STRATEGIES FOR THE DEVELOPMENT OF HIV VACCINE TRIAL SITES IN AFRICA: CHALLENGES AND OPPORTUNITIES
REPORT OF THE WHO-UNAIDS SPONSORED SECOND FORUM OF THE AFRICAN AIDS VACCINE PROGRAMME (AAVP)

“STRATEGIES FOR THE DEVELOPMENT OF HIV VACCINE TRIAL SITES IN AFRICA: CHALLENGES AND OPPORTUNITIES”

Addis Ababa, Ethiopia
16–18 June 2003
**TABLE OF CONTENTS**

1. Introduction ........................................................................................................... 6

2. The African AIDS Vaccine Programme (AAVP) ........................................ 7

3. Opening Ceremony .................................................................................................. 8

4. Advocacy and Resource Mobilization ............................................................... 9
   (a) A strategy roadmap for advocacy and communication ............................. 9
   (b) The development of international partnerships and support for AAVP ....... 10

5. Biomedical Sciences ............................................................................................. 10
   (a) The AAVP policy statement on “Implications of HIV genetic variability
       for the development of HIV vaccines suitable for use in Africa” ............. 11
   (b) How basic science could provide guidance for the development of
       HIV vaccines suitable for use in Africa .............................................. 12
   (c) Pipeline of candidate HIV vaccines targeted for Africa ....................... 13
   (d) National regulatory procedures – perspectives from African countries ... 17
   (e) Clinical and laboratory requirements for Phase I, II and III trials .......... 18

6. Community Preparedness ..................................................................................... 19
   (a) Involving the community in vaccine preparedness .................................. 19
   (b) From AIDS Vaccine Community Task Force to the Community
       Preparedness Working Group ............................................................. 20

7. Ethics, Law and Human Rights ........................................................................... 21
   (a) Ownership of research ............................................................................ 21
   (b) Issues in informed consent: Culture and implications for HIV
       vaccine trials in developing countries .................................................... 22
   (c) Access to treatment, care and support for HIV vaccine trial participants
       who acquire HIV infection during the conduct of a trial ....................... 23

8. National Strategic Planning ................................................................................. 24
   (a) Inventory of HIV/AIDS control programme policy/plans for HIV/AIDS
       vaccine research ..................................................................................... 24
   (b) Country experiences ............................................................................... 25

9. Population-Based Studies ................................................................................. 27
   (a) Overview of HIV prevalence and incidence in Africa ........................... 27
   (b) Global perspectives of HIV vaccine development ................................. 29
   (c) Lessons learned from HIV vaccine trials – experiences from Africa
       (Phase I/II trials) ..................................................................................... 32
(d) Collaborative efforts in cohort development in preparation for HIV vaccine efficacy trials in Africa ........................................... 33
(e) Facilitating multi-site collaboration in HIV efficacy trials in Africa ....... 36

10. **Lessons Learned from the First HIV Vaccine Efficacy (Phase III) Trial** ................................................................. 37
(a) Results from the first efficacy trial with rgp120BB (VaxGen) candidate vaccine (AIDSVAX BB) in the USA, Canada and the Netherlands ............ 37
(b) AIDSVAX B/B efficacy trial follow-up ...................................... 38

11. **Working Group Recommendations** ..................................... 39
(a) Policy frameworks ................................................................... 39
(b) Ethics, care and support .......................................................... 40
(c) Site development .................................................................... 41
(d) General recommendation ....................................................... 41

**ANNEX**
**LIST OF PARTICIPANTS** ......................................................... 42
1. INTRODUCTION

The Second AAVP Forum (“Strategies for the development of HIV vaccine trials sites in Africa: challenges and opportunities”) was held at the Hilton Hotel in Addis Ababa, Ethiopia from 16–18 June 2003. The Forum was organized by the WHO-UNAIDS HIV Vaccine Initiative (HVI), WHO Regional Office for Africa and the African AIDS Vaccine Programme (AAVP).

The Forum was cosponsored by 15 partner organizations that provided technical, logistical and/or financial support: The Canadian International Development Agency (CIDA), The Centers for Disease Control and Prevention (CDC), the Ethiopian Netherlands AIDS Research Project (ENARP), the European Union (EU), the French Agency for Research on AIDS (Agence Nationale de Recherche sur le SIDA (ANRS), The Bill and Melinda Gates Foundation, the Harvard AIDS Institute, the Istituto Superiore di Sanita (National Institute of Health) in Rome, the International AIDS Vaccine Initiative (IAVI), The National Institutes of Health of the United States of America (NIH) and their HIV Vaccine Trials Network (HVTN), the US Military HIV Research Programme (US MHRP), the Swedish Agency for International Development (SIDA/SAREC), the South African AIDS Vaccine Initiative (SAAVI), and the World Bank.

The multiplicity of cosponsors of the workshop, and the different professional backgrounds of participants served to indicate the complexity of what is required to ensure that a HIV vaccine is developed and made available in Africa. By bringing so many people together from different countries, disciplines and interest groups, an opportunity was created to increase understanding and collaboration between partners interested in promoting the development and evaluation of HIV vaccines for Africa. Similarly, increased interaction and collaboration was afforded between those interested in continuing the process of developing a policy framework that will ultimately facilitate the implementation of HIV vaccine trials in Africa with the highest scientific and ethical standards.

Africa is home to more than 80% of all HIV-infected people globally and the development of a HIV vaccine suitable for Africa has been recognized as an urgent priority. Facing this challenge, the WHO-UNAIDS is sponsoring an African AIDS Vaccine Programme (AAVP), which was launched at the First AAVP Forum in Cape Town, South Africa in June 2002. One of the major recommendations that emerged from that Forum was the need to “develop strategies and plans supporting the ongoing efforts to implement multiple HIV vaccine trial sites in Africa”. The Second AAVP Forum has been organized as a follow-up to this recommendation.

The specific objectives of the Forum were to:

- Increase understanding and collaboration between all partners interested in promoting the development and evaluation of HIV vaccines for Africa;
- Collectively identify the needs and commit support to strengthen the existing trial sites in Africa and identify possibilities to develop new ones;
- Continue the process of developing a policy framework to facilitate the implementation of HIV vaccine trials in Africa with the highest scientific and ethical standards; and
- Develop recommendations for the further development of AAVP activities, with specific milestones to assess progress and success.

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A copy of the report of the First AAVP forum can be obtained at: http://www.who.int/HIV-vaccines/Documents/Forum_proceedings/secondpages/toc.htm
The workshop presentations were varied and the topics covered were of critical importance to understanding issues related to HIV vaccine research, development and access, and the task ahead will require significant levels of goodwill, commitment and intense international collaboration and coordination.

This report provides a narrative of the presentations and discussions that took place during the Forum. A full copy of all presentations can be found at www.who.int/HIV-vaccine.2

2. THE AFRICAN AIDS VACCINE PROGRAMME (AAVP)

The AAVP is a network of African scientists and community personnel, working to promote and facilitate HIV vaccine research and evaluation in Africa, through capacity-building and regional and international collaboration. The AAVP promotes vaccine development and evaluation of promising HIV candidate vaccines in Africa, by building on local knowledge and resources and by encouraging collaboration between African countries, as well as with other countries and partners internationally.

The AAVP is a response to an appeal for a HIV vaccine for Africa launched in Nairobi, Kenya in June 2000, which was articulated in The Nairobi Declaration. The goal of the AAVP is to advocate and support a coordinated effort to contribute to the global HIV vaccine development goals, ensuring that appropriate and affordable vaccines are developed for Africa in the shortest possible time.

The objectives of the AAVP are to:3

- Promote development, facilitate evaluation, and address future availability of HIV/AIDS vaccines for Africa;
- Serve as a forum for collaboration and coordination;
- Assist countries in strengthening research infrastructures and setting up scientific and ethical standards;
- Promote exchange of information by facilitating networking; and
- Promote targeted training.

The AAVP is developed under the guidance of the WHO-UNAIDS HIV Vaccine Initiative (HVI). The programme is coordinated by a Steering Committee and the work is planned, facilitated and implemented through six working groups:

- Advocacy and Resource Mobilisation;
- Biomedical Sciences (Laboratory/Clinical);
- Community Preparedness;
- Ethics, Law and Human Rights;
- National Strategic Planning;
- Population-Based Studies (Epidemiology/Socio-Behavioural).

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2 This report was prepared by Shaun Mellors, Inis – www.inis.ie
3 As stipulated in the African AIDS Vaccine Programme brochure.
3. OPENING CEREMONY

The Opening Ceremony saw the high level political commitment that is undoubtedly required to advance and integrate all aspects related to HIV vaccine research, development and future access. There were examples of political commitment being translated into political action on the national and regional levels. In addition, this commitment permeated into the public arena through the establishment of common research agendas, and the creation of effective coalitions, partnerships and networks that facilitate and encourage stakeholder participation.

His Excellency Girma Woldegiorghis, President of the Federal Democratic Republic of Ethiopia, officially opened the workshop, and called for a strong commitment to find a HIV vaccine suitable for use in Africa.

The Honourable Raphael Tuju, M.P., Minister for Information and Tourism of the Republic of Kenya, reminded participants that the reality of the AIDS epidemic is with us. The sub-Saharan African region accounts for approximately 75% of those living with HIV/AIDS worldwide. He went on to say that vaccine development is a complex process that requires interplay between science and technology, industry, communities and other sectors.

The Honourable Minister highlighted why the AAVP is an imperative rather than a choice, as it is a platform for African scientists, leaders and communities to become active members of the global quest for a HIV vaccine. He called upon all leaders of African countries to give more support to AAVP as future work required is enormous – and the war against AIDS is a war that we must win.

Dr Angela Benson, the Acting WHO Representative in Ethiopia, stated that one of the goals set for the AAVP is to promote and facilitate HIV vaccine research through capacity-building and through regional and international collaboration. The WHO promotes the integration of vaccine research into national AIDS control programmes, and subscribes to the principles of AAVP that aspire to the highest ethical and scientific standards and ensure full participation of all African communities. WHO supports increased collaboration between African scientists and international colleagues to make a safe vaccine available and accessible to the people of Africa and the rest of the world.

Dr Aberra Geyid, Director of the Ethiopian Health and Nutrition Research Institute (EHNRI), welcomed participants to Ethiopia and highlighted strategies that were used in the establishment of the Ethiopian AIDS Vaccine Initiative (EAVI). He also stressed the importance of developing national strategic plans to address the challenging issues of HIV vaccine development, research and access.

Dr José Esparza, Coordinator of the WHO-UNAIDS HIV Vaccine Initiative (HVI), stated that the presence of His Excellency, the President of Ethiopia, testifies to the high priority that Ethiopia and Africa give to the efforts of AAVP in contributing to the development of a preventive vaccine against AIDS – the disease that kills more Africans than any other disease. He indicated that while the challenges that lie ahead are difficult, we have no choice other than to succeed. The challenge may be bigger than any one individual working separately, but it is not bigger than all of us working together.
4. ADVOCACY AND RESOURCE MOBILIZATION

The AAVP Advocacy and Resource Mobilization Working Group (ARM)\(^4\) manages the overall image dynamics of the programme and actively mobilizes resources and builds organizational support for the AAVP goals. A major output for this group is the development of a strategic framework that will help to:

- Define advocacy goals;
- Identify target audiences;
- Outline approaches to promote and support the goals of AAVP among partners and collaborators; and
- Develop key messages for each target group.

The specific objectives of the ARM are:

- To position the AAVP as having a vital role to play in the global efforts to develop HIV vaccines; and
- To mobilize the necessary resources to build support for the AAVP goals.

4(a) A strategy roadmap for advocacy and communication\(^5\)

Accomplishing the mission of AAVP depends on creating an environment that is highly supportive of research, evaluation and rapid access to an effective HIV/AIDS vaccine. Advocacy can be described as strategic outreach to gain support of key audiences in order to influence policies and spending and, thereby, bring about political, economic and social change.

The objective of the advocacy plan of the AAVP is to create a roadmap for advocacy and communications that clearly supports the mission and potential of the programme. The AAVP has specific “added value,” has representation from the top leadership of a variety of stakeholders and has a unique role as advocator and facilitator in Africa. The plan seeks to define and strengthen collaboration, partnership and networking to ensure more effective outreach and advocacy on the national level.

The key themes of the advocacy strategy are:

- Combined with HIV/AIDS prevention and treatment, an HIV vaccine is the ultimate hope for protecting present and future generations of Africans against HIV/AIDS.
- Overcoming the scientific, political, ethical and cultural challenges associated with HIV/AIDS vaccine research and access to future vaccines which requires collaboration on every level of the global society.
- AAVP provides the most credible platform from which to promote and evaluate vaccine trials in Africa and champion public policies to ensure rapid access.

A communication guide\(^6\) has been developed by members of this Working Group, which is intended to assist organizations and stakeholders at a national level. It includes specific examples of how to work with communities and different opinion leaders and stakeholders on the issue of advocacy.

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\(^4\) Excerpt from the African AIDS Vaccine Programme workplan and budget.
\(^5\) Presentation by Dr Malaki Owili (Kenya) on behalf of the Working Group on Advocacy and Resource Mobilization.
\(^6\) A copy of the AAVP communication guide can be obtained from [www.who.int/HIV-vaccines](http://www.who.int/HIV-vaccines).
4(b) The development of international partnership and support for AAVP

The vision and goals of the AAVP include the need to advocate and support a coordinated effort to contribute to the global HIV vaccine development goals, ensuring that appropriate and affordable vaccines are developed for Africa in the shortest possible time. Since its development, the AAVP has played a key role in facilitating HIV vaccine activities and focusing on collaboration with various African countries.

Several donors have expressed and shown interest in supporting the AAVP, and some of these partnerships involve collaboration with the International AIDS Vaccine Initiative (IAVI), which has resulted in financial support of US$ 200,000 for a two-year period. Financial support of CAN$ 5 million over a three-year period was also secured from CIDA and collaborative activities that address issues of future availability of HIV vaccines were instigated with the CDC. Several other donors and sponsors have expressed interest in the AAVP and a pledge has been received from the Swedish International Development Agency and Swedish Agency for Research Cooperation with Developing Countries (SIDA/SAREC).

Some of the challenges and opportunities highlighted for the AAVP include establishing the community preparedness working group, creating and sustaining a media network in Africa and refocusing the activities within AAVP to include:

- Developing and strengthening partnerships with international HIV vaccine research groups;
- Focusing on national strategic planning;
- Strengthening regulatory capacity at national and institutional level;
- Addressing and incorporating community issues;
- Strengthening laboratory research capacity and increasing knowledge of young African scientists through training in specific techniques.

5. BIOMEDICAL SCIENCES

The overall objective of the Biomedical Sciences Working Group (BMS) is to define and strengthen priority areas in biomedical sciences for the purposes of accelerating the development of broadly effective and affordable HIV vaccines through regional and international collaboration. To achieve this goal, it will be important to identify potential areas for collaborative research and to strengthen the capacity of centres/laboratories in Africa that could serve as regional reference/training centres for detailed characterization of HIV strains and immune responses relevant for vaccine design and monitoring.

A plan for capacity-building is being developed to ensure that:

- Standard laboratory procedures are established with necessary equipment provided;
- A quality assurance and proficiency testing programme is established for a network of laboratories; and
- Short-term and long-term training programmes to train African scientists in different aspects of HIV vaccine research and development are established.

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7 Presentation by Coumba Toure of WHO-UNAIDS HVI.
8 Excerpt from the African AIDS Vaccine Programme Workplan and Budget.
5(a) The AAVP policy statement on “Implications of HIV genetic variability for the development of HIV vaccines suitable for use in Africa”

The development of a safe, broadly effective and widely accessible HIV vaccine represents the best hope for the long-term control of the HIV epidemic, in particular for developing countries. The development of a HIV vaccine suitable for use in Africa represents a special challenge in this regard. This reflects the fact that Africa exhibits the broadest range of HIV genetic diversity, as well as widely diverse epidemiological patterns of HIV subepidemics with varying health, ethnic, social and economic factors, all of which may have important implications for HIV vaccine efficacy (VE).

Acknowledging the lack of scientific knowledge with regard to the potential implications of HIV genetic diversity for HIV VE, the AAVP has developed a policy statement, which encourages the parallel development of multiple candidate HIV vaccines based on globally prevalent HIV genetic subtypes.

The patterns of HIV genetic diversity in Africa are already very complex. It is anticipated that genetic diversification and the complexity of emerging circulating recombinant forms (CRF) of HIV will continue to increase over time. Due to the high HIV genetic diversity in Africa, it will be essential to determine the relevance of HIV-1 subtypes for vaccine protection by conducting parallel trials with candidate vaccines that are matched or mismatched to prevalent HIV strains. The available scientific data provides arguments in favour of either type of trial. However, the matched approach is more readily accepted by scientists, communities and policy-makers. Nevertheless, it is not realistic to expect that the number of subtype-specific vaccine candidates that is developed would be sufficient to match all prevalent HIV-1 strains.

In the absence of appropriate vaccine candidates that are matched to prevalent HIV-1 strains in a specific population, initial phase I and II trials could be considered with promising candidate vaccines. Mismatched trials should be based on the best state-of-the-art knowledge and scientific logic, and designed in such a way that they maximize the probability of generating scientific data on cross-protection or lack of such protection. Proceeding with phase I/II trials, irrespective of their subtype specificity, also has its own scientific merits in validating the vaccine design for induction of expected immune responses in a given population. Scientifically and ethically sound trials could contribute significantly not only to gaining important scientific data, but also to capacity-building, infrastructural development and training.

The most difficult decision is with regard to mismatched phase III efficacy trials. These trials could be considered with candidate vaccines that have undergone extensive pre-clinical and clinical evaluation in matched trials, including demonstration of reasonable levels of efficacy against homologous HIV-1 strains. These could be considered as bridging trials.

Trials with cocktail/multivalent candidate vaccines represent a special scenario, and these limit the possibilities of obtaining clear-cut information on homologous or heterologous protection. This could be addressed by incorporating highly sophisticated laboratory methodologies (e.g. “sieve analysis”) into the study design. Such information will be of utmost importance for the development of improved second-generation HIV vaccines.

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9 Presentation by Alash’le Abimiku on behalf of members of the Biomedical Sciences Working Group. A copy of the Policy Statement can be obtained from www.who.int/hiv-vaccines.
Conclusions:

- HIV vaccine development and clinical trials in Africa will need to adhere to a sensible strategy, which should be practical in its expectations, but at the same time move forward as a multi-pronged approach.
- Considerations for testing mismatched vaccines should emphasize safety issues, generation of scientifically relevant information within the national context, and other positive outcomes (such as capacity-building).
- Rational decisions on mismatched vaccine trials should be made only in a conducive environment, which must be created as part of an overall plan for strengthening HIV vaccine evaluation sites in Africa (e.g., national AIDS vaccine plans). This strategy should emphasize the need for parallel development of both approaches, with a priority being given to the development and testing of candidate vaccines based on HIV subtypes and CRFs, which are common in Africa.
- A good, safe and highly immunogenic heterotypic vaccine could offer a better chance of broad protection than a poor vaccine based on a homologous subtype.

5(b) How basic science could provide guidance for the development of HIV vaccines suitable for use in Africa

HIV is classified into genetic subtypes. Circulating recombinant forms are also common and each of these has specific geographic locations. The unique recombinants also have the potential to reach epidemic proportions depending on different circumstances. Within these epidemics, three subtypes have the highest prevalence, namely A, C and D.

Subtype B has a moderate global presence (mostly in industrialized countries) and the other subtypes have a circumscribed geographic location. CRF01_AE and CRF02_AG are the most important circulating recombinant viral strains of the epidemic. AE is found in south-east Asia and AG is found in west and west-central Africa. Central Africa exhibits a complex viral pattern with most of the viral strains detected and no subtype being prominent. Since three of the globally prevalent strains are present in east Africa (A,C,D), this could provide an opportunity to test different candidate vaccines.

### TABLE 1. Global Distribution of HIV - 1 Subtypes and Recombinants

<table>
<thead>
<tr>
<th>Number</th>
<th>Region</th>
<th>Subtype/Recombinant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>North Atlantic</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>South Pacific</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>South Pacific</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>South Pacific</td>
<td>D</td>
</tr>
<tr>
<td>5</td>
<td>South Pacific</td>
<td>CRF01_AE</td>
</tr>
<tr>
<td>6</td>
<td>South Pacific</td>
<td>CRF02_AG, other recombinants</td>
</tr>
<tr>
<td>7</td>
<td>South Pacific</td>
<td>A,B,AB</td>
</tr>
<tr>
<td>8</td>
<td>South Pacific</td>
<td>B, BF recombinant</td>
</tr>
<tr>
<td>9</td>
<td>South Pacific</td>
<td>B, C, BC</td>
</tr>
<tr>
<td>10</td>
<td>South Pacific</td>
<td>F, G, H, J, K, CRF01 other</td>
</tr>
<tr>
<td>11</td>
<td>South Pacific</td>
<td>insufficient data</td>
</tr>
</tbody>
</table>

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10 Presentation by Francine McCutchan – US MHRP, USA.
11 Graphic developed by Francine McCutchan – US MHRP, USA.
Main geographic concentration

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Main geographic concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>East Africa and Former Soviet Republics</td>
</tr>
<tr>
<td>B</td>
<td>The Americas and western Europe</td>
</tr>
<tr>
<td>C</td>
<td>Southern Africa, eastern Africa, India and China</td>
</tr>
<tr>
<td>D</td>
<td>East Africa</td>
</tr>
<tr>
<td>CRF01_AE</td>
<td>South-east Asia</td>
</tr>
<tr>
<td>CRF02_AG</td>
<td>West and west-central Africa</td>
</tr>
</tbody>
</table>

HIV vaccine development is currently focusing on the six globally prevalent strains: Subtypes A, B, C and D, as well as CRF 01_AE and CRF 02_AG. Subtypes A, C and D are intermixed in east Africa and this has resulted in the generation of a great variety of inter-subtype recombinants. The spread of CRF02_AG in west-central Africa is intermixed with many other recombinant strains, some of which also contain subtypes A and G, plus a variety of other subtypes.

Preparations for HIV vaccine trials in Africa must address the seemingly conflicting requirements of high throughput HIV-1 genotyping in populations with high proportions of inter-subtype recombinant strains, including many unique and complex recombinants of unpredictable structure. Although genome sequencing capacity is expanding, it cannot yet meet sampling requirements at the population level. Multi-region hybridization assay was presented, and this provides the required capacity to fully support vaccine development.

5(c) Pipeline of candidate HIV vaccines targeted for Africa

At the time of the AAVP launch in June 2000, there was a limited amount of vaccine research on African HIV strains and subtypes. To address this issue and make a significant impact on the epidemic in Africa, scientists called for future vaccines to be designed for effectiveness against virus subtypes prevalent in Africa.

Collaborative efforts to conduct HIV vaccine trials on the continent have increased and these have highlighted that the development of a HIV vaccine for Africa requires the full support, cooperation and collaboration of many partners around the world. International partnerships and collaboration have been strengthened by the expansion of technical, logistical and financial support for HIV vaccine research and development. This has also facilitated the global exchange of information among scientists and other stakeholders globally with a view to advancing Africa’s contribution to vaccine development.

National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIAID/NIH) – USA¹²

Advances in multi-clade candidate vaccines are in the pipeline, and the NIH has recognized the need to support the expansion of the vaccine pipeline. It has achieved this through investment and through strengthening partnerships with various USA and other international partners in different and specific areas. These partners include corporate partners, as they are critical to the successful manufacturing of large quantities of vaccine.

¹² Presentation by Margaret (Peggy) Johnston, NIAID.
The HVTN supports trials (or preparation for future trials) at 14 sites in the USA, 7 in Latin America and the Caribbean, 5 in Africa and 4 in Asia. The NIAID/NIH partnership involves ANRS (clinical trials), CDC (product development and site development), EuroVac (clinical trials), IAVI (antibody consortium), CAVI (product development), SAAVI (product development), and US MHRP (all aspects).

Candidate vaccines in, or soon to enter, Phase I in Africa (American Government Sponsor)

- Adenovirus-vector (Clade B) Merck: Malawi, South Africa and seven other countries
- Canarypox (Clade A) (Aventis Pasteur): Uganda
- DNA-multi epitope (Epimmune): Botswana
- DNA-adeno-multi gene (A,B,C): Botswana, South Africa, Malawi and others
- NIH Vaccine Research Center (VRC): Botswana, South Africa

Candidates vaccines for Africa in earlier stages of development (American Government Support)

- DNA + Env/PLG (clade C): Chiron
- DNA + MVA (Clades A, D): USMHRP
- DNA + MVA (Clades A,B,C): Emory, GeoVax, CDC, NIAID
- DNA + Env (multiple): ABL
- DNA + MVA (Clade C): SAAVI

Centers for Disease Control and Prevention (USA)

The main activities of the CDC HIV Vaccine Section related to Africa are HIV-1 CRF02_AG vaccine development, field site development in Kenya (Nairobi and Kisumu) and the selection of additional African field sites.

US Military HIV Research Programme (USMHRP)

The overall strategy for HIV vaccine development in Africa is a two-prong approach that involves (i) Accelerating the development and testing of candidate vaccines by facilitating phase I/II clinical safety and immunogenicity evaluation in Africa and facilitating rapid progression to phase III in Africa (in collaboration with DIAIDS/NIAID-VRC); and (ii) Continuing research efforts to define correlates of protection and improve vaccine candidates for next efficacy trials in Africa.

The technical approach is to:

- Characterize incident strains and molecular epidemiology of the epidemic;
- Utilize state-of-the-art vector strategies incorporating appropriate HIV genes;
- Perform pre-clinical vaccine safety, immunogenicity, and primate challenge studies;
- Manufacture vaccine candidates for clinical evaluation;
- Evaluate safety and immunogenicity of candidate vaccines in early clinical trials;
- Establish capacity for phase III trials in compliance with International Conference of Harmonisation (ICH) and good clinical practice (GCP) and provision of appropriate prevention and medical care services;
- Design and perform phase III trials, which incorporate the determination of correlates of immunity and assessment of breadth of protection across different HIV-1 sub-types and CRFs.

The USMHRP can help the global HIV vaccine initiative by bringing all products to the table for broader discussion, and developing field sites and capabilities with the general view of revisiting

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13 Presentation by Charles Vitek (HIV Vaccine Section, Epidemiology Branch) CDC.
14 Presentation by Deborah L. Birx, Director, US MHRP.
opportunities previously discussed. The American Government should also bring its resources
together and optimize candidate comparisons and explore novel combinations of immunogens,
as well as contributing to a coordinated and non-duplicative government plan. Ideally, all HIV
vaccine efforts should be centrally coordinated and several candidates and combinations should
rapidly move forward into large human trials so that direct comparisons can be facilitated.

**International AIDS Vaccine Initiative (IAVI)**\(^{15}\)
IAVI’s approach to vaccine trials in Africa is to have multiple products in development in order
to advance the field and to move the best products forward. Africa is included in trials in their
very early stages, and two phase I/II trials have been started in Africa (Kenya and Uganda) with a
view to looking at prevention or control of HIV infection with relevant HIV subtypes (cross-clade
protection).

IAVI sponsored products include:

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Clade</th>
<th>Status</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA + MVA</td>
<td>A</td>
<td>Phase I/II</td>
<td>East Africa</td>
</tr>
<tr>
<td>Bacterial Delivery (DNA)</td>
<td>A</td>
<td>GMP*</td>
<td>East Africa</td>
</tr>
<tr>
<td>rAAV</td>
<td>C</td>
<td>GMP</td>
<td>South Africa</td>
</tr>
<tr>
<td>MVA</td>
<td>C</td>
<td>GMP</td>
<td>India</td>
</tr>
<tr>
<td>DNA + MVA</td>
<td>C</td>
<td>GMP</td>
<td>China</td>
</tr>
<tr>
<td>SFV (DNA, particle)</td>
<td>A, C</td>
<td>Design</td>
<td>India</td>
</tr>
<tr>
<td>VEE replicon particle(^{16})</td>
<td>C</td>
<td>GMP</td>
<td>South Africa</td>
</tr>
</tbody>
</table>

\(^{15}\)Presentation by Nzeera Ketter, Director, Efficacy Trials, Research and Development – IAVI.

\(^{16}\)IAVI is no longer an active partner in this trial.

IAVI is trying to broaden its scope so that products can be moved quickly into phase III trials, and
is supporting technology transfer for the manufacture of the vaccine in other countries such as
India.

**The South African AIDS Vaccine Initiative (SAAVI)**\(^{17}\)

SAAVI is tasked with developing an affordable, effective and locally relevant preventive HIV
vaccine for southern Africa. SAAVI has two national mandates: (i) Create an enabling environment;
and (ii) Develop a biotechnology incubator, which involves pushing SAAVI products and creating
opportunities for scientific and clinical collaboration.

It is the intention to move many HIV-1 subtype C products to phase I trials. Scientists working on
the development of a suitable vaccine do not believe that one vaccine alone will be sufficient.
They are, therefore, working on one vaccine to prime the immune response and another vaccine
to boost the vaccine response, thereby culminating in a broader immune response. Some
candidate vaccines were fast tracked, and three vaccines are being taken forward. These are:

- DNA vaccine expressing *gag-rt-tat-nef*;
- DNA vaccine expressing *env*;
- MVA vaccine *gag-rt-env-nef-tat*.

\(^{17}\)Presentation by Enid Shepard, University of Cape Town – SAAVI.
European Union HIV Vaccine Programme (EU HIV)\(^ {18}\)

The EU HIV Vaccine Programme has a new funding policy that involves clusters of researchers that can react more effectively and that involve complementary products.

Collaboration with different partners and stakeholders has resulted in the development of the European Developing Countries Clinical Trials Partnership (EDCTP). The aim of this partnership is to accelerate the clinical development of effective interventions (drugs and vaccines) against three infectious diseases: AIDS, tuberculosis and malaria. The functions of this partnership are to: coordinate clinical trials; stimulate trials; strengthen capacity and knowledge transfer; and make trial sites attractive for industry.

Istituto Superiore di Sanita (National Institute of Health) – Italy\(^ {19}\)

The Istituto Superiore di Sanita (National Institute of Health) believes that within HIV/AIDS vaccine development, the control of infection and the block of disease onset are the more achievable end-points. This approach can also effectively block virus transmission to healthy individuals. New concepts of “reverse technology” must be applied which identify key and unconventional vaccine targets by:

- Gene structure/function;
- Role in virus life cycle and pathogenesis;
- Conservation in different subtypes and induction of cross-clade immune responses in natural infection;
- Capability alone or with proper delivery systems to include T cell responses.

Based on this rationale, the Institute developed the HIV-1 tat regulatory gene product as a candidate HIV vaccine prototype. Phase I clinical trials with Tat protein are about to enter both preventive and therapeutic vaccines in Italy. Phase II trials will continue in Italy (Milan 1 site, Rome 2 sites) and Africa (South Africa and Uganda). Site preparation, feasibility studies and technology transfer are ongoing.

Karolinska Institute – Sweden\(^ {20}\)

A collaborative project, known as the HIV Immunogenicity Study (HIVIS) was developed between various partners in Tanzania (Muhimbili University College for Health Science, Dar es Salaam), Sweden (Karolinska Institute and South Stockholm General Hospital), Germany (Ludwig-Maxmillian Universität, Munich), South Africa (University of Cape Town) and the USA (Walter Reed Army Institute of Research - WRAIR).

The objectives of the study are to optimize the immunization schedule for DNA vaccine priming and MVA vaccine boosting in the development of HIV-1 preventive vaccines and to develop expertise and capability for studying HIV-1 vaccines in Tanzania. Stockholm will perform phase I trials and Tanzania will participate in phase I/II trials.

The study is a three-year programme funded by the EU, and an important objective of this collaboration is to strengthen the capacity and infrastructure of Tanzania so that it can participate effectively in these trials. This includes developing capacity related to regulatory issues, clinical

\(^{18}\) Presentation by Hans Wolf – EU HIV Vaccine Programme.

\(^{19}\) Presentation by Steffano Butto – Istituto Superiore di Sanita, Italy.

\(^{20}\) Presentation by Eric Sandstrom, Karolinska Institute – Sweden.
issues, education and informed consent (IC), and phase II and phase III capacity-building within the police force infrastructures.

**Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases, National Institutes of Health – USA**

The VRC is a new concept within NIH. The major rationale behind it is to locate all relevant expertise at a single site and allow it to be self-contained. The VRC is publicly funded, mission-oriented and has broad capability and capacity. The concept is to shorten the time from basic concept to early phase clinical trials. A number of novel vaccine concepts are being pursued by VRC, including the development of vaccines targeted for use in Africa.

The VCR believes that vaccine development still remains the best hope of controlling the HIV epidemic and that current candidate HIV vaccines are more likely to control infection than prevent infection and are, therefore, likely to be only partially effective. Measuring efficacy will be a complex issue, and success requires global coordination of multiple private and public agencies, and an unprecedented level of community education and involvement.

**5(d) National regulatory procedures – perspectives from African countries**

The WHO organized a Southern African Regional Workshop in Gaborone, Bostwana in November 2001 on “Scientific guidance for the regulation of research and development of microbicides and HIV vaccines”. The meeting brought together representatives of Institutional Review Boards (IRBs) and National Regulatory Authorities (NRAs) from 14 countries in southern Africa.

It was evident from the workshop that IRBs and NRAs are at different levels of development and understanding. Some countries may be reluctant to host clinical trials at the present time because they lack capacity and infrastructure to approve and/or monitor clinical trials. Countries with insufficient infrastructure are vulnerable to the introduction of unethical and/or poorly designed clinical trials. The meeting discussed various challenges and issues faced by NRAs and IRBs and identified priority areas that need to be addressed. The participants also devised clear recommendations that include:

- WHO-UNAIDS should establish a regional technical group drawn from regional experts, to:
  - Assist countries in the evaluation of HIV vaccine trials (microbicides and antiretroviral drug trials);
  - Coordinate training activities for NRAs/IRBs to develop capacity in the evaluation of HIV vaccines;
  - Develop a reference set of guidelines for NRAs/IRBs;
  - Provide a forum to coordinate evaluation of clinical trials at regional level, by exchanging reports on clinical trials review, evaluating multi-centre trials and facilitating meetings between NRAs/IRBs.
- Encourage/facilitate governments to recognize the role and status of ethical review boards and processes;
- Conduct capacity-building needs assessment, followed by courses tailored to local and regional needs;
- Sponsor dialogue/resolution of significant differences among IRBs in different countries and develop networking opportunities;

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21 Presentation by Barny Graham VRC, USA.
22 Presentation by Joseph T Karashani Research Ethics Committee, University of Zambia.
• IRBs should generate their own guidelines, based on the Council of International Organisations of Medical Sciences (CIOMS) and other international guidelines, with relevant variables to be determined locally;
• Improve awareness of IRB activities.

5(e) Clinical and laboratory requirements for Phase I, II and III trials

Well-managed clinical trials are essential in biomedical research. Guidelines that have been issued by various organizations could be followed in order to meet the clinical and laboratory requirements for trials. These include WHO, ICH, and the NRA from each individual country. Good manufacturing practice (GMP), good laboratory practice (GLP) and good clinical practice (GCP); (see below) specify the general guiding principles and practices necessary to achieve quality and safety of biological products. They are in place to set quality standards and to ensure quality control in the laboratory, manufacturing and clinical trial settings.

These guidelines also emphasize the need for training or the existence of qualified personnel and the development of adequate facilities. Moreover they highlight the importance of documenting what happened, what should happen and what did not happen. GMPs also assure data quality and reliability upon which to make regulatory decisions and develop assurances around patient safety, rights and confidentiality.

When do the GMPs need to be implemented?

Good manufacturing practice:

Many investigational products are novel and so relevant processes or tests may not be well established, optimized or validated at the outset. Before the product is administered to large numbers of individuals in pivotal clinical trials, full GMP should be in place. Prior to that, certain aspects should be implemented, even for phase I in which smaller patient numbers are used. These include ensuring that there are adequate facilities, environmental monitoring, batch record maintenance and trained operators.

The WHO has identified six essential functions to be undertaken by an effective vaccine regulatory system: a published set of requirements for licensing; surveillance of vaccine field performance; a system of lot release; the use of a laboratory when needed; regular inspections for GMP; and evaluation of clinical performance. This definition is the basis for designation of vaccines of assured quality and for WHO activities concerned with strengthening vaccine regulation and capacity of Member States.

Good laboratory practice:

Pivotal pre-clinical animal studies should be performed according to GLP (even to support Phase I). Manufacturing quality control (MQC) assays, which may be under development in early clinical phases, should be in place by Phase III (before pivotal trial). Clinical assays, which may be under development in early clinical phases should be in place at least prior to being used on pivotal Phase III trial samples and, preferably, should be in place before pivotal decisions are made regarding dose, route, schedule etc.

23 Presentation by Rebecca Sheets, VRC/NIH.
Good Clinical practice:

Most aspects of GCP should be in place for all clinical trials. In order to increase the quality of trials, all stakeholders need training and guidance. Training assures that investigators are aware of their responsibilities and that sufficient time is devoted to the conduct of trials. GCP measures are intended to assure subjects rights, confidentiality and safety and, therefore, should be implemented for all trials.

6. COMMUNITY PREPAREDNESS

The aim of the Community Preparedness Working Group of the AAVP is to define and strengthen appropriate community participation and preparation in HIV vaccine research, development and access, and within the AAVP structure.

The working group's specific objectives are to:

1. Ensure the development of relevant and understandable information on HIV vaccine research and development, delivery, access and usage for community groups and communities;
2. Facilitate a participatory process of sharing appropriate information;
3. Enhance collaboration by forming strategic partnerships and alliances;
4. Establish and strengthen mechanisms for coordination of various community efforts at global, regional and national levels;
5. Advocate the meaningful participation of communities in the process of HIV vaccine research and development.

This working group is newly established, and has officially been in existence since 2003.

6(a) Involving the community in vaccine preparedness

The underlying principle for community involvement and preparedness should be that it can, and does, result in better science. There are various different models of community involvement and preparedness, and partnerships have to be created and strengthened among all the different stakeholders to develop an appropriate model for the respective trial site. Successful HIV vaccine development and access will require a coordinated and concerted effort over the coming years. Defining and sustaining this effort will involve clarifying roles and responsibilities, resources and developing timeframes, as well as creating mechanisms for accountability and coordination.

There is a need to advocate comprehensive national plans for countries that are now engaged in HIV vaccine development. These plans should cover strategies and timelines for pre-clinical and clinical research, vaccine development and manufacture, regulatory review and approval of new clinical research and new vaccines, public health use and accessibility. They should also address issues related to standards of care and treatment and to the development of an infrastructure that will leave communities better off than before the trial started – irrespective of whether or not the trial proceeds to the next phase. It is necessary to ensure that these plans form part of a broader national response and are not perceived as being separate from each other. It is ineffective for discourses or programmes to have to compete against the other. There is an opportunity to define

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common agendas and lessons that can be learned since vaccine and microbicide treatment are both directed to the achievement of common goals. In addition, there is need to promote the attitude that giving funding and priority to one does not, and should not, preclude giving to the other.

HIV vaccine trials must be used as an opportunity to expand access to treatment and prevention in communities where trials take place. They must be used as a catalyst for making treatment a reality for many communities, it is an opportunity to develop infrastructure within communities and ensure that trials do, in fact, leave communities better off than before the trial started. We have an opportunity to learn from history to ensure that future prevention efforts are culturally appropriate, and are not biased against women – as they have been in the past. There is need to integrate vaccines (and microbicides) into prevention strategies and education. Community and vaccine preparedness is not just about clinical trial implementation, but also about the broader process of vaccine development and access. It is about public understanding, public support and public participation. Community advocates, especially from Southern Africa, need to broaden their capacity to become more effective and to articulate vaccine advocates. There is a need to be able to demonstrate how, and where, the vaccine agenda fits in with other national and regional agendas. In addition, it is necessary to integrate the principles of benefit and justice, because if this does not occur history may ultimately reveal that there was a failure in capitalizing on opportunities and in learning lessons.

6(b) From AIDS Vaccine Community Task Force to the Community Preparedness Working Group

Communities in Africa have been at the frontline of the AIDS epidemic. The community response in Africa has been characterized by the formation of three regional networks: the African Council of AIDS Service Organisations (AfriCASO), The Society of Women and AIDS in Africa (SWAA) and the Network of African People living with HIV/AIDS (NAP+). The community issues in the past were addressed in the Ethics Law and Human Rights working group of the AAVP. In March 2000, a community consultation was held in Pretoria, South Africa to develop strategies for effective community preparedness within a broader HIV vaccine agenda.

In May 2002, a meeting was held in Nairobi with 39 partners from 17 different countries. Five key priorities were adopted at the Nairobi meeting. These were to know, to disseminate, to advocate, to negotiate, and to interact. The AIDS Vaccine Community Task Force (AVCTF) was formed and had a clear mandate until November 2002. A series of meetings held in New York and Tunis led to the development of a comprehensive work plan. The Community Preparedness Working Group has developed five programmatic lines as part of its workplan. These are:

1. Ensure the development of relevant and understandable information on HIV vaccine research, development and delivery for use by groups and communities;
2. Facilitate a participatory process of sharing information among all community stakeholders on HIV vaccine research, development and delivery;
3. Increase community involvement within the AAVP structures;
4. Increase the ability of the community to contribute meaningfully to the HIV vaccine development process from basic research to development and access;
5. Establish a strong coordinating secretariat in order to enhance communication and design/conduct of activities related to the workplan.

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27 Presentation by Abdel Kader Bacha – Interim Focal Point for the Community Preparedness Working Group.
The Community Preparedness Working Group consists of representatives of the five sub-regions of Africa, and is in the process of employing a coordinator to facilitate its work and ensure effective and appropriate community preparedness in Africa.

7. ETHICS, LAW AND HUMAN RIGHTS

The overall objective of the AAVP Working Group on Ethics, Law and Human Rights (ELH) is to define and strengthen priority areas in the context of ethics, law, human rights and HIV vaccine research, to ensure the conduct of lawful and ethical HIV preventive vaccine trials in Africa.

The ELH working group is researching existing ethics and human rights resource needs in Africa, and aims to form and resource a strong network of concerned persons and organizations who can receive further training, share information, experiences and resources, and build the capacity of key constituencies to prepare for and respond to ethical-legal considerations of HIV vaccine trials in Africa. The ELH working group is currently in its second formal year of operation.

7(a) Ownership of research

There are growing concerns in developing countries about access to, and use of, tissue that is stored for specific studies and subsequently re-accessed for other studies. This often occurs without the consent of the participants or the original principal investigator (PI). There are also parallel concerns about access to tissues stored for new and ongoing research. Moreover, ethical and public policy questions arise on access to human tissue following its removal from the human body, and these are made more challenging by the absence of a clear framework in African countries for the regulation of access to tissue samples. Genome studies create both new opportunities and ethical problems for work with African sources of DNA.

There is a need to strengthen the capacity of African researchers and communities in this area, and it is important to include local stakeholders from the very beginning in the discussion of this important issue. The ownership of tissue, so defined, should be clarified as early as possible in the design of the study. The principle of exchange should be designed within a framework of agreement through a Materials Transfer Agreement (MTA). An MTA is a legal contract that specifies that the host retains samples but that under certain conditions these may be “lent” or made available to others for research.

Essential elements of an MTA are the specification of: the parties to the agreement; the materials being used; the purpose and usage of the materials; authorized uses; location where it will be used and stored; specific restrictions (e.g. not to be used in human cloning, not to be used as per country X law); time period; ownership of derivatives; ownership of products; commercial rights; public limitations and acknowledgements.

There is a need for an audit of relevant legislation in African countries in order to clarify and develop a clear policy statement on the legality of ownership concept. Local researchers and institutions must participate at all stages of the research. Capacity of sites and countries (including training and storage facilities) should be developed and effective monitoring mechanisms should be put in place. IRBs will require guidance on issues regarding requests for further use of tissues, and this could be clarified in an MTA. The issue of ownership of research should strike a balance.

28 Presentation by Femi Soyinka. Obafemi Awolowo University, Nigeria.
between human protection and the development of science and healthcare. National and institutional interests also need to be balanced and protected.

The AAVP is in the process of developing a position statement on the ownership of biological samples.

7(b) Issues in informed consent: Culture and implications for HIV vaccine trials in developing countries

There is little dispute about the ethical imperative for informed consent in HIV vaccine trials. However, there have been some claims that insistence on individual informed consent (IC) reflects western cultural bias and “imperialistic” insensitivity. There is, therefore, growing awareness of the need for cultural sensitivity in the conduct of IC processes in developing countries (e.g. UNAIDS, 2000). However, there is little agreement on what cultural sensitivity means and how it should be implemented in the IC process.

There is relatively little argument for discarding the IC principle altogether. The real questions relate to procedural variations to the IC process to tailor it to local culture. The HIV/AIDS Vaccines Ethics Group (HAVEG) at the University of Natal is conducting research to explore these issues in the interest of recommending culturally appropriate and sensitive IC processes, which will improve the validity and reliability of IC in African settings. This research distinguishes the legal aspects of IC from the psychological and moral aspects of truly informed decision-making, although these are not mutually exclusive.

Cultural sensitivity can operate at many levels of the decision-making and IC process – semantically, procedurally and with regard to principles. Cultural sensitivity also depends on how culture is defined – is it confined to race, ethnicity, language, religion, education, socio-economic status, occupation? This is a much-contested concept that is subject to a number of popular misconceptions. Some of these misconceptions are that:

- Cultures are homogeneous;
- Individual persons are only members of single cultures;
- Decision-making consistently refers to a constant cultural frame of reference;
- All African cultures are collectivist, such that individual IC can be discarded.

HAVEG views culture as the frame of reference used by individuals to inform their decision-making. There is enormous diversity within and between African cultures, requiring careful local study of assumptions underlying the decision-making frame of reference used in local settings for specific types of decisions. Individuals within cultures may differ as much regarding their values and decision-making preferences as do individuals from another culture.

There are various procedures for incorporating cultural values and practices into IC without altering their substantive aspects. For example, it may be necessary to negotiate community entry before attempting to enrol individuals. Community assent and individual IC need not be seen as mutually exclusive. Researchers report that conventional IC procedures used in African settings are not truly understood, and that a range of other social factors (social desirability, submission to power, hopes of benefits) impact on enrolment.
The language and procedures for IC need to be tailored on the basis of local social research to enhance understanding and voluntary involvement. Conventional tests of understanding tend not to be reliable measures of such understanding. More research effort must be expended on developing culturally-sensitive IC procedures to improve the validity of individual decision-making. This will improve enrolment and retention of participants in HIV vaccine trials and thereby improve the scientific quality of the study. Such research could include:

- Psychological/cognitive research in assessing genuine understanding, retention and recall of information over the short, medium and long term;
- Studies of autonomous decision-making to ensure maximal voluntary involvement in IC processes;
- Cultural/anthropological research e.g. local understandings of community and individual participation and of vaccination.

Such research is currently being undertaken by the AAVP HAVEG/ELH group, in collaboration with various partners in the field.

7(c) Access to treatment, care and support for HIV vaccine trial participants who acquire HIV infection during the conduct of a trial

There are two main arguments that can be made in support of the premise that sponsors and investigators should be obliged to provide treatment to infected volunteers. It has been argued that sponsors are obliged to treat HIV infection acquired during a trial because this could constitute a research-related injury. However, evidence to date suggests that a general behavioural disinhibition (i.e. increased risk behaviour) does not occur over the course of trials, or that increases in risk behaviour over the course of trials are not sustained.

There is evidence to suggest that volunteers can be helped to understand that a HIV vaccine cannot afford protection, (this is an under-researched area), although this educational process is likely to be challenging and would require resources and commitment. If it can be demonstrated that HIV infection is related to an individual’s trial participation, then conceivably this would present grounds for compensation at an individual level. However, not all infections acquired during a trial should be considered research-related. It could be argued that trial participants should be provided with access to high quality treatment on grounds of justice.

Attention to considerations of distributive justice should ensure that there is a fair distribution of research-related risks and benefits among collaborators, i.e. knowledge, products, capacity-building, and medical care required for the performance of the research. It is controversial to suggest that sponsors are obliged to provide access to medical care that falls beyond that required for the conduct of research. However, it can be argued that HIV vaccine trials occur in a context of vast inequalities between sponsors and host countries in terms of access to resources. Thus, trial participants from developing countries will, in general, undergo lower levels of treatment for HIV infection that their foreign (e.g. USA) counterparts, and sponsors should contribute resources aimed at reducing these inequalities. It is likely that there will be much debate about the most appropriate, or just, manner in which to use finite sponsor resources to combat disadvantage.

30 Presentation by Catherine Slack (Stobie M, Lindegger G, Milford C, Wassenaar D, Strode A, Ijseelmuiden C) HAVEG, School of Psychology, University of Natal Pietermaritzburg, South Africa
8. NATIONAL STRATEGIC PLANNING

The National Strategic Planning Working Group (NSP)

The objectives of the NSP\(^1\) are to:

- Promote and facilitate HIV vaccine research and evaluation in Africa;
- Establish a database for African countries regarding national responses to HIV/AIDS vaccine preparedness;
- Identify strengths and weaknesses in national responses and provide technical expertise where required.

8(a) Inventory of HIV/AIDS control programme policy/plans for HIV/AIDS vaccine research\(^2\)

The NSP carried out a survey regarding national responses to HIV/AIDS vaccine preparedness. The objectives of the survey were to collect information on health sector responses to HIV/AIDS and to establish a database by undertaking an inventory of HIV/AIDS control programmes and plans for HIV/AIDS vaccine research in Africa. The methodology used was a standard questionnaire that was distributed via WHO country representatives to key informants in Africa. The completed questionnaires were returned to and analyzed by the AAVP secretariat.

15 African countries responded to the survey, although it was pointed out that there were challenges in some countries actually receiving the questionnaire. The sub-regional breakdown included Southern African (four countries), East Africa (four countries) and West Africa (seven countries). The survey found that characteristics of countries involved in HIV vaccine research include:

- Strong collaboration exists with local and international institutions/organizations;
- Funding in place from public, private, local and international NGOs, bilateral and multilateral agencies;
- Strong and appropriately qualified human resources;
- Conducting and involving diverse research in STD and HIV/AIDS;
- Defining national HIV/AIDS strategic plans with a component on HIV vaccine development.

The survey defined a number of recommendations to be incorporated and implemented. These include the need for:

- Countries to be encouraged to develop and incorporate HIV vaccine programmes in the national HIV/AIDS strategic plan;
- Provision of guidelines on conducting research on HIV vaccines;
- Implementation of specific HIV vaccine plans in collaboration with local and international institutions/organizations;
- Training and hiring of qualified and experienced personnel in HIV research and development;
- Use of proactive leadership in mobilizing public, private, NGO, bilateral and multilateral partners in HIV vaccine research.

A limited number of HIV vaccine trials are currently being undertaken in three countries in Africa – Uganda, Kenya and Botswana – with trials in Malawi and South Africa under way since 2003.

\(^{1,2}\) Presentation by Job Bwayo, KAVI.
International organizations should, therefore, support efforts in the development of HIV/AIDS vaccine plans and strategies in more African countries. The AAVP should provide a pivotal leadership and facilitative role in this endeavour.

8(b) Country experiences

The development of a national HIV vaccine plan in Uganda

The objectives for developing a national HIV vaccine plan include:

- Building national consensus on a comprehensive, well-coordinated, long-term strategy for the development of a safe, immunogenic, efficacious and affordable preventive, therapeutic and perinatal HIV vaccine;
- Clarifying the legal framework for regulatory approval, manufacture and licensing of HIV vaccine products;
- Providing guidelines for scientific and ethical review of HIV vaccine trial proposals and protocols;
- Providing guidelines for monitoring the conduct of HIV vaccine trials according to scientifically and ethically acceptable standards;
- Proposing ways and means to build local infrastructure and transfer knowledge and technology;
- Proposing ways and means of ensuring availability and accessibility of an efficacious vaccine to the general population.

The essential elements of a national HIV vaccine plan are that it should:

- Address political, social and policy issues;
- Define regulatory, scientific and ethical issues;
- Review guidelines and the nature of preparatory research that is required for HIV vaccine trials;
- Tackle implementation issues in Phase I/II and III trials;
- Address operational and logistical issues.

Uganda has a long history of mobilizing effective responses from all different levels of society. The President of Uganda expressed political commitment in 1986, and the country developed its National HIV Vaccine Plan in 1991. Presidential clearance and approval from the cabinet and parliament was obtained for vaccine research between 1995 and 1997, and the first volunteer was vaccinated in 1999.

The development of a national plan has provided a unique opportunity to build consensus in the country, and has attracted national and international partners by providing “clear rules of the game.” A well conceived plan could be presented to donors and to international agencies for collaboration and support.

Presentation by Roy Mugerwa, Department of Medicine, Makerere University Medical School, Uganda.
The development of a national HIV vaccine initiative – The South African AIDS Vaccine Initiative

SAAVI was established by the South African Cabinet and Eskom (Southern African Electricity Supplier) in 1999 as a lead programme of the South African Medical Research Council. Its primary funding is from the South African Government and Eskom. SAAVI is assigned with developing an affordable, effective and locally relevant, preventive HIV vaccine for southern Africa. SAAVI awards multi-million-rand funding annually to South African research groups at leading institutions to develop and test candidate HIV vaccines. It also funds researchers investigating the ethical issues involved in testing HIV vaccines, and a community education project.

SAAVI is a broad-based community research initiative that supports programmes at various South African academic institutes, which focus on specific areas. These include:

- Teams at the National Institute of Communicable Diseases (NICD) and other laboratories, examining complex immune responses to HIV vaccines;
- Two large laboratory research teams at the Universities of Cape Town and Stellenbosch dedicated to the development of novel HIV vaccines based on characterization of many local isolates of HIV;
- HAVEG at the University of Natal which is responsible for researching and developing ethical guidelines that are locally relevant and facilitate ethically sound vaccine trials;
- Multiple trial site clinical teams. These include: (a) the HIV/AIDS Division of the Perinatal HIV/AIDS Research Unit in at the Chris Hani Baragwanath Hospital in Soweto; (b) the SAAVI Vaccine Trial Division at the Medical Research Council in Durban; (c) the Cape Town Clinical Trials Consortium – a consortium of the Medical Research Council and the Universities of Cape Town and Stellenbosch, aiming to develop clinical trial sites in the Western Cape; and, (d) Aurum Health Research, a subsidiary of Anglo American, that will develop trial sites in the North-West Province.

Additional trial sites will be developed as the need arises. SAAVI also has an extensive vaccine community preparedness group – a consortium focusing on community education, legal and human rights, education and media and communications. This group has received funding from the EU since 2000 and has recently received an additional grant to increase and extend its activities.

SAAVI underestimated the steep learning curve that was required to educate the regulatory bodies with regard to the various issues related to vaccine development. Partners of SAAVI collaborated with the joint body of life insurers in South Africa, and the Life Officers Association agreed to amend their protocol/policy on HIV testing being required for life insurance. The standard ELISA test which cannot distinguish infection with the virus from a “false positive” immune reaction (because it measures antibodies to HIV and not HIV itself) currently applies to all applicants. However, the PCR test, which can make this distinction, will be provided in the last analysis for anyone participating in a HIV vaccine trial. On this basis, HIV vaccine trial participants could certify that they are participating in a trial. As their contribution to HIV vaccine development, the life insurance industry will provide the PCR test at their own expense.

34 Presentation by Tim Tucker, SAAVI.
35 Further information about this amendment can be found at www.loa.co.za.
Current status of HIV/AIDS vaccine research and development in Ethiopia

In March 2000, the ENARP/EHNRI (Ethiopia-Netherlands AIDS Research Project, Ethiopian Health and Nutrition Research Institute) organized the first international workshop on HIV/AIDS vaccine research in Ethiopia. The workshop provided an excellent opportunity for the initiation of national consensus building for vaccine-related activities in Ethiopia.

The workshop agreed that the availability of an effective and affordable HIV vaccine would provide the best hope for the future control of the epidemic in Ethiopia, and also emphasized that the activities in the area of HIV vaccines should be complementary to, and not in competition with, other HIV prevention programmes. In preparation for future vaccine trials, it is important to strengthen national capacity, develop appropriate infrastructure and train Ethiopian scientists in areas of HIV vaccine research and development. The Ethiopian AIDS Vaccine Initiative was formed in February 2003 and specifically aims to:

- Promote the development and evaluation of HIV candidate vaccines in Ethiopia with high scientific and ethical standards;
- Develop a national HIV vaccine strategic plan (in collaboration with other relevant stakeholders);
- Foster and develop national and international collaboration;
- Facilitate the review of protocols pertaining to HIV/AIDS vaccine research and clinical trials;
- Organize workshops and conferences as deemed appropriate and necessary;
- Establish different working groups to deal with specific issues such as scientific/technical, legal/ethical and community/advocacy issues.

9. POPULATION-BASED STUDIES

The Population-Based Studies Working Group (PBS) promotes involvement of HIV vaccine development research groups and industry to join partnerships with networks of population groups, to share information on ongoing and planned multi-centre studies, and to identify potential sites for vaccine evaluation.

Standard strategies will be developed to:

- Establish and maintain a register of available cohorts/populations for vaccine evaluation in the region; and
- Conduct socio-behavioural studies that are necessary to assess the feasibility of recruiting volunteers, as well as to explore their willingness to participate in vaccine trials.

9(a) Overview of HIV prevalence and incidence in Africa

In 1992, 42 million people worldwide were living with HIV, 69% of them in sub-Saharan Africa. During 2002, there were 5 million new cases of HIV (70% in sub-Saharan Africa) and 3 million deaths (80% in sub-Saharan Africa). By the end of 2002, there were 4 countries in Africa where over 30% of all adults were infected with HIV and this situation is not improving. The number of new cases each year in this region is approximately 4 million, contributing to the ever-rising total number of HIV cases.
HIV prevalence provides a good indication of the overall state of the epidemic. Prevalence data are derived from sentinel surveillance sites at antenatal clinics, from smaller-scale surveys of communities, hospital or clinic attendees, or from special groups such as patients attending STD clinics or factory workers. An increasing amount of information is emerging from national sero-surveys. In low-risk (unselected) urban populations within all of east and southern Africa, Cameroon, Central African Republic and Liberia, HIV prevalence is above 10%, with lower rates elsewhere. In high-risk (selected) urban populations in much of eastern and southern Africa, and in Ghana, Benin and Sierra Leone, HIV prevalence is above 40%, with lower rates elsewhere. Prevalence data indicates who is infected and, therefore, not suitable for enrolment into prophylactic vaccine trials. However, it does not give a clear picture of recent epidemic trends. This is because the average survival after infection is about 9 years, and so the number of new cases is always just a small proportion of the total number of cases. Prevalence represents a balance between the number of new cases, the number of deaths, the number of migrants in and out of a survey area and any changing selection biases in the survey.

The incidence of new cases of HIV infection gives a better indication of recent epidemic trends, but it is difficult and complicated to measure because of the need to link results from the same individual from one year to the next. It is unfeasible to collect incidence data on a national level or on a regular basis, thus this has been done at only a few sites in Africa. The incidence rate in general populations with established epidemics is usually approximately 1–2%, meaning that 1 or 2 new cases of HIV occur each year for every 100 uninfected adults.

Higher rates are seen in high-risk groups, for example sero-discordant couples (one partner is seronegative, the other is seropositive), where annual incidence has been measured at 5–12%. Higher rates also occur transiently in expanding epidemics, such as the current one in southern Africa, but by the time the expanding nature of the epidemic becomes apparent, the incidence has generally already started to decline. In conclusion, because the rate of new cases is quite low, large sample sizes are needed to measure incidence with any degree of accuracy.

Currently, incidence is measured directly by collecting paired samples from individuals following a one-year time-lapse, but are there alternative methods? Detuned assays based on "sensitive–less sensitive" testing techniques show some promise. These techniques exploit the progressive development of antibodies in recent HIV infections (within the first 120–180 days). However, there is little published, validatory data for these assays for detection of the non-subtype-B viruses which predominate in Africa. Forty-nine specimens from individuals newly infected with A, C and D subtypes were tested in one study, and 20 C-subtype specimens were compared with a computer generated model. This detuned assay approach could be of great benefit in identifying high-incidence populations suitable for vaccine trials, however further validation of these assays is urgently required.

Considerations for calculating the sample size required for a vaccine trial include: The length of follow-up and expected rate of losses to follow-up; the required power and significance level for the study; the type of randomization (community or individual); the number of arms in the study; the background HIV incidence and the minimum VE anticipated. Of these, the most critical are length of follow-up, background incidence and minimum VE. The numbers required under these varied circumstances can vary significantly, ranging from as few as 555 for a study with 80% power, 2-year follow-up, 5% background HIV incidence and 70% VE, to 45,196 for a study with 90% power, 1 year follow-up, HIV incidence of 1% and VE of 30%.
Other factors that need to be taken into account are:

- Risk behaviour of individuals, once in the cohort, may change. Overall it may increase, decrease or remain the same. There have been studies where risk behaviour has decreased, and others where it remained unchanged, but it is theoretically possible that risk behaviour could increase if participants felt themselves to be protected by an experimental HIV vaccine.

- There are many different HIV subtypes and circulating recombinant forms in Africa, although A and C are the most common. It is likely that an efficacious vaccine developed from one subtype will be more effective against natural infections of the same subtype than against other subtypes. But the extent of this subtype specificity is not known. Vaccine trials will need to be powered so that the efficacy of a vaccine against the same subtype can be measured, and so that useful information can be generated about protection against other subtypes. This will require knowledge of the distribution of HIV subtypes in each prospective vaccine trial population.

9(b) Global perspectives of HIV vaccine development

Exciting opportunities and challenges are presented to all stakeholders involved in HIV vaccine research, development and testing. AAVP is in a perfect position to provide that critical bridge between challenges and opportunities. Some of the lessons learned and critical events in international HIV vaccine development include:

- Early development of country-specific scientific leadership. This has been initiated over the last 10 years by UNAIDS – WHO, and the NIH PAVE Sites;
- Those initial countries, with WHO-sponsored national AIDS vaccine plans – Thailand, Uganda and Brazil – have assumed a global leadership role;
- Scientists have the ability to influence their respective governments for political support (The ability to transition HIV-1 vaccine national plans has resulted in productive debate);
- Long-term support by sponsors – EU, NIH, CDC, IAVI, US Department of Defense (DoD) – includes the ongoing provision of training, physical infrastructural development and capacity-building;
- Biotech and pharmaceutical companies willingness to develop non-HIV-1 B products is critical;
- A transfer from biotech to big pharmaceutical companies may also be required.

It is one thing to talk about cooperation and collaboration but translating that into reality is difficult. The USA partners all have different strengths and weaknesses and a collaborative partnership has been formed among various partners not only to avoid duplication, but also to establish a Department of Defence tri-service programme that is executed through the WRAIR and the Henry M. Jackson Foundation in partnership with the Division of AIDS (DAIDS), NIAID and Health and Human Services (HHS).

New opportunities have been created by this joint collaboration and the various parties share a common mission – the development of a globally effective HIV vaccine. This shared vision has led to an expanded effort in the Americas and a continued effort in the USA and Europe that together have a concentrated and comprehensive focus on sub-Saharan Africa. Although the collaboration has created a unique opportunity, it has also presented new challenges to all sponsors which include the need to: coordinate efforts; optimize collaboration, including site development; share
knowledge, expertise and sites; and to unify by developing a comprehensive immunological evaluation platform.

HIV-1 sequencing has resulted in many branches being added to the strain tree.\(^4\) Defining the depth and breath of HIV-1 molecular diversity and its significance will elucidate the relationship between immunity, HLA, escape mutants and recombinants as well as allowing for careful “in vitro” dissection of immune responses and their breath. There is also a need to revisit neutralization and cellular responses using carefully defined effectors (pure vs. recombinant subtypes) and viruses.

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**Challenges of collaboration and vaccine development:**

- The challenges have moved from immunogen development to site selection, comprehensive training and immune assessment. (There is a need for continued effort on the generation of primary isolate neutralization);
- Common comparable immunogenicity and true collaborative development of vaccine sites should be the goal;
- The need to integrate HIV care and treatment, prevention activities, and vaccine development under a comprehensive site development umbrella;
- The establishment of prevention platforms (water, blood, VCT);
- The development of candidate vaccines that induce both humoral and cellular immunity;
- Comparison of multiple combinations of promising immunogens using a common platform.

\(^4\) Diagram developed by Deborah Birx, Director US Military HIV Research Programme.
**Trials Planned for Africa**

1. Botswana
2. Kenya
3. Nigeria
4. South Africa
5. Tanzania
6. Uganda

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41 Table developed by Deborah Birx, Director, US MHRP.
9(c) Lessons learned from HIV vaccine trials – experiences from Africa (Phase I/II trials)

Kenya: Omu Anzala

The Kenya AIDS Vaccine Initiative (KAVI) was established in 1999, and is based within the Department of Medical Microbiology at the University of Nairobi. KAVI brings together scientists from the Departments of Paediatrics, Medicine and Medical Microbiology. The initiative has three collaborators: Medical Research Council (MRC) UK, IAVI and the Department of Medical Microbiology at the University of Nairobi.

The objective of KAVI is to participate in the development of a safe, effective and affordable HIV/AIDS preventive vaccine. KAVI currently has two candidate vaccines in phase I/II trials: **aked – DNA vaccines and a live recombinant vaccine (viral vector modified Vaccinia Ankara)**. KAVI has also initiated a roll-over trial in which volunteers from the DNA vaccine trial were enrolled into the MVA trial. Enrolment in this trial has been completed and KAVI is now in the process of developing a cohort at high risk of infection in the Kangemi Division in Nairobi.

Uganda: Pontiano Kaleebu

With assistance from WHO, Uganda developed a national vaccine plan in 1991, and has since participated in two phase I/II vaccine trials; ALVAC vCP 205 (Canarypox vector with HIV-1 subtype B **gag/protease/env**) which was successfully completed in 2001, and the DNA-MVA (Prime-boost) vaccine trial that started in February 2003.

The Ugandan national vaccine initiative has been effective in that it receives government commitment and support, has created and strengthened international partnerships and has brokered effective linkages with community groups due to a strong community response to the epidemic. Although there were challenges related to regulatory and ethical approval in the implementation of the first trial, there has been opportunity for improvement, most notably in the review process that incorporated lessons learned from the first trial. These lessons included a quicker review process, with fewer committees for the review of different protocols, as well as an increase in media and public awareness and in response to the vaccine trials.

One of the challenges highlighted from the Ugandan experience is the low rate of women that are enrolled in vaccine trials. Some of the explanations given for this phenomenon are that most of the recruitment/information materials are in English, husbands do not give permission for their wives to participate, and that cultural differences permeate. Retaining potential volunteers has also proved to be challenging, as some volunteers participate in the pre-screening study, and once they know that their medical test results are normal they do not return for further participation.

The need to identify normal laboratory values for African sites and to evaluate tests listed in the protocol in African communities was also illustrated by the Ugandan experience, as there was an abnormally high rate of hepatitis C amongst potential volunteers. This may be because the tests and normal laboratory values determined elsewhere may not be appropriate for the Ugandan population.
The Ugandan experience has shown that each trial is a learning process, and that there is an interest and ownership of the process by effective recruitment strategies, high ratio of screening enrolment and good follow-up rates.

**Botswana: Ibou Thior**

The Botswana/Harvard partnership will be testing the Epimmune Vaccine – EP HIV 1090 (Subtypes A–G), which is predicted to induce cellular immune responses across many subtypes. It is Botswana’s first HIV vaccine trial, and is also the first vaccine trial in Africa for the HVTN.

Botswana has received high levels of political support, which has been turned into effective action. A collaborative research agreement was signed in 1996, and Ministry of Health officials have been involved in “vaccine think tanks” on an ongoing basis. The Government built (and funded) a new HIV clinical and research laboratory in 2001, at a cost of US$ 5 million, and rolled out a national antiretroviral programme in 2002. This programme currently has 3000 enrolled patients.

Botswana listed a number of challenges encountered in the preparation of their first vaccine trial. These included the lack of appropriate investigator-led research, reflecting the fact that Botswana does not have its own Medical School, and so ended up recruiting appropriate scientific staff from Kenya, Zimbabwe, Senegal and Trinidad and Tobago. Finding appropriate populations to participate in the study was difficult, as Botswana is a country with a small population and a high HIV prevalence (35% among women attending in 2002). The site has looked at health care workers and a diamond mining company to assist in phase II trials.

Although the country has had experience in ongoing clinical trials (prevention of mother-to-child HIV transmission and antiretrovirals), there are still challenges associated with training and developing the capacity of new staff and Community Advisory Board (CAB) members. The HVTN is assisting with this through GCP training programmes for relevant staff, international collaboration and support for CAB members. Similar to many other countries, Botswana found it a challenge to involve and recruit women into HIV vaccine trials. The high level of disempowerment of women in Africa is undoubtedly leading to the high rates of infections and low rates of participation of women in trials. Women need to be targeted specifically in the trial, and HIV vaccine recruitment information should be targeted specifically to women.42

**9(d) Collaborative efforts in cohort development in preparation for HIV vaccine efficacy trials in Africa**

Preparing for phase I/II and plans for phase III HIV vaccine trials in South Africa

The Perinatal HIV/AIDS Research Unit (PHRU) was set up to strengthen capacity for conducting phase I/II trials with different candidates. The PHRU is part of a multi-site initiative of SAAVI and is based at the Chris Hani Baragwanath Hospital in Soweto. The other sites are in Cape Town, Durban and Orkney.

The strategies adopted by the PHRU include the provision of quality voluntary counselling, testing, education and information workshops, the hosting of outreach events and the establishment of a CAB. The functions of the CAB include being a “watchdog” and they are also bearers of information to the community living in Soweto. The CAB members are actively involved in outreach activities and also contribute to the development of research protocols. The CAB

42 Comment from the floor - Elizabeth Ngugi, Kenya.
members have suggested a research agenda for the PHRU, which includes therapeutic vaccines, standards of care and the regulatory process.

A Voluntary Counselling and Testing (VCT) clinic was set up in February 2002, and started with a pre-screening protocol that aimed to prepare a cohort of well-informed low-risk healthy potential volunteers. Although in excess of 60% of people attending the VCT clinic are men, most of the potential volunteers are women. In order to prepare for Phase III trials, the PHRU requires political and regulatory support, multi-site capability and capacity, community mobilization on a larger scale, research and intervention study expertise. In addition, it must address the issue of special groups, such as adolescent participation – working groups have been set up in South Africa to tackle this issue. The PHRU is interested in strengthening and developing partnerships with other African collaborators.

**Cohort development in Uganda**

The work of the MRC (UK) programme is based at different sites in Uganda. Most of the MRC work related to cohort development is being carried out in the Masaka district (another large cohort is in the Rakai District). An intervention trial was carried out in different parishes between 1994 and 2000. One thousand people were recruited from 18 different parishes into the cohort. The conclusions of the trial were that HIV prevalence and incidence vary widely within the rural district, highest incidence rates tend to occur in communities with highest prevalence and investigators expect to be able to identify community characteristics associated with higher rates.

The proposed selection strategy for Phase III trials is to recruit from rural communities and small trading centers in the Masaka district, select communities with known high HIV prevalence/incidence, add further communities with risk factors known to be associated with high HIV incidence, and randomize by community rather than by individual.

**Phase III trial feasibility – Community awareness and acceptance:**

Participation rates were high in previous long-term studies in the Masaka district, and had a follow-up rate of approximately 80%. The relationship between study communities and the research programme (MRC) has been strong, and the community perceives that the programme is beneficial for the broader community. Political support from the district and other local authorities has been excellent.

**Phase III trial feasibility – Service and other important aspects:**

VCT services are in place with a modest uptake (about 75% of those counselled wish to know their test results). The medical services are functional and sustainable and have been integrated into the existing primary health care system. These services include STI care, condom provision and general health care. The literacy rate of the study population in women is approximately 70% and in men approximately 75%.

**Phase III trial feasibility – Research capacity:**

There is a field trial team in place that has substantial experience in intervention trials and other longitudinal studies. The field team includes a behavioural research team that has extensive background data on reported sexual behaviour, and the behavioural data can be correlated.

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43 Presentation by Heiner Grosskurth, MRC Programme on AIDS in Uganda/Uganda Virus Research Institute.
44 A parish is a small administrative division of a district.
with biological markers. The basic science laboratories have expertise in virology, immunology and microbiology, and the statistical section is experienced in the analysis of community-based, controlled trials.

The expected outcome of the proposed selection strategy is that HIV prevalence in the trial cohort will be approximately 15%, with an HIV incidence of approximately 1.2/100 person years. Coefficient of variation of HIV incidence between communities is 0.2, and it may be reduced further by stratification or matching of communities. There is a possible 25 000 population at enrolment, and a follow-up of 2–3 years is feasible with an expected loss to follow-up of 10%. The selection strategy should be sufficient to detect VE of 30%. It was noted, however, that it is important to carefully select a promising candidate vaccine, as there may only be one opportunity for phase III trials on this cohort.

**Cohort development in Tanzania**

Tanzania has a population of 34 million, and one official language (Swahili). HIV/AIDS has been declared a national disaster by the President, and HIV vaccines form part of the national HIV/AIDS strategy. However, in the absence of a safe and immunogenic candidate HIV vaccine relevant to the Tanzanian situation, the development of population cohorts designed for VE trials has been a challenging undertaking.

A feasibility study was undertaken to determine if an open cohort of police officers in Dar es Salaam could be suitable for possible HIV VE trials. This was done by:

- Carrying out epidemiological prevalence and incidence studies as well as determining possible social behavioural factors of HIV infection;
- Including pre-test and post-test HIV counselling and provision of general health check on each of the consenting police officers.

The police officer cohort was considered to be a good cohort, as police officers comprise a highly disciplined, easily accessible, quite well educated subpopulation of the general Dar es Salaam population and include a good representation of both genders. In 1994, when recruitment into the cohort started, there were between 15 000 and 20 000 police officers in the city from which a suitable cohort could be recruited. Between 1994 and 1998, sero-prevalence and sero-incidence of HIV infection in the cohort were determined. HIV prevalence in approximately 2800 police officers aged between 18–55 years was 13% (with women having a higher prevalence than men), and HIV incidence in the cohort was 2% per year.

There are several suitable cohorts for HIV vaccine trials in Tanzania (female bar workers in southwest Tanzania, several MTCT cohorts, and several demographic surveillance projects that include adult morbidity and mortality projects AMMP and TANESA), and what is now needed is the availability of a suitable, appropriate and potentially safe and immunogenic vaccine for trials. The planned HIVIS project offers the first opportunity for participation in HIV vaccine trials in Tanzania where several HIV subtypes and recombinants are found. Even in the absence of suitable HIV candidate vaccines, establishing cohorts provides many opportunities for the conduct of several HIV vaccine trial preparatory activities, as well as for the facilitation of HIV prevention and control activities in the study sites. Such studies are considered to be essential capacity-building opportunities.

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45 Presentation by Fred Mhalu, Muhimbili University College of Health Sciences, Dar es Salaam, Tanzania.
9(e) Facilitating multi-site collaboration in HIV efficacy trials in Africa

**United States of America collaboration**

Multi-site collaboration is important, as no one site will have all the capabilities and capacity to implement an efficacy trial in addition to trying to deal with and answer various scientific questions. An inter-agency steering committee has been formed between the US MHRP, CDC (USA), VRC and the HVTN with the shared mission of identifying a safe and effective HIV vaccine. The objectives of this collaboration are to accelerate vaccine development and use available resources efficiently and effectively. The overall approach is to work together in areas of common interest, share and compare data and use joint and/or complementary funding.

The key aspects of this collaborative initiative are to: ensure host country and community input; guarantee that data are acceptable to regulatory agencies; ensure coordination with other prevention and treatment research and prevention and care programmes; and facilitate different partners in maintaining their individual identities. The initial areas of coordination will be:

- **Training**: Ensuring uniform, quality training across sites, and developing and utilizing shared training modules;
- **Site development**: Developing/sharing fundamental criteria and principles for site readiness (GCP) and shared mentoring programmes/initiatives;
- **Laboratories**: Developing/sharing common regional and/or national laboratories (GLP, quality control/quality assurance).

There are currently 10 sites collaborating with, and being supported by, CDC, DoD/US MHRP and NIAID/HVTN. These are located in Côte D'Ivoire, Uganda, Cameroon, Kenya (2 sites), Botswana, Tanzania, Malawi and South Africa (2 sites). The future aims of this effort are: to expand to include working partners (such as AAVP, IAVI, SAAVI), particularly around the area of site preparations; to adapt new technologies to facilitate HIV vaccine evaluation; to make data-driven decisions in order to make the best decisions for the use of public funding; and to link vaccine trials to global efforts – such as the proposal from the Gates Foundation to establish a global HIV vaccine enterprise and the American President’s Emergency Plan for AIDS relief.

The President’s plan involves US$15 billion over five years and targets 14 countries (Nigeria, Côte D'Ivoire, Rwanda, Zambia, Namibia, South Africa, Botswana, Mozambique, Tanzania, Kenya, Uganda, Ethiopia, Guyana and Haiti). Its goals are to prevent seven million new infections, treat two million HIV-infected people, and care for 10 million HIV infected individuals and AIDS orphans. The President’s Emergency Plan will not provide funding for research, but will support research for the development of infrastructure. The plan will be implemented by in-country mechanisms, which include coordination with ambassadors, health ministries, national AIDS councils and country coordinating mechanisms (CCM). It will also build upon existing African and Caribbean health structures.

The American Government’s HIV vaccine development efforts are now better coordinated, with collaboration initially focusing on developing and utilizing quality phase III trial capacity. The collaboration is open to other vaccine developers, and it will also link with prevention and care.

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46 Presentation by Margaret (Peggy) Johnson, Director Vaccine and Prevention Research Programme, DAIDS, NIAID.
programmes (including the President’s Emergency Plan) and will ensure input from host countries in setting priorities.

**International AIDS Vaccine Initiative – IAVI**

The goal of IAVI is to accelerate work in the field of HIV/AIDS vaccines and to address the following issues:

- Challenges in vaccine research;
- Design of immunological assays – this is very important, especially for the evaluation of neutralizing antibodies;
- Development – the lack of capacity for production of candidate vaccines under GMP is a major obstacle;
- Clinical trials – the major impediment is the restricted number of suitable infrastructures in Africa and Asia;
- Regulatory aspects – it is important to define an efficacy end-point for licensing.

IAVI focuses on vaccines that can be used in the developing world. Contracts are, therefore, established with IAVI-sponsored investigators in order to assure tiered pricing and access of countries where the disease is endemic to future HIV vaccines. As most HIV strains prevalent in developing countries belong to the A or C clades, vaccines must be designed to meet the specific needs of these countries.

**10. LESSONS LEARNED FROM THE FIRST HIV VACCINE EFFICACY (PHASE III) TRIAL**

**10(a) Results from the first efficacy trial with rgp120BB (VaxGen) candidate vaccine (AIDSVAX BB) in the USA, Canada and the Netherlands**

The results from the first HIV VE trial with the rgp120BB’ (VaxGen) candidate vaccine in the USA, Canada and the Netherlands were presented. Prior to this trial, the rgp120-based candidate vaccines underwent intensive evaluation in all preclinical phases, as well as phase I and II human trials, conducted mostly in the USA and Thailand. These studies demonstrated that rgp120B is able to protect chimpanzees from HIV infection. The subsequent phase I and II trials using a bivalent form (AIDSVAX B/B) of the candidate vaccine also demonstrated its safety and immunogenicity.

The first HIV VE phase III trial was initiated in June 1998, using a bivalent rgp120BB’[MN+GNE8] candidate vaccine formulated with alum. The trial had a multi-centre, placebo-controlled, double-blind, randomized (vaccine:placebo 2:1) design. The trial enrolled 5417 volunteers from 61 sites in the USA, Canada and Netherlands, comprising 5109 non-IDU men who have sex with men (MSM) and 308 women at heterosexual risk. The majority of men participating in the trial were white (86.3%) and the women were mostly non-white (70.5%). Immunization included seven doses administered at 0, 1, 6, 12, 18, 24 and 30 months.

It was demonstrated that the trial was well controlled, well randomized and well conducted. The candidate vaccine was well tolerated and induced specific humoral responses. There was no
evidence of enhanced susceptibility to infection or increased disease progression in vaccinated individuals with concurrent HIV infections. Self-reported baseline risk behaviour correlated with infection rate: HIV infection occurred in 9.3% of 3006 volunteers with high-risk behaviour versus 3.7% of 2397 with lower-risk behaviour.

The primary end-point for VE was defined as risk of HIV infection in vaccine recipients compared to risk in placebo recipients expressed as \([1-\text{relative risk}] \times 100\%\). The secondary end-point in this trial was defined either as the reduction of viremia in vaccinated individuals or as time to starting antiretroviral treatment in vaccinated individuals, as compared to placebo group. The overall results of this trial did not demonstrate significant VE, which was calculated at 3.2% level. However, further subset analysis revealed that apparent VE varied significantly in different race and gender groups – increasing to 50.6% in a “non-white” group, 77.6% in blacks and up to 86.5% in women, although the number of women was too small to generate statistical significance. Also, estimates of VE, overall and within subgroups, were significantly higher in the higher-risk group compared to the lower-risk group. Multivariate analysis, controlling for age, education, geographic region and risk behaviour, showed similar VE estimates.

The detailed analysis of data generated by this trial is under way. This will attempt to explain differences between different treatment arms and will consider both host-related and virus-related factors (levels of neutralizing antibodies, sieve analysis, etc). Final analysis of data generated in this trial should help justify the need for additional further research and clinical trials to confirm or further clarify the indicative vaccine effects detected in this trial.

10(b) AIDSVAX-B/B efficacy trial follow-up
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10(b) AIDSVAX-B/B efficacy trial follow-up

This trial raised some initial questions that need to be answered in an attempt to understand the results better. Media reports were conflicting and carried mixed messages. The questions raised are: Whether the subset efficacy is ‘real’; whether differences in immune responses to the vaccine explain the result; and whether there are other factors that might explain the result?

VaxGen should be complimented for the enormous effort, openness and frankness in which they put data on the table for external review. The data was somewhat surprising in that they showed no efficacy in the overall population, but in a subset analysis tended to produce significant results. Thus the current questions are as follows: Was there some biological plausibility that would/could explain the results in the subset; what was the scientific message from the trial; and what further research was required?

The NIH–CDC held a meeting in April 2003 to independently examine the results, and to determine whether further government support for research and development is warranted. There were 32 participants from USA Government agencies (CDC, DoD, NIH), non-profit organizations (Gates, IAVI), academia (HVTN, AVRWG), international agencies (WHO) and the community (AVAC, Black AIDS Institute). The outcome of the meeting was that additional independent analysis was needed and the specific next steps included the need to:

49 Presentation by Margaret (Peggy) Johnson, Director Vaccine and Prevention Research Programme, DAIDS, NIAID.
• Review a report of the analysis team that looks at efficacy data and the biological plausibility;
• Weigh up the strength of data suggesting additional research and development is warranted vs. opportunity cost;
• If additional research and development is warranted, identify a funding source(s).

The indication for ongoing or planned efficacy trials is what is needed to apply the insights and hypothesis generated from the VaxGen trial. Lessons learned from VaxGen should be used and applied to future efficacy trials. VaxGen has set a high bar for the next efficacy trial, and has generated critical data related to behaviour change during the conduct of an efficacy trial. The VaxGen trial had excellent enrolment and follow-up in hard to reach populations.

However, AIDSVAX conundrum does pose a number of important questions:
• Is there a need to conduct another large trial with existing formulation (race, gender)?
• Is there a need to ‘improve’ the design before further testing?
• Is there a need to evaluate AIDSVAX in combination with other candidate vaccines?
• Is there a need to invest in other candidate vaccines?

Further questions were posed by Roy Mugwera of Uganda on behalf of the AAVP:
• Are these results statistically correct and significant?
• Do the data justify further development of this vaccine concept in Africa?
• Is there a good rationale to conduct small-scale trials to confirm safety and immunogenicity of gp120 in African populations (including women)?
• Should these trials be done with African clade vaccines (A, C or D gp120)?
• Should they proceed with any available gp120?
• Should we move to an efficacy trial in Africa (with gp120)?
• Should we wait for the Thai results (end of 2003) to further test the concept?

11. WORKING GROUP RECOMMENDATIONS

The meeting broke up into three working groups in order to come up with clear recommendations related to the AAVP. The three working groups were (i) Policy frameworks, (ii) Ethics, care and support and (iii) Site development.

11(a) Policy frameworks

HIV vaccine development is critical for Africa, and is the best long-term hope of controlling the epidemic. Each African country must eventually have an HIV vaccine policy or plan, which should be included in the national strategic policy as an integral part of all HIV intervention programmes. The implementation of the policy or plan must be ensured by governments.

Critical issues to be covered in national vaccine policy or plan, include:
• Government responsibility and commitment;
• The establishment of vaccine advisory committees/working groups at the highest level, which consist of different stakeholders and list roles and responsibilities;
• Regulatory authorities must ensure accelerated review and approval process for HIV vaccine studies, licensing and manufacturing (AAVP could potentially play a role in supporting countries that do not currently have regulatory authorities);
• Training/advocacy (including top level);
• Standards of treatment and care;
• Regional alignments/collaboration/cooperation (South-south collaboration and multi-site collaboration should be included).

WHO-UNAIDS and AAVP must assist countries in the development of national vaccine plans or policies, for example, by supplying a template for their development. In the early 1990’s, WHO assisted Brazil, Rwanda, Thailand and Uganda in the development and implementation of the first generation of national AIDS vaccine plans.

WHO-UNAIDS and AAVP should facilitate the establishment of national vaccine policies or plans at the highest political levels nationally, and through the African Union and the New Partnership for African Development (NEPAD).

The meeting recognized a need to develop sustainable research infrastructures in Africa to support the vaccine development effort. This would require participation and coordination from national institutions and international collaborators to sustain capacity on a long-term basis. Organizations such as ENARP have been a successful example of this type of collaboration, and similar collaborations merit further support from international and national partners.

11(b) Ethics, care and support

• There is currently no general legislative framework in Africa within this area, so there is a need to understand what legislative frameworks exist nationally. Training workshops should be developed according to the needs assessment, and these should build on experiences of research ethics committees and/or institutional review boards that have been involved in reviewing HIV vaccine trials;
• There is a need for more effective coordination of research ethics training activities in Africa;
• Standard and endorsed ethical guidelines documents should be circulated among member countries;
• AAVP should support and strengthen “ethics” monitoring capacity, and should encourage sharing of information and lessons learned among and between different research ethics committees and/or institutional review boards;
• WHO–UNAIDS should establish an expert group of research ethics committee members that could be referred to for independent advice and assistance. Clear terms of reference should be established for this expert group;
• The Community Preparedness Working Group should be separate from the Ethics, Law and Human Rights group, although there is a need for close collaboration;
• Communication between and among different working groups of the AAVP should be improved;
• AAVP should develop an information pack to strengthen community preparedness. It should include lessons learned, what has worked, what has maximized community preparedness and provide a list of useful resources and guidelines. AAVP could assist in the development of a resource packet with community friendly documentation;
• There is a need to assess community needs on issues related to IC and standards of care/ access to treatment;
• AAVP should develop policy documents on the issue of standards of care, and a policy document that ensures gender equality at all levels of research and all structures of the AAVP;
• AAVP should develop discussion documents on the issues of enrolment of adolescents, the ownership of research specimens (tissue, blood, etc.) and the continuity of care;
• AAVP should develop a prioritized social science research agenda;
• There is a need for a more outcome-driven annual review process, and recommendations between meetings need to be followed through and reported on;
• AAVP needs a dedicated website.

11(c) Site development

• AAVP should play a leadership role in mediating negotiations between donors and potential or existing sites to bring them together for a wide range of research initiatives;
• AAVP should ensure that vaccine trial cohorts are not monopolized but instead are used for the benefit of science and host countries and are linked with capacity-building. There is a need to establish prolonged sustainability, and to develop local expertise while also exploiting existing expertise;
• AAVP should determine what resources are available at sites and what is required to strengthen sites. It is important that all sites throughout Africa are represented, even those which are not represented at this meeting. Long-term sustainability is a responsibility of both the host country and the donor/sponsor;
• AAVP should facilitate collaboration with reference centres between African countries.

11(d) General recommendation

There is a need for appropriate human and financial resources to be identified in order to implement and prioritize recommendations and activities of the AAVP.
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