunteers, mostly injecting drug users. Efficacy data from these two Phase III trials may be available within the next 2-3 years.

But there are several other candidate vaccines in the pipeline. The National Institute of Health in the United States is planning to launch within the next two years their first Phase III trial, using a prime-boost regime utilising a canarypox-HIV live recombinant vector (ALVAC, produced by Pasteur Mérieux Connaught) followed by gp120.

Other vaccine concepts are being developed in the laboratory and some are progressing to Phase I/II clinical trials. These include synthetic peptides representing critical HIV epitopes, "naked" nucleic acids (especially DNA), different live vectored vaccines (using BCG, Salmonella, the modified Ankara strain of vaccinia virus, and a Venezuelan Equine Encephalitis replicon).

**THE NEED TO CONDUCT MULTIPLE VACCINE TRIALS**

In order to accelerate the development of a much-needed vaccine, multiple efficacy trials will have to be conducted in parallel. These multiple trials will be necessary to test the efficacy of several vaccine concepts (or products) against different virus subtypes and in different populations (which may differ in the route of transmission of the virus, the genetic makeup of the population, or its nutritional status and exposure to other infectious or parasitic agents).

Many of these trials will have to be conducted in developing countries. These trials will be important because (1) the large majority of HIV infections are occurring in these countries, where an effective vaccine would eventually be used and have the most benefit; (2) efficacy trials will need to be conducted in populations with a high incidence of HIV infection; and (3) the antigenic variability of HIV may require that candidate vaccines are tested in different areas of the world.

The implementation of these multiple efficacy trials will require intense international coordination and collaboration.

**NATIONAL AND REGIONAL AIDS VACCINE PLANS AND STRATEGIES**

The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have collaborated with selected developing countries in the preparation of future HIV vaccine trials. In 1992 the WHO collaborated with national authorities and scientists in Brazil, Thailand, and Uganda, leading to the adoption of National AIDS Vaccine Plans in these countries. These plans, which were developed through a consensus building process, served to define national policies and to develop mechanism for the submission, review, approval, and monitoring of vaccine-related research. This led to the establishment of vaccine committees or subcommittees in these countries and to the strengthening of their scientific and ethical review processes.

In addition, National AIDS Vaccine Plans identified research priorities necessary to support the appropriate design and implementation of future HIV vaccine efficacy trials, including virus isolation and characterisation, epidemiology and cohort develop-

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***Capacity building is a long-term, continuous effort, in which all stakeholders participate.***

ment, data management, vaccine-related social and behavioural research, strategies for public information and communication, and Phase I/II clinical trials.

The existence of these plans have attracted international partners, by providing "clear rules of the game" and avoiding situations in which decisions are taken on an ad hoc basis.

In fact, most HIV vaccine trials to date in developing countries have been conducted in countries with WHO/UNAIDS sponsored National AIDS Vaccine Plans. The first Phase I HIV vaccine trial in Thailand started in June 1994. Since then five other preventive HIV vaccine trials have been conducted in that country, including the only Phase III trial in the developing world. Brazil conducted a Phase I/II trial in 1994 and Uganda started the first phase I/II trial in Africa in February 1999. Other Phase I/II trials have been conducted in China and in Cuba.

National AIDS Vaccine Plans have contributed to building capacity for the long-term involvement of these countries on HIV vaccine research activities. In support of these initiatives multiple training workshops have been organized in areas such as virus sub-typing, Good Clinical Practice, research ethics, social and behavioural research (informed consent, willingness to participate in trials, monitoring risk behaviour of trial participants), and communication and public information. At the same time, capacity building is conceived as more than simply training. According to a UNDP definition, it is the creation of an enabling environment with appropriate policy and legal instruments. It includes institutional development and community participation, with attention to human resources mobilization and strengthening of managerial systems. Capacity building is a

long-term, continuing effort, in which all stakeholders participate (ministries, local authorities, communities, non-governmental organizations, professional associations, academics) and should be developed in close collaboration with international partners.

UNAIDS and WHO have also played an important role by providing independent and authoritative scientific and ethical advice to developing countries considering the implementation of HIV vaccine trials.

***The implementation of these multiple efficacy trials will require intense international coordination and collaboration.***

Based on the experience accumulated over the last seven years, National AIDS Vaccine Plans have been revised, reflecting the growing HIV vaccine expertise in these countries. Other countries, such as South Africa and India, have recently developed National AIDS Vaccine Strategies, and UNAIDS and WHO are assisting other developing countries to do so. In addition, through a Joint UNAIDS-WHO "HIV Vaccine Initiative", activities in these countries will increase, including the development of regional AIDS vaccine networks, aimed at facilitating "peer-support", exchange of information, training, research, and capacity building.

**AN INTERNATIONAL ETHICAL FRAMEWORK**

In addition to the scientific issues discussed above, the conduct of HIV vaccine trials will have to deal with important ethical concerns, including the substantial risks of social and psychological harm for

human subjects participating in HIV vaccine research.

For this reason, UNAIDS embarked on a comprehensive process to develop ethical guidance for the conduct of HIV vaccine trials. The process included a series of workshops conducted in Geneva (Switzerland), Washington (United States), Entebbe (Uganda), Ouro Preto (Brazil), and Bangkok (Thailand), with the support of more than 120 participants from 33 countries, including ethicists, scientists, activists, government officials, community representatives and lawyers. The product of this process is a "Guidance Document" stating the UNAIDS position on ethical considerations in HIV preventive vaccine research. The document relies on ethical principles articulated in the Nuremberg Code, the Declaration of Helsinki, the CIOMS/WHO International Guidelines for Biomedical Research Involving Human Subjects, and the WHO and ICH Good Clinical Practice Guidelines.

The UNAIDS "Guidance Document", which will be released soon, seeks to provide more specific guidance on issues that are unique to HIV vaccine research, including: (1) potential for benefit and harm in trials; (2) international collaboration; (3) safeguards to the rights and welfare of research subjects; and (4) issues related to justice and the availability in the future of safe and effective HIV preventive vaccines.

**CONCLUSION**

The evolving history of HIV vaccine research shows a progressive understanding of the importance of community involvement and capacity building in developing appropriate research protocols. While AIDS may be rightly considered 'only one serious disease among several', the WHO and UNAIDS experiences in addressing this disease have led to a new appreciation of the importance of international partnership in biomedical research alongside a greater awareness of the need for local capacity building. ■

**Dr José Esparza  
Claire Pattou  
Saladin Osmanov**

Department of Policy, Strategy  
and Research, UNAIDS  
20 avenue Appia, CH-1211  
Geneva 27, Switzerland  
E-mail: [unaids@unaids.org](mailto:unaids@unaids.org)