

# REPORT FROM THE MEETING OF THE UNAIDS VACCINE ADVISORY COMMITTEE (VAC)

Geneva, 14-16 June 1999

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## 1. Introduction

A new “Vaccine Advisory Committee” (VAC) was appointed by Dr Peter Piot, Executive Director of UNAIDS in December 1998, with representation of the major AIDS vaccine development programmes in industrialized and developing countries (Members of the VAC are listed in Annex I).

The new committee met for the first time in Geneva, 14-16 June 1999, with participation of 12 out of 15 members of the committee, 7 special invitees from the European Commission, the French National Agency for Research on AIDS (ANRS), the Japanese National Institute of Infectious Diseases (NIID), the World Bank (WB) the World Health Organization (WHO), and 4 members of the UNAIDS Secretariat (Meeting participants are listed in Annex II). Dr Werasing Sittitirai, Associated Director of the UNAIDS Department of Policy, Strategy, and Research opened the meeting on behalf of Dr Peter Piot. Dr José Esparza, Leader of the UNAIDS Vaccine Team, welcomed the participants and described the objectives of the meeting, which was chaired by Dr Barry Bloom.

The meeting had the following objectives:

to briefly review the state of the art on HIV vaccine development; to review plans and activities of major AIDS vaccine research programmes in industrialized and developing countries, to identify possibilities for coordination and collaboration between institutions and with UNAIDS; to review and discuss the plan of activities proposed by UNAIDS in the area of HIV vaccine development for the biennium 2000-2001, and to make recommendations for prioritization; and

to make recommendations concerning the proposed partnership between UNAIDS and WHO in the area of HIV vaccines.

## 2. Scientific review: “towards an AIDS vaccine”

(Presented by Dr Neal Nathanson)

The path “Towards an AIDS vaccine” was discussed, according to the following scheme:

- Why it is so difficult to make an effective vaccine
- “Partial” vs. “sterilizing” immunity
- The mechanisms of protection
- The importance of mucosal immunization
- The next steps

### Why it is so difficult to make an effective vaccine

Factors contributing to the difficulty of developing an AIDS vaccine are related to the lifelong persistence of the virus. This persistence is the result of evasion of the immune system (cell-to-cell spread, latency), HIV-specific immune exhaustion (gradual attrition of CD4<sup>+</sup> cell population, deletion of HIV-responsive clones), viral immunobiology (poor induction of neutralizing antibodies), and complexities in the conduct of clinical trials (e.g. long incubation period and no immune correlate of protection).

### Partial vs. sterilizing immunity

The question was discussed as to whether ‘partial’ immunity would suffice for protection or whether ‘sterilizing’ immunity would be necessary. For viruses causing acute infections, subjects who have been adequately immunized usually undergo a transient sub-clinical infection when exposed to a potentially virulent wild type virus (“partial” protection). In the case of HIV vaccines, the question is “Will such ‘partial’ protection lead to viral persistence?” If so, will “partial” protection confer adequate resistance to an HIV challenge or is “absolute” protection (“sterilizing immunity”) needed? Do studies of viral set points and survival curves in HIV-infected humans provide a useful reference? Relevant to that question are animal experiments, which show that immunized monkeys challenged with simian immunodeficiency virus (SIV) exhibit reduced virus set points, and those might correlate with eventual slower progression to disease.

## The mechanisms of protection

Discussions on mechanisms of protection lead to consider two possibilities. The first is a *correlate hypothesis*, in which protection correlates with a specific immune parameter (such as antibodies, CTL killing, or CD<sup>+</sup> proliferation). The second is the *barrier hypothesis*, which suggests that a combination of antibody plus CTLs, plus associated cytokine responses, might act in concert to constitute a sufficient barrier. An important question to consider is if different immunizing protocols could protect by a different mix of immune responses.

## The importance of mucosal immunity

The possible importance of mucosal immunity was discussed, considering issues related to the protection of vaccinees (following sexual transmission, the virus first replicates in T cells and monocytes in the vaginal mucosa, and mucosal immunity could provide an additional protective barrier), transmission by vaccinees—“altruistic” vaccinee—if a vaccinee subsequently infected with wild-type virus excretes less virus, transmission could be reduced), efficacy of mucosal immunity (comparison of mucosal immunization vs. systemic immunization).

## The next steps

The following next steps were identified as important:

- gp120 phase III (VaxGen) initiated in 1998: Recombinant monomeric gp120 produces primarily antibody responses (neutralization limited to T cell-adapted strains).
- Avipox (Pasteur-Merieux-Connaught,PMC) plus gp120 boost (VaxGen or Chiron) Phase II trials to be completed in spring 1998: Non-replicating poxvirus vector expressing HIV proteins followed by monomeric gp120 produces neutralizing antibody (limited to T cell-adapted strains) plus inconsistent CTLs (25%–70%).
- Venezuelan Equine Encephalitis (VEE) replicons: Development of GMP for phase I trial (AlphaVax, sponsored by IAVI), trials to start in 2001?: Recombinant VEE pseudovirion expressing HIV *gag* and *env* proteins.
- DNA and Modified Vaccinia Ankara (MVA) expressing T cell epitopes (Oxford, sponsored by IAVI): Trial to start in 2000?: DNA and MVA expressing selected HIV epitopes will be used to induce MHC-specific CTLs.
- MVA development of Good Manufacturing Practices (GMP) for phase I trials (sponsored by NIH), initiated in 2001? Recombinant poxvirus expressing *gag*, *pol*, *env* proteins, possibly with a DNA prime.

## In summary

- (a) Why is it so difficult to make an effective vaccine?: *Pathogenesis*: virus persistence, continual virus spread, attrition of CD<sup>4+</sup> cells.; *Vaccinology*: HIV resists neutralization, no immune correlate of protection, difficult efficacy trials.
- (b) Proof of protection. In macaques, best candidate immunogens provide substantial, if partial, protection against severe challenges with SIV or SHIV (chimeric SIV/HIV)
- (c) Next steps. Compare many candidate immunogens in primates, prepare GMP candidate vaccines, initiate phase I human trials, and prepare for phase III efficacy trials.

## 3. Review of plans and activities of major AIDS vaccine programmes.

### 3.1 The European Commission, Belgium

(Presented by Dr Lieve Franssen).

The European Union believes that a global effort to make an AIDS vaccine accessible and available quickly to all who need it is required and that the need for public sector involvement is likely to be temporary, but critical. A preventive AIDS vaccine will be an international public health good of inestimable value to the people of the world.

### **European Commission consultation on making an AIDS vaccine available in the developing world**

The European Commission (Directorate General for Development VIII/A/2: Social, human, cultural development; gender' unit) organized in Brussels, March 1999, a consultation on "Making an AIDS vaccine available in the developing world: economic and financing issues". The consultation identified a range of potential actions worthy of future consideration and issues where more information was required. These were in the following areas:

- (a) research and development to identify a candidate vaccine for trial in Africa;
- (b) public health and economic research;
- (c) vaccine preparedness;
- (d) manufacturing capacity;
- (e) strengthening distribution capacity and infrastructure;
- (f) creating a supportive political environment and political will at the highest levels; and
- (g) addressing barriers represented by intellectual property and regulations.

### **The European Union identifies AIDS vaccines as area for priority funding 1999-2000**

The European Union has identified AIDS vaccines as an area for priority funding for 1999-2000, to develop a better understanding of the capacities, demand, ability and willingness to pay for a potential HIV/AIDS vaccine by households, governments and donors.

Proposals are being sought for studies to analyse and quantify potential public-sector and private-sector demand in developing countries, and the determinants of demand in these sectors, and specifically to:

- provide information about ability and willingness to pay by individuals, households, government and donor agencies in a range of developing country settings;
- determine how potential public and private sector demand may be affected by vaccine characteristics;
- determine how potential demand may be affected by the size and characteristics of the population at risk;
- determine how potential demand may be affected by price and pricing structures, such as tiered pricing; and
- determine how potential demand may be affected by costs of delivery and the capacity of health services to deliver vaccines.

Proposals are also being sought for a series of studies in a range of developing country settings to improve understanding of the context of vaccine policy and delivery, in order to contribute to the development of national strategies for a preventive AIDS vaccine, including:

- review of current national vaccine policies and implications for policies should a preventive AIDS vaccine become available; and
- review of current systems for vaccine delivery, to assess existing capacity and determine requirements for strengthening capacity, including analysis of affordability.

### **3.2 The World Bank, the United States of America**

(Presented by Ms Amie Batson)

#### **World Bank establishes Bank-wide multidisciplinary AIDS vaccine task force**

In 1998 the World Bank (WB) established a Bank wide multidisciplinary AIDS Vaccine Task Force with the following objectives:

- (a) identify why private investment is so low;
- (b) identify ways to address the market failure; and
- (c) work with industry, industrial country partners and developing country partners to create feasible approaches/financial instruments.

The initial activities of the WB Task Force were supported by the Innovation Marketplace programme, and include the following:

- (a) industry study (to explore perceptions and motivations of industry and reactions to possible Bank interventions);
- (b) demand study (to estimate developing country potential demand and willingness to pay for an HIV/AIDS vaccine);
- (c) consultation with donor partners (to explore findings and discuss partners perspectives on most feasible ways forward); and
- (d) instrument development (to develop a financing mechanism based on the work with the industry and developing and industrial country partners).

### **Industry study**

The industry study revealed that the number of candidate vaccines and the rate of progress are a function of cost and risk of development. Few companies are pursuing multiple approaches, whereas a number of approaches are “sitting on the shelf”, untested, while the big pharmaceutical industry has limited interest in biotechs with novel ideas.

### **Perceptions of market for HIV vaccines in industrialized countries**

Perceptions about a market for HIV vaccines in industrialized countries were not uniform. Some manufacturers (e.g. Merck and Chiron) assume that a market will exist. Other manufacturers (SKB) doubt that such a market will be significant, because at-risk groups in industrial countries are small and it is unclear if the vaccine will ever be perceived as sufficiently “safe” for broad distribution. Moreover, it is unclear at the present time what vaccine characteristics will be required to serve the market.

### **Perceptions of developing-country market**

Regarding the perceptions of a developing country market, some small biotechs with no supply experience assume that money will be found and that a market will exist. On the other hand, major vaccine manufacturers with supply experience (SKB, PMC, and Chiron), point to today’s weak market and doubt that it will be different for HIV/AIDS vaccines. Thus, the credibility of promise of future financing for HIV/AIDS vaccines will be determined by today’s market for other vaccines. In addition, there is a need to define the characteristics required for HIV vaccines to be used in less developed countries.

### **Industry focuses on development problems—high cost and risk of failure**

Industry focuses on development problems, and in particular the high cost and risk of failure in late stage development. The estimated cumulative investment to develop an HIV vaccine is in the order of US\$ 120 million. Up to US\$ 30 million may be required for basic, pre-clinical and early clinical research, which can take up to five years. A first decision gate, which will be taken based on the probability of success, is the initiation of phase III efficacy trials, which may required an investment of US\$ 30 to 40 million through a 3 to –4-year period. The second critical decision gate, which must be decided even before efficacy trials are completed, is related to manufacturing and scale-up, a process which may require an additional US\$ 50-60 million over five years. In summary, after more than ten years of research and development, the potential for commercialization in the target population is essential in the decision-making process. In addition, the high costs and perceived low probability of success are important disincentives to invest in early stages of product development.

