The highlighted countries are those with ongoing or completed HIV Vaccine trials.
“Since the vision was first conceived, the Enterprise has developed from a concept on paper to an alliance of leading HIV vaccine researchers, funders, and advocates dedicated to accelerating the discovery, development, and testing of a vaccine against HIV through the implementation of a shared scientific strategic plan.”
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Executive Summary

The search for an HIV vaccine, one of the most important and challenging scientific endeavors of our time, demands a new approach to biomedical research. The best scientific minds must be engaged in a well-resourced, international effort that fosters innovative research while promoting collaboration and which systematically tackles the most pressing scientific questions before the field.

The Global HIV Vaccine Enterprise was conceived in 2003 to bring new focus, cooperation, and expanded resources to HIV vaccine research. Since its inception the Enterprise has formed an alliance of independent organizations that includes many of the leading AIDS vaccine research institutions in the world.

Together, this group has developed and begun to implement a shared scientific strategic plan, helped mobilize significant new resources, promoted collaborative work among researchers, and sponsored dialogues on major scientific challenges. The Enterprise has also established an interim Secretariat and laid the foundation for expanded activities under the leadership of a soon to be appointed Executive Director.

The Enterprise concept was first proposed in a June 2003 article in Science signed by 24 leaders in HIV vaccine research. They called for a revitalized, more collaborative research effort that would increase the scale and accelerate the pace of research, establish common standards for comparing products, expand manufacturing capability, and improve the capacity of clinical trials sites. The Enterprise proposal was further developed at a meeting of leading scientists, public health experts and policy makers in August 2003. In 2004, at their annual Summit, the Group of 8 nations endorsed the Enterprise concept and pledged their support.

The Enterprise is now engaged in a broad range of activities, but science is its core business. The initial stakeholders in the Enterprise began work on their Scientific Strategic Plan (SSP) in 2004, convening six expert working groups and conducting a comprehensive review of the state of HIV vaccine research. The SSP was published in PLoS Medicine in February 2005.

Putting the scientific plan into action

Enterprise partners are now aligning many of their activities and launching new projects to address the six priority areas identified in the SSP: vaccine discovery, laboratory standardization, product development and manufacturing, clinical trials capacity, regulatory capacity, and intellectual property issues.

In this initial phase of the Enterprise, most partner research activities have focused on the “upstream” components of the scientific plan, particularly vaccine discovery and laboratory standardization. Examples of partner activities include:

+ The U.S. National Institute of Allergy and Infectious Diseases (NIAID) has created the Center for HIV/AIDS Vaccine Immunology (CHAVI), a consortium of 95 investigators in 36 institutions in 8 countries.
+ The Bill & Melinda Gates Foundation has supported creation of the Collaboration for AIDS Vaccine Discovery (CAVD), a network of 16 research consortia, with more than 180 investigators in 22 different countries.
The International AIDS Vaccine Initiative (IAVI) has expanded its Neutralizing Antibody Consortium (NAC), created a consortium to address correlates of immunity, and established an AIDS Vaccine Development Laboratory.

The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) are preparing principles for community engagement and revising ethical guidelines for clinical research.

The European Commission (EC) is supporting several cooperative HIV research projects, including the EUROPRISE network that brings together vaccine and microbicide researchers.

The European & Developing Countries Clinical Trial Partnership (EDCTP) is strengthening clinical trials capacity through multi-center projects in Africa.

The Wellcome Trust supports a variety of HIV vaccine research projects consistent with priorities identified in the SSP and is convening scientists to discuss novel approaches to vaccine design.

The French National Agency for Research on AIDS and Viral Hepatitis (ANRS) is funding research on a variety of HIV vaccine approaches within the scope of the SSP.

The AIDS Vaccine Advocacy Coalition (AVAC) provides policy, advocacy and community perspectives and helps connect civil society to the work of the Enterprise.

Addressing key scientific challenges

The Enterprise SSP will be continually revised as scientific knowledge evolves and partners advance their understanding of the challenges and opportunities in HIV vaccine research. To help guide revision of the SSP, the interim Secretariat has convened three expert working groups to discuss key scientific issues.

The first workshop, Approaches to expediting HIV vaccine efficacy evaluation, was held in April 2007 and included 42 participants. The group discussed how to interpret forthcoming results from intermediate-sized vaccine efficacy trials, as well as the advantages and disadvantages of different clinical trial designs. Participants identified the need to expedite product testing in an industry-like manner and more clearly define criteria for selecting appropriate trial designs for different candidates.

The second workshop, Humoral responses to HIV and approaches to the design of antigens that induce neutralizing and other potentially protective antibodies, was held in May 2007 and attended by 25 scientists. Participants agreed on the need for expanded research attention to isolating and characterizing new broadly neutralizing monoclonal antibodies against various HIV clades; to obtain crystal structures of additional envelope molecules; to understand the potential protective role of “non-neutralizing” antibodies; to better characterize the significance of in vitro assays in relation to in vivo protection; and to obtain additional information on relevant B cell immunology. Ultimately, the design of new immunogens either with stabilizing mutations in gp120, scaffolds of conserved neutralization epitopes on
other proteins, or other structurally-based approaches (e.g., env-CD4 chimeras or mimics of them) may lead to more promising products. Significantly improving HIV vaccine design is still of the highest priority.

The third workshop, Improving defenses at the portals of entry: innate and mucosal immunity, was held in June 2007 and included 26 scientists. Participants identified the need for better understanding of mucosal T cell responses and the mechanisms of infection in mucosal surfaces, and improved techniques to evaluate mucosal immune responses. They agreed that insufficient understanding of innate and mucosal immunity is a significant bottleneck in vaccine development and they called for additional research in several areas. Substantial effort needs to be devoted to designing and developing novel vaccine candidates that target mucosal tissues, both at the portal of entry as well as within the mesenteric lymphatic system, where the “battle” with the virus takes place.

Creating a base for expanded activities

The Secretariat is the central coordinating body of the Enterprise: monitoring, implementing, and updating the SSP; convening stakeholders; and advocating for new resources for HIV vaccine research. In the first years of the Enterprise, the Bill & Melinda Gates Foundation has served as the interim Secretariat. Since January of 2005, the interim Secretariat has managed development of the SSP, sponsored the three scientific workshops, launched an international Executive Director search, developed a business plan, and created an Enterprise website and other communication materials.

The interim Secretariat is involved in a variety of HIV vaccine-related events, and now plays a central role in organizing the annual AIDS Vaccine conferences. It has also organized several meetings in addition to the scientific workshops, including:

- Satellite and roundtable sessions at the International AIDS Society pathogenesis meeting in 2005, at the First Eastern European and Central Asia AIDS Conference in 2006, and at the AIDS 2006 conference,
- A Stakeholders Forum that brought together over 50 advocates, social scientists, researchers and others from developing and developed countries, and,
- A Funders Forum that will become an annual event.

As soon as the Executive Director is appointed, a permanent Secretariat will be established. An Enterprise Council will provide strategic guidance on the Enterprise mission, objectives and policies and a Scientific Stewardship Committee will provide scientific guidance to the effort.

Since the vision was first conceived, the Enterprise has developed from a concept on paper to an alliance of leading HIV vaccine researchers, funders, and advocates dedicated to accelerating the discovery, development, and testing of a vaccine against HIV through the implementation of a shared scientific strategic plan. In the coming years, the Enterprise expects to recruit new partners from the private and public sectors and continue to build a well-resourced, collaborative global effort to develop one of the most urgently needed health technologies of this century.
Introduction

Soon after HIV was identified as the cause of AIDS in 1983-1984, there was an expectation that an effective vaccine would be tested, developed and deployed within several years. The intense research effort conducted during the last 20 years has produced important information on the virus and the disease, but an effective vaccine remains elusive (Douek et al., 2006; Esparza et al., 2006; Johnston and Fauci, 2007; Berkley and Koff, 2007). To confront this challenge, in June 2003 a group of leaders in the field of HIV vaccines published a Policy Forum article in the journal Science proposing the creation of the Global HIV Vaccine Enterprise (Klausner et al., 2003). The authors recognized that current attempts to develop such a vaccine were insufficient in scale and focus, and that a renewed HIV vaccine research effort was required.

This is the first full report of the activities of the Global HIV Vaccine Enterprise (the Enterprise). During the two years since the Enterprise Scientific Strategic Plan was published, we have been diligently working to translate the vision into a set of actions to accelerate the development of a much needed HIV vaccine (Figure 1). The development of the Enterprise has gone through three phases: conceptualization (2003), planning (2004), and initiation of activities (2005-2007).

The conceptualization phase was completed in August 2003 when the authors of the proposal published in Science invited a group of leading scientists, public health experts, and policy makers to meet at the Airlie House in Virginia, United States, to refine the vision of the Enterprise. The meeting participants agreed that the Enterprise should be developed, not as a new organization, but as an alliance of independent organizations committed to accelerating the development of a preventive vaccine for HIV through the implementation of a shared strategic plan, mobilization of additional resources, and greater collaboration among HIV vaccine researchers worldwide. The Human Genome Project provided an interesting model for international coordination with many funders agreeing on a scientific road map, voluntarily dividing the work, and agreeing to an evolving set of production standards (Collins et al., 2003; Klausner et al., 2003).
The Enterprise model represents a new way of thinking about problems and approaches to resolving them through the formulation of a shared scientific strategic plan. The plan is based on the identification of gaps and opportunities, the use of common tools, optimized resources, and iterative learning. Most importantly, it represents a new way for scientists to engage as a global community of problem-solvers, sharing materials and information, and balancing collaboration with healthy competition.

In 2004, the Enterprise moved from conceptualization to planning as the Scientific Strategic Plan (SSP) was developed through a process of international consultation. Six expert Working Groups were convened, involving a total of 140 scientists from 15 countries, to focus on the most critical issues in HIV vaccine research and development. The Working Groups conducted a comprehensive review of the state of HIV vaccine research, and published the initial SSP for the HIV vaccine field in early 2005 (Coordinating Committee of the Global HIV Vaccine Enterprise, 2005).

Initial activities to contribute to the implementation of the SSP were launched in 2005 and 2006, including the NIH-supported Center for HIV/AIDS Vaccine Immunology (CHAVI), and the Bill & Melinda Gates Foundation-supported Collaboration for AIDS Vaccine Discovery (CAVD). During this early implementation phase the Enterprise also established an interim Secretariat that provides administrative infrastructure.

Science is the core business of the Enterprise and has been the focus of activities thus far. Section I of this report summarizes the scientific contributions of initial Enterprise stakeholders to the implementation of the SSP, as described in their reports to the Secretariat. These activities demonstrate that the collaborative vision of the Enterprise is becoming a reality. Increasingly, activities implemented by different Enterprise stakeholders will benefit from improved cooperation, minimizing unnecessary duplication, and encouraging complementary exploration of key scientific challenges.
**Figure 2** shows the constellation of organizations and individuals working together to implement a shared plan. These include funding agencies, research organizations, non-government organizations, international agencies, and individual scientists supported by different programs that have been launched or realigned to target SSP research priorities.

The full implementation of the Enterprise SSP will require the increasing commitment and participation of many organizations, from industrialized and developing countries, from the public and private sector, and civil society.

Enterprise partners recognize that science evolves and that new concepts emerge, and this will require ongoing review and updating of the SSP. Section II of this report summarizes the recommendations of three Enterprise Working Groups that met in 2007 to discuss current critical issues and new opportunities in HIV vaccine research. Their recommendations will inform a future full revision of the SSP.
The Enterprise calls for complementing current investigator-led efforts with large-scale, well-funded, collaborative efforts across institutions and disciplines, tackling major scientific problems that have proven too difficult for any one group to tackle alone. In addition, Enterprise stakeholders are also exploring a variety of new approaches to encourage innovation and support novel high-risk/high-reward ideas to the HIV vaccine discovery effort.

A small interim Secretariat based at the Bill & Melinda Gates Foundation has been developing the infrastructure necessary to establish an independent, permanent Secretariat in anticipation of the appointment of the Enterprise’s first Executive Director (ED). The work of the interim Secretariat and plans to establish the permanent Secretariat are summarized in Section III of this report.

We hope that this report helps provide a greater understanding of the work of the Enterprise to date and its promise for advancing progress towards the development of a safe and effective vaccine. We also hope that the information provided in this report demonstrates that our initial decision to concentrate on science, rather than on the administrative aspects of the Enterprise was appropriate. And, more importantly, we hope that by reading this report you will become a supporter of the goals of the Enterprise.

August 2007

José Esparza MD, PhD*

Helene D. Gayle MD, MPH**

Head, Interim Secretariat of the Enterprise, and President of the Enterprise Board of Directors

Chair of the Enterprise Coordinating Committee, and Vice President of the Enterprise Board of Directors

* Senior Adviser on HIV Vaccines, Bill & Melinda Gates Foundation
** President and CEO, CARE USA (Formerly Director of HIV, TB and Reproductive Health, Bill & Melinda Gates Foundation)
Section I: Implementing the Scientific Strategic Plan

1. Contributions of initial Enterprise stakeholders

Several Enterprise stakeholders are making significant contributions to the implementation of the SSP, aligning some of their activities with SSP priorities and, in some cases, launching new activities which directly target gaps in the global HIV vaccine research and development effort (Esparza, 2005; IAVI, 2006; Lau et al., 2007).

The National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), part of the U.S. Department of Health and Human Services, is one of the founding members of the Enterprise. NIAID contributes to the Enterprise through both its intramural program, particularly the Dale and Betty Bumpers Vaccine Research Center (VRC), and its extramural program, established and overseen by the Division of AIDS (DAIDS). The HIV vaccine program within the VRC acts as a self-contained HIV Vaccine Development Center (VDC) such as those called for in the June 2003 Policy Forum in Science magazine proposing the establishment of the Enterprise (Klausner et al., 2003). The NIAID extramural program’s main direct contribution to the Enterprise is through a virtual VDC called the Center for HIV/AIDS Vaccine Immunology (CHAVI), which was designed to help address some of the Enterprise scientific priorities. Following a peer-reviewed competition, an award for CHAVI was made in July 2005 to a consortium led by Barton Haynes at Duke University.

In addition, NIAID manages a large portfolio of grants and contracts that align with the priorities of the Enterprise SSP to the extent possible, and operates according to the Enterprise principles of collaboration, coordination, and transparency. This includes an innovation grant program, which enables successful research to evolve into a phased expansion program, as well as other multi-group, collaborative grants and contracts, many of which foster public-private partnerships. Finally, DAIDS leads the Partnership for AIDS Vaccine Evaluation (PAVE), a voluntary consortium of U.S. Government agencies and key U.S. Government-funded organizations involved in the development and evaluation of HIV preventive vaccines and the conduct of HIV vaccine clinical trials. PAVE’s formation predates the proposal of the Enterprise, and PAVE’s Working Groups have made significant progress toward several goals outlined in the Enterprise SSP.

One of the key priorities of the Bill & Melinda Gates Foundation is to promote the development of a preventive HIV vaccine. The Gates Foundation is one of the founding stakeholders of the Enterprise and one of its strongest advocates. The Gates Foundation agreed to serve as the interim Secretariat of the Enterprise until a permanent Secretariat could be formally established. Acting as the interim Secretariat, the Gates Foundation has coordinated the development and updating of the Enterprise SSP, and has convened a number of scientific and stakeholder meetings, including meetings of the Coordinating Committee where key Enterprise stakeholders are represented. In order to not loose momentum, the interim Secretariat has also established the basic administrative infrastructure that will support the functioning of the permanent Secretariat (see Section III of this report). The Gates Foundation has been supporting research in the field of HIV vaccines since 1998, when it provided the first of several grants to the International AIDS Vaccine Initiative (IAVI). When the Enterprise SSP was developed, the Gates Foundation expanded its HIV vaccine activities, aligning them with the Enterprise plan. This led to the launching of several new initiatives, in particular the Collaboration for AIDS Vaccine Discovery (CAVD), which was launched in late 2006. Other activities include a col-
laborative effort with the European and Developing Countries Clinical Trials Partnership (EDCTP), to support capacity building in Africa for future HIV vaccine trials. Presently the Gates Foundation is partnering with the Wellcome Trust and IAVI to support new programs in innovative research for HIV vaccines.

The International AIDS Vaccine Initiative (IAVI) is another founding member of the Enterprise. In their “AIDS Vaccine Blueprint 2006” IAVI, as a partner of the Enterprise, provided a comprehensive look at the achievements and challenges facing HIV vaccine science and policy making. The Blueprint makes a series of recommendations that IAVI believes will move the field closer to achieving the goal of an effective HIV vaccine. IAVI’s recommendations were built upon the Enterprise process, focusing on initiatives to address key scientific challenges and integrating these efforts to create a more effective enabling environment to accelerate AIDS vaccine research and development.

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The Joint United Nations Programme on HIV/AIDS (UNAIDS), a founding member, and the World Health Organization (WHO) have been actively involved in the Enterprise since its inception, participating in both the formulation of the SSP and its implementation, and fully supporting the spirit of collaboration, cooperation, and transparency embodied in the goals and objectives of the Enterprise. UNAIDS has convened a number of consultations on effective partnerships for biomedical HIV prevention research; developed “Good Participatory Practice Guidelines”, with assistance from AVAC; and is leading the revision of the 2000 UNAIDS guidance document on Ethical Considerations for HIV Preventive Vaccine Research. The WHO-UNAIDS HIV Vaccine Initiative (HVI), located in the WHO Initiative of Vaccine Research (IVR) in Geneva, Switzerland, has five priority activity areas: 1) Technical guidance and coordination; 2) Policy development; 3) Regional networking and strategic planning; 4) Capacity building; and, 5) Support to selected collaborative projects. The outcomes of these activities align with the objectives of the Enterprise SSP.

The European Commission (EC) is supporting a number of co-operative research projects in HIV, currently focusing on drugs, microbicides, and vaccines. The EC believes that co-operation is central to winning the battle against HIV, and that philosophy is in line with the Enterprise. In recent years the EC has concentrated efforts on finding new innovative approaches to vaccine development, covering basic, preclinical, and early clinical testing. Funding of small-scale, highly innovative approaches has been implemented with the aim of opening new avenues for research in this field. In order to better synergize European research on new preventive technologies, the EC is financing EUROCRISE, a Network of Excellence that includes both microbicides and vaccine researchers. This newly funded project includes about 15 European research projects funded by both the EC and the Bill & Melinda Gates Foundation, representing more than 132 institutions from 22 countries. EUROCRISE will promote an integrated program for European research on new preventive strategies.

The main objective of the European Developing Country Clinical Trials Partnership (EDCTP) is to support the development of new or improved clinical interventions to fight HIV/AIDS, malaria and tuberculosis, to promote European research integration, and to foster strong partnership with and between scientists in African countries. In addition, EDCTP aims to strengthen capacity for carrying out clinical trial activities in Africa. EDCTP supports multicenter projects which combine phase II or III clinical trials with capacity building and networking. In projects supported by EDCTP, these three components are closely integrated. In this regard, EDCTP ensures that the capacity building
and networking established are utilized to successfully conduct clinical trials under the best practices and promote sustainability of the clinical trials capacity in Africa. EDCTP also promotes an enabling environment for the conduct of trials through support and strengthening of ethics review and national regulatory frameworks. The EDCTP objectives for vaccine development are to establish the capacity to measure HIV incidence in defined cohorts; prepare selected sites to conduct Phase II trials with candidate vaccines; and conduct of phase II and III studies at African sites. Therefore EDCTP’s contribution to the implementation of the Enterprise SSP at this stage covers two of its priority areas, namely, clinical trials capacity and regulatory considerations.

The Wellcome Trust, whose mission is to foster and promote research with the aim of improving human and animal health, is another of the founding stakeholders of the Enterprise. Its broadly defined mission allows the Trust to respond flexibly to medical needs and scientific opportunities, as well as tackling immediate priorities. This independence and long-term perspective enables the Trust to support additional research that will benefit future generations. As part of their program, the Trust is supporting HIV vaccine R&D in a way that is consistent with the Enterprise SSP. The Trust and the Gates Foundation convened a joint brainstorming meeting in late July 2007 to discuss novel approaches to identify and support innovative ideas in biomedical research. The meeting explored general approaches that could be applicable to any biomedical research field, but focused on how those approaches could be immediately used to support innovative (high risk/high reward) research to accelerate the development of an HIV vaccine. The impetus for the meeting was based on the recognition by the scientific community that new research paradigms need to be explored, but that there is very little consensus on how to do it in a practical way. The recommendations from this meeting will be used by Enterprise partners to develop pilot programs that would expand innovative research on HIV vaccines.

The French National Agency for Research on AIDS and Viral Hepatitis (ANRS), an Enterprise founding stakeholder, participates in a number of international initiatives designed to draw up a scientific timetable for the development of a vaccine against HIV, and its activities will be within the scope of priority areas identified in the Enterprise SSP.

The AIDS Vaccine Advocacy Coalition (AVAC) is a founding stakeholder of the Enterprise, and its staff and board members have participated actively in the Enterprise activities, including participation in Working Groups and members of various Enterprise committees. While the focus of the Enterprise has been on key scientific areas, AVAC continues to provide policy, advocacy and community perspectives to support and influence the Enterprise and its stakeholders. Since the idea of the Enterprise was first proposed in 2003, AVAC has provided updates and critiques in each of its Annual Reports.

Additional Enterprise stakeholders are aligning some of their activities with the Enterprise SSP. As the Enterprise develops with time, it is expected that other organizations, both in industrialized and developing countries, and in the public and private sector, will increasingly contribute to the implementation of the Enterprise SSP.
2. Implementation activities

This section of the report provides a summary description of the activities implemented by different Enterprise stakeholders in support of the SSP, based on the reports each submitted to the interim Secretariat. The SSP identified the major roadblocks in vaccine research and the most promising avenues for addressing these, making recommendations in six priority areas (Coordinating Committee of the Global HIV Vaccine Enterprise, 2005):

1. Vaccine discovery
2. Laboratory standardization
3. Product development and manufacturing
4. Clinical trials capacity
5. Regulatory capacity
6. Intellectual property issues

During this initial phase of the Enterprise, most of the activities focused in the more upstream components of the plan, especially in the areas of Vaccine Discovery and Laboratory Standardization, which were considered to be the main priorities. However, activities to implement other components of the SSP have also been initiated.

2.1. Vaccine discovery

The immediate priority of the field is to design candidate vaccines that cause the immune system to produce protective responses using both of its major arms—cellular immunity and neutralizing antibodies.

There are major challenges to discovering vaccines capable of eliciting both types of responses. Researchers have developed vaccine candidates capable of eliciting cellular immunity against HIV in animal studies and small clinical trials, and three candidates are currently in phase II or III trials. While researchers have identified antibodies that can bind to and neutralize a broad range of primary HIV isolates, they have thus far been unsuccessful in designing vaccine candidates to elicit those antibody responses.

The Enterprise SSP makes a number of recommendations for overcoming some of these obstacles:

- Research teams currently developing vaccine candidates based on cellular immunity should coordinate their efforts and share data to increase knowledge and better guide the development of new candidates capable of eliciting more potent responses.
- Large-scale research consortia should be created to focus on the problem of designing vaccine candidates capable of eliciting neutralizing antibodies. Many scientists believe that this problem can be solved by bringing together immunologists, structural biologists, and scientists from other disciplines.
- To fill gaps in scientists’ understanding of the interplay between HIV and host, large-scale studies should be conducted of people who have very recently become infected with HIV, to learn important information about the role of a vaccine in the initial stages of infection and how the body prevents or controls infection.

Three of the founding members of the Enterprise have launched major programs to design vaccines to elicit broadly protective immune responses, elucidate the correlates of protective immunity, and explore whether infecting viruses have unique features than can be exploited in vaccine design:
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

CHAVI, funded by NIAID, is a consortium of scientists in universities and academic medical centers which is trying to solve major problems in HIV vaccine development and design through the work of 10 highly collaborative Discovery Teams supported by 12 cores. CHAVI now involves 95 investigators in 36 institutions in 8 countries.

CHAVI’s Viral Biology Discovery Team under the leadership of Beatrice Hahn is studying recently transmitted viral sequences in an effort to identify unique signatures of transmitted viruses. They are generating panels of transmitted viruses and creating and making available a CHAVI transmitted HIV-1 sequence database for vaccine design and viral biology studies. This team has developed a novel method to sequence virus from a single genome (Single Genome Amplification or SGA) and thereby avoid artifacts arising from recombination during PCR. From August 2006 through April 2007, 4,260 complete B clade envelope sequences isolated from 192 individuals using SGA (including 2,590 sequences from 96 acute infections) were added to the publicly accessible Los Alamos National Laboratory (LANL) HIV Sequence Database by CHAVI (Hahn and coworkers, unpublished). This is more than the total number of complete envelope sequences submitted to the LANL database in the previous 19 years of its existence. The CHAVI Host Genetics Discovery Team led by David Goldstein is employing candidate gene and genome-wide screens in specimens from cohorts of AHI and exposed and uninfected (EU) individuals to define genes that may contribute to resistance to HIV-1 infection. Coupled with the screens of candidate genes will be the capacity to study the biology of gene associations in an effort to understand mechanisms of immune control of HIV-1. Whole genome analysis of HIV-infected individuals has already confirmed the association of a specific HLA-B allele (or an endogenous retrovirus sequence tightly associated with it) with the early ability to contain virus replication. Early genomic data also suggests that there is a strong correlation between the level of HLA-C expression and viral set point (Fellay et al, 2007)

CHAVI’s Discovery Team in Non-Human Primate Correlates of Immunity of Live Attenuated SIV under the leadership of Norm Letvin is working to define the correlates of immune protection to live attenuated SIV and to super-infection, while CHAVI’s T Cell Immunology Discovery Team, led by Andrew McMichael, is working to perform a comprehensive analysis of the ontogeny of anti-HIV-1 cellular responses in patients with AHI compared to chronically infected patients.
in an effort to understand successful T cell based immune control of HIV-1. In AHI studies, they are attempting to define “good” and “bad” anti-HIV-1 T cells using stimulating peptide sets that are both autologous and heterologous to the patient. This team will also study samples from EU individuals compared to unexposed and uninfected (UU) samples. In EU studies, they will work to determine if, in a subset of EU samples, anti-HIV-1 immune responses are correlated with protection from HIV-1 infection.

In the area of neutralizing antibodies, CHAVI’s Structural Biology Discovery Team under the leadership of Joseph Sodroski focuses on the structural properties of the HIV-1 trimer in order to develop a comprehensive picture of the conformational changes the virus undergoes during AHI. This research will assist investigators in the design of stable envelope forms of HIV-1 that could potentially induce broadly reactive neutralizing antibodies. To date, this team has determined the crystal structure of a fully glycosylated Simian Immunodeficiency Virus (SIV) gp120 envelope glycoprotein in an unliganded (native, non-CD4 bound) form, providing information on how neutralizing antibodies may react to this molecule and ultimately providing information leading to vaccine design for inducing neutralizing antibodies (Sodroski and coworkers, unpublished). CHAVI’s B Cell Immunology Discovery Team led by George Shaw is working to define the ontogeny of epitope-specific anti-HIV-1 binding and neutralizing antibodies as well as antigen specific B cells during AHI in order to determine why broadly neutralizing antibodies are rarely observed in AHI. This team has developed B-cell tetramers as a new way to quantitate the presence of epitope-specific B lymphocytes in various compartments of the body (Haynes, Shaw and coworkers, unpublished).

Investigators in CHAVI’s Adjuvant Development Discovery Team led by Norm Letvin are working to develop novel adjuvants that optimize the immunogenicity of candidate HIV-1 vaccines produced by CHAVI. This team has demonstrated that formulation of plasmid DNA vaccines with polyethylenimine can result in enhanced immunogenicity and may result in mucosally-focused responses (Letvin et al, unpublished). In 2006 CHAVI established two new discovery teams, Innate Immunity and Mucosal Immunity. Investigators in the Innate Immunity Discovery Team led by Andrew McMichael are studying the functional properties of peripheral blood natural killer (NK) and dendritic cells (DC) during the acute stages of HIV infection, to ascertain their T cell stimulatory capacity and their ability to suppress HIV replication. This research aims to develop vaccines that can recruit an accelerated innate immune response to HIV-1. The Mucosal Immunity Discovery Team led by Robin Shattock is working to define the acquired immune responses and innate host defenses at mucosal surfaces that may act during HIV-1 transmission in order to develop vaccines that prevent mucosal transmission of HIV. CHAVI’s Vaccine Design Discovery Team led by Barton Haynes will use the results of CHAVI’s clinical and non-human primate studies to inform the design of vectors, inserts and composite immunogens for testing in the Non-Human Primate Core. Viable immunogens resulting from these studies will be considered for vaccine development.

Peter Kwong and colleagues at the NIH VRC recently published the atomic level structure of the neutralizing anti-CD4 binding site monoclonal antibody IgG1b12 bound to gp120. This structure illustrates how an antibody can access the structurally conserved CD4 binding region of gp120 (Zhou et al, 2007). In the area of Immune Correlates of Protection, another of the priority areas of the Enterprise Plan, scientists from the VRC have developed reagents and procedures for complex multifunctional analysis of immune responses to vaccines and natural infection for identification of immune correlates of protection. These new techniques were employed to demonstrate that polyfunctional T cells have been shown to correlate with greater control of HIV replication among chronically HIV-infected people (Betts et
In addition, in 2006 VRC scientists demonstrated that a DNA prime, recombinant adenovirus vector boost vaccine can protect against the destruction of the CD4 memory compartment following acute SIV infection, and that this protection correlates directly with longer life-span of infected animals (Mattapallil et al., 2006). VRC scientists have determined the immune responses to the VRC clade A Env insert used in clinical trials of multi-clade DNA and adenoviral HIV vaccines. This immunogenic insert has been made available to multiple organizations for comparative HIV vaccine studies.

During 2006, the VRC signed a Cooperative Research and Development Agreement with IAVI, formally joining IAVI’s Neutralizing Antibody Consortium, and will provide new information on the molecular structure of broadly neutralizing antibodies and how they recognize the virus.

Since the establishment of the Enterprise, NIAID has funded over 30 unsolicited research grants and contracts that are studying areas identified as priorities in the SSP (see www3.niaid.nih.gov/research/topics/HIV/vaccines/funding). The DAIDS’s Integrated Preclinical/Clinical AIDS Vaccine Development Program (IPCAVD) supports the later stages of preclinical preventive HIV vaccine concept refinement and testing, culminating in human studies. IPCAVD studies can include later stage preclinical research (vaccine optimization studies, immunogenicity/challenge studies, etc), GMP vaccine production, GLP preclinical toxicology and safety studies, pre-IND/IND preparation and submission, and clinical testing. In 2006, Dan Barouch and colleagues reported the creation of new chimeric vaccine vectors based on adenovirus serotypes 5 (Ad5) and 48 that circumvent pre-existing antibodies to Ad5, making it possible to use such vectors in populations with high Ad5 sero-incidence (Roberts et al., 2006).

The DAIDS’s HIV Vaccine Research and Design (HIVRAD) Program supports multidisciplinary HIV preventive vaccine-related studies. In 2005, Bart Haynes and colleagues discovered that several human broadly neutralizing monoclonal antibodies (MAbs) previously isolated from HIV long-term infected individuals bind to cardiolipin and may be poly-reactive autoantibodies. This finding may explain why these antibodies are difficult to induce (Haynes et al., 2005). In 2006, this group went on to describe an HIV-1 envelope-based immunogen, based on a consensus envelope gene sequence, that induced antibodies that neutralize subsets of subtype B and C HIV-1 primary isolates, demonstrating that immunogens can be created that have better immunogenic properties than those of wild-type envelope (Liao et al., 2006). James Binley and collaborators showed that non-neutralizing antibodies bind nonfunctional forms of envelope protein on the surface of HIV, and suggested that these forms of Env may divert the antibody response and help the virus evade neutralization (Moore et al., 2006).

The CAVD was launched in July 2006 with support from the Bill & Melinda Gates Foundation and is being developed as a highly collaborative network of 16 research consortia, comprising more than 180 investigators, in almost 90 institutions in 22 different countries. Eleven of the consortia are working on different approaches to developing HIV vaccines, six of which focus on vaccine concepts designed to induce cell-mediated immunity, and the other five on vaccine concepts designed to induce protective antibody responses. Those 11 Vaccine Discovery Consortia (VDC) are supported by five Central Service Facilities (CSF), which conduct standardized immunological evaluations and data and statistical analysis for the whole network, allowing for real-time comparison of the results. The CAVD projects are not intended to focus on basic discovery research. Instead, they target a perceived strategic gap in the HIV vaccine research and development continuum, which is the translational or “maturation” phase. This phase is aimed at
harnessing the vast amount of knowledge derived from basic research to produce the “proof-of-concept” experiments required to proceed with confidence to the product development phase. To ensure that the whole effort is bigger than the sum of its parts, the 16 CAVD consortia and centers are bound together by a robust communication and alliance management strategy, and by legal agreements to share materials and data among the different CAVD laboratories and, in time, with the rest of the Enterprise alliance and the scientific community at-large. In less than 12 months of work, the CAVD teams have made considerable progress, and the following paragraphs provide only a cursory description of their main goals.

The five CAVD VDCs focusing on humoral immunity are exploring different approaches to solving the challenge of developing candidate vaccines that induce antibodies capable of neutralizing clinical (or primary) isolates of different subtypes and strains of HIV-1. The VDC lead by Robin Weiss (University College London) is using three different and complementary approaches to isolating a significant number of novel broadly neutralizing MAbs against different HIV subtypes, especially those circulating in Africa (subtypes A and C). Dr. Weiss’ group is searching for these monoclonal antibodies in humans with high titers of broadly neutralizing antibodies, in immunized transgenic mice that express human antibodies, and in immunized llamas, which produce natural single chain functional antibodies. These MAbs will then be used to identify and characterize conserved regions of the HIV envelope proteins in order to design candidate vaccines that induce broadly neutralizing antibodies.

Leo Stamatatos (Seattle Biomedical Research Institute) has put together a unique collaboration of HIV scientists and experts in computational protein design from the University of Washington (lead by Bill Schief) to engineer novel protein immunogens in which different non-HIV protein scaffolds are used to optimally present HIV epitopes to the immune system. Dr. Stamatatos’s team is also isolating additional neutralizing MAbs from HIV subtype B, which will complement those obtained by other investigators. The computational design expertise of this group could be of value to other groups working on the design of epitope-based vaccines for the induction of neutralizing antibodies.

The VDC lead by Bart Haynes (Duke University) builds on the already mentioned observation that some of the broadly neutralizing MAbs against HIV (such as 4E10 and 2F5) are poly-specific antibodies that also recognize human (“self”) proteins and are sometimes present in different autoimmune diseases. Their goal is to acquire proof of concept data that manipulation of the immunoregulatory controls of B cell immune responses to HIV-1 Env, coupled with enhanced immunogen design, can lead to safe induction of broadly reactive neutralizing antibody responses. To do this they are using a two armed approach to the problem of induction of antibodies that broadly neutralize HIV: one strategy is to develop immunogen formulations that trigger B cells normally tolerant to the desired envelope epitopes and regions, and the other is to develop immunogens that are more native and will preferentially induce the desired antibody types. Although most investigators are trying to identify conserved HIV epitopes that can induce broadly neutralizing antibodies (including the above three VDCs lead by Drs. Weiss, Stamatatos, and Haynes), two VDCs are exploring different and novel approaches to the induction of neutralizing antibodies against HIV.

The VDC lead by Susan Zolla-Pazner (New York University) is assessing the potential use of the third hypervariable region of the major envelope protein of HIV (the V3 loop of gp120) as a vaccine candidate. Although the HIV-1 V3 loop is highly immunogenic, its extreme genetic variability (and inaccessibility in the envelope protein) has precluded its use as a potential candidate vaccine. This project is somewhat outside of the current HIV vaccine paradigm and is based on preliminary observations suggesting that despite its genetic variability, the V3 loop exhibits functional and structural conservation that translates into immunological similarities which could be harnessed to develop a practical HIV vaccine.
Thomas Lehner (Kings College London) and collaborators are systematically exploring the role of alloimmunization (immunization with “self” HLA proteins) as a potential approach for HIV vaccine development, including protection experiments in non-human primates (NHP). This project builds on previous clinical, epidemiological and experimental observations suggesting that immune responses against host proteins can play a role in preventing HIV infection.

Six CAVD teams are addressing the challenge of developing better approaches to inducing cell-mediated immunity. Three of these VDCs focus on the improvement of viral vectors that are currently being explored as potential candidate vaccines for HIV, namely non-replicating adenovirus and poxvirus vectors. The VDC lead by Norman Letvin (Harvard Medical School) is designing novel candidate vaccines that circumvent pre-existing immunity against two potential HIV vaccine vectors (adenovirus and *Mycobacteria*). This group is constructing a series of chimeric adenovirus vectors, combining components from different adenovirus serotypes which will hopefully maintain the vaccine immunogenicity of the Ad5 vector while eliminating its susceptibility to neutralization from pre-existing naturally occurring antibodies (complementary work is supported by NIAID and close coordination has been established). The second component of this project will explore novel BCG and *Mycobacterium smegmatis* vectors to further assess the potential use of novel mycobacterial vectors for HIV vaccine development.

Steven Patterson (Imperial College London) and coworkers are testing a novel ‘stealth’ adenovirus vector vaccine based on Ad5 and Ad11 that is formulated with a polymer shield to evade pre-existing natural immunity to adenoviruses. The vaccine will be designed to elicit both systemic and mucosal immunity, enhancing antigen delivery to DCs in the skin via a topical patch delivery device as well as through the use of a novel adjuvant. Giuseppe Pantaleo (Centre Hospitalier Universitaire Vaudois) has assembled a VDC of largely European investigators focused on improving current poxvirus vector vaccines aimed at generating cell-mediated immune responses. Poxviruses (including different strains of the vaccinia virus such as MVA, as well as the avian canarypox viruses) have been used in different constructs of HIV vaccines, with mixed results. Dr. Pantaleo’s group is conducting a systematic study of these poxvirus vectors to bring forward “best-in-class” constructs and combinations for clinical evaluation. The group is exploring different modifications in the genetic backbone of the poxvirus vectors, different ways to improve antigen expression, and the capacity of different vectors to trigger innate immune mechanisms.

Timothy Zamb’s (IAVI) VDC is developing and will study in NHP a range of less explored viral vectors that are not currently being used in clinical trials of HIV vaccines, including recombinant vectors based on adeno-associated virus (AAV), avian Newcastle Disease Virus, reovirus, and chimeric constructs of HIV and Venezuelan Equine Encephalitis virus (VEE) or Vesicular Stomatitis Virus (VSV). This is a collaborative project with IAVI in which selected candidate vaccines will be tested in large NHP experiments using a low-dose mucosal challenge model to determine a rank order of efficacy. Two additional VDCs deal with more upstream aspects of vaccine development. David Ho (Aaron Diamond AIDS Research Center) and his coworkers are exploring approaches to designing second-generation vaccines tailored to present HIV antigens to DCs to enhance the level and duration of immune response. After interacting with an antigen, DCs mature and migrate to the lymphoid tissues, where they communicate with T- and B-cells to initiate and shape the immune response.

Julie McElrath (Fred Hutchinson Cancer Research Center) is systematically exploring and comparing how various adjuvants and vectors stimulate innate immunity, including attempts to obtain in vitro markers of in vivo function. Innate immunity refers to the non-specific mechanisms by which pathogens are recognized and responded to by the
immune system, mostly mediated by different Toll-Like Receptors (TLRs). It is increasingly recognized that different adjuvants and vectors work through stimulation of different TLRs, and these studies promise to bridge the gap between innate and adaptive immunity (represented by the humoral and cell-mediated responses to specific antigens). If successful, this type of information would potentially benefit the whole field of vaccinology.

As mentioned earlier, five Central Service Facilities (CSF) provide scientific support to the 11 VDCs of the CAVD network. Two CSFs are “Vaccine Immune Monitoring Centers” (VIMCs) which focus on standardized and comparative evaluations of either humoral or cell-mediated immune responses and one is a “Mouse Immunology Laboratory” (MIL), to guide preclinical development of candidate vaccines (the Laboratory Standardization facilities of the CAVD will be described in the next section of this report).

The CAVD also established a Vaccine Immunology Statistical Center (VISC) and a HIV Specimens Cryorepository (HSC). The VISC is lead by Steve Self (Fred Hutchinson Cancer Research Center) and it is developing a robust web-based interface to support the efficient sharing and analysis of data and a state-of-the-art Vaccine Immunology Data System for the creation of common data standards to facilitate efficient data-sharing and management of data emanating from the work of the CAVD (including both preclinical and clinical studies). Likewise, the VISC provides a data management and statistical consultative service that supports the establishment of IT and data management systems infrastructure for the CAVD, as well as high-quality statistical support for pre-clinical and clinical study design and analysis. Through SCHARP (The Statistical Center for HIV/AIDS Research & Prevention) Dr. Self provides a strategic data and statistical analysis link with other HIV vaccine programs such as the NIH-sponsored HIV Vaccine Trials Network (HVTN) and CHAVI. Hagen von Briesen (Fraunhofer Gesellschaft, Institute for Biomedical Engineering) is the PI of the cryobank and repository for the storing and distribution of materials generated by the CAVD including, as appropriate, clinical samples and virus strains, reagents developed by vaccine discovery centers (e.g. hybridomas, clones, peptides), and samples from preclinical and clinical trials of HIV candidate vaccines. This CSF also focuses on the development of novel cryopreservation techniques to further optimize the quality of long-term storage for these highly valuable research samples and reagents.

In addition to the original CAVD projects described above, the Gates Foundation is supporting other relevant HIV vaccine research projects, including several Grand Challenges in Global Health projects, and will continue identifying new areas in need of support. In this regard, in May 2006, the Gates Foundation awarded a grant to the Elizabeth Glaser Pediatric AIDS Foundation to develop and test candidate vaccines to prevent HIV infection in children.

**INTERNATIONAL AIDS VACCINE INITIATIVE**

IAVI supports the design, development, and clinical evaluation of HIV vaccine candidates applicable for use in developing countries through a range of partnerships and agreements with more than 40 academic, biotechnology, pharmaceutical, and government institutions around the globe. To accelerate the discovery and development of promising HIV vaccine candidates, IAVI has established an *AIDS Vaccine Development Laboratory* in Brooklyn, New York. This laboratory is closely linked to IAVI’s AIDS Vaccine Consortium, a network of laboratories focused on solving key scientific problems impeding HIV vaccine development. The laboratory consists of three interlinked programs: vector design, protein, and medicinal chemistry and pre-clinical core immunobiology. The Vector Design group systematically creates, tests and prioritizes novel vectors with the goal of advancing the most promising candidates to clinical development. In 2006 the Vector Design Group initiated activities to establish parameters for assessing
promising new vectors against current leading candidates (e.g., DNA, Adenovirus) and gold standards (e.g., live attenuated). The goal of the Protein/Medicinal Chemistry group is to create HIV surface proteins and peptides to stimulate production of antibodies capable of neutralizing the broad spectrum of HIV isolates circulating worldwide. The Protein Group also serves as a resource for the IAVI-sponsored Neutralizing Antibody Consortium (NAC), and has begun purification of reagents to support the organization’s scientific program. The Preclinical Core Immunobiology Lab assesses the immunogenicity and efficacy of vaccine candidates by creating standardized trials and rigorously-controlled in vivo assays.

IAVI’s AIDS Vaccine Consortium (AVC) is a program of three consortia, each focused on solving critical scientific challenges. In 2006, the NAC was expanded and focused its efforts on: characterization of broadly neutralizing sera; identification of new broadly neutralizing MAbs; determination of structure of MAb-Env complexes; and immunogen design. Achievements included initiation of a protocol to identify broadly neutralizing sera, characterization of broadly neutralizing sera with intensified focus on the CD4 binding site, and the production and screening of first-generation carbohydrate and scaffold immunogens. As mentioned earlier, IAVI established a Cooperative Research and Development Agreement with the NIH’s VRC, the first of its kind with a not-for-profit agency. The cooperative agreement brings additional research expertise to the consortium to accelerate the design of immunogens to elicit broadly neutralizing antibodies. IAVI and The Scripps Research Institute jointly purchased their own fully-integrated and automated crystallography platform that enables rapid and consistent protein crystallization. This robot will accelerate and optimize the NAC’s HIV vaccine development initiatives by dramatically improving the efficiency and speed of HIV envelope protein structural studies. Systematically determining the molecular crystal structures of HIV envelope proteins that induce neutralizing represents a significant bottleneck in the overall effort (complementary studies are being conducted by the VRC and the CAVD). IAVI also developed an agreement, in conjunction with the Indian Department of Biotechnology, to launch a program for high throughput antigen design modeled after those found in the pharmaceutical industry.

IAVI’s Live Attenuated Consortium (LAC) was established to determine how the human body can control HIV and the mechanism of protection conferred by live attenuated SIV and to translate these findings into vaccine design. Through a series of focused research questions geared to inform vaccine design, the LAC is structured to elucidate the mechanism of efficacy of live-attenuated SIV in the non-human primate model including which antigens are necessary for protection, and what is the mechanism by which a live-attenuated SIV vaccine protects against SIV challenge in non-human primates. IAVI also established a collaboration with Bruce Walker (Harvard University) to develop more effective assays to assess cell mediated immune responses and to utilize these assays in the evaluation of “elite controllers” to determine which antigens are required to control HIV in humans.

IAVI’s Vector Consortium was initiated in 2006 for the systematic prioritization of vector-based vaccines that elicit persistent and mucosal immune responses. Vectors under study include paramyxovirus, reovirus, cytomegalovirus, adeno-associated virus and chimeric viruses. A subset of IAVI’s Vector Consortium is supported by the Gates sponsored CAVD (through the VDC led by Timothy Zamb).
EUROPEAN COMMISSION

The EC promotes and funds European-wide collaborative efforts to develop an HIV vaccine and calls on the Member States to coordinate their national research policies. Some of the projects supported by the EC include: DC-targeted vaccines, recombinant measles virus as a vector for HIV vaccines, generation of broadly cross-neutralising antibodies for innovative active-passive HIV vaccination strategies based on modified Ig-gene transgenic mice, exploration of innovative and promising vaccine delivery systems and adjuvants, newly developed technologies to improve DNA vaccination against HIV, induction of mucosal immunity including adsorption of antigens on biodegradable PLA micro-particles in order to strengthen uptake and presentation by antigen-presenting cells, studies of HIV-positive individuals who do not progress to AIDS, as well as several relevant highly innovative projects aimed at developing new viral vaccine vectors by harnessing knowledge obtained from basic immunology.

The EC has recently published a call for proposals to finance large collaborative research projects aimed at designing HIV immunogens that can induce broadly reactive neutralizing antibodies, combining vectors, immunogens and adjuvants. The projects could also address standardized measurement of immune responses, identification of correlates of protection, appropriate animal model testing, preclinical validation, and proof of principle testing in humans. The evaluation process is ongoing and decisions are expected before the end of the year.

WELLCOME TRUST

In the area of HIV vaccine discovery, the Wellcome Trust supports a number of projects relevant to the priorities identified in the Enterprise SSP. Researchers at Imperial College London are working on a project which aims to characterize T cell mediated immune responses in groups of HIV-1 infected individuals in whom differences in the ability to control VL are reflected by discordant T cell mediated responses. These studies will aid the development of therapeutic strategies to control and ‘steer’ T cell responses towards a desired phenotype. Another investigation being carried out at the Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, South Africa is looking at whether or not T cell responses at the cervix of HIV-infected women differ from those present in the blood during early and established infection. The comprehensive approach outlined in this project and the development of methodologies to evaluate genital T cell responses against HIV will be useful in the understanding of virus transmission and in future HIV vaccine studies. Another team at the National Institute for Virology in South Africa is studying the HIV-1 subtype C, the predominant HIV-1 subtype in South Africa, to better characterize and understand how HIV-1 subtype C viruses enter human cells. Additionally, immunogenic sites within HIV subtype C will be identified that are able to elicit neutralizing antibodies against primary isolates. This information will then be used to assist in the design of candidate vaccines that are being designed specifically for use in regions where HIV-1 subtype C circulates.

Investigators at the National Institute for Communicable Diseases in South Africa are carrying out a study to characterize immune capability in mother and infants, to assess alterations in numbers and immunophenotypes of specific innate and acquired immune cell subsets, and to analyze HIV-specific (acquired – CD4 and CD8 T cell) and non-specific (innate – natural killer cell) immune responses in HIV-1 infected mothers and their infants at birth and at six weeks post-delivery. Understanding maternal influences on cellular immune capacity of the infant is important as this will contribute to further characterizing protective immune processes in the infant, providing essential information for the rational design of HIV-1 vaccines, and will help to define cellular immune alterations in the HIV-1 exposed uninfected infants that may affect responses to antigenic challenge in early and later life. This study will therefore provide much

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needed baseline data on uninfected and HIV-1 infected mothers and infants that will also contribute to the future study of other infectious agents or vaccines in early infancy, and will serve to inform decisions around maternal immunization strategies and vaccination strategies (HIV-1 or other) for the newborn.

The Wellcome Trust is currently co-funding a research program with the Bill & Melinda Gates Foundation, as part of the Grand Challenges for Global Health initiative. This project has a large consortium which includes St George’s, University of London (lead Institution), Imperial College London, Universities of Oxford and York, Queen’s University Belfast, NIBSC and a number of biotechnology companies in the US (Particle Sciences) and Europe (Polymun Scientific). The research proposes to develop novel strategies for repeated and/or sustained vaccine delivery to the vaginal mucosa. The project is based on the hypothesis that sterilizing immunity at the site of HIV entry will be required for protection, as immunological memory will not be sufficient. To this end the goal of the project is to develop a low-cost vaginal gel or silicone ring that can be used for vaccine delivery, that can be self administered, and available to developing countries.

**FRENCH NATIONAL AGENCY FOR RESEARCH ON AIDS AND VIRAL HEPATITIS**

For over 15 years the ANRS has been committed to a research program on HIV vaccines that covers all experimental fields: upstream research for the definition of immunogens, animal research, and clinical research to evaluate candidate vaccines. Since 1994, the ANRS has been developing an epitope-based vaccine strategy with the use of lipopeptides which consist of large synthetic HIV peptides coupled with a lipid tail and designed to induce cell-mediated immune responses. The new stage in the ANRS vaccine research program calls for increased resources to harness opportunities generated by recent scientific advances, responding to the need to adapt ANRS vaccine research to the latest challenges. A key issue is the transition from empirical approaches to the formulation of questions that emerge from knowledge acquired in various fields of vaccine development. Areas that will be explored by the ANRS include: evaluation of *in vitro* and *in vivo* in non-human primate models of the immunogenicity of lipopeptides alone or combined with recombinant vectors, the identification of innate immunological correlates of protective immunity, and development of a vaccine approach targeting HIV antigens to DCs using recombinant antibodies to DC receptors.

**AIDS VACCINE ADVOCACY COALITION**

AVAC continues to play an active role in communicating about the Enterprise and the field at large, especially to civil society partners around the world. The 2006 AVAC Report *Understanding the Cosmology of the Global HIV Vaccine Enterprise* included an update on the Enterprise and diagrams to show the relationships between Enterprise partners, especially with the new funding streams of NIH’s CHAVI and the Gates Foundation’s CAVD. The focus of this report was to describe the vaccine discovery and laboratory standardization components of the Enterprise and how the new funding mechanisms would contribute to them.

### 2.2. Laboratory standardization

In the early stages of research, vaccine candidates are judged on their ability to stimulate immune responses in animals and humans. However, the laboratory assays that researchers use to assess immune response may not be comparable, severely hampering decisions about which candidates to pursue for further testing. In addition, new knowledge about the immune response to HIV is raising concerns that current assays overlook important aspects of those immune responses.
The Enterprise SSP recommends that current efforts to standardize how laboratories conduct assays for measuring cellular immunity are expanded and extended to neutralizing antibody assays, with the ultimate goal of an international network of standardized laboratories. The plan also proposes that new research efforts be launched to create new immune response assays, and to test whether these assays can help researchers more accurately assess vaccine candidates’ promise.

**NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES**

NIAID has made several contributions to the Enterprise SSP’s laboratory standardization goals. The PAVE Laboratory Working Group has collaborated to develop a peripheral blood mononuclear cell (PBMC) program, as consistent quality of PBMCs is of critical importance to the detection of cellular immune responses in immunogenicity assays such as ELISpot and ICS (Intracellular Cytokine Staining) (Bull et al., 2007). The PBMC Quality Program is designed to monitor training, competency and quality for PBMC cryopreservation, and the critical elements of this program have been adopted by PAVE partners. NIAID/VRC is developing the NIAID Vaccine Immune T Cell and Antibody Laboratory (NVITAL, operated by Henry Jackson Foundation) to perform state of the art end-point immunogenicity tests from specimens obtained from HIV vaccine clinical trials. This facility receives funds from the Bill & Melinda Gates Foundation as part of the CAVD consortium lead by Richard Koup, to provide capacity to perform cross-trial comparisons of various candidate vaccines from global partners using standardized methodologies.

There are multiple organizations conducting HIV-1 vaccine trials globally. In the current absence of a single central laboratory to perform endpoint assays, it is imperative that the data from multiple laboratories can be compared to inform product advancement decisions. This will require standardized assays, common reagents and SOPs and Good Clinical Laboratory Practice (GCLP) guidelines to measure and monitor laboratory performance. Toward this goal, DAIDS has established External Quality Assurance (EQA) programs for the ELISpot, ICS, and Ad5 neutralization antibody assays to compare proficiency across multiple laboratories. DAIDS has also developed GCLP guidelines to share with partner organizations. DAIDS supported researchers generated standard virus panels for measuring neutralizing antibodies against HIV-1 by constructing pseudoviruses containing cloned envelope genes from subtype B and C viruses. These panels make it possible to compare neutralizing sera from any vaccine trial.

**BILL & MELINDA GATES FOUNDATION**

As mentioned previously, the VDCs that are part of the Gates Foundation sponsored CAVD are supported by three CSFs that provide standardized evaluations of immune responses induced by the candidate vaccines they develop. One of the two CAVD’s Vaccine Immune Monitoring Centers (VIMCs), lead by David Montefiori (Duke University) focuses on humoral (antibody) immune responses. This international network of collaborating laboratories is in the process of optimizing and standardizing the best laboratory assays for general distribution and use in comparing different pre-clinical and clinical vaccine platforms. This VIMC will also establish systems for proficiency testing, quality assurance, centralized provision of reagents, and training support. The second CAVD’s VIMC, lead by Richard Koup (Foundation for the National Institutes of Health and Vaccine Research Center) is focusing on cell-mediated immune responses. Its international network of collaborating laboratories is optimizing assays for comparative vaccine evaluation, as well as establishing systems for proficiency testing, quality assurance, centralized provision of reagents, and training. They will also develop and validate novel and more relevant laboratory assays to quantitatively measure cell-mediated immune response.
responses to candidate vaccines. Finally, Phil Greenberg (University of Washington) has established a Mouse Immunology Laboratory (MIL) to provide a service to the VDCs working on candidate vaccines that induce cell-mediated immunity, developing and utilizing novel and sensitive mouse models to quantitatively evaluate the immunogenicity of candidate HIV vaccines, with the ultimate goal of providing additional accurate screening information to determine what vaccines and formulations should be selected for testing in non-human primates and humans.

**INTERNATIONAL AIDS VACCINE INITIATIVE**

IAVI’s Human Core Laboratory in the UK was selected as a central core laboratory, leading assay validation, standardization and laboratory certification for the Gates Foundation sponsored CAVD. The Immunobiology Laboratory at the IAVI AIDS Vaccine Development Laboratory is closely linked to IAVI’s Human Core Laboratory, and will provide standardized reagents and assays to ensure preclinical immunogenicity studies are in synergy with clinical studies. In 2006, the group established and standardized assays across collaborators in the IAVI’s AIDS Vaccine Consortium.

**WHO-UNAIDS**

Over the period of 2004-2007, the WHO-UNAIDS HIV Vaccine Initiative (HVI) facilitated the implementation of a European Union-sponsored NeutNet Project on comparative evaluation and standardization of HIV-neutralization assays. The project successfully concluded producing important scientific results and recommendations on the performance of various assays suitable for use in HIV vaccine trials (to be published).

### 2.3. Product development and manufacturing

Once researchers have identified a vaccine design that is believed to be promising, a critical phase of vaccine research is developing a manufacturing process that yields consistent batches for clinical trials and is practical and affordable for eventual large-scale production. Manufacturing issues are particularly challenging for HIV vaccines—and may require different technologies depending on the nature of the vaccines. While a number of HIV vaccine candidates have been successfully manufactured in small batches for trials, the production processes are complex or cumbersome, and may not be optimal for large scale production capable of meeting global needs.

The Enterprise SSP calls for creating a network of vaccine manufacturing experts to engineer improved HIV vaccine production processes; these experts would be closely linked to vaccine discovery consortia and clinical trial sites. Such an effort will be particularly important as more HIV vaccine candidates are discovered and advance through clinical trials. Private industry involvement in such a network is critical, because most vaccine manufacturing expertise resides in the private sector.

**NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES**

The VRC’s Vaccine Production Program (VPP) carried out significant process development research, including development of novel viral vectors, formulation, delivery, and manufacturing process research, as well as analytical development research including development of potency assays for candidate vaccines. The VRC’s VPP completed
the Vaccine Production Plant, developed cGMP manufacturing capability, produced Phase II and Phase IIb clinical material, and continued development of procedures to scale-up production.

DAIDS supports a diverse product development pipeline, including support for HIV vaccine production, all IND-required preclinical studies, and IND preparation and submission. DAIDS helped advance 11 products into phase I trials in 2005-2006. This includes DNA-, peptide-, protein-, MVA-, and vaccinia-based products developed by ABL, Therion, St. Jude's Children Hospital, Wyeth, Epimmune, and GeoVax.

BILL & MELINDA GATES FOUNDATION

In February 2007 a partnership was announced between the Gates Foundation and the Government of Canada to support the Canadian HIV Vaccine Initiative, a new effort to accelerate the development of an HIV vaccine and to address critical research gaps identified by the Enterprise. This initiative will support Canadian researchers and institutions to work with collaborators around the world, including in developing countries, on a range of HIV vaccine research activities, including: discovering new vaccine candidates, strengthening clinical trials capacity, manufacturing promising vaccine candidates for trials, and addressing policy, regulatory, and social issues related to HIV vaccine development. Discussions are underway to define more specifically how this initiative will address the recommendations made in the Enterprise SSP in relation to product development and manufacturing.

INTERNATIONAL AIDS VACCINE INITIATIVE

IAVI currently has a diverse product development pipeline with five different candidates in clinical trials, including AAV vectored vaccines, MVA vectors alone or in combination with DNA, and a collaboration with the VRC to participate in the evaluation of the VRC’s DNA+Ad5 candidate clinical trials in developing countries. Regulatory meetings in Europe and the US were held with these candidates in order to prepare for IND submission. In order to effectively develop and manufacture adenoviruses for clinical trials, IAVI licensed the HER cell line (AdVac® technology) from Crucell. In 2006 IAVI completed characterization of this cell line and received favorable regulatory feedback from the US FDA.

FRENCH NATIONAL AGENCY FOR RESEARCH ON AIDS AND VIRAL HEPATITIS

The ANRS is currently developing, in collaboration with Transgene, a recombinant MVA vector coding for clade B HIV-1 epitopes homologous to those contained in lipopeptide formulations. This vector will be tested in phase I/II, alone and in combination with HIV LIPO-5 vaccine in 2008. A collaboration between ANRS and Eurovacc consortium was launched in 2007 to accelerate the development of DNA and recombinant NYVAC vectors. In addition to the development of new products (MVA vector, fusion protein that targets DCs), experiments have been conducted by ANRS in order to improve the production yields for the synthesis of LIPO-5. A new process has been developed that enables large scale production.
2.4. Clinical trials capacity

Three phases of clinical trials in humans are required to fully test a vaccine candidate. Large scale trials must be conducted in the populations that would eventually use the vaccine. For HIV, this means conducting trials both in industrialized and developing countries (95% of new HIV infections occur in developing countries).

A number of developing countries have participated in small-scale phase I/II trials of HIV vaccine candidates to test safety and immunogenicity, and Thailand has participated in two of the four large-scale phase IIB and III trials initiated to date. Many countries, however, lack sufficient infrastructure to conduct HIV vaccine trials, especially large-scale trials; far more capacity will need to be developed to support a growing number of future trials, some potentially requiring thousands of participants.

The Enterprise SSP proposes the development of a network of training centers in developing countries to provide technical assistance in the following areas:

- Enhancing research infrastructure, including trial sites and laboratories,
- Training and supporting qualified staff,
- Educating the public about vaccine trials to help with recruitment of informed study participants,
- Ensuring coordination with the medical systems that provide prevention, care and treatment services to people in communities where trials will take place,
- Developing HIV vaccine trial sites that can also be used to test other new HIV prevention technologies, such as anti-HIV microbicides, as well as other biomedical interventions relevant to the host communities.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

In 2006, NIAID made awards to the leadership groups of six new HIV clinical trials networks, and earlier this year awards were made to the clinical trial units of these networks. Notably, the new networks were designed to encourage the development of research sites with the capacity to do research in multiple areas, as had been suggested in the Enterprise SSP. Three studies to evaluate safety and immunogenicity of the VRC DNA prime and Ad5 boost strategy were launched in Africa and the Americas by the HVTN, the US Military HIV Research Program, and IAVI, sponsored by DAIDS. This triad of studies is significant to the Enterprise because it represents the first multi-group cross-harmonization of protocols. NIAID is facilitating the collaboration of four partners, integrating their sites on three continents in 12 countries under a single protocol (PAVE 100, currently in the planning stages), which is the product of the partners’ joint intellectual, technical, and logistic contributions. This partnership hopes to execute a large phase IIB study spanning diverse populations, sponsored by DAIDS. The expansive and integrated capacity needed for the trial was achieved through the cooperation of the partners and their mutual flexibility and willingness to serve in a united effort, often providing complementary components. The PAVE Site Development Working Group developed a standardized tool for surveying HIV vaccine trial sites according to a set of required and desired “critical elements” for efficacy trial preparedness and used it to assess the readiness of the PAVE partners’ international sites.
INTERNATIONAL AIDS VACCINE INITIATIVE

Over the last five years IAVI has established clinical trial sites and capacity in developing countries, resulting in the conduct vaccine clinical trials and laboratory work. IAVI has proven that high quality clinical trials can be completed in resource poor settings. IAVI conducts clinical research at the sites to prepare for efficacy trials as well as to inform vaccine design. In this regard, IAVI is conducting five different studies to prepare for future HIV vaccine trials in Africa. One study evaluated the HIV prevalence among 6532 volunteers at four sites in Kenya and Uganda. Another study, conducted at seven sites in Kenya, Rwanda, South Africa, Uganda and Zambia studied HIV incidence and volunteer retention, including heterosexual transmission in HIV-discordant couples. IAVI is also implementing a multi-center study of HIV early and acute infection and the evolution of both virus and immune response. Another study is defining laboratory reference ranges research study for hematology and biochemistry values, information which will benefit the whole field as traditional clinical trial reference ranges are based on western ranges of health normal volunteers. IAVI is also screening HIV infected volunteers who remain healthy after at least three years of infection, with the goal of identifying those individuals with broadly neutralizing antibodies to HIV for further investigation by the NAC.

EUROPEAN AND DEVELOPING COUNTRIES CLINICAL TRIALS PARTNERSHIP

To address the urgent need for developing and preparing sites to conduct HIV vaccine trials in countries seriously affected by the epidemic, EDCTP and the Gates Foundation announced in December 2006 a joint call for proposals to fund capacity building for HIV vaccine trials in sub-Saharan Africa. This call is part of the collaborative effort proposed by the Enterprise, and its initial focus is for the preparation of phase II clinical trials of HIV candidate vaccines, but where appropriate, it may also be used to conduct other trials. The call requested specific research plans (which could include non-HIV vaccine projects) a capacity building plan, including a description of training activities, upgrading of infrastructure activities and networking activities and a consortium of competent investigators committed to the project. Decisions about specific projects to be funded will be made by the third quarter of 2007.

The South African Medical Research Council-Cochrane Centre received an EDCTP grant for the establishment of an international registry of randomized clinical trials focusing on HIV/AIDS, TB and Malaria in Africa. This "ATM registry" is the first clinical trials database in Africa, and will serve as an important global resource for researchers, clinicians, policy makers, and the lay public. The database provides reliable information on the efficacy and safety of prevention and treatment measures. It identifies research gaps that should be addressed in future trials and it provides a ‘laboratory’ for studying the scope, quality and funding patterns of trials. It also keeps track of on-going trials.

With regards to capacity building for ethical review, EDCTP launched in 2005 and 2006 two calls for proposals to support courses and seminars on ethics and support for the establishment and the strengthening of African National Ethics Committees or Institutional Review Boards.

WHO-UNAIDS

The WHO-UNAIDS HVI provides continuous technical advice and guidance to low- and middle-income countries, producing policy documents and providing comments on submitted protocols for the conduct of HIV vaccine trials. Examples of recent policy issues addressed by WHO-UNAIDS include: Novel strategies for HIV vaccine trials (Phase IIB-TOC) (WHO/UNAIDS/IAVI International Expert Group, 2007); Access to care & treatment in vaccine trials (Tarantola et al, 2007); Strategies for involvement of adolescents in HIV vaccine trials (AIDS, in press).
In March 2007, HVI, in collaboration with the Enterprise, convened a consultation on “Preparing for vaccine efficacy results”, which was attended by key stakeholders and representatives of the current phase III trial in Thailand (Sanofi Pasteur canarypox with VaxGen rgp120 boost) and two Phase IIB trials (Merck Ad5 vaccine). The final report contains recommendations and a framework of priority activities to be implemented within next 6-12 months. One of the key recommendations was to establish an ad-hoc Enterprise Coordinating Group (in collaboration with WHO/UNAIDS) to begin preparing for the eventual release of HIV vaccine efficacy trial results (the current members of the Coordinating Group are listed in Appendix 1). The specific tasks proposed for this Group include: communicating among the trial sponsors to become informed of potential results scenarios, supporting partners in identifying communications needs and managing post trial expectations, facilitating dissemination and understanding of trial results when they become public, facilitating information exchange among partners of different trials to optimize clarity of trial communications and results, and supporting developing country efforts to develop post trial plans.

Since 2000, WHO and UNAIDS have provided technical guidance and support for the development and functioning of the African AIDS Vaccine Programme (AAVP), a network of African scientists and communities working together to promote and facilitate HIV vaccine research and clinical trials in Africa through capacity building and regional and international collaboration. AAVP’s key highlights in 2006-2007 include: (a) conduct of the AAVP Forum (November 2006, Yaoundé, Cameroon), with subsequent printing and widespread distribution of the meeting report and the Yaoundé Statement which explicitly supports the Enterprise; (b) development of a new Five-Year Strategic Plan for 2007-2011; and (c) tendering for and selection of four AAVP Resource and Coordinating Facilities/Centres in Africa. In November 2006, HVI supported organization of a consultation in Sapporo, Japan on “The development of a regional HIV vaccine trial network in Asia” (Report to be published).

Eight capacity building training workshops were supported by HVI on the preparation and conduct of HIV vaccine trials in low- and middle-income countries, focusing on ethics and regulatory aspects, laboratory technologies, Good Clinical Practice, mathematical modelling, and media communications. Three countries were supported in the development of their National AIDS Vaccine Plans (Cameroon, Rwanda, and Tanzania).

HVI continued providing support for the implementation of a project on “Future access, mathematical modelling, and public health use of HIV vaccines” with participation of five low- and middle-income countries (Brazil, Peru, Kenya, China, and Thailand). The project included the development of the VacSim model, a practical manual and training workshops targeting application of this model by public health experts. IAVI has collaborated in the implementation of a number of activities within this project.

WELCOME TRUST

Scientists at the Wellcome Trust’s Centre for the Epidemiology of Infectious Diseases at Oxford University are developing a cost-effectiveness analysis (CEA) framework for HIV-1 prevention, vaccination, and AIDS combination therapy. The general objective of this proposal involves the elaboration of a CEA framework to assess and compare the costs and impacts of different HIV/AIDS prevention and treatment strategies. Firstly, the authors evaluated competing strategies for HIV prevention via STD control and for comparing different ARV combination therapies. Additionally, the CEA framework will also be developed to consider HIV prevention through different possible HIV vaccination programs. It is thought that by developing the CEA framework for HIV prevention and ARV treatment programs, current knowledge gaps can be identified and filled, where appropriate, with the view to standardize approaches for CEA to facilitate
comparisons across competing strategies, and to foster the collection of epidemiological, clinical and costing data necessary to execute CEA of HIV/AIDS interventions with confidence.

**FRENCH NATIONAL AGENCY FOR RESEARCH ON AIDS AND VIRAL HEPATITIS**

Over the last three years, ANRS has extended the number of clinical trial sites in France with standardized procedures for phase I and II clinical trials and the recruitment of healthy volunteers. Over the last 10 years, ANRS has established clinical trial sites and has built capacity in developing countries for laboratory work. This has allowed ANRS to conduct clinical trials in the field for ARV treatment (first line, second line), prevention of mother to child transmission, and on the impact of circumcision on HIV transmission. In collaboration with developing countries and local investigators, ANRS has proven that high quality clinical trials can be completed in resource-poor settings. Discussions within the ANRS network of clinical sites in developing countries (Burkina Faso, Côte d’Ivoire, Senegal, Cameroon, Vietnam, Cambodia, Brazil) are starting in preparation for phase I and large phase II clinical trials. The partnership will commence with an upstream review of regulatory considerations, ethical questions, local politics, and benefit-to-risk considerations in vaccine trials.

**AIDS VACCINE ADVOCACY COALITION**

AVAC worked closely with the UNAIDS Secretariat to convene a working group to develop draft “Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials.” In 2004, AVAC developed the “Correlates of Readiness” as a checklist of specific, quantifiable goals that trial networks, policymakers, and communities can use to determine readiness for the long road of vaccine development. These correlates include readiness for recruiting and retaining participants; manufacturing; long-term relationships with sites and communities; staffing and support; managing expectations; and collaboration. Consistent with the Enterprise, these correlates are aimed at building site capacity generally rather than preparing for specific trials. AVAC is now working with in-country civil society partners to validate and adapt these “correlates” as a tool for monitoring national vaccine activities, planning for the future and advocating for national prevention research plans.

During the International AIDS Conference in Toronto in July 2006, AVAC hosted a special satellite session entitled “Community Matters: Engaging, Mobilizing, and Sustaining Community Involvement in HIV Vaccine and Prevention Research” during which AVAC provided a platform for the Enterprise Interim Secretariat to present an update on the Enterprise to civil society partners and for the Enterprise to hear about community priorities and expectations. AVAC and the Enterprise Interim Secretariat also organized a community forum in the Global Village on “Everything you ever wanted to know about AIDS vaccines...”.

AVAC is currently developing terms of reference for the Communication Subgroup of the Enterprise Coordinating Group on Efficacy Trial Results (described earlier), for which AVAC will serve as convener. This group will prepare strategically for the complex communications challenges presented by large-scale trial results and ensure maximum information sharing across agencies, countries, and networks.
2.5. Regulatory capacity

National regulatory oversight of clinical trials is the cornerstone of safe and scientifically valid medical research. However, many developing countries lack expertise and well-defined processes for reviewing and approving clinical trials and assessing results—a critical roadblock for HIV vaccine research, given that many trials will need to be conducted in developing countries.

The Enterprise SSP calls for regulatory experts in industrialized and developing countries to share their experiences through training curricula and programs. Improving regulatory capacity would minimize bottlenecks in conducting clinical trials of HIV vaccine candidates, and accelerate licensing of vaccines that prove safe and effective.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

NIAID staff contributed to several international consultations on HIV vaccine trial regulatory processes and principles and provided technical assistance to vaccine developers and foreign officials in the area of vaccine trial regulations. DAIDS developed a paper outlining considerations for conducting HIV vaccine trials in adolescents and will soon complete another about vaccine trials in newborns.

INTERNATIONAL AIDS VACCINE INITIATIVE

IAVI believes that the clinical trial paradigm must change in order accelerate the development of an HIV vaccine. IAVI is piloting a model to accelerate the acquisition of preliminary efficacy data on vaccine candidates, thus allowing efficient use of resources and prioritization of candidates. In the Screening Test of Concept (STOC) trials model, preliminary efficacy data are yielded from trials of small numbers (360-600) in high-risk individuals. Early on 2006 IAVI hosted a WHO/UNAIDS workshop to develop consensus on how to use Test of Concept (TOC) trials as a tool in vaccine development, how to interpret them, and how to communicate to constituencies regarding these trials (WHO/UNAIDS/IAVI International Expert Group, 2007). A follow-up Enterprise meeting was organized in April 2007, to discuss issues related to clinical development of HIV vaccines, and the role of phase IIA, IIB, and III trials in the pathway to determining efficacy (see Section II of this report).

EUROPEAN AND DEVELOPING COUNTRIES CLINICAL TRIALS PARTNERSHIP

EDCTP, in collaboration with WHO, is involved in capacity strengthening of the national regulatory environment in various African countries through training and, where possible, by developing a common regulatory framework at the regional level. Key activities include:

- Regulatory pathways (both in-country and inter-country),
- Joint review of clinical trials applications,
- Joint inspection of clinical trials involving selected African National Regulatory Authority (NRA) managers,
- Establishment of the African Vaccine Regulatory Forum (AVAREF),
- Training on regulatory monitoring and inspection of clinical trials, and
- The Global Training Network (GTN) course on authorization and evaluation of clinical trials, targeting key African managers of NRAs, ethics committees and national immunization programs together with se-

**AIDS VACCINE ADVOCACY COALITION**

The purpose of AVAC’s regulatory advocacy project is to ensure that HIV vaccine trials are conducted safely, equitably and ethically and that there are no unnecessary regulatory roadblocks to rapid licensure and distribution. AVAC has submitted comments on a range of proposed and final regulations in the US and elsewhere, for example, to influence the development of protocols for clinical trials; to advocate for regulations permitting adolescent trials; to open access to government funded research; and to urge more rapid review of potential HIV prevention technologies. Copies of these documents are available on AVAC’s website.

### 2.6. Intellectual property issues

Researchers routinely seek patents and other intellectual property protections for their inventions. Intellectual property protections provide an important incentive for innovation by rewarding researchers and companies for their efforts. But if not properly managed, intellectual property protections can impede innovation by preventing researchers from sharing information and working together to solve major problems.

The Enterprise SSP calls on the HIV vaccine field to agree on intellectual property arrangements that balance the need to incentivize and protect individual researchers or companies, and the need to promote greater and more rapid sharing of information among scientists that can lead to potential breakthroughs in HIV vaccine research.

These may include agreements against litigation, mutually beneficial license and patent ownership arrangements, and legal counsel to Enterprise participants on patent and intellectual property issues. In addition, the plan recommends that intellectual property arrangements be used to recognize the important contributions of developing countries to HIV vaccine research—for example, by granting rights to affordable access to effective vaccines.

**NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES**

The CHAVI consortium is in the process of reviewing and revising its governing documents to ensure the integration of its science and the resulting intellectual property (IP) into the Enterprise efforts. Key to this is the harmonization of CHAVI’s strategy with the critical elements of the Global Access Policy proposed by the Gates Foundation (described below). Specific elements of the CHAVI strategy include:

- A requirement that global access be addressed in all aspects of IP management,
- A requirement that certain inventions of value to the Enterprise as a whole be made available for licensing only on a nonexclusive basis,
+ Recognition of the contribution of clinical samples, including those from developing countries, to CHAVI's research in the form of royalty sharing arrangements, and

+ The implementation of memoranda of understanding and similar agreements between CHAVI and other Enterprise stakeholders such as EuroCHAVI, the CAVD, and IAVI to facilitate the sharing of information and resources.

In addition, to ensure data accessibility to the rest of the HIV vaccine development community, CHAVI is making an effort to deposit online all CHAVI publications through PubMed Central and will provide access to all HIV sequence information through the publicly-accessible DAIDS-sponsored LANL HIV database.

BILL & MELINDA GATES FOUNDATION
A principal goal of the Gates Foundation in its funding of HIV vaccines (and of other of drugs, vaccines and diagnostics for neglected diseases) is to ensure that innovations (and related rights) are managed and public health solutions are optimized for the purpose of facilitating: (a) the broad availability of data and information to the scientific community; and (b) the access to affordable health solutions for the benefit of people most in need within the developing world. The Gates Foundation refers to this goal as achieving “Global Access,” and sees it as critical to accomplishing the fundamental objective of reducing health inequities in developing countries. To further these objectives, the CAVD grantees were each required to develop a global access strategy, in addition to including related global access commitments within their respective Collaboration Agreements. The strategy describes how Global Access will be achieved through the course of conducting the particular research project as well as in their structuring of subsequent product development activities. In addition, all of the CAVD grantees and their collaborators collectively entered into an unprecedented set of Data & Material Sharing Principles outlining and facilitating how the participating organizations will transfer materials and share data and information among the consortia and with the broader scientific community.

INTERNATIONAL AIDS VACCINE INITIATIVE
IAVI’s intellectual property strategy includes: (a) the licensing-out of key technologies to advance HIV research (such as the sublicensing of its HER96 cells to advance its new adenovirus vector research program into a phase 1 trial); (b) ensuring global access provisions as a part of all vaccine development programs; and (c) improving communications with HIV research collaborators (in this regard, IAVI has launched a new web site for all of the AIDS Vaccine Consortium researchers to use that will expedite the review of manuscripts, presentations, and patent disclosures).

AIDS VACCINE ADVOCACY COALITION
AVAC legal counsel participated actively in the IP Working Group that contributed to the Enterprise SSP. These ideas were subsequently expanded and published in AVAC’s 2005 Report, “Intellectual Property at the Crossroads” in which AVAC recommended modest, small steps that can help foster workable IP arrangements among the many groups involved in HIV vaccine research and development. AVAC subsequently met with key stakeholders to assess the relevance and applicability of implementing these steps and convened symposium along with the Center for Health Policy at Brooklyn Law School for legal practitioners, industry, drug access advocates, and academics to discuss IP collaboration. Various Enterprise partners participated in this session.
“The Enterprise model represents a new way for scientists to engage as a global community of problem solvers, sharing materials and information, and balancing collaboration with healthy competition.”
Section II: Enterprise Working Group Meetings On Key Scientific Issues

When the Enterprise SSP was being developed in 2004, those engaged in the process recognized that the SSP would require continuous revision and updating based on new scientific understanding and the work of partner organizations.

To help guide revision of the SSP, the interim Secretariat of the Enterprise convened three Working Groups to debate key scientific issues in HIV vaccine research (participants of these three Working Groups are listed in Appendix 2). This section summarizes the discussions and recommendations of these three Working Groups. Full reports of each of the workshops will be published in appropriate scientific journals.

1. Approaches to expediting HIV vaccine efficacy evaluation

The workshop on “Approaches to Expediting HIV Vaccine Efficacy Evaluation” was held in April 2007 and hosted in IAVI’s offices in New York. A major goal of the workshop was to increase cohesion among different clinical trial groups and vaccine developers regarding the designs and potential interpretation of results from different types of intermediate-sized vaccine efficacy trials that have been initiated or proposed.

The workshop mapped the different clinical trial designs onto different objectives and discussed a potential roadmap for the rapid advancement of promising HIV vaccines. The workshop, which was attended by 42 participants, was organized by Ripley Ballou (Co-Chair), Jerome Kim, Steve Self, Katharine Kripke, Pat Fast, and Nina Russell (Co-Chair).

The workshop included presentations and invited commentaries from 15 participants. The topics covered in the presentations included:

- Mapping of the primary trial objectives for different trial designs,
- Lessons learned from advanced phase malaria vaccine trials,
- Goals and objectives of test of concept phase IIB in contrast to phase III trials, and the sequence of trials leading up to a phase IIB,
- Goals and objectives of IAVI’s proposed comparative screening test-of-concept (STOC) trials, and the sequence of trials leading up to them,
- Statistical considerations for test-of-concept (TOC) trials,
- Adaptive trial designs: Bayesian approaches,
- Role of efficacy trial designs in the broader context of vaccine development programs,
- Efficiency and feasibility: Challenges to identifying appropriate cohorts and to planning, analysis, and coordination of information,
- Ethical challenges, and
- Regulatory considerations.
Previous workshops have addressed related issues, including the primary and secondary objectives of efficacy trials, potential endpoints for acquisition of HIV infection and disease progression, and the design and role of phase IIB TOC trials as part of an overall product development plan (WHO/UNAIDS/IAVI International Expert Group, 2007).

However, the landscape of HIV vaccine clinical trials has changed significantly since some of the previous efficacy trial workshops. There is a robust pipeline of candidate vaccines designed to stimulate cell-mediated immunity (CMI), including one in phase III and two that are in, or soon to be in, phase IIB trials, as well as a number of vaccines in earlier phases of development:

+ **Phase III** –
  - RV 144 - USMHRP/Sanofi canarypox + VaxGen rgp120 (final results 4Q09).

+ **Phase IIB** –
  - Merck adenovirus (Ad5) trials:
    - STEP (Merck V520-023/HVTN 502) (interim analysis 3Q07, final results 1Q09), and
    - Phambili (HVTN 503/Merck V520-026) (interim analysis 4Q08, final results 1Q10).
  - PAVE 100 – Vaccine Research Center (VRC) DNA + Ad5 (opens 2007, two interim analyses, final results in 1Q11).

All of this activity and the multiple possible clinical trial outcome scenarios require planning for the potential impact of results from ongoing trials and their effect on the design of future vaccine trials. Consequently, the workshop focused primarily on the potential design of efficacy trials that might follow the current or planned trials, including a proposal introduced by IAVI in their 2006 Blueprint to conduct STOC trials (IAVI, 2006).

The following questions were posed to frame the broader discussion: If the current class of T cell vaccine candidates has a moderate effect on VL set point, how do we continue to optimize this approach while we are waiting for the next major improvement with a better T cell vaccine or a neutralizing antibody-inducing vaccine? How do we make decisions about the value of incremental improvements in vaccine candidates without exhausting major resources?

The ongoing Merck Ad5 vaccine trials were discussed as an example of the differences between phase IIB TOC and phase III trials. Phase IIB TOC trials are intended as an initial assessment of efficacy in the face of substantial uncertainties (for example, about correlates of protection, regulatory requirements, manufacturability). Phase IIB TOC trials allow for a triage approach. If the results are negative, the candidate can be reformulated or discarded. If positive, the trials will generate data about endpoints and immune responses that will inform the design of phase III trials. Phase IIB TOC trials guide development and can use a prototype product in a limited population, making them smaller, less expensive, and faster. Phase III trials are designed to support licensing and must use the final formulation and manufacturing process in the target population. Consequently, detailed process development for manufacturing scale-up, more precise measurements of efficacy, and true clinical endpoints in addition to surrogate markers of disease are required. Therefore, phase III trials are larger, longer, and more expensive.
The current Merck phase IIB-TOC designs evaluate both acquisition of HIV infection and VL set point among those who become infected, beginning (in the STEP study) in a population with the best chance of success (high-risk men and women in subtype B areas with low Ad5 antibody titers) and then expanding to include a subpopulation with high Ad5 antibody titers. The HVTN 503, or Phambili study, was recently initiated in a subtype C population in South Africa to evaluate the potential for cross-clade efficacy. The trials are sized to detect with 80% power a 50% reduction in HIV acquisition and/or at least a 0.5 log$_{10}$ reduction in VL. The trials will evaluate short-to-medium term persistence in reduction of VL or protection from acquisition, but not long-term reduction in VL, and are unlikely to be able to detect direct evidence of clinical benefit (e.g., decreased mortality, decreased rate of AIDS cases).

In addition to the Merck studies, the proposed PAVE 100 trial is a phase IIB TOC trial to evaluate the NIH VRC’s multiclade DNA/rAd5 vaccine candidate. It is an endpoint driven study that will enroll an estimated 8500 subjects in three geographic regions with equal distribution between genders. It will have 90% power to detect a 40% reduction in acquisition of HIV infection and/or at least a 0.4 log$_{10}$ reduction in VL. It will also allow for properly powered sub-group analysis (by gender, region and pre-existing anti-Ad5 antibodies) and selected analysis of potential correlates of protection.

IAVI proposed the potential use of even smaller, less expensive and faster trials to ‘screen’ candidate vaccines (screening test of concept or STOC trials) concurrent with ongoing phase IIB TOC trials in order to evaluate alternative antigens, vectors, routes of delivery, and single vs. prime-boost regimens. The goal would be to increase the efficiency of product clinical development, help set priorities for further testing, and possibly guide decisions about manufacturing investments. STOC trials would be used for vaccines that are unlikely to impact HIV acquisition and would be limited to a single endpoint, namely VL set point, and would not be powered to detect a significant effect on acquisition.

STOC trials would be designed to start after phase I and would substitute for pivotal phase II immunogenicity studies. They would rely heavily on enrollment of cohorts with very high annual incidence of HIV infection (2-7%) and would require approximately six months for enrollment. The primary endpoint in STOC trials is defined as mean VL set point at three to six months after infection, and acquisition of infection would be included as a secondary endpoint. STOC trials could potentially roll over to longer trials to collect data on CD4+ responses or potential immune correlates of protection. A very positive finding from a STOC trial could theoretically trigger a phase III follow-up study and accelerate the development of a licensable vaccine. There is potential cost savings with STOC trials—the cost per participant would be the same as for phase IIB-TOC trials but STOC trials would aim to follow less than half the number of volunteers, mostly by powering the studies to detect a 1-log difference in VL without the power to detect a significant effect on acquisition. This design could possibly detect a highly efficacious vaccine after only 20 events, although there is less risk at 30 events. For a minimum post-vaccination follow-up period of 12 months (with total time for the trial of about two years), the sample size required to achieve 30 endpoints would range from 388 participants for a population with annual HIV incidence of 7% to 1,312 participants for a population with annual HIV incidence of 2%.

A number of challenges associated with the STOC approach to accelerated efficacy evaluation were identified. STOC trials are not designed or powered to conduct concurrent “comparative” evaