

Meeting of the Vaccine Advisory Committee (VAC) Geneva, 21-23 February 2000

Summary Report and Recommendations

INTRODUCTION

WHO activities in the area of HIV vaccines were initiated in 1989, under the guidance of a “Biomedical Research Steering Committee”, chaired by Dr. Geoffrey Schild. In 1990 the former WHO Global Programme on AIDS established a Vaccine Development Unit guided by a “Vaccine Development Steering Committee”, which was chaired by Dr Hans Wigzell. With the establishment of UNAIDS in 1996, HIV vaccine activities were continued by the UNAIDS Vaccine Team, guided by its “Vaccine Advisory Committee” (VAC), chaired by Dr. Barry Bloom.

The WHO-UNAIDS HIV Vaccine Initiative was established from January 2000, to take advantage of the complementary expertise of WHO and UNAIDS in the area of HIV vaccines.

This was the first meeting of the VAC to provide guidance to the new WHO-UNAIDS Initiative, and it was attended by all 15 members of the Committee (Annex I).

OPENING REMARKS

The meeting was opened by Dr. Peter Piot, Executive Director of UNAIDS. Dr. Jose Esparza, Coordinator of the WHO-UNAIDS HIV Initiative, informed that the new initiative is based at the Health Technology and Pharmaceuticals (HTP) Cluster in WHO, and presented the apologies of Dr. Michael Scholtz, Executive Director of HTP, who could not attend the meeting. Dr Bjorn Melgaard, Director of the WHO Department of Vaccines and Biologicals, briefed the group on the recently launched Global Alliance for Vaccines and Immunization, of which WHO is a partner.

SUMMARY OF THE MEETING

The meeting, which was chaired by Dr. Barry Bloom, had three open scientific/briefing sessions and a closed session restricted to members of the VAC. For the open scientific sessions a total of 54 additional participants attended the meeting, including representatives from industry, UNAIDS co-sponsors and other agencies (Annex II).

Open session 1: “Approaches to the development of broadly protective HIV/AIDS vaccines: HIV subtypes and cross-reactive anti-HIV immune responses”. This session was co-sponsored by the Office of AIDS Research (OAR) of the National Institutes of Health (NIH) of the United States of America, and covered the following topics:

- Genetic variability and molecular characterization of HIV-1 strains;
- Lessons learned from studies on natural history and pathogenesis of HIV/AIDS;
- Role of cell-mediated immunity as potential mechanism of HIV vaccine-induced protection;
- Humoral anti-HIV responses as potential mechanisms of protection against HIV/AIDS;
- HIV envelope structure and function; and
- HIV vaccine design, immunogenicity and protection studies.

Open session 2: Therapeutic vaccines

Open session 3: Developing an “African AIDS Vaccine Strategy”.

A comprehensive technical report of sessions 1 and 2 is being prepared. Session 3 provided useful information to plan follow-up activities aimed at the development of a comprehensive “African AIDS Vaccine Strategy”.

Closed session: VAC members analyzed the presentations and discussions which took place during the open scientific/briefing sessions and made the following comments and recommendations to WHO-UNAIDS:

COMMENTS FROM VAC MEMBERS:

The increase in the AIDS epidemic emphasizes the urgency of developing new and more effective preventive tools against HIV. Vaccines represent an important component of future global strategies to combat the epidemic, and perhaps the best long-term hope for the control of HIV/AIDS, especially in developing countries. However, the development of HIV/AIDS vaccines is still facing a number of difficult scientific challenges.

Great scientific progress has been made over the past year, providing unprecedented opportunities for developing and evaluating new candidate vaccines:

- (1) genetic characterization studies of viral strains and variants sponsored by several agencies, including WHO-UNAIDS, have provided abundant information regarding geographical distribution and dynamics of HIV-1 subtypes and their recombinants;

- (2) a significant number of candidate vaccines have been developed, and are entering clinical trials for safety and immunogenicity, and two large scale trials have been initiated to test protective efficacy;
- (3) new methodologies have been developed to assess immunological outcomes in vaccinees in a more precise way than previously available;
- (4) the introduction in some countries of highly active antiretroviral therapy, that can significantly reduce viral load, has opened new opportunities for the development of therapeutic vaccines; and
- (5) a guidance document on ethical considerations relevant to HIV preventive vaccine research, based on extensive discussions with interested parties from many countries, was developed by UNAIDS, providing an ethical framework for the design and conduct of clinical trials.

WHO/UNAIDS recognizes that vaccine development is an iterative process, which may require several trials and gradual improvement of candidate vaccines, before a highly effective vaccine is developed. Many agencies and organizations, in developed and in developing countries, and from the public and private sectors, are essential partners on this collaborative effort.

The first two trials to test vaccine efficacy are underway in the United States and Thailand, and it will take some time before results are available. Several new candidate vaccines remain to be tested for safety and immunogenicity, before being considered for large-scale efficacy trials. It is therefore essential that every effort be made to support and increase current HIV prevention efforts, because still it could take several years before we have an effective HIV vaccine (especially one with high protective efficacy). Consequently, funding for AIDS vaccine research should be additive to that already being used for other interventions, including care.

RECOMMENDATIONS FROM VAC MEMBERS:

1. While candidate vaccines entering Phase III evaluation are expected to show some level of protective efficacy, many questions remain regarding what antigens, and what immunological mechanisms, are necessary and sufficient for protection. In addition to continuing studies in animal models, it will be **essential to learn from human clinical trials, including efficacy trials**, what are the essential requirements and immunological correlates of protection.
2. Informative clinical vaccine trials will require **genuine and equal partnerships between scientists in developing and industrialized countries**. These partnerships should be developed at the earliest possible time, and should include planning for capacity building and infrastructure development.

It is also essential to strengthen **partnerships between WHO-UNAIDS and other sponsors of vaccine research**, including national AIDS research programs in industrialized countries, the International AIDS Vaccine Initiative, the World Bank, the European Community, the pharmaceutical industry, and others. Likewise, building on previous work spearheaded by WHO-UNAIDS in 1992-1993, National AIDS Vaccine Programs and/or Strategies in developing countries should be stimulated and supported. Because of the nature of HIV vaccine research, these collaborations and partnership should be conceived as **long-term and sustainable efforts**.

Vaccine research for different diseases (especially the three major killers: HIV/AIDS, malaria, TB) could benefit from a coordinated approach, tackling common problems with common strategic approaches. This could be especially important in the preparation of sites for the conduct of trials in developing countries. WHO-UNAIDS, through the Intercluster Vaccine Research (IVR), should establish the necessary links with the Global Alliance for Vaccines and Immunization (GAVI), the Children Vaccine Programme (CVP), the International Vaccine Institute (IVI) and other relevant agencies.

3. Despite the lack of scientific evidence on the immunological relevance of the HIV-1 genetic diversity, it **remains reasonable to initially design candidate vaccines based on the strains prevalent in the country in which the trials are to be conducted.** However, because of the uncertainty of how important virus variation is for vaccine-induced protection, and because of the complexities of developing multiple vaccine candidates, it would be also important initially, wherever possible, to test vaccine efficacy against more than one strain in multiple arms of the trials. **Ideally, every Phase III trial should aim at testing more than one hypothesis or scientific question, so that maximum information could be obtained from each trial.**
4. **In every Phase I, II or III trial, one goal should be to gain the most information relevant to the identification of immunological correlates of protection,** that could ultimately predict the effectiveness of future vaccine candidates, and reduce the time for development of second and third generation vaccines. This should include at least activities to develop protocols and reagents to assess:
 - a. Antibodies, particularly neutralizing and mucosal antibodies;
 - b. Cell mediated immunity, including cytotoxic T lymphocytes
 - c. T helper cells and immune memory
 - d. Antigenic characteristics of intercurrent viruses that might indicate some immune escape as evidence for selective pressure following immunization
5. To facilitate the comparability of data from trials of different vaccines in different countries, WHO-UNAIDS should consider mechanisms to **assess the needs for providing reference reagents and possibly standardized protocols** for immunological and epidemiological measurement methods, quality assurance and control.
6. With the introduction in some countries of highly active antiretroviral therapy for HIV/AIDS, capable of reducing viral loads to low levels in HIV infected individuals, there may be an **opportunity to learn whether after reduction of viral burden, it is possible to immunize with vaccines** to engender a virus free state, reduce viral loads, or reduce the chances of emergence of drug resistant strains. Such studies could also be helpful for the design of preventive vaccines, by more rapidly identifying immune correlates of protection, as well as effective candidate vaccines. However, at the present time it is **not recommended that such trials be undertaken in countries not using combination antiretroviral therapy** in their national programs.

7. WHO/UNAIDS should contribute to **supporting trials in developing countries by assisting in the planning process, and in strengthening their capacity, including opportunities for training.** Among the areas in which there is a need for expertise are: ethics, epidemiology, biostatistics, trial design and analysis, Good Clinical Practices, data management, culturally appropriate counseling to avoid risk behavior and provide prevention information, laboratory tests for virus and immune parameters assessment, economic analysis, intellectual property rights, and biological regulatory procedures. WHO-UNAIDS should also provide advice for the development of proposals for vaccine trials in developing countries, including plans and budgets for improvement of scientific facilities and ethical review capacity. An area in need of additional support is in relation to the natural history of HIV/AIDS in different populations, which may be required to interpret data from future efficacy and effectiveness trials.

WHO-UNAIDS should **also facilitate the establishment of South-North and South-South collaborative networks** for exchange of information and experiences. Information on training opportunities should be made widely available.

It is recognized that the human and financial resources needed to strengthen infrastructures for vaccine trials in developing countries would be very significant. **WHO-UNAIDS could only provide seed funding to some of these activities, encouraging other partners to contribute to the effort.** In addition, **WHO-UNAIDS is encouraged to seek additional funds for their HIV vaccine activities.**

8. **The WHO-UNAIDS Network for HIV Isolation and Characterization,** aimed at isolating and characterizing viral strains and variants from different parts of the world and providing strains to all interested researchers and vaccine manufacturers, **should be maintained and strengthened.**
9. WHO-UNAIDS should **establish an information base, focusing on clinical trials (especially those conducted and planned in developing countries)** that would minimize unnecessary duplication of efforts, conserve human resources and maximize the new information to be gained from each trial. It would be helpful to learn which countries are planning to carry out trials, what are the participating institutions, industrial partners and scientists implementing the various aspects of the research, which vaccine candidates are to be tested, and the design and end points of the trials.
10. WHO-UNAIDS **should provide reliable and readily understandable scientific information to the public, media and advocacy organizations that can serve to mobilize support in countries for vaccine trials.** Of particular importance are epidemiological surveillance information on the burden of disease, incidence and prevalence rates, mortality rates from AIDS, and effectiveness of other non-vaccine interventions, which will ultimately be required to assess the impact of any vaccine on transmission and reduction of disease burden. Since many more HIV vaccine trials will be conducted in the future, it is important to develop information strategies targeting the media and advocacy groups, to educate the public on the rationale for conducting multiple HIV vaccine trials.

Annex I:

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Annex II

OTHER PARTICIPANTS:

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