### **Phase III efficacy trials—a significant barrier**

Phase III efficacy trials represent a significant barrier given their expenses and risk. They are critical to finding out what vaccine concepts induce protective immunity, and what the level of protection is. However, conduct of phase III trials is plagued by a poor understanding of immune responses required to successfully protect against HI/AIDS, and by the expenses and risk involved in the conduct of these trials. (They are lengthy and expensive, of uncertain outcome, and may require major investments in manufacturing capacity.) These real or perceived obstacles, related to both science and business, act as disincentives to move candidate vaccines into phase III trials.

## **World Bank explores potential mechanism to accelerate development of AIDS vaccines for less developed countries**

Based on the above analysis, the WB is exploring potential mechanism to accelerate the development of AIDS vaccines for less developed countries:

- (a) policy dialogue;
- (b) “pull” mechanisms, including expand lending for existing vaccines, providing better information on less-developed country markets, and assuring a market (through a vaccine purchase fund, contingent lending, or high-profile signing of intent); and
- (c) “push” mechanisms, directly supporting vaccine R&D (through grants to organizations like IAVI or UNAIDS, or lending to countries), or reducing the economic risks of vaccine clinical trials.

The WB Task Force continues implementing the demand studies in developing countries. This is accomplished through the identification of country backgrounds (economic impact of AIDS, spending on vaccines, size and accessibility of risk groups for vaccine utilization); modelling exercises (the impact of vaccines vs. other interventions, and the cost-effectiveness of vaccine use); and assessment of potential markets (through willingness to pay studies given vaccine characteristics, including estimated number of doses demanded). This is proceeding through a consultative process, which started in March 1999, with a meeting in Paris. The meeting consisted of industrial country partners (and UNAIDS participants), to update partners on activities and findings, to identify possible strategies and to obtain feedback (role of the WB, possible strategies, next steps). Developing country consultations are planned in Thailand (conducted in May 1999, with collaboration of UNAIDS), South Africa, India, and Brazil, to update policy-makers on findings, to discuss possible actions of the WB, and to obtain feedback on the value of proposed strategies.

### **3.3 World Health Organization, Department of Vaccines and Other Biologicals, Geneva, Switzerland**

(Presented by Dr Teresa Aguado)

#### **Collaborative project between WHO and UNAIDS exploring novel approaches for HIV vaccine development**

A collaborative project between WHO and UNAIDS to explore novel approaches for HIV vaccine development has been implemented since June 1997, with financial support from the Government of Japan. These provided funds have been used to organize a major scientific meeting, two technical consultations, and to provide catalytic funding to selected target research proposals.

This collaborative project is geared to developing countries’ needs, identifying opportunities, with limited funding, to have an impact. The project is targeting: “easy”/inexpensive approaches; technologies that can facilitate development of candidate vaccines for different HIV-1 subtypes; promoting the development of candidate vaccines that could rapidly move to phase I trials; and involving scientists from developing countries.

#### **Technical consultations support further exploration of BCG-vectored HIV vaccines**

A technical consultation held in Geneva (August 1997) recommended to encourage and support work aimed at further exploring BCG-vectored HIV vaccines, including:

- collaboration with Dr Honda (NIID, Tokyo) to: study the neutralizing ability of antibodies induced in monkeys, assess the stability of rBCG plasmids in vaccinated monkeys, and to prepare for a future IND application;
  - assessment of the capability of the BCG vectors to accommodate larger and multiple genes; and
  - comparison of episomic constructs to other type of constructs.
- In addition, the 1997 consultation recommended work related to: the identification of CTL epitopes and HLA restrictions in subtypes other than B;
  - pre-clinical work on mucosal immunization with DNA vaccines; and

- generation of subtype A SHIVs.

A second technical consultation, held in September 1998, recommended concentrating the effort on the BCG approach, specifically:

- to continue work in the areas recommended before; and
- to accelerate progression of candidate vaccines to phase I trials.

Different projects are being supported along the recommendations made by the two technical consultations.

### **NIID joint meeting on AIDS vaccine research in Asia**

In addition, UNAIDS, WHO and the NIID of Japan, organized a joint meeting on “AIDS Vaccine Research in Asia: Needs and opportunities” (Tokyo, October 1998), attended by 59 scientists from 8 countries in the region and co-workers from the US and Europe. A full report of this meeting has been published (AIDS 1999, 13:UNAIDS1-UNAIDS13).

The Committee was also briefed about the WHO plans to create an “Intercluster Vaccine Research” (IVR) activity, to better coordinate vaccine activities, which are presently located in two different WHO clusters (Health Technology and Pharmaceuticals and Communicable Diseases).

### **3.4 International AIDS Vaccine Initiative (IAVI), United States of America**

(Presented by Dr Seth Berkley)

#### **The International AIDS Vaccine Initiative (IAVI) mission**

The International AIDS Vaccine Initiative (IAVI) mission is to accelerate the development of safe, effective, accessible preventive AIDS vaccines for use throughout the world. To achieve this, IAVI works with public and private sector institutions to accelerate progress on three fronts: (a) speeding up scientific progress towards a vaccine; (b) mobilizing political support through advocacy and education; and (c) encouraging industrial involvement in AIDS vaccine development.

#### **Creating AIDS vaccines for developing countries**

The IAVI was established in 1996 as new independent organization, focusing on creating AIDS vaccines for developing countries. Launched by the Rockefeller Foundation, IAVI is now supported by private foundations, multilateral institutions (including UNAIDS), corporate sponsors, and individuals. IAVI operates through a secretariat in New York City, with representation in several industrialized and developing countries. An international Board of Directors guides IAVI’s overall strategy and an international Scientific Advisory Committee advises Its scientific programme agenda..

#### **Vaccine development partnerships teams**

In 1998 IAVI created two vaccine development partnerships teams, which received awards to pursue the development of candidate vaccines based on the T-cell epitopes of subtype A strains, expressed by the Ankara strain of Vaccinia (a collaboration between scientists in the UK and Kenya), and the use of the VEE replicon to express subtype C sequences (a collaboration between US and South African scientists). New projects will be considered for funding in the near future. In creating these vaccine development partnerships, the IAVI acted as a social venture capitalist, using financing to secure intellectual property agreements to ensure that these vaccines are available in developing countries at a reasonable price.

#### **Industry’s participation in AIDS vaccine effort critical**

IAVI believes that industry’s participation in the AIDS vaccine effort is critical. It will continue to meet with leaders and scientists in all major vaccine companies, working with them to identify barriers and create solutions. IAVI also believes that depending on the technology, developing country manufacturers may be critical to rapid distribution and inexpensive manufacturing. IAVI and its partners (especially the World Bank) are also

exploring the possibility of establishing vaccine development and purchase funds, or related financial instruments intended to encourage the commercial sector's investment in the AIDS vaccine enterprise.

### **Main communication objectives**

IAVI's main communication objectives are to raise national and international understanding about the need for an AIDS vaccine, to foster scientific cooperation and collaboration, and to leverage growing financial support for the development of all promising experimental vaccines. IAVI produces "The IAVI Report", devoted exclusively to global news about HIV vaccine development, which is distributed free of charge to more than 10 000 people in over 100 countries.

### **3.5 National Institutes of Health (NIH): Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), United States of America**

(Presented by Dr Margaret Johnston)

The NIH Vaccine and Prevention Research Programme supports the discovery and development of vaccines and other biomedical and behavioural interventions to prevent AIDS. For the last few years vaccine activities have been coordinated through three branches (Pre-clinical Research, Clinical Development, and Efficacy Trials), but the programme is currently being re-organized and novel programmes are being designed:

#### **Innovation Grant Programme**

An Innovation Grant Programme has been launched to encourage entrance of novel and innovative concepts into the research pipeline. The programme supports exploratory/developmental research, providing short-duration grants (one to two years) for a maximum of US\$ 150000 for preliminary studies of highly speculative nature. Areas of emphasis have been: envelope structure and function, creation of new animal models, antigen processing, cellular immunity, live vectors, adjuvants, and optimization of nucleic acid expression cassettes. Areas on emphasis for the new funding period (September 1999) include induction of T cell memory and whole-inactivated approaches.

#### **HIV Vaccine Research and Design Programme (HIVRAD)**

The HIV Vaccine Research and Design programme (HIVRAD) replaced the National Cooperative Vaccine Development Groups (NCVDG) programme and funds traditional hypothesis-driven, mid-stage, targeted research on vaccine design: correlates of immunity, animal model development and utilization, immunogen structure, design and pre-clinical testing of novel candidates, and antigen processing.

#### **The Integrated Pre-clinical/Clinical AIDS Vaccine Development (IPCAVD)**

The Integrated Pre-clinical/Clinical AIDS Vaccine Development (IPCAVD) programme encourages multidisciplinary, iterative refinement and optimization of candidate vaccines to bridge pre-clinical and clinical research in the following areas: pre-clinical research (vaccine design, delivery systems, methods to enhance or direct immune responses, vaccine production and IND-related testing, and human testing). Substantive preliminary data are required in the applications and human testing is expected to begin within the five-year period of the award.

#### **The HIV Vaccine Design and Development Teams**

The HIV Vaccine Design and Development Teams encourage advancement of candidate vaccines through a focused, multidisciplinary, development-based, milestone-driven-oriented approach, supporting the complete range of studies from research through product development, pre-clinical development, and clinical trials.

#### **The HIV Vaccine Development and Production Programme**

The HIV Vaccine Development and Production Programme assists investigators in developing clinical lots of meritorious candidate vaccines and obtaining the data and approvals necessary for clinical testing.

### **Additional research and development resources**

In addition to the above activities, three additional research and development resources are available: simian evaluation units (to evaluate promising SIV/HIV candidates in non-human primates), vaccine reagents (to procure or produce reagents essential to AIDS vaccine development and evaluation) and assay support (to adapt, standardize and perform virological and immunological analysis).

Field activities have been conducted through the domestic AIDS Vaccine Evaluation Units (AVEU) and the international HIVNET (dealing with vaccines, microbicides, behavioural change, STD interventions, and perinatal transmission). These networks are in the process of transitioning to two network concepts: The Vaccine Trial Network (VTN) and the Prevention Trial Network (PTN). The VTN will include a leadership group, support to laboratory studies, support to data management and analysis and national and international sites.

### **Vaccine Research Center (VRC)**

A Vaccine Research Center (VRC) is being established at the NIH campus (building under construction). Its mission is to conduct research that facilitates the development of vaccines for human disease, with an initial primary focus on vaccines for AIDS. The VRC will have the following activities:

- (a) Basic research to establish mechanisms of long-lasting protective immunity against HIV and other pathogens that present special challenges to vaccine development;
- (b) The conception, design, and preparation of vaccine candidates for HIV and other diseases;
- (c) Laboratory analysis, animal testing, and clinical trials of such candidates. The VCR will conduct a comprehensive programme of research on the NIH intramural campus and work with scientists in academic, clinical, and industrial laboratories through a programme of national and international collaboration.

The VRC will actively seek industrial partners for the development, efficacy testing, and marketing of vaccines and focus the development of new methodologies and training opportunities that will benefit all vaccine researchers.

During the discussions, it was pointed out that the NIH sees its HIV vaccine development mission not only as having a domestic focus, but also as an international responsibility.

### ***3.6 Military programme: The US Military HIV Vaccine Research & Development Program. Department of Defence (DoD) Program: a cooperative agreement between the Walter Reed Army Institute of Research (WRAIR) and the Henry M. Jackson Foundation (HMJF), United States of America***

(Presented by Dr Deborah L. Birx)

#### **HIV poses a significant threat to the US military**

HIV infection is epidemic in almost every less well developed and potentially unstable region of the world, and the risk of exposure to HIV by DoD personnel is high. In response to this military-relevant infectious disease threat, a US congressionally mandated research programme was begun in 1986 to assess and mitigate the impact on the US military readiness by monitoring the spread of HIV infection in military forces and by developing methods to prevent infection. As lead agent for infectious disease research in DoD, the US Army has a highly targeted programme to address the military concerns of HIV: surveillance of infectious rates and HIV subtypes around the world; development of vaccines and other countermeasures to prevent infection; and clinical studies to avoid immune deficiency. The primary focus of this programme is the prevention of HIV infection in military personnel. The programme recognizes that HIV infection is relevant to today's US military and that, ultimately, the administration of an effective vaccine may be needed to protect military forces against HIV infection. Success in achieving this goal will have broad-reaching application for HIV prevention in civilian populations worldwide.

## **Vaccine discovery, development and evaluation programme**

In addition to education, surveillance, and threat assessment, a vigorous programme of vaccine discovery, development, and evaluation is being implemented. The programme collaborates with multiple US and international agencies and a network of DoD Overseas Biomedical Research laboratories to provide an effective surveillance network to monitor the emergence of virological trends in the pandemic and to serve as permanent platforms for evaluation of candidate vaccine in overseas endemic settings. The programme has effectively leveraged its vaccine R&D funding and resources to pursue a number of novel candidate vaccine approaches and formulations. Extensive use of Cooperative Research and Development Agreements (CRADAs) with private industry greatly extends the resources of the US Military HIV Research programme.

## **US Department of Health and Human Services efforts**

The US Military HIV Vaccine Research and Development efforts augment and complement efforts of the US Department of Health and Human Services. Domestic clinical trials of candidate vaccines based on the strains of HIV indigenous to the USA (genotype B) are conducted. This is done to gain familiarity with these novel constructs and to develop an initial safety database to facilitate transition of specific vaccine approaches for evaluation overseas with candidate vaccines. Such vaccines are specifically designed from the HIV strains, which circulate overseas, and, importantly, to harmonize (with the US National Institutes of Health) assays that are critical for evaluating the effects of candidates on the human immune system.

## **The US Military HIV vaccine programme**

Currently, three distinct classes of HIV vaccine candidates (recombinant subunit envelope, canarypox-vectored genes with subunit envelope boost, and facilitated plasmid DNA) are in clinical trials conducted by the US Military HIV vaccine programme. Clinical evaluation of these constructs is underway in the USA and in Thailand. The focus is to select and then evaluate the most immunogenic of safe candidate vaccines for their ability to protect individuals from HIV infection. The current lead candidate is canarypox-vectored HIV (vCP1521) manufactured by PMC, boosted by a recombinant subunit envelope (genotype E). Large-scale field efficacy testing is planned to begin in collaboration with Thailand during 2001.

## **Pre-clinical R&D of novel candidates**

Pre-clinical R&D of a number of novel candidates is being pursued, primarily through CRADAs with industry partners. In addition to small animal and macaque studies of novel immunogens (many of which are conducted under the auspices of an NIH contract as a Simian Evaluation Unit), the programme is poised to play a role in the initial manufacture (by good manufacturing practices (GMP)) of several of these new-candidate vaccines. This is possible through the Walter Reed Army Institute of Research bioproduction facility at Forest Glen, Maryland. Currently, the programme plans to produce (with corporate partner AlphaVax and the IAVI) HIV particles based on the VEE replicon platform, and (with corporate partner AVANT Immunotherapeutics) recombinant anthrax antigen-vectored HIV core polypeptides, which are called Therapore<sup>TM</sup>HIV.

## **Field efforts to prepare for large-scale testing of promising HIV candidate vaccines underway in Thailand since 1991**

Field efforts to prepare for large scale testing of promising HIV candidate vaccines have been underway in Thailand since 1991. During this period, there has existed an effective alliance with multiple US Government agencies (CDC, NIH, and USAID). Efforts in collaboration with the Royal Thai Government have been extensive: national HIV surveillance; development of multiple field sites as potential venues for efficacy testing of promising candidates; creation of a phase I/II AIDS vaccine evaluation network at four academic and Government sites; development of extensive in-country laboratory capability and technology transfer to conduct vaccine evaluations; and successful planning, implementation and completion of large multicenter human clinical trials. All vaccine development in Thailand is conducted with candidates incorporating elements of indigenous Thai HIV (genotype E).

More recent efforts, beginning in 1998, have focused on development of a similar field capability in collaboration with Government and academic collaborations in Uganda. Vaccine development opportunities in Uganda are unique and complementary to other programme efforts. Distinct genotypes of HIV (A and D) co-circulate in this region of the world. The ability to address efficacy and its breadth requires access to sites with such viral diversity. This is a critically important question to be answered in developing vaccines. Again, close coordination with other US Government agencies is envisioned, and will be critical to the success of US-sponsored vaccine development in Uganda.

### **3.7 The US Centers for Disease Control and Prevention (CDC)**

(Presented by Dr William L. Heyward)

#### **Long history in vaccine development, evaluation, and programme implementation**

CDC has a long history of involvement in vaccine development, evaluation, and programme implementation, including vaccines for the prevention of smallpox, polio, hepatitis B, *Haemophilus influenzae* type B, Japanese B encephalitis, meningococcus, rotavirus, and others. Once a safe and effective vaccine is licensed and available, CDC has a major role in the USA in the development and evaluation of strategies and recommendations for vaccine use; surveillance of infection/disease and vaccine-related adverse events; the implementation and evaluation of vaccine programmes; in epidemic investigations, and the development and standardization of laboratory methods and reagents. The CDC also has an important role in providing health care education and communication, as well as technical assistance to states, international agencies and developing countries. Although some vaccine-related basic research activities are conducted at CDC, most of CDC's vaccine-related efforts are directed toward the latter states of vaccine development, including phase III efficacy field evaluation of candidate vaccines and post-licensure evaluation (phase IV demonstration projects) and programme implementation.

#### **Establishment of HIV vaccine unit in September 1998**

To date, CDC has not had a major role in the ongoing basic research to develop HIV vaccine candidates. However, as HIV vaccine candidates are now entering large-scale phase III trial field testing, CDC is committed to the HIV vaccine development and evaluation effort, both nationally and internationally. In September 1998, the HIV Vaccine Unit was formally established to provide a focal point for the conduct and coordination of HIV vaccine activities at CDC. The HIV Vaccine Unit is in the Epidemiology Branch, Division of HIV/AIDS Prevention, of the National Center for AIDS, STD, and TB Prevention. The Unit works closely with the Division of AIDS, STD, and TB Laboratory Research of the National Center for Infectious Diseases, which conducts HIV vaccine-related laboratory research and support of field activities, the National Immunization Program, the National Vaccine Program Office, and other CDC offices and programmes.

#### **CDC's HIV vaccine activities are primarily focused around the following programmatic areas:**

- (a) Phase III efficacy trial in the USA;
- (b) Phase III efficacy trial in Bangkok, Thailand;
- (c) Development and evaluation of an HIV vaccine in Africa; and
- (d) Programme support and evaluation: ethics, partnerships, education, and communication.

#### **CDC to co-sponsor the trial with VaxGen beginning September 1999**

In June 1998, a phase III efficacy trial was begun to evaluate the safety and protective efficacy of rgp120 B/B vaccine (AIDSVAX™, VaxGen, Inc., Brisbane, CA, US) among 5000 homosexual men and women at high risk of HIV infection in approximately 60 sites in the USA. This trial is a randomized, double-blind, placebo controlled trial and is expected to last 3 years. Starting in September 1999, CDC will co-sponsor the trial with VaxGen. In a selected number of sites, CDC will also sponsor other trial-related epidemiologic, laboratory, and social/behavioural research. These studies will include determination of HIV incidence in the community (using the "sensitive/less sensitive" testing strategy developed by CDC) and

genetic characterization of incident viruses; assessment of the frequency and impact of post-exposure prophylaxis and anti-retroviral therapy; evaluation of the informed consent process; characterization of the extent and determinants of unblinding and development of interventions to minimize unblinding; identification of determinants to minimize loss to follow-up; assessment of HIV risk behaviour change among trial participants to determine if increased HIV risk behaviour is associated with perceived vaccine protection; development of methods to optimize the identification, recruitment and retention of persons at greatest risk of HIV infection; and evaluation of the impact of a phase III trial on communities, trial participants, and researchers. In conjunction with this efficacy trial, CDC is also collaborating with the NIH's AIDS Vaccines Evaluation Groups (AVEG) to develop and evaluate a simple serologic assay to differentiate vaccine-induced antibody from antibody due to infection.

Since 1994, CDC has collaborated with the Bangkok Metropolitan Administration (BMA), the World Health Organization (WHO), and UNAIDS to develop a cohort of injecting drug users (IDUs) to determine the feasibility of conducting a phase III efficacy trial in this population. These studies included determination of HIV incidence and risk behaviours leading to HIV infection, genetic characterization of incident viruses, ability to successfully follow IDUs over time, and assessment of their willingness to participate in a phase III trial. In March 1999, a phase III efficacy trial was initiated in Bangkok among 2 500 IDUs attending 17 drug treatment clinics to evaluate the safety and protective efficacy of rgp120 B/E vaccine (AIDSVAX™, VaxGen). This trial is being conducted by VaxGen, Inc., the BMA, the Mahidol University, Faculty of Tropical Medicine, and CDC's HIV/AIDS Collaboration (a joint collaboration between CDC and the Thailand Ministry of Public Health) in Bangkok. This trial is a randomized, double-blind, placebo-controlled trial and is expected to last three years. CDC will be assisting the Thai institutions by providing epidemiologic and laboratory technical assistance including assessing the vaccine's primary protective effect, secondary endpoints (CD4<sup>+</sup> cell counts, viral load), and evaluation of secondary HIV transmission from the infected IDU to their sexual partner. Social-behavioural studies as described above will also be conducted.

### **CDC initiating research to promote development of DNA vaccine for Africa**

In collaboration with Yerkes Primate Research Center and the Emory Center for Vaccine Research, CDC is initiating research to promote the development of a DNA vaccine for Africa utilizing HIV subtypes A, C or D. Currently, CDC and Yerkes are conducting experiments of various DNA vaccine constructs and combinations in macaque monkeys. In conjunction with this pre-clinical research, CDC is exploring the potential for conducting vaccine trials in several African sites where CDC is currently working (Botswana, Côte d'Ivoire, Kenya, South Africa and Uganda). In the laboratory, CDC is developing rapid methods to determine HIV genetic subtype in populations being considered for HIV vaccine trials. These methods include subtype-specific serologic tests, restriction-fragment-length-polymorphism (RFLP) analysis, and heteroduplex mobility assays. Evaluation of the "sensitive/less sensitive" testing strategy to determine HIV incidence in populations with non-subtype B HIV infection is also being evaluated.

Certain programme and evaluation activities are fundamentally necessary to support and promote the research activities described above. These ongoing and future activities are required in order to efficiently and effectively conduct successful HIV vaccine trials and related research. These broad activities are in the areas of ethics, partnership, and education/communication.

### **CDC assists UNAIDS with development of international guidelines for vaccine trials**

CDC has assisted UNAIDS with the development of international guidelines for the ethical conduct of HIV vaccine trials, as well as development of guidelines for developing countries to assess comprehension and willingness to participate in vaccine efficacy trials. CDC will also evaluate the current ethics knowledge base regarding the design and implementation of HIV vaccine efficacy trials and identify resources to meet accepted standards.

In addition, CDC will be working with many national partners, including the NIH, the DoD, the US Agency for International Development (USAID), the Advisory Council on Immunization Practices (ACIP), the National Vaccine Advisory Committee (NVAC), the Association of State and territorial Public Health Laboratory Directors (ASTPHLD), the Association of State and Territorial Health Officers (ASTHO), the Council of State and Territorial Epidemiologists (CSTE), and others to develop guidelines and strategies for the implementation of an HIV vaccine (on availability of a licensed vaccine). Internationally, CDC works with WHO, UNAIDS, USAID, the World Bank to provide technical assistance when necessary.

### **CDC work with community representatives and action boards**

Working with community representatives and action boards, CDC is developing and evaluating strategies to promote the understanding among communities of the need for HIV vaccine development and the biomedical and social challenges that such development entails. Using various means of communication, including a website, the *Morbidity and Mortality Weekly Report*, and other strategies. CDC is disseminating information on and results from all CDC's HIV vaccine research activities.

### **3.8 The National Agency for Research on AIDS (Agence Nationale de Recherches sur le SIDA .-ANRS-), France**

(Presented by Dr Michel Kazatchkine).

ANRS provides financial support to:

- (a) peer-reviewed programmes originating from research laboratories (INSERM, CNRS, Institute Pasteur, Universities);
- (b) a joint programme with Pasteur-Mérieux-Connaught (PMC); and
- (c) to a Network of volunteers for vaccine trials.

In addition, ANRS has supported the organization of the “Cent Gardes Meetings” and is planning to co-sponsor a yearly conference on HIV vaccines, alternating between USA and France (or other European venues).

The work is being conducted through a Vaccine Research Network (Réseau d'Investigations Vaccinales ANRS –RIVac) with a task force composed of 13 research laboratories, 13 programmes, and 153 scientists. The network includes a Neutralization Group (9 projects, exploring the usefulness and breadth of neutralizing antibodies); a Facilitation Group (4 projects, exploring the biological significance of facilitating antibodies); a Cellular Immunity Group (13 projects, exploring how to improve cellular immune responses); and a Mucosal Immunity Group (6 projects, exploring how to generate mucosal responses). These activities are conducted through six programmes: basic research, animal models (macaque and cat), constructs, standardization of methods, phase I vaccine trials, and active immunotherapy trials.

### **Different HIV vaccine approaches explored with ANRS support**

Different HIV vaccine approaches are being explored with ANRS support, including: Vector based vaccines (canarypox, adenovirus in macaques, Semliki Forest Virus in macaques, BCG), peptide vaccines, subunit vaccines (oligomeric gp160), lipopeptides and DNA vaccines. In collaboration with PMC, candidate vaccines are being developed, not only based on subtype B strains, but also on subtypes A, C, D and E.

Immunogens developed with ANRS support include different canarypox constructs: vCP125 (gp160MN), vCP205 (gp120MN/gagLAI/protLAI), vCP300 (gp120MN/gagLAI/protLAI/CTL domains *nef* and *pol* LAI); vCP1452 (gp120MN/(tm/gag/prot/CTL domains *nef* and *pol*)LAI); and lipopeptides: LP& (*nef*66-97, *nef*117-147, *nef*182-205, *gag*183-214, *gag*253-284, V3c), LP4T (*nef*/TT, *gag*/TT, *pol*/TT, RT/TT), and CLTB.36 /T(p24E-LAI | B (V3MN)) .

Several phase I HIV vaccine trials have been conducted in France with ANRS support, including trials to assess memory induction, as follows:

Primo-Vaccination	01	vCP125 + gp160 (PMC)
	02	gp160 + peptide V3 (PMC)
	03	vCP205 + peptide V3/gag (PMC)
	07	vCP300 (PMC)
	04	6 lipopetides
	10	vCP1452 + 6 lipopeptides
Memory-induction	11	5 lipopeptides
	05	01 + vCP205 (PMC)
	06	02 + vCP205 (PMC)
	08	03 + vCP205/peptide V3/gag (PMC)
	09	03/07 + 6 lipopetides
	04bis	Boost
	09bis	Boost

In addition, a number of trials have been conducted (or are being conducted) in the USA in collaboration between ANRS and Industry (PMC), as follows:

ACTG 326	vCP205	27 vol (ongoing)
WRAIR-RV124	vCP205/gp169MN-LAI-2/PCPP or alum	68 vol (ongoing)
AVEG 012A	vCP125/vcp65/gp120 Chiron	30 vol (finished)
AVEG 012B	vCP125/vCP65/gp120 Chiron	101 vol (finished)
AVEG 0122	vCP205/vCP65/gp120 Chiron	75 vol /finished)
AVEG 026	vCP300/gp120 Chiron	140 vol (finished)
AVEG 029	vCP205/vCP65/gp120 Chiron	34 vol (finished)
AVEG 022A	vCP2095/gp120 Chiron	150 vol (follow-up)
AVEG 027	vCP205/vCP65/gp120 MN VaxGen	84 vol (follow-up)
AVEG 032	vCP205(/vCP65/p24/gp120 Chiron	64 vol (follow-up)
AVEG 033	vCP205/GM-CSF	36 vol (follow-up)
AVEG 034	vCP205/vCP1433/vCP1452/gp160 MN/LAI-2	100 vol (follow up)
AVEG 202	vCP205/gp120 Chiron	420 vol (follow up)

In addition, in February 1999 a trial with vCP205 was initiated in Uganda, with support from the US NIH (HIVNET 007).

A Network of volunteers for HIV vaccine trials was organized independently of industry. It was developed through public announcements. Volunteers are not remunerated, and low-risk volunteers are selected based on their individual decision, not influenced by group pressure. A cohort (expoCI) has also been developed in Abidjan, Côte d'Ivoire.

ANRS is planning to spend approximately US\$ 8 million dollars a year on vaccine research over the coming two to three years, and the entire French programme will be reviewed in the autumn of 1999 by an international advisory committee, which will issue specific recommendations.

### **3.9 The National Institute of Infectious Diseases (NIID) and other vaccine research, Japan**

(Presented by Dr Yoshiyuki Nagai)

#### **BCG-HIV recombinant vaccines**

HIV/AIDS vaccine projects that started several years ago and are ongoing in Japan include the use of recombinant BCG-based vectors expressing the V3 loop of HIV-1 (subtypes B and E) (Honda *et al*, at the NIID, Tokyo), live attenuated SHIV chimera viruses with the accessory genes deleted (Hayami *et al*, Kyoto University), and DNA vaccines with various HIV-1 structural genes (Okuda *et al*, Yokohama City University).

Animal protection experiments have been conducted with the BCG-V3 recombinant candidate vaccine, using cynomolgus monkeys challenged with SHIVs containing a homologous V3 sequence. Immunization failed to induce complete protection, but reduced the virus load by two logs. Although the virus load was reduced by vaccination, virus production appeared to persist longer in vaccinated monkeys when compared with controls. Recombinant BCGs expressing various other epitopes in addition to V3 are being developed, in the hope that their use in combination will confer stronger protection.

### Recent new approaches explored

More recently, the following new approaches are being explored:

- (a) Large quantity production of HIV-1 structural proteins using recombinant Sendai viruses (SeV) (Nagai *et al*, NIID, Tokyo);
- (b) Host responses to and immunogenicity of deglycosylated SIV envelope protein (Nagai *et al*, NIID, Tokyo);
- (c) Co-injection of an infectious DNA clone encoding the FSIV chimera SIVmac239 envelope with the ecotropic Friend murine leukaemia virus (FLV) and the DNA encoding the FLV receptor (mouse cationic amino acid transporter 1, mCAT1) (Matano *et al*, NIID, Tokyo).

SeV is an envelope virus with a negative sense RNA genome of about 15.4 kb, and it has a broad cellular host range, reaching quite a high copy number in infected cells. A technology has been developed, which allows infectious virus recovery from the SeV cDNA, and hence the expression of foreign genes from recombinant SeV. The quantity of HIV-1 gp120 expressed by this recombinant technology is as high as 6 mg per liter of culture medium, the highest among available mammalian cell systems. Expressed to date are various modules (gp120, gp140, and gp160) of HIV-1 Env of different genetic subtypes (B and E), as well as SIV Gag. The SeV-based expression system thus facilitates large quantity production of HIV-1 proteins, which could be used as immunogens directly, or after various chemical and genetic modifications. As SeV causes a surface infection localized to the respiratory tract, a generalized mucosal immunity could potentially be induced if SeV vectors are used as a live recombinant vector vaccine. Studies on the feasibility of using SeV-based expression systems, to both produce sub-unit vaccines, or as a live vectored vaccine, are being conducted in mice and monkeys.

The Env protein of HIV-1, and that of SIV, is heavily glycosylated. The clustered sugar chains on the virion surface are thought to mask potential epitopes. In designing Env-based vaccines, it has to be evaluated how far the heavy glycosylation contributes to immune evasion of these viruses. There is also a need to define whether or not the removal of sugar chains from the Env will increase its immunogenicity and ability to induce protective immunity. To address these issues 5 of the 23 N-linked sugar chains from SIVmac239 gp120 have been removed by site-directed mutagenesis, without impairing viral infectivity, and these products are presently being evaluated in macaques. Immune responses to the wild type and deglycosylated gp120 are also being compared in mice expressing the proteins by recombinant vaccinia viruses.

### FLV-SIV chimera a potential approach to safer and effective live vaccine

The FLV-SIV chimera is a potential approach to a safer and effective live vaccine. The previous concept of live attenuated SIV and HIV vaccines was based mainly on virus attenuation by deletion of accessory genes such as *nef*, *vif*, and *vpr*. Such deletion mutants, however, retain some pathogenicity or can potentially revert to wild type. On the other hand, antigen production levels from DNA vaccines appear to be generally low and, in some situations, may not be sufficient to confer appropriate protective immunity. The receptor (mCAT1) of FLV is expressed in murine cells and tissues, but not in cells from humans and non-human primates. The idea of co-injection of FLV-SIV chimera DNA and mCAT1 DNBA involves the construction of an infectious DNA clone encoding the FIV Env in place of SIV Env in the SIV background, and the replication of the generated chimeric virus from the DNA in a restricted site of rhesus macaque, where FLV receptor is expressed by the co-injected mCAT1 DNA. A preliminary study suggested that such restricted chimera virus replication can induce some protection against SIV in rhesus macaques.

### **3.10 The National Institute of Biological Standards and Control (NIBSC), United Kingdom**

(Presented by Dr Geoffrey Schild)

AIDS vaccine research activities in the UK were greatly stimulated in the past through the Medical Research Council (MRC) AIDS Directed Programme (1986-1994). Its legacy is a variety of AIDS vaccine activities being conducted in multiple institutions, including the National Institute of Biological Standards and Control (NIBSC), in London.

The NIBSC includes several laboratories directly or indirectly working on HIV vaccine-related activities, and hosts the “AIDS Reagents Project”, which is one of the two repositories of the UNAIDS Network for HIV Isolation and Characterization (the other being located at the NIH).

The NIBSC has made important contributions, especially in the area of animal models, having described for the first time the effect of anti-host immune responses in eliciting protection against SIV challenges in monkeys. The NIBSC could be a valuable resource for future studies aimed at comparing results from vaccine trials in humans and in experimental models.

Because of its regulatory expertise, the NIBSC could also contribute to collaborative studies to standardize reagents and assays for HIV vaccine research.

### **3.11 The HIV vaccine development programme, Thailand**

(Presented by Dr Natth Bhamarapravati)

The Thai national policy regarding HIV vaccine development and evaluation has passed through different phases.

#### **First phase**

During the first phase (1994-1995), Thailand was willing to facilitate trials of HIV vaccines that were safe and immunogenic, provided that phase I trials had been conducted in the country of origin, and that Thai investigators were responsible for the conduct of the trial with assistance and support from investigators from abroad. During this phase, the AIDS vaccine subcommittee made recommendations to the National AIDS Commission, which gave the final authorization for the trials.

#### **Second phase**

During the second phase (1995-1996), Thailand further developed the criteria for conducting HIVB vaccine trials in the country, including the following:

- (a) availability of animal data;
- (b) the candidate vaccine includes components or genes which are derived from the local E subtype;
- (c) assistance is provided to help strengthening the existing capacity for HIV isolation and characterization (including genetic, immunological and biological studies), GLP and GCP, data management (analysis, evaluation and presentation), and repositories;
- (d) under the above circumstances no requirement exists to have phase I trials conducted in the country of origin;
- (e) early dialogue on measures to ensure accessibility of vaccines to Thais and population of neighbouring countries; and
- (f) the Subcommittee would recommend that the proposal should be authorized by the Communicable Disease Control (CDC) Department, without having to return to the National AIDS Commission.

#### **Third phase**

The third phase (1996-1998) is similar to the previous one, with two additions:

- (a) that Thai investigators are encouraged to work at the pre-clinical development stage with the group that wants to conduct vaccine trials in Thailand, with an expectation to also share Intellectual Property Rights (IPR); and
- (b) serious dialogue should be conducted on vaccine availability and affordability prior to the conduct of phase III efficacy trials, obtaining a preliminary agreement or letter of intent.

### **Process of submission, review, and approval of vaccine research proposals well established**

The process of submission, review, and approval of vaccine research proposals in Thailand is well established:

- Vaccine Subcommittee briefing on the prospective trial by investigator from abroad;
- Submission of early draft proposal (not a formal submission);
- International review (such as UNAIDS);
- Domestic review by Thai investigators not necessarily connected with AIDS research;
- If the proposal is considered scientifically sound, then it is sent to the Ethical Review Committee of the Ministry of Public Health;
- Completion of approval by relevant Institutional Review Boards (IRB);
- Repeated briefings and discussions between investigators and reviewers, for possible improvements of the protocol;
- Organization of a “readiness” workshop;
- Submission of final protocol (Formal submission);
- Decision and recommendation made to the CDC (within one month of receiving the final protocol); and
- Dialogue and letter of intent from the manufacturer regarding future availability of the vaccine.

Nine HIV vaccine trials have been conducted in Thailand since 1994, including preventive (P) and therapeutic (T) trials:

- MN synthetic V3 peptide (UBI)(P).....Phase I started in June 1994.
- MN gp120 (Genentech) (P).....Phase I/II, started in February 1995.
- SF2 gp120 (Chiron) (P).....Phase I, started in August 1995
- HIV Immunogen (Immune Response) (T)....Phase II, started in March 1996.
- HIV Immunogen (Immune Response) (T)....Phase II, started in August 1997.
- HIV E/B gp120 (Chiron) (P).....Phase I/II, started in November 1997.
- HIV E/B gp120 (Vax Gen) (P).....Phase II, started in 1998.
- HIV E/B gp120 (VaxGen).....Phase III, started in March 1999.
- HIV E canarypox/gp120 .....Phase I/II pending.

### **Lessons learned**

A number of lessons have been learned:

- (a) Need to build consensus among policy/decision-makers, medical community, and the mass media;
- (b) Need to build up a sense of partnership and collaboration with investigators and manufacturers from abroad, through continuing briefing, consultation rather than using an authoritarian approach, expressing reasonable needs and expectations for infrastructure and capacity-building, advising national investigators for moderation in budget requests, and placing manpower development as a priority issue.
- (c) Consideration of ethical problems must be mandatory from the early phases of planning, using ethics to leverage many issues which are controversial, in order to get optimum and harmonizing decisions.
- (d) Use of HIV vaccine trials to foster cooperation between Thai scientists themselves and with foreign scientists, to develop policies at the National AIDS Commission and the Ministry of Public Health, and to establish close cooperation among a number of Thai institutions and Universities.
- (e) Vaccine trials have contributed to developing a number of infrastructures: Network for virus isolation and characterization, GLP and GCP training, laboratory capacity to assess immune responses, network for data management, repository for material generated from vaccine trials, molecular epidemiology, and counselling services.

- (f) Experience with the “therapeutic vaccine” trial was relevant and more demanding at the phase I/II level. Vaccinees were not healthy and trials required better and more comprehensive GLP/GCP. In the early stages of the trial, clinical endpoints were used, but new laboratory endpoints, such as virus load, can be used. Randomization was more complicated.
- (g) The role of UNAIDS was important for advocacy, as an honest broker in negotiations, providing opinion on scientific and ethical issues. UNAIDS should encourage HIV vaccine trials in countries with a reasonable level of manpower and infrastructure. Too small a country may result in “exploitative” situations. The UNAIDS catalytic funding is essential, and can be used to negotiate appropriate counterpart funding.
- (h) The process of reviewing protocols and approval of trials must be transparent. High officials of the Ministry of Public Health or of the Government, should be updated periodically on the status of reviews.
- (i) Confidentiality of volunteers should be strictly enforced. Press releases rather than press conferences are preferred, if possible.
- (j) Good explanations must be given of why more than one HIV vaccine trials are conducted.
- (k) Positive reasons for manufacturers for the selection of countries to conduct clinical trials include: high HIV incidence, limited therapeutic interventions, better education of volunteers, good compliance, no racial/ethnic/religious conflicts, political and economic stability, reasonable level of medical and health, manpower and infrastructure, and cost-effectiveness.
- (l) Among the problems identified are the following:
  - need to better understand and harmonize roles of the IRB of different institutions in multicenter trials;
  - manpower; too few scientists, long term to develop one, rapid changes in technology;
  - extra financing for the infrastructural unit(s) is essential.

#### Future activities of HIV vaccine development programme in Thailand

- a) Phase I/II of a prime boost trial, using Canarypox-HIV-E, followed by gp120 or gp160. 1
- b) Workshop to evaluate access to future volunteers to support HIV vaccine trials (phase I/II, and phase III on high risk cohorts or on community based trials);
- c) Planning for trials with BCG-vectored candidate vaccines;
- d) Planning to incorporate subtype A, and possibly subtype C, components in the trials;
- e) Preparation for accessibility issues;
- f) Development, with the Thai FDA, of guidelines for phase IV trials, with limited imports to be paid by public/private financing;
- g) Development of alternate models for vaccine delivery, and determination of impact and cost/benefit for interruption of transmission (i.e. in an effectiveness trials involving 500 000 young soldiers).

### **3.12 National plan for AIDS vaccines—activities, Uganda**

(Presented by Mrs Sophia Mukasa Monico)

With the assistance of WHO, Uganda developed in 1992 a National Plan for AIDS Vaccines, which provided the framework for implementing multiple activities, leading to the initiation of a phase I/II HIV vaccine trial in February 1999. This trial is being conducted with a canarypox-HIV candidate vaccine (vCP205) and supported by the US NIH.

A progress report of this trial was presented. Twenty-two participants were randomized (17 males and 5 females and are following the protocol schedule of immunization (6 completed three doses, 12 have received two doses, and four have received only the first dose). An additional 39 volunteers were screened for EBV cell-line transformation, with anticipated start of clinical screening by first half of July. To date only three serious adverse events have been reported, and all have been resolved without continuing sequelae. A revised protocol is currently being discussed to correct operational issues related to screening, and to modify eligibility criteria considerate of endemic health problems in Uganda.

The trial began on 8 February 1999 with the initial recruitment of six eligible volunteers. Considerable publicity was given to the launching of the trial. This generated widespread public interest and debate. Some of the pertinent issues raised included:

- whether the volunteers would be experimentally infected (challenged);
- need to carry out the vaccine trials to have their positive conclusion;
- pride of Ugandans to be participating in such an important and crucial step in the control of HIV;
- fears that vaccine was not based on strains circulating in Uganda;
- confidence in the manufacturer's ability to take care of any possible side-effect arising from the vaccine;
- caution regarding possible compensation in case of side-effects; and
- danger of complacency and need to gear up traditional preventive methods.

No logistical problems have been experienced concerning the vaccination schedule. All procedures and processes related to randomization, vaccination and follow-up have been followed according to the protocol. The final hurdle related to the protocol will be to identify, screen, and enrol the remaining 18 participants.

### **3.13 National STD/AIDS Programme, Brazil**

(Presented by Dr Jose R. Carvalheiro)

Since 1980, and until June 1999, Brazil has officially reported 155 590 cases of AIDS, and UNAIDS estimates that by mid-1998 there were 580 000 adults and children infected with HIV in the country. A National STD/AIDS Programme is functioning in all 26 states and in the Federal Capital City. It has undertaken most AIDS prevention and control actions, with limited participation of the private sector. The National Programme is responsible for epidemiological surveillance, and provides combination antiretroviral therapy to patients meeting the criteria defined by a panel of experts. (In 1998 alone, more than US\$ 600 million were spent for that purpose). The National Programme also maintains Anonymous HIV Testing Clinics and distributes condoms free of charge. Social communication has been intense and continuous and a Network of Human Rights of People Living with HIV/AIDS has played an important role in acquiring and preserving social rights.

The Brazilian authorities' initial response to the GPA/WHO suggestion in 1991 to involve Brazil in the international effort to develop and test HIV vaccines was initially rejected. A change of national authorities, however, led to a recognition of the severity of the HIV/AIDS problem, and to the importance of Brazil joining the international AIDS vaccine effort.

#### **The National AIDS Vaccine Plan**

The Ministry of Health established a National HIV/AIDS Vaccine Committee, and with the assistance of GPA/WHO, developed the first National AIDS Vaccine Plan in 1993. The Plan (similar to those also developed with assistance of GPA/WHO in Rwanda, Thailand, and Uganda), analysed the epidemiological situation and the state-of-the-art on HIV vaccines. It also provided recommendations for preparatory research in laboratories (virus isolation and characterization); clinical aspects (to develop the capacity to conduct phase I/II trials); epidemiology (to identify and characterize potential populations for the future conduct of efficacy trials); and social/behavioural issues (to investigate issues related to trial participation and public acceptance to vaccine trials).

#### **Brazilian network for HIV isolation and characterization**

A Brazilian network for HIV isolation and characterization was established, modelled after, and having a close working relationship with the WHO/UNAIDS Network for HIV Isolation and Characterization. The Brazilian Network is coordinated from FIOCRUZ (Salvador, Bahia) and is composed of six laboratories distributed throughout the country. The Brazilian Network has contributed much to the understanding of molecular epidemiology in Brazil, having identified the presence and distribution of different HIVV genetic subtypes in Brazil

(B, B', F, C and D). The Virus Network also contributes with the characterization of incident virus from the cohort studies.

Three cohorts to assess the feasibility of conducting efficacy trials were established in Belo Horizonte (*Horizonte* project), Rio de Janeiro (*Rio* Project) and Sao Paulo (*Bela Vista* Project), with joint support from the Ministry of Health and WHO/UNAIDS. A fourth cohort, also in Rio de Janeiro (*Praca XI* Project), is being supported by the US-NIH. A total of 3000 volunteers, mostly men-who-have-sex-with-men, are enrolled in the four cohorts. HIV prevalence at enrolment varied from 10% to 23%, indicating the heterogeneity of these populations. That heterogeneity is also evident from HIV- incidence data, which go from 1.3% to 3.1% per year. Followed up for over four years, these cohorts have shown the technical and logistical feasibility of this type of study in Brazil. A problem that needs to be addressed relates to follow-up, which can be as high as 20-50%, depending of the duration of the study. These cohort studies are perceived as a national resource, and a great number of volunteers have expressed the willingness to participate in potential efficacy trials, generally moved by reasons associated with altruism, as well as the possibility of benefits to themselves.

Since the approval of the National Plan, Brazil participated in a phase 1-2 clinical trial of the UBI V3 peptide candidate vaccine, involving 30 volunteers. The trial was carried out in Rio de Janeiro and Belo Horizonte.

### **Much learned during six years of Brazil National AIDS vaccine plan implementation**

Much has been learned during the first six years of the Brazil National AIDS Vaccine Plan implementation. The National Virus Network is running smoothly. Clinical investigators working with the cohorts have gained much experience with the clinical follow-up of seroconvertors (many of whom are receiving antiretroviral treatment), an experience which is essential for future assessment of secondary end-points of vaccine efficacy. Two groups gained experience on vaccine trials conducted in accordance with GLP and GCP.

There is much excitement for a new phase of AIDS vaccine activities in Brazil. Investigators from the *Praca XI* Project in Rio de Janeiro, in association with the US-NIH, are planning to conduct a phase I/II trial of a canarypox-HIV recombinant vector boosted with rgp120. Preliminary contacts have been made with a manufacturer working on DNA vaccines. There has been some discussion regarding the possible testing of therapeutic vaccines in the context of antiretroviral therapy. The National AIDS Vaccine Committee and the Ministry of Health are open to suggestions from manufacturers, scientists, and agencies considering HIV/AIDS vaccine research, development, and evaluation activities in collaboration with Brazil.

### **Revision of 1993 National AIDS Vaccine Plan in the light of experience gained**

To take advantage of the experience gained, the 1993 National AIDS Vaccine Plan is being revised. Special attention is being paid to the gaps existing between national expertise and the "state-of-the-art" knowledge, worldwide, in the different disciplines relevant to HIV vaccine research and development. The intention is to make a formal presentation of the revised plan to the international community, probably in November 1999, for which the support of UNAIDS and of other institutions will be requested.

### **Civil society gives strong support to HIV vaccine effort**

In Brazil, civil society has given strong support to the HIV vaccine effort. Nongovernmental organizations (NGOs) are significantly represented at the National AIDS Vaccine Committee. NGOs have organized three national workshops on AIDS vaccines (1994, 1996, 1998, with support from WHO/UNAIDS), and have published three special bulletins on vaccines. Brazilian NGOs are frequent participants in international vaccine fora. These include those concerning ethical considerations for the international conduct of HIV vaccine trials. They have maintained the position that HIV-seroconvertors, anywhere in the world, should have access to the "best proven therapy" (in Brazil, the "highest attainable" is already the "best proven" level of therapy).

### **On Brazilian agenda—future availability of HIV vaccines, intellectual property, and technology transfer issues**

Future availability of HIV vaccines, intellectual property, and technology transfer issues, are also on the Brazilian agenda for future discussions. The vaccine manufacturing capacity of Brazil, mostly located at Biomanguinhos (Rio de Janeiro) and Butantan (Sao Paulo) should be considered for future production of HIV vaccines.

### **International financing institutions may consider the provision of zero interest funding to developing countries conducting HIV vaccines trials**

Finally, because of the global characteristics of the HIV epidemic, international financing institutions may consider the provision of zero interest funding (as a grant not a loan) to developing countries willing to conduct trials of HIV vaccines, the results of which will benefit all mankind. If properly stimulated, local R&D funding agencies will contribute to the effort.

### **3.14 South Africa AIDS Vaccine Initiative (SAAVI), Republic of South Africa**

(Presented by Dr William Malegapuru Makgoba).

#### **HIV/AIDS epidemic in Republic of South Africa having major impact on health and economy**

The HIV/AIDS epidemic in the Republic of South Africa is already having a major impact on health and the economy, which will worsen in the future. A vaccine is perceived as an important tool to control the epidemic.

The economic impact of HIV/AIDS in the Republic of South Africa has stimulated the private effort to contribute to a national HIV/AIDS vaccine development effort. Such effort is coordinated by the South Africa AIDS Vaccine Initiative (SAAVI). It is focusing in four areas:

- (a) biology of HIV (genotype C is the prevalent strain associated with heterosexual transmission, but genotype B is still prevalent in homosexual transmission );
- (b) clinical trials;
- (c) ethics (building infrastructure); and
- (d) public education and advocacy.

#### **SAAVI successful in raising significant level of financial support**

SAAVI has been successful in raising a significant level of financial support from Government sources and from the private sector in the Republic of South Africa. It is planning to launch a research programme based on a request for applications.

SAAVI is currently linked to the IAVI, through the IAVI-supported project to develop a VEE-vectored subtype C candidate vaccine (in collaboration with AlphaVax). Other projects that are relevant to HIV vaccine development and evaluation in the Republic of South Africa are:

- (a) HLA distribution and immune responses;
- (b) Follow-up of commercial sex workers in Johannesburg (some of whom remain seronegative); and
- (c) possible consideration of testing subtype B candidate vaccines among men-who-have-sex-with-men.

### **3.15 The Indian Council of Medical Research (ICMR), The National AIDS Research Institute (NARI, Pune), The National Institute of Virology, and other institutions, India**

(Presented by Dr Nirmal K. Ganguly).

## **Out of some 7 million HIV-infected persons in South East Asia, over 5 million believed living in India**

Out of almost 7 million HIV infected persons in South East Asia, over 5 million are believed to be living in India. Moreover, India is still experiencing a rapid and extensive spread of HIV and the availability of a safe, effective and affordable HIV vaccine may be essential for the control of the epidemic.

Scientists from different institutions conducted a brainstorming session in New Delhi in November 1998 to discuss issues related to HIV vaccine development and testing in India.

The Indian Council of Medical Research (ICMR) has a network of laboratories with a track record of studies on epidemiology, virology, immunology, and molecular biology of HIV.

The National AIDS Research Institute (NARI, Pune) has an active virology laboratory and an HIV repository.

### **Detailed knowledge regarding virus subtypes essential**

A detailed knowledge regarding virus subtypes is essential for developing vaccine candidates or for selecting appropriate vaccine candidates from the ones currently available. Several studies conducted in India have shown that the genotype C is the most prevalent in the country, although subtypes A and B have also been reported in a small number of patients. NARI conducted a study among recently infected persons that indicated the presence of HIV-1 genotypes C2 and C3, which are closer to the Zambian and the Indian prototypes, respectively. The majority of infected persons with unknown date of seroconversion carried the subtype C3 genotype, with only 20% carrying the C2 genotype. Most of the C3 strains were closely homologous to each other, while more nucleotide sequences divergence was seen in C2 samples. Full-length clones of six isolates from seroconverters in Pune have been cloned. This NARI study revealed the presence of an A/C recombinant strain.

NARI has also conducted studies of immune responses to HIV infection. Cross-subtype CTL sensitization was shown among recently infected patients in Pune. This cross-CTL response was polyvalent and comparable to the one seen in patients infected with homologous B subtype infections. The studies have also shown that while some patients exhibit cross-subtype CTL response, some showed HIV-1 subtype C specific CTLs only. NARI is also undertaking studies in neutralizing antibodies and HIV-specific lymphocyte proliferation assays. These are also used as indicators of vaccine immunogenicity.

### **Role of other research institutions in India**

The National Institute of Virology, NARI, and other institutions have expertise in various molecular biology techniques, which are central to vaccine development. It has been proposed to develop subtype C based candidate vaccines using this infrastructure available within the ICMR. In the Indian scenario, isolated attempts have been carried out in the past with certain vaccine concepts.

Testing of an indigenous or other vaccine candidates would require community preparedness for vaccine trials, cohorts of appropriate populations, laboratory facilities, and expertise for supporting the development of candidate vaccines and also for conducting vaccine trials.

NARI has established three state-of-the-art STD clinics. It has excellent infrastructure and trained personnel in clinical investigations and follow-up, large-scale epidemiological studies, behavioural and intervention research, and modern data management facilities. NARI has conducted the single largest prospective cohort study of STD patients in India, enrolling over 2000 HIV-negative STD clinic patients. NARI experience and expertise in conducting large-scale epidemiological studies, data management, and behavioural research, will be used for any proposed vaccine trial.

Besides NARI, the Tuberculosis Research Centre (TRC) and the Institute of Research in Medical Statistics, have also shown their capability of conducting large-scale trials of BCG

and anti-leprosy vaccines, respectively. In addition, the TRC has a well-developed immunology laboratory, which can support trials.

### **Conducting HIV vaccine efficacy trials requires population willing and able to participate**

To conduct HIV vaccine efficacy trials, it will be necessary to identify a population willing and able to participate. There should be clear decisions regarding the type and doses of the vaccine, and the infrastructures required to implement the study protocol and to evaluate the results. It is also imperative that the national authorities, scientific fraternity, and community be prepared for the vaccine trial.

While assessing the preparedness of the community for the vaccine trial, an understanding of the community and individual concerns is required. The community may have concerns about whether or not issues like confidentiality, consent, and non-discrimination, will be observed, and whether the community will be assured a continued supply of the vaccine even after completion of the trial. Participating individuals might be concerned about adverse reactions, confidentiality, post-vaccination HIV seropositivity or infection or both, discrimination and problems related to insurance, freedom to travel, employment, and immigration.

### **Community preparedness assessment**

Community preparedness assessment would mean finding out if the community perceives the need for a vaccine trial. If it is not perceived, it might be necessary to stress advocacy and information. The decisions about who will give the information, which information, and by using which strategy, will all be very crucial. If there are barriers, fears or reluctance, qualitative behavioural research will have to be conducted to understand, and then to take appropriate corrective measures. It is also necessary to ensure a continued support and participation of the community. It may be necessary to take help from coordinating agencies, involving community representatives and by giving timely feedback to the community. Community involvement is possible if a “Community Advisory Board” (CAB) is established, a close contact with Community-Based Organizations (CBOs) is maintained, and public fora are conducted to discuss ethical, scientific, and social issues.

HIV vaccine trials can be undertaken in India under the leadership of the ICMR, with participation of its various institutions. However, there is a need for sensitizing the community and policy-makers towards the need to conduct HIV vaccine trials. The issue of HIV vaccine development is complex and sensitive, and hence a threadbare discussion on the choice of vaccine development strategies, the choice of candidate vaccine for trials, ethical and social issues, and the design of future trials, needs to be carried out to develop national consensus and policy.

## **4. Review and discussion of UNAIDS proposed activities**

### **4.1 Brief report of past activities**

(Presented by Drs. José Esparza and Saladin Osmanov).

### **Vaccine activities in UNAIDS derived from activities initiated by former WHO Global Programme on AIDS (GPA)**

These activities started with a major consensus meeting organized in March 1998. GPA established a Vaccine Development Unit in 1990 and a Steering Committee on Vaccine Development in 1991.

When UNAIDS was created in 1996, the GPA/WHO vaccine agenda was adopted and adapted by the new programme. A Vaccine Team and a Vaccine Advisory Committee (VAC) were established in 1997 and, in 1998, “Vaccines” were identified as one of the five thematic priorities for UNAIDS work. Collaborative work between UNAIDS and the WHO Global Programme on Vaccines was initiated in 1997, to promote the development of novel

approaches for HIV vaccines, with support from the Government of Japan. UNAIDS has also been collaborating with the WHO Programme on Research and Training in Tropical Diseases (TDR) in the organization of training workshops on Good Clinical Practices.

### **UNAIDS-VAC recommendations**

At its first meeting in April 1997, the UNAIDS-VAC provided a series of recommendations for UNAIDS work in the following areas:

- collection, exchange, and analysis of information;
- creation of collaborative networks;
- assistance with capacity-building in developing countries;
- provision of independent and authoritative advice;
- identification of ethical, regulatory, and legal barriers; and
- advocacy for HIV vaccines.

The WHO and UNAIDS vaccine programmes have implemented a large number of activities, and only a few examples will be provided here.

### **National plans for AIDS vaccine research, development, and evaluation**

National plans for AIDS vaccine research, development, and evaluation were developed in 1992-1993 in Brazil, Rwanda, Thailand, and Uganda, with the assistance of WHO/GPA. These National plans describe National policy procedures for submission, review, approval, and monitoring of research proposals; and specific recommendation for a research agenda to prepare for future HIV vaccine efficacy trial, including virus isolation and characterization, base epidemiology and cohort development, social and behavioural research and repeat phase I/II trials of candidate vaccines, which have already been tested in the country of origin. UNAIDS provided technical and financial support for the implementation of these activities, including the establishment of cohorts of HIV-negative volunteers in the four countries. WHO and UNAIDS have also provided continuous advice to National authorities regarding the conduct of HIV research, especially clinical trials.

### **The WHO/UNAIDS Network for HIV Isolation and Characterization**

The WHO/UNAIDS Network for HIV Isolation and Characterization was established to systematically collect and analyse strains from potential sites for HIV vaccine trials. It has successfully linked laboratories in industrialized and developing countries. In addition, the Network has developed standard procedures (including a manual for virus isolation and characterization); trained investigators from developing countries (genetic characterization by HMA, virus isolation, neutralization assays); established repositories (with the collaboration of the US NIH and the NIBSC in London); developed and widely distributed reagents for HIV vaccine research (HIV strains, molecular clones, sera, etc); and coordinated collaborative studies (virus subtypes in potential vaccine evaluation sites, characterization of prevalent C/A strains). One of the collaborative projects of the Network provided the first evidence that genetic subtypes do not define neutralization immunotypes.

During the last two years UNAIDS has been deeply involved in the development of new ethical guidance for the international conduct of HIV vaccine trials. To that end, six consultations were organized (in Brazil, Switzerland (Geneva), Thailand, Uganda and the USA (Washington)) to collect views from interested parties, including the affected community. A "Guidance Document" is being finalized, defining UNAIDS policy on this important topic.

Since capacity-building in developing countries is one of the UNAIDS priorities, a number of training workshops have been organized (most of them in Africa, Asia and Latin America), in the following disciplines: virus isolation and characterization, ethics; GCP; communication and public information; and social and behavioural research.

### **4.2 Proposed activities for 2000-2001: Comments and suggestions**

The proposed UNAIDS Unified Budget & Workplan 2000-2001 includes in its Programme Component<sup>10</sup> (Development and promotion of prevention methods), activities "To promote

and support development, evaluation and future availability of HIV vaccines”, to be jointly implemented by UNAIDS and WHO.

In preparation for this meeting, a questionnaire was sent to all members of the VAC, requesting their comments and suggestions regarding the proposed activities. VAC members were also requested to provide “scores (Lower/Medium/Higher priority) for each proposed activity. All VAC members provided comments and their replies were analysed and used to guide the discussions.

**Goal:** The overall goal of the UNAIDS/WHO strategy and activities is “To promote the development, facilitate evaluation, and address future availability of preventive HIV vaccines, with a focus on the need of developing countries”.

**Comments:**

- It was considered very clear, concise, comprehensive, and with the correct focus;
- In addition to preventive vaccines, it could also consider “therapeutic” vaccines;
- Consider deleting the reference to “developing countries”;
- Consider changing the word “availability” for “accessibility”;
- Should mention “ethics” and “capacity-building”;
- There is a need to be clear on what UNAIDS does, and what will be done by partners;
- Extensive multi-sectorial efforts urgently needed to promote vaccines in developing countries, since therapeutic interventions are unaffordable or inaccessible;
- Involvement of local industries (in developing countries) and community is critical for long-term sustainability;
- This will need strong and sustained advocacy initiated through UNAIDS and others.

**The proposed activities are grouped in five categories:**

- (a) Advocacy
- (b) Guidance and coordination
- (c) Promotion of vaccine development
- (d) Facilitation of trials through capacity-building
- (e) Future availability.

**(a) Advocacy:** UNAIDS (and WHO) will continue advocating for the development of HIV vaccines as a long-term (and complementary) approach to control the HIV/AIDS epidemic, especially in developing countries, through policy statements, dissemination of information to different audiences, and direct contacts/negotiations with key people in the private and public sector.

- Include “vaccine “messages” in policy statements and presentations from UNAIDS and Co-sponsors.
- Develop and produce documents and information on HIV vaccines (targeted to different audiences);
- Prepare a biannual (one every two years) “State of the HIV/AIDS Vaccines”, with a summary of progress (including trials) in developed and developing countries (with the assistance of members of the VAC);
- Contact/visit key players (including political and opinion leaders and pharmaceutical industry).
- Include “HIV vaccines” in the agenda of regional and international initiatives on HIV/AIDS.

**Comments:**

- Advocacy is an essential function of an honest broker as UNAIDS;
- Do not overestimate UNAIDS advocacy capacity: target journalists, and health and scientific leaders in developing countries;
- Target (1) policy-makers, scientists, industry, regulatory authorities, and (2) local opinion leaders, NGOs, PWA, and community at large;
- Important in establishing positive and meaningful community participation;
- UNAIDS advocacy is an important but perhaps under-appreciated role of UNAIDS;
- Critical for UNAIDS/WHO is to advocate and not to do (to maintain neutrality);
- Consider cultural value of advocacy;

- Present “vaccines” in the context of other preventive interventions, distinguishing between immediate and long-term goals;
- UNAIDS advocacy should also stimulate additional involvement from national authorities and pharmaceutical industry;
- Impartial biannual “State of the HIV/AIDS Vaccines” (including all agencies and countries) is a great in; should be placed on the Internet.

**(b) Guidance and coordination:** UNAIDS (and WHO) will continue providing for coordination and consensus-building through its Vaccine Advisory Committee, which is composed of representatives of key institutions involved in HIV vaccines from industrialized and developing countries:

- Maintain an effective Vaccine Advisory Committee (VAC), to provide advice to national authorities, industry, and the scientific community;
- Establish effective working relationships with all UNAIDS co-sponsors; and
- Organize consensus workshops and meetings on key issues related to HIV vaccine development (including ethics, strategic planning, virology and immunology, trial design, social/behavioural issues, etc).

**Comments:**

- A functioning VAC is very important in this rapidly moving area;
- The UNAIDS Vaccine Committee should be a consensus body to decide on which trials go from phase II to phase III;
- As vaccine activities proceed, international coordination is essential;
- UNAIDS must take or assume a leadership role in this area;
- In this contentious area, UNAIDS/VAC can provide balanced and independent judgement;
- Priority is to provide advice to national authorities and for inter-agency strategic planning (including future availability);
- Support to developing countries should be major UNAIDS focus;
- UNAIDS has provided critical leadership organizing consensus workshops;
- Support for social-behavioural activities is essential, but need to bring relevant expertise to the VAC;
- Media training sessions are needed, to increase knowledge about vaccine research and trials;
- Interagency working group is a good idea, but need to discuss selection of representatives;
- The challenge is to encourage others to be active and not to try to “control”;
- Guidance and coordination is essential at all stages of HIV vaccine development and trials, mainly because there are many international agencies who have broad experience in various activities. Their experience will be useful in averting problems and hurdles;
- UNAIDS, being a neutral and acknowledged agency, should coordinate all these activities.

**(c) Promotion of development of appropriate vaccines:** Although UNAIDS (and WHO) is not now proposing to be involved in basic research or product development, it will continue promoting and facilitating the manufacturing of appropriate candidate vaccines for testing and future use in developing countries, through provision of information and reagents collected by its Virus Network, and supporting targeted research in innovative vaccine approaches more suitable for developing countries:

- Increase level of activities of the UNAIDS Network for HIV Isolation and Characterization (sample collection in developing countries, virus genetic characterization, neutralization assays and immunotyping, CTL and HLA studies, repositories, reagent production and distribution, reagents and assays standardization);
- Support targeted research for selected vaccine development projects (this refers to small catalytic grants to stimulate neglected areas, directed to investigators in industrialized and developing countries. These small grants are not intended to support “product development” and are to complement funding provided by other agencies.

**Comments:**

- Excluding Virus Network Activities (which received full support), UNAIDS cannot compete with industry or other funding agencies (in product development). However, it must go ahead to promote the development of new vaccine concepts;
- Virus Network activities must include efforts to determine the biological and immunological significance of genetic variability;
- Virus Network sample collection should be improved, to expand to cellular immunology;
- Access to information and reagents derived from the Virus Network should be broadened;
- Promotion (of product development) is important, but not UNAIDS comparative advantage. If UNAIDS/WHO promotes/develops specific products, it loses neutrality. The main advantage of UNAIDS/WHO is to advise developing countries on what products should be developed/tested;
- NIH will be doing much of this (product development) and they are well funded;
- Leave this (product development) to the USA and other countries;
- Doubts about impact of small funding. Small grants are relatively useless, since they overlap with activities of national agencies;
- Where is the comparative advantage of UNAIDS (in promoting development of new vaccines)?;
- Main activity should be to promote coordination and collaboration among investigators (actual research should be supported by others, and encouraged by UNAIDS);
- Current UNAIDS strategies are adequate and fruitful;
- There is a need to involve more developing country scientists in basic research, including funding to promote vaccine concepts which are more appropriate for these countries;
- Programmes to develop indigenous HIV vaccines (in economically developing countries with sufficient scientific infrastructure) must be accorded primacy. This will not only promote research, but will offer the potential to discover newer approaches. At the same time, testing efficacy of other, whenever feasible, should also be given due priority. UANIDS should coordinate these efforts.
- Would UNAIDS increase support for targeted research, including clinical trials in developing countries (through co-sponsors)?

**(d) Facilitation of trials in developing countries through capacity-building:** Since multiple trials of HIV vaccines would have to be conducted within the next few years, many of these in developing countries, UNAIDS (and WH) will assist these countries developing sustainable capacity for the conduct of such trials, *through* the design and implementation of National AIDS Vaccine Plans and Strategies, and regional AIDS Vaccine Networks for information exchange, peer support, training, research and capacity-building :

- Continue supporting implementation of ongoing UNAIDS-assisted national AIDS vaccine plans (Brazil, Thailand, Uganda), through targeted funding in several areas (national consensus workshops, ethical review capacity building, virus monitoring, cohort development and associated research, data management, social/behavioural studies, clinical trials);
- Assist additional selected countries in the development of National AIDS Vaccine Plans; and
- Establish three Regional Networks for AIDS Vaccines (Africa, Asia, Latin America and the Caribbean), in close coordination with “National Plans” and fostering South-South and South-North links.

**Comments:**

- All activities listed in this section with regard to developing countries are urgent and of the highest priority;
- This is the most important area of UNAIDS activities.
- UNAIDS should provide training, capacity-building (through targeted research) and foster exchanges between countries;
- Training should also include modern vaccine production technologies (to allow future transfer);
- Proposed training activities essential and applicable to all vaccine research;
- Infrastructure development is one of the most important activities of UNAIDS/WHO;
- UNAIDS support has facilitated the conduct of the only international HIV vaccine trials thus far: this should be continued;

- Facilitation of trials can best be undertaken after intensive efforts to sensitize policy-makers, NGOs, and community (including PWA). Simultaneously, preparation of “sites” training of scientists and establishing quality control, shall reduce the time lag in undertaking HIV vaccine trials;
  - UNAIDS should provide for exchanges between developed and developing country scientists; also, to increase general understanding of vaccine development and future deployment;
  - Activities should also include community mobilization, sensitization, and discussion on potential use of vaccines;
  - Although social-behavioural/ethical issues are important, activities should focus on scientific capacity-building (especially in situations where sources of funding are limited);
  - Not clear what is the comparative advantage of UNAIDS in providing support to training and targeted research (not enough funds to do it well; perhaps select only a couple of activities);
  - Cohort development is important, but no UNAIDS comparative advantage;
  - Would expand activities to create regional rather than country specific activities (that way, countries will not feel isolated when they move forward);
  - Regional workshops will help capacity-building among developing country researchers;
  - In planning trials, UNAIDS should assist countries in using “science” to guide “political” decisions.
- (e) Addressing future availability of HIV vaccines:** UNAIDS (and its co-sponsors) will explore approaches to make future vaccines available in developing countries, through the design of vaccination strategies based on multiple scenarios, to be implemented with the mobilization of multiple partners and resources from the public and private sector:
- assess potential vaccination strategies based on different scenarios (i.e. vaccine efficacy, HIV incidence, access to target populations, and costs.) to model future demand and potential utilization; and
  - explore alternatives to increase access to future HIV vaccines, including financial and cost reducing strategies (i.e. transfer of technology, local production, intellectual property issues) and planning phase IV effectiveness trials.

**Comments:**

- Considering current stage of HIV vaccine development, it is too early to consider this issue;
- This will only be relevant when the matter can be addressed in practical terms;
- There is a need to avoid creating false expectations about vaccine availability;
- Should be maximum priority: should be addressed not as a philanthropic exercise, but as a negotiation with industry. Related social, economic and public health research is important. Need to discuss intellectual property issues.
- This may, perhaps, be the most important function of UNAIDS/WHO over the next years;
- This is an excellent and realistic approach;
- The proposed strategy is extremely important to increase future access in developing countries;
- This issue should be explored intensively. Lead time to make products available may be three to four years once a vaccine comes up on the scene (three years?);
- The scenario issue is critical to obtain World Bank and others’ support;
- UNAIDS/WHO should assist by providing technical assistance to WB, UNAICEF, and others in this task;
- This strategy only makes sense in the context of working with the WB, WHO, and other players in vaccines;
- Identification of industrial partners is crucial in establishing future availability. Some developing countries that have comparatively lower production costs could provide a suitable industrial base to optimize cost of future vaccines. These vaccines can then be exported to other countries. In order to avoid intellectual property rights-related issues, agreements to this effect should be made prior to initiation of these trials.

**(f) General comments regarding the proposed UNAIDS strategy and activities:**

- UNAIDS has found a critical gap and has filled it with innovative thinking, substantially advancing international AIDS vaccine development. Has developed extensive scientific outreach in developing countries, which is being extended to developed country scientists and industry;
- UNAIDS priorities should remain: advocacy, guidance to developing country national authorities, capacity-building, and international coordination. No role in research, excepting targeted activities and stimulating other agencies;
- UANIDS/WHO has a critical role as the only neutral scientific body on AIDS vaccines. Should preserve neutrality: develop guidelines, provide advice, review protocols, monitor ethics, ensure international standards. Should not dilute itself by making small inconsequential efforts in other areas;
- UNAIDS should identify comparative advantages: impartial review of protocols and capacity-building to carry out meaningful trials. Use others' funds. An incremental funding issue;
- Need to consider interactions with HIV vaccine activities of other UNAIDS co-sponsors (such as with the AIDS Vaccine Task Force of the World Bank);
- Need to complement and avoid duplicating activities of other programmes. Focus on activities that are essential and that require international leadership;
- Must be extremely focused to have an impact;
- UNAIDS should remain a neutral broker in the midst of competing agendas;
- Overall excellent: Emphasis in three areas: Virology (strain immunotyping), epidemiology (prepare for phase III trials in Africa), policy (how to use a future vaccine; link with the WB);
- Research is needed on correlates of protective immunity and parallel evaluation of candidate vaccines in human trials and in animal models;
- The proposed UNAIDS activities will ensure a wider participation of different countries in HIV vaccine development activities. These activities are comprehensive and well organized, If UNAIDS takes the initiative to provide leadership and to support HIV vaccine development, the promotion of these strategies will be facilitated.

**(g) Suggestion for other activities:**

- Given present budget situation, no further activities are encouraged;
- UNAIDS should provide a forum to understand how all agencies involved in HIV vaccine research "articulate" their efforts;
- Stronger coordination of international trials among NIH, WRAIR, ANRS, IAVI, MRC, others;
- Create regional collaborative networks among scientists (would help to bring along other countries that are lagging);
- Establish regional molecular epidemiology networks for monitoring and surveillance;
- Facilitate inter-country consultation (could be independent of UNAIDS intervention);
- Ensure adequate ethical and DSMB (Data and Safety Monitoring Board) expertise in developing countries, emphasizing local decision-making (because of different risk/benefit ratios);
- Foster developing country leadership in controlling activities in their own countries;
- Consider doing "something" to look into the possibility of developing whole inactivated vaccines;
- UNAIDS must also undertake activities to establish international quality control for various laboratory tests. It should assist in establishing regional laboratory bases in certain regions.

#### **4.3 Prioritization of activities**

Although the proposed range of activities was considered to be appropriate and realistic, certain activities were identified as having higher priority.

- There is a need to increase the knowledge base on HIV vaccines in developing countries. This requires strategies based on information, advocacy, and education. Appropriate strategies should include information, advocacy, and education components, and should target different audiences. The advocacy effort should be "honest", without creating false expectations.

- Capacity-building through the establishment of the Regional AIDS Vaccine Networks is essential. There is also a need to identify new countries for a new round of assistance in the developing of National AIDS Vaccine Plans. Experience from other countries can be shared, accepting the principle of “learning by doing”. It is important that UNAIDS continues providing targeted support to selected activities (seed money) with a long-term vision and commitment. Funding, however, should not be considered as an “entitlement programme” and funds should be provided through a competitive process. In addition to supporting specific research proposals, it is also important to support organizational capacity (such as scientific and ethical review capacity). Partners (donors, agencies) can assist UNAIDS with the provision of technical and financial support to developing countries. Prioritization of activities should be based on country-specific needs and sustainability. The development of a strategy to accelerate the development of HIV vaccines for Africa is an urgent need.
- The Virus Network should be expanded to include activities related to immunological characterization of HIV isolates (both neutralization and CTL) as well as standardization of reagents and assays relevant to HIV vaccine development and trials. A system should be put in place to allow for free exchange of reagents and information, stressing collaboration and reciprocity.
- Strategies to plan for future availability are also urgently needed and should be developed with partners, such as the World Bank and the European Commission. These strategies should be comprehensive and credible, dealing with issues related to the capacity to produce and deploy vaccines, financing, pricing, and intellectual property rights issues. Modelling vaccine use is important, both as a general exercise, as well as concerning specific candidate vaccines which may become tested (and hopefully available) in the immediate future.

## **5. Recommendations for the proposed UNAIDS/WHO partnership on vaccine development.**

Dr Peter Piot (Executive Director of UNAIDS) and Gro Harlem Brundtland (Director-General of WHO) have announced their decision to establish a joint UNAIDS-WHO AIDS Vaccine Programme, and details of this collaboration are being discussed.

The UNAIDS Vaccine Advisory Committee discussed the proposed collaboration, suggested the following:

### **Points to be considered concerning a partnership between UNAIDS and WHO in the area of HIV vaccines:**

1. AIDS is a global epidemic, now the largest cause of death from any infectious disease worldwide, with 90% of the burden falling in developing countries. The magnitude of the epidemic demands a commensurate international response. Effective and safe vaccines currently represent the best hope to control the epidemic in developing countries. They are an international public good requiring international investments.
2. UNAIDS and its Vaccine Advisory Committee has played a targeted but useful role at several levels, and this essential work should be continued and enhanced through collaboration with WHO.
3. The social, cultural, and political environment in which HIV vaccine research and future deployment takes place is unique and requires quite different approaches from classic childhood vaccines, although, if successful, vaccines could be useful in both children and adults.
4. Developing vaccines against HIV must be given high visibility and priority, if the financial, ethical, and scientific problems are to be addressed with the intensity required by the epidemic.
5. To achieve that goal, we would support a Joint UNAIDS-WHO Programme on AIDS Vaccines based on the following principles:
  - (a) The joint programme should serve as an independent voice and objective and impartial international broker to facilitate development, testing, and deployment of AIDS vaccines.

- (b) To increase its effectiveness, a joint external UNAIDS-WHO AIDS Vaccine Advisory Committee should guide the activities of this joint programme. It will need to establish its priorities, comparative advantage and identity, and the joint committee will require increased financial and human resources to make a greater impact.
- (c) Flexibility of action, and ability to provide for rapid response in this rapidly evolving, and often controversial field will require a significant degree of freedom and autonomy, and a clear delineation of the decision making process.
- (d) To take advantage of their respective experience and expertise, close working relationships with other activities WHO and UNAIDS, will be essential to a joint vaccine activity, and this will have both practical and symbolic importance. Links to UNAIDS need to be retained to integrate vaccines with other prevention approaches.
- (e) The UNAIDS-WHO vaccine programme should be focused principally on international scientific, policy and strategic issues, that will encourage and accelerate development of AIDS vaccines, e.g. expanding the existing virus and immunologic networks; ethical, regulatory, licensing, public health strategies and collaborations with industry.
- (f) The UNAIDS-WHO Vaccine Programme will be most effective by working together with countries planning vaccine trials and developing vaccines, the cosponsors and other international agencies; IAVI, NGOs and community groups supporting or advocating vaccines against AIDS.”

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