Scientific considerations for the regulation and clinical evaluation of HIV/AIDS preventive vaccines


The consultation was jointly organized by the WHO-UNAIDS HIV Vaccine Initiative and the Quality Assurance and Safety of Biologics Team of the World Health Organization (WHO). Thirty-four experts from 16 developed and developing countries attended the meeting, bringing together expertise from academic institutions, clinical trial centres, national and international regulatory authorities. Representatives of major pharmaceutical companies were also invited.

The primary objective of the meeting was to identify gaps that need to be addressed from regulatory perspective to ensure appropriate progress of HIV vaccine development from basic research to human trials, licensing and future application, with a special focus on needs of developing countries.

As a result of discussions, the following priority needs were identified and recommendations were made in order to establish an appropriate regulatory framework for the development and evaluation of preventive HIV/AIDS vaccines, which were divided in two main areas: (a) standardization and control of candidate HIV/AIDS vaccines, and (b) approaches to the conduct of clinical trials of candidate HIV/AIDS vaccines.© 2002 Lippincott Williams & Wilkins


Keywords: HIV/AIDS vaccines, product development, clinical trials, regulatory requirements

Introduction

The discovery and characterization of HIV as the causative agent for AIDS, in the mid 1980’s was followed by intensive efforts to develop a vaccine, which have continued to the present time and accelerated as the massive impact of the AIDS pandemic has become increasingly obvious. In the past 15 years many clinical and academic scientists, research institutes, pharmaceutical and biotechnology companies have participated in an unprecedented volume of research and development work aimed at vaccine development. At the same time, the consensus view held by the scientific community and public health experts is that the best hope of prevention and control in the face of the HIV/AIDS pandemic is by the development of a safe, affordable and effective vaccine. Although the mobilization of scientific resources towards vaccine development has been far greater than that previously applied to any other single infectious agent, progress has not been rapid and it was recognised early that the challenge of HIV vaccine development would be a difficult one, given the unique and complex biological and genetic characteristics of the infectious agent and the absence of a precedent for successful vaccine development against a lentivirus. Nevertheless, a great deal has been learned about the characteristics of HIV and many innovative approaches to HIV vaccine

*This report contains the collective views of an international group of experts (list of participants in Annex 1), and does not necessarily represent the decisions or the stated policy of the World Health Organization. The Contribution of the Chair (Dr H. Rees), Co-Chairs of the Working Groups (Dr K. Goldenthal and Dr G. Schil) and Rapporteurs (Dr N. Almond, Dr J. Darbyshire and Dr R. Sheets) during the meeting and in the preparation of this Report is much appreciated.

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development are currently in progress. Recently, political and financial initiatives have accelerated the progress of several vaccine candidates into clinical trial (Table 1). The results of the first Phase III clinical trials are expected by the end of the year 2002. Efforts towards vaccine development and evaluation target mainly preventive vaccines, designed to protect individuals from HIV infection or reduce the likelihood of transmission in the community. Therapeutic vaccines, designed to modify the progression of the disease in HIV-positive subjects, are also under consideration.

Vaccines must be licensed as a pre-requisite for widespread use. Consequently, in parallel with efforts to develop and clinically evaluate candidate vaccines, it is of critical importance that consideration of the scientific basis for the regulation and licensing of vaccines and the appropriate design and ethical aspects of clinical trials should also be given urgent attention. Smooth and effective progress towards licensing necessitates the development of practical guidelines to identify and address the regulatory issues and, since in many cases AIDS vaccine development projects are international in nature and involve collaboration between member states in industrialized and developing countries, an international consensus on regulatory aspects is important. It is recognised that the countries in greatest need of vaccines may be those with less experience of regulatory processes. In consequence WHO and UNAIDS are taking action to co-ordinate and guide the development of regulatory advice.

The meeting was held at WHO Headquarters, Geneva on 13–16 March 2001, bringing together experts in the field of HIV vaccine research, those involved in the regulation and licensing of vaccines and in clinical trials of vaccine candidates. The key goals of the meeting were to highlight the need for a consistent global regulatory framework for the licensing of HIV/AIDS vaccines and identify the gaps in the scientific understanding that need to be addressed to establish a robust regulatory framework. The scope of the consultation was divided into two main areas:

A. Standardization and control of candidate HIV/AIDS vaccines.

B. Approaches to the clinical evaluation of candidate HIV/AIDS vaccines.

This report highlights the key issues identified during the meeting that need to be addressed in order to establish an appropriate regulatory framework for HIV/AIDS vaccines, as well as a consensus on aspects of the design of clinical trials. In the process, several areas were identified where targeted regulatory research may assist in providing guidance.

**The standardization and control of candidate vaccines**

Since its establishment in 1946, the WHO has had an important traditional role in providing guidance and technical advice to the Member States with regard to the production, standardization and quality control

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Sponsor</th>
<th>Location</th>
<th>Progress</th>
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<tbody>
<tr>
<td>gp120 (subtype B)</td>
<td>VaxGen, US CDC</td>
<td>USA, Canada and The Netherlands</td>
<td>Phase III, results expected November 2002</td>
</tr>
<tr>
<td>gp120 (subtype B/E)</td>
<td>VaxGen, Thai Ministry of Health</td>
<td>Thailand</td>
<td>Phase III, results expected November 2003</td>
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<tr>
<td>Canarypox gag/pol/env/nef plus gp120 boost (subtype B or subtype B/E)</td>
<td>Aventis Pasteur, VaxGen, US NIH, Medical Research Foundation, Trinidad, National Laboratory of Research Haiti, Federal University of Rio de Janeiro, US DoD</td>
<td>Haiti, Trinidad and Tobago, Brazil, USA (using subtype B boost) and Thailand (using subtype B/E boost)</td>
<td>Phase II, three trials</td>
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<tr>
<td>DNA plus MVA boost, gag and T cell epitopes</td>
<td>IAVI, University of Oxford, University of Nairobi</td>
<td>UK and Kenya (subtype A)</td>
<td>Phase I, underway</td>
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<tr>
<td>Lipopeptides (plus Canarypox gag/pol/env/nef)</td>
<td>ANRS</td>
<td>France</td>
<td>Phase I, underway</td>
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<tr>
<td>VEE gag (plus pol/env)</td>
<td>Alphavax, IAVI, NIH, John Hopkins University, University of Natal</td>
<td>USA and South Africa</td>
<td>Phase I, Q2, 2002</td>
</tr>
<tr>
<td>Adenovirus gag, DNA gag</td>
<td>Merck, ISS, Italy</td>
<td>USA</td>
<td>Phase I, Q1, 2002</td>
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<tr>
<td>Recombinant tat protein</td>
<td>Chiron, NIH</td>
<td>USA</td>
<td>Phase I, Q1, 2002</td>
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<td>DNA-PLG, Δ2 gp120 boost</td>
<td>Wyeth, NIH</td>
<td>USA</td>
<td>Phase I, Q3, 2002</td>
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<tr>
<td>DNA, peptide boost</td>
<td>ABL, NIH</td>
<td>USA</td>
<td>Phase I, Q1, 2002</td>
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<tr>
<td>DNA, envef</td>
<td>UNSW, NIH</td>
<td>Australia</td>
<td>Phase I, Q3, 2002</td>
</tr>
<tr>
<td>DNA, Fowlpox boost</td>
<td>HIV, IAVI, NIH</td>
<td>USA, Uganda and Kenya</td>
<td>Phase I, Q3, 2002</td>
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<tr>
<td>DNA (Salmonella delivery)</td>
<td>EuroVac</td>
<td>Switzerland, UK</td>
<td>Phase I, Q3, 2002</td>
</tr>
<tr>
<td>NYVAC/MVA/SIV gag/pol/env/nef gp120 boost</td>
<td>Merck Research Laboratories, NIH, IAVI</td>
<td>USA</td>
<td>Phase I, Q1, 2003</td>
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testing of vaccines. The WHO Recommendations and Guidelines are advisory rather than mandatory and have served a valuable purpose in providing authoritative guidance in relation to best practice and consensus based approaches in ensuring that products are of acceptable quality, safety and efficacy.

The development of guidelines for HIV/AIDS vaccines will be particularly demanding because of the wide variety of innovative approaches being taken, several of which have no precedent in other licensed vaccines. It will require a multi-disciplinary approach involving virologists, immunologists, molecular and genetics scientists, vaccine manufacturers and public health experts working together.

The consultation recognised that a wide range of guidelines are available from WHO and other international or national regulatory bodies covering 'generic' aspects of the production and quality control of biological products. For example, guidelines on recombinant derived biological products, on synthetic peptides and on nucleic acid vaccines, and others already exist. However, some of the new approaches that are being taken for HIV/AIDS vaccine development, e.g. vectored vaccines, are not adequately covered by existing guidelines.

The development of guidelines for the standardisation and control of HIV/AIDS vaccines presents a greater problem than for many vaccines in part because we do not know the types of response an effective vaccine needs to elicit. For most current licensed viral vaccines, serological responses following vaccination correlate with vaccine efficacy. For HIV/AIDS vaccines, however, many experts believe that vaccine efficacy will correlate only with cellular immune responses or local immune responses elicited at mucosal sites. As a result, a variety of vaccine strategies have been proposed and are being developed (see Table 1). These distinct approaches often present different sets of problems in ensuring the quality of material and its production. For some strategies there have been precedents through the development of vaccines for other diseases. As a result, pertinent regulatory documents exist already (see Table 2). For other approaches novel issues present themselves and need to be addressed. These will be discussed in greater detail below.

It is of crucial importance that any vaccine that is to be subject to Phase III trials should be shown capable of consistent, lot to lot production, and should be fully characterized with defined and reproducible specifications.

**Issues associated with specific vaccine strategies**

**Inactivated vaccines**

This is a classical vaccine approach used to prepare a number of effective viral vaccines, including for example influenza and polio vaccines. With respect to inactivated HIV vaccines, the key issue would be to ensure complete inactivation of any biological activity

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**Table 2. Existing documents that will be of value in the development of regulatory guidelines for AIDS vaccines**

<table>
<thead>
<tr>
<th>Title</th>
<th>Source and reference</th>
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<tbody>
<tr>
<td>Guidelines for National Authorities on Quality Assurance for Biological Products</td>
<td>WHO, TRS 822 (1992)</td>
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<tr>
<td>Animal Cells, as In Vitro Substrates for Production of Biologicals</td>
<td>WHO, TRS 822 (1992)</td>
</tr>
<tr>
<td>Synthetic Peptide Vaccines</td>
<td>WHO, TRS 878 (1996)</td>
</tr>
<tr>
<td>Notes for Guidance on the Quality of Pre-Clinical and Clinical Aspects of Gene Transfer Medicinal Products</td>
<td>EMEA, CPMP/BWP/3088/99</td>
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<tr>
<td>Adopted April 2001</td>
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**Documents Related to Clinical Evaluation of HIV Vaccine**

<table>
<thead>
<tr>
<th>Title</th>
<th>Source and reference</th>
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<tr>
<td>Good Clinical Practice</td>
<td>WHO, TRS 850 (1995)</td>
</tr>
<tr>
<td>Regulation and Licensing of Biological Products in Countries with Newly Developing Regulatory Authorities</td>
<td>TRS 858 (1987)</td>
</tr>
<tr>
<td>Ethical Considerations in HIV Preventative Vaccine Research</td>
<td>UNAIDS Guidance Document</td>
</tr>
<tr>
<td>Operational Guidelines for Ethics Committees that Review Biomedical Research</td>
<td>TDR/PRP/ETHICS/2000.1</td>
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and the safety of the cell substrate, be they continuous cell lines or primary cell cultures.

Recombinant protein vaccines
Vaccines of this type have progressed further in clinical development than other products and current Phase 3 vaccine studies involve recombinant envelope vaccines. Generic guidelines that are relevant to such vaccines are available. However, there are two particular points worthy of further consideration. In the case of a vaccine based upon HIV regulatory proteins, e.g. Tat, the potential toxicity of the protein should be carefully considered. The second issue is the need to ensure comparability and consistency of production so that the vaccine materials used in the definitive clinical trials should be fully characterized and specified and shown to be capable of consistent lot to lot production.

Recombinant DNA vaccines
This novel vaccine strategy has interesting potential for HIV/AIDS vaccine development. The key features that appear to ensure the quality and safety of DNA vaccines are the physical properties and formulation of material. Fortunately, regulatory guidelines exist that are pertinent in guiding generic issues regarding the production and quality control of DNA vaccines. Special considerations may apply in the case of DNA vaccines expressing a regulatory gene product. A key issue is the biological activity of a transgene expressed by the vaccine. This is relevant whether it be a viral regulatory gene such as tat that is known to have toxic effects in vitro or an immunomodulatory gene co-expressed with a viral antigen to enhance anti-HIV responses.

Recombinant viral vector vaccines
A number of viruses have been genetically engineered in order to allow high level expression of foreign transgenes and act as vaccine vectors. Examples include vaccinia virus (and its derivatives, such as NYVAC and MVA), Fowl pox virus, adenovirus, adeno-associated virus, Semliki Forest virus and Venezuelan Equine Encephalitis virus. Some of the regulatory issues associated with this approach have been addressed in documentation produced by the FDA and EMEA with regards to gene therapy. However, there are no biologicals based upon viral vectors licensed for use as preventive vaccines in humans. Due to the diverse nature of each viral vector system, for example, in terms of mode and site of replication of the vector, it may not be possible to produce a set of generic guidelines. As a result, more specific guidelines may need to be developed focusing on the needs for HIV/AIDS vaccines or focusing on each vector system employed. A particular issue that is worth noting with regards to the production of recombinant viral vectors is the cell substrate employed. Particularly in the situation where replication defective viruses are delivered because many of the helper cell lines used to produce the viral structural protein used to package the viral nucleic acid are derived from continuous cell lines that may be tumorigenic.

Recombinant bacterial vectors
Vectors based upon attenuated mycobacterium, such as BCG vaccine or on attenuated Salmonella strains are being explored in HIV/AIDS vaccine development. Guidelines for this type of product will be required.

Live attenuated HIV virus
Although this is a conventional approach in the production of other viral vaccines, there are strong reservations about the development of such HIV vaccines for use in humans at the present time, given the current limitations of knowledge on the biology and genetics of HIV in relation to virulence and attenuation. Studies in model systems have so far failed to disassociate the pathogenic potential of HIV (or SIV) from its replicative capacity in vitro, i.e. there are no specific genes for pathogenicity of HIV in vitro. Moreover, the degree of vaccine induced protection appears to correlate with the replicative capacity of the virus. As this vaccine approach provides potent vaccine protection in model systems, it remains a valuable tool in laboratory research, but considerable further work would be required before it could be considered appropriate for clinical studies.

Generic issues
Beyond issues that apply to a specific vaccine approach, there are a number of considerations that need to be addressed to ensure the quality of HIV/AIDS vaccine, whatever the details of the vaccine strategy.

Standardisation of HIV assays
Virological, immunological and molecular assays are necessary both in the development and clinical testing of new vaccines and also to assess the quality of each batch of vaccine produced subsequently. Technical progress in the standardization and validation of key assays is an important necessity. Reference reagents will be needed for international distribution to ensure comparability of results from these assays.

Serological assays are essential as a diagnostic tool for detection of clinical infection. In addition, serological responses are measured in vaccine studies, for example by ELISA where selected viral components are used as antigens to determine antiviral antibodies elicited following immunization. Alternatively, assays are designed to assess virus neutralising activity in vitro. As a result, during clinical trials care is required to select appropriate serological assays that will be capable of differentiating between immunization and infection. Thus, the selection of serological assays will depend upon those viral antigens formulated in the vaccine. In addition, prior to and during clinical trials in particular,
it is essential to ascertain background responses in local populations and where more than one sero-diagnostic assay is being used, that they generate comparable data.

For most viral vaccines the correlate of protection is a serological response generated by the vaccine. As a result, particular importance is ascribed to binding antibody or neutralizing antibody measured in serum. Whilst technically relatively simple, the measurement of binding antibodies by ELISA is dependent upon the quality of the protein employed. These are often produced by recombinant technology. The quality of the results generated is dependent upon the quality of the antigen preparation. Standardised assays and the availability of reference antigens and antibody materials would be beneficial. The detection of neutralising activity is considered a valuable guide to function serological response that could have biological effect. In animal models a beneficial role for the transfer of potent neutralising antibodies prior to virus expression has been described by more than one group. However, evidence for a beneficial role of neutralizing antibodies in vaccine induced protection is currently lacking. There are considerable technical issues associated with the standardization of neutralizing assays for HIV-1 and clearly the availability of reference panels of antibodies and sera will be essential to enable data to be compared.

Another challenge for the standardization of AIDS vaccines is the need to develop methods to compare cellular immune responses. A number of vaccine approaches are being developed primarily because of their ability to elicit cellular immune responses, particularly cytotoxic T cell responses mediated by CD8+ lymphocytes. Recent advances in immunology allow measurement of T cell responses without the need for maintaining cells in culture for two to three weeks, as was the case for chromium release assays. However, ELISPOT and intracellular cytokine staining assays require cells to respond to antigenic re-stimulation. As a result, the accuracy of these latter assays is dependent upon the viability of cells. Only the analysis of CD8+ cell responses by measuring binding of peptides loaded onto fluorescently labelled MHC Class I tetramers is not dependent upon cellular viability. Developing assays to maximize comparability of results from CD8+ T cell assays is a challenge, but even relatively simple measures such as the application of common peptides or peptide pools of a defined size, quality and from a single source may have marked effects on the comparability of results. Reference preparations of tetramers may also prove useful. Certainly a key challenge will be the development of reference cell preparations for these types of assays.

Measurement of viral load is believed to be important in many clinical trials because it is not anticipated that

at least the first generation of HIV/AIDS vaccines will confer "sterilizing immunity". The introduction of quantifiable gene amplification technologies such as RT-PCR, NASBA, bDNA allow the viral RNA load (vRNA) to be determined with a high degree of accuracy. On the introduction of this new technology in diagnostic virology problems were encountered particularly over the reproducibility and accuracy of assays. Many of these have been overcome through the establishment of external as well as internal quality control schemes and in particular the introduction of a WHO International Standard. Measuring loads as International Units is considered to be preferable as it enhances comparability of data. However, additional reference materials are required to underpin this genetic diagnostic technology. In particular, there is a need to develop reference panels that will permit evaluation of the influence of genetic variability of HIV isolates on the sensitivity of assays.

**Genetic variation of HIV**

The classification of HIV isolates from a number of geographical areas into genetic sub-types or clades has been valuable in mapping the epidemiological spread of infection. This has led to the rationale of selecting local isolates from trial sites as the basis of immunogens in vaccine clinical trials. However, as the pandemic has developed, the complexity in the pattern of distribution of viruses has increased, as well as the emergence of recombinant circulating forms (CRFs). As discussed above, genetic variation impacts upon the sensitivity of molecular diagnostic assays, but this issue is being addressed through the development of reference panels. However, the quality of these reagents is dependent upon effective monitoring of HIV isolates from key regions likely to act as trial sites. In this regard, the WHO-UNAIDS Network for HIV Isolation and Characterisation provides a valuable mechanism of acquiring current information. Its value is dependent upon the scale of sample collection and the speed at which this information is generated and disseminated.

Compared to the emphasis and speed of characterising HIV based upon genetic criteria, relatively little progress has been made to understand the implication of genetic variation and HIV-1 subtypes upon antigenic variation, particularly at key epitopes of the virus involved in protection. It is quite possible that characterising viruses based upon antigenic variation may result in a very different grouping of viruses based upon genetic variation, but that would depend upon the type of vaccine employed. It is urgent that more information on the implications of genetic variation for the biological and immunological properties of HIV is gained as rapidly as possible and correlates made in respect of the protective efficacy of vaccines.
Potency

Vaccine potency provides a measure of the ability of a vaccine to elicit appropriate responses. For many current viral vaccines, measurement of potency does not always involve a study of immunogenicity. The properties of well-established vaccines are reproducible that surrogate biological markers such as antigen content may be appropriate and sufficient. Appropriate methods of determining potency for HIV/AIDS vaccines will depend on the vaccine approach used. A vaccine based upon a recombinant viral vector presents the greatest number of issues since currently there are no licensed vaccines based upon the strategy. Further research will be required to evaluate whether standardized assay for immunogenicity measuring serological or cellular immune responses will be necessary, or whether titre of the vector or levels of protein expression may be used such as the surrogate markers. If immunogenicity studies are selected to assess the potency of vaccine lots, then even here pitfalls may be encountered as for some vectors, significant variation in the susceptibilities of different laboratory animal species have been described that could affect the results.

Animal models

In the absence of clear information as to the type of response an effective AIDS vaccine needs to elicit, then the application of appropriate animal models would be expected to continue to play an important role. The key value of a useful model is the ability to challenge immunized subjects and assess their ability to control virus replication in comparison with unvaccinated controls. Although there is considerable investment and investigation in and investigation using model systems, there seems to be a reluctance by vaccine developers to use model systems as a key checkpoint of pre-clinical evaluation of vaccine efficacy prior to entry into humans. This is due to uncertainty of the model that reflects the situation in man most clearly. HIV-1 has a highly restricted host range in laboratory animals. Chimpanzees are susceptible, but cost and ethical issues frequently restrict the numbers available for study below those needed for robust statistical validity. In addition, replication of HIV-1 in chimpanzees is seldom to high levels questioning whether it represents a robust challenge for any vaccine. Transgenic and immunodeficient mice reconstituted with components of the human immune system are also susceptible to HIV-1, but unfortunately the length of immunization studies precludes their use. Another lentivirus infection with the Feline Immunodeficiency Virus (FIV) is a natural infection of cats and the development of an effective FIV vaccine is a veterinary issue in its own right. The ability to translate results to clinical studies remains unclear because of the distinct genetic organisation of FIV and aspects of its biology, e.g. 1° cellular receptor. As a result many people regard that the experimental infection of macaques with HIV-2 or the closely related simian immunodeficiency virus (SIV) is most appropriate for vaccine studies. A key reason leading some to question the relevance of animal models is that in some situations different models have yielded conflicting observations on the efficacy of specific vaccine strategies. For example, protection has been reported to be conferred by recombinant envelope protein in the HIV/chimpanzee model, but limited or no protection has been seen with equivalent vaccines in the SIV/macaque model. In this situation, whilst positive data may facilitate progress, the failure to achieve protection with a vaccine in one model system should not be interpreted that the vaccine is of little use in man.

Clearly, there is a need for model systems to develop our understanding of vaccinating against HIV/AIDS. Therefore, it is important that models are developed in conjunction with clinical studies (para-clinical testing) to ensure that there is clear understanding as to which model is most appropriate for the vaccine strategy being evaluated and developed.

The key issue that can be addressed in animal models is the identification of correlates of protection and the understanding of mechanisms of vaccine protection. These are valuable in the development of regulatory issues associated with a particular vaccine approach and as a result identify methods to ensure the quality of each batch of material. The restricted availability of appropriate facilities for animal model studies and their high interest cost, indicate that efforts should be made to ensure that these resources are used effectively.

Summary recommendations of the working group on standardization and control

WHO/UNAIDS should:

1. Commission a thorough review of current guidelines and related documents to assess existing material for completeness, and consistency and relevance to HIV/AIDS vaccines regarding the issues described above; identify 'gaps' and the need for the development of additional guidelines of specific relevance to HIV/AIDS vaccines;

2. Develop generic or specific guidelines on viral and bacterial vectored vaccines for prophylactic use and encourage and support research on the issue of vaccine potency;

3. Disseminate information on available regulatory documents relevant to HIV/AIDS vaccines;

4. Develop fora of experts to provide appropriate advice to countries that need specific regulatory advice and to assist in strengthening National Regulatory Authorities (NRA);

5. Encourage enabling research that will facilitate the development of further guidelines on cell substrate and other issues as they pertain to HIV/AIDS vaccines;
6. Seek a consensus on methods to assess serological and cellular immune responses and virus load;
7. Identify appropriate reference reagents that should be prepared for standardized immunological and virological assays;
8. Encourage the further development of the WHO-UNAIDS Network for HIV Isolation and Characterisation and the timely dissemination of molecular, biological and immunological information on incident viruses;
9. To convene at appropriate times further international meetings of experts to advise on regulatory issues and identify future needs.

Approaches to clinical evaluation of preventive HIV/AIDS vaccines

Discussion of the issues related to clinical evaluation addressed only those specific to preventive HIV/AIDS vaccine Phase III efficacy trials. It was recognized that many countries where HIV/AIDS vaccine trials may be performed have limited regulatory resources. Regardless of the participating organizations, trials should be performed only in countries where adequate provisions can be made to ensure proper ethical and regulatory oversight.

HIV/AIDS vaccine trials are complex and likely to attract considerable community attention and it is essential that there is strong political and community support before starting. A number of documents are currently available which address general issues which are for clinical trials in considerable detail (see Table 2 and also references 4-6). However, there are many issues specific to HIV/AIDS vaccine trials that need to be considered.

Clinical trial design

The primary end-point of the two ongoing Phase III preventive HIV vaccine efficacy trials is prevention of infection. Based on animal model data, however, it is anticipated that some vaccines may not prevent infection by inducing “sterilizing immunity”, but could result in a significant and substantial reduction in viral load (in vaccinees who subsequently are exposed to HIV and become infected). Thus, evaluation of viral load is also of great interest for vaccine efficacy trials. However, there is a need for much more research on this topic. The persistence of very low or undetectable levels of viral load in those vaccinees who have become HIV infected as demonstrated in the context of a randomized controlled trial compared to a control group could potentially provide a public health benefit, if this lead to a reduction in HIV disease progression.

If viral load is used as an end-point, a number of issues need to be considered, including validation of laboratory methods for viral load measurement with different HIV-1 subtypes and, possibly, in different target populations, as well as a number of measurements of viral load to be made to determine the “set point” before HAART initiation, if it is to be initiated. Long-term follow-up of infected trial participants in order to assess delay in disease progression may be needed. It is emphasized that as well as viral load, CD4 counts should be included in trial endpoints as a composite prognostic measure.

Some participants expressed the view that a vaccine that is capable of controlling the viral load at a very low or undetectable levels in a vaccinated group compared to the control group, in the context of a randomized controlled trial, may be of public health benefit in heavily affected developing countries, if this leads to reduced disease progression. However, current understanding of the natural history of HIV disease suggests that a reduction in viral load of the order of 1 to 2 logs would have relatively little potential benefit to the individual.

More data should be obtained on the natural history of HIV disease in developing countries from acute infection onward, including viral load as a function of time and its relation to both CD4 cell counts and AIDS defining clinical events. The impact of concurrent infections (e.g., malaria, TB, and sexually transmitted infections) on HIV disease progression should also be investigated.

For vaccinated individuals who subsequently become HIV infected, there is uncertainty about whether a decrease in plasma viral load would be associated with a decrease in HIV transmission. Thus, data are needed which correlate viral load in semen and vaginal secretions with plasma in (i) HIV infected individuals, (ii) vaccinees who subsequently become infected, and (iii) immunized non-human primates who subsequently become infected. CD4 cell counts should be obtained in parallel with viral load assessments. A potential beneficial outcome for preventive HIV vaccine trials would be the clinical demonstration that vaccinees who subsequently become HIV infected are less likely to transmit HIV than those who become infected in the control group. The use of anti-retroviral drugs would be expected to affect the assessment and interpretation of this outcome. This concept should be explored by statistical modelling, sample size estimates and feasibility issues for trial design.

Discussions in the host country regarding the use of anti-retroviral drugs in trial participants who become infected, should be held prior to initiating a trial, in order to formulate a plan. The trial sponsor can facilitate the community implementation of national
guidelines for use of anti-retroviral drugs and opportunistic infection therapies. It should be noted that use of drugs may affect the interpretation of trial data and should always be accompanied by appropriate disease monitoring and counselling with regard to adherence. These policies are important in assuring patient well-being while on therapy and to minimize therapeutic failure with the emergence of drug resistant virus.

Sponsors and investigators will need to have a plan to address what services will be offered to individuals found to be HIV infected at baseline screening, as well as those who become infected during the trial. This plan should be clearly described in the consent forms, and should include counselling and referral, as appropriate. If trial participants who become HIV infected during the course of the trial receive anti-retroviral therapy, the impact of this therapy will need to be factored into the interpretation of viral load data.

It is recommended that modelling techniques, based on observational cohort data are used to estimate the potential impact of anti-retroviral therapy on trial outcomes such as a decreased viral load of varying degrees (e.g., one log decrease, undetectable, etc.). This will help to elucidate the public health utility afforded by the various trial outcomes including combinations of outcomes.

All HIV infections that occur during clinical trials should be extensively characterized by subtyping and sequencing. In this regard, the findings for HIV vaccines should be compared to those for the local population, including the control group. Proviral DNA should be quantified in cells such as PBMC's as well as from relevant mucosal sites. Data on proviral DNA may be of special interest in persons with an undetectable viral load.

An important issue is the minimum duration of protection afforded by an HIV vaccine which would support its use in public health programs. The acceptable criteria for this parameter are likely to be country and vaccine specific. The need for booster doses is closely related to this issue.

Long-term clinical follow-up of trial participants who become HIV infected would be critical to determine whether, a "vaccine-induced" decrease in viral load is associated with clinical benefit in terms of delay in disease progression and death.

**Clinical trial conduct**

In some regions, it is recognized that there is a shortage of local Investigators with sufficient training and/or experience to undertake preventive HIV vaccine trials. Additional training opportunities and resources should be provided for Investigators and other essential trial personnel to increase their practical experience with vaccine trials.

In some instances, experienced Investigators have extensive commitments with other research projects. A clear trial management plan with sufficient research staff, appropriately qualified and experienced must be in place to ensure sufficient, competent site management for each trial.

Sites for vaccine clinical trials require careful preparation and consultation prior to initiating clinical trials. In many countries, there are shortages of potential clinical trial sites. Resources should be provided to address this problem. Sites with experience in other HIV intervention studies should be considered as possible vaccine trial sites.

Generic Standard Operating Procedures (SOP) should be developed for key procedures in HIV vaccine clinical trials and should be widely available. Examples may include SOP's for:

- Subject recruitment and enrollment;
- Obtaining and documenting Informed Consent;
- Pre- and post-HIV test counseling; and
- Ongoing HIV risk reduction counseling.

In relation to Good Clinical Practices (GCP) clear policies and procedures on monitoring and inspection are important:

- Procedures should be in place to assure GCP, with special attention to appropriate monitoring;
- Training should be provided to NRA in the area of GCP inspections. NRA's may not need to perform routine inspections, but should have the capacity to inspect a site in case of problems. Liaison with other regulatory authorities is encouraged.

**Target population**

Once safety and immunogenicity have been evaluated in healthy adults, performing safety and immunogenicity trials in selected high risk populations should be considered. Potential safety issues for the specific type of product (e.g., live vector, recombinant, etc.) are important considerations before proceeding to Phase III trials. Efficacy trials might be conducted in infants from populations at high risk for HIV infection.

Adolescents are a potential target population for HIV vaccination because of their high risk of infection, at least in some regions. Once safety and immunogenicity have been evaluated in adults, safety and immunogenicity trials in adolescents should be considered in parallel with adult efficacy trials. In addition, there should be an evaluation of how vaccine trial participation affects
risk behavior, and special consideration should be given to the target age group and the details of informed and assent consent. Also, from a biological perspective, adolescents may have a different response to vaccination or susceptibility to HIV infection, compared to adults, because of their maturing anatomy and physiology.

In a comprehensive immunization program (i.e., following licensing/regulatory approval), significant numbers of HIV infected persons in high prevalence areas may receive the HIV vaccine, as pre-vaccination screening is unlikely to be feasible. Thus, prior to approval, consideration should be given to evaluating vaccine safety in HIV infected persons in a controlled trial(s). The extent and timing of this clinical evaluation will depend on factors such as (i) the type of product (e.g., live vector, recombinant, etc.) and its anticipated safety profile based on pre-clinical and clinical data, (ii) experience with similar products, and (iii) plans for pre-vaccination screening for serostatus post-licensure.

Facilitating the regulatory process
A sponsor should provide evidence that a vaccine has biological plausibility in order for that product to be advanced to Phase I clinical development. Evidence of biological plausibility may include animal immunogenicity data and animal challenge/protection data. The extent of this supporting data may be related to the perceived risk/benefit for the host country. Other useful information may include data on similar products.

To support Phase I clinical trials, on-site laboratory facilities with adequate Quality Assurance and Quality Control should be in place to perform the necessary screening and safety assessments of the volunteers and SOP’s for specimen handling must be available.

Infrastructures should be in place or under development in the region or country to undertake immunogenicity and virological testing for Phase II and III trials. For a Phase III trial, there should be on-site capacity for the testing of key samples. However, this does not preclude the testing of samples outside the country for any clinical trial.

Phase I trials may be performed simultaneously in both the country of origin of the product and in the host country(s) where future efficacy trials are planned. However, trials could also proceed in the host country without a Phase 1 trial in the country of origin, and vice versa.

Ideally, in a clinical development, there is usually a need to test multiple doses, schedules and formulations. For the purpose of efficiency, most of this work may be performed in countries with strong clinical research infrastructures.

The first HIV seronegative trial participants should be healthy HIV seronegative subjects with normal laboratory values (e.g., chemistry, haematology, etc.), even if minor abnormalities in such values are common in the normal population at that site. Subsequently, individuals with mildly abnormal laboratory values commonly observed in the country, but who are otherwise healthy, can be included in Phase I and II studies.

Prior to proceeding to Phase III efficacy trial(s), sponsors should provide NRAs with all available Phase I and II safety and immunogenicity data, as well as supporting epidemiological data. Prioritising candidate vaccines for clinical trials, if applicable, may be facilitated by national or international advisory groups.

Dialogue among regional officials and regulators should be supported and encouraged. This should include sharing national HIV/AIDS vaccine plans, which ideally should be part of a regional HIV/AIDS vaccine plan.

For those countries with minimal resources, WHO-UNAIDS could play an important role by obtaining outside expert advice on a case-by-case basis, for both the investigational and licensing stages. Consideration should be given to the establishment of an international regulatory advisory group convened by WHO, which can advise and support countries as needed.

Regional regulatory harmonization could potentially speed up the process as well as disseminate knowledge. In some regions, harmonization for purposes of registration is already under discussion. WHO and UNAIDS could facilitate such initiatives and support regional harmonization for the purposes of clinical trial review and approval, as well as for licensure.

Additional international and national funding should be directed toward developing countries for the specific purpose of strengthening regulatory expertise and building the infrastructure so that they are in place to facilitate swift approval of safe, effective vaccines particularly those for life-threatening diseases.

Summary recommendations of the working group on approaches to the conduct of clinical trials of candidate HIV/AIDS vaccines
1. Highly sophisticated HIV/AIDS vaccines present novel concepts for regulatory approval which need to take into consideration the design and ethics of clinical trials.
2. International and National requirements need to be considered from the earliest clinical develop-
ment stages to the post-licensure production and clinical utilization.

3. National Regulatory Authorities in developing countries will need advice, training and scientific support both for clinical trial review and approval, and for licensing.

4. Providing advice may be insufficient; host countries for clinical trials will need proactively to involve experts with experience in evaluating trials, as well as evaluating the dossier in their regulatory review process.

5. For the regulatory approval of preventive HIV/AIDS vaccines, close collaboration between countries within the region with the most experienced National Regulatory Authorities and those with little experience is strongly recommended.

6. There is a need for more extensive dissemination of information on HIV vaccines and trials to member states by organizations such as WHO-UNAIDS, IAVI, EMEA, etc.

7. Clinical trials are technically demanding and expensive to conduct; the need for international support, both financial and technical, for trials in the less wealthy countries needs to be addressed as a matter of urgency.

Selected References


7. http://www.who.int/biologicals


Annex I

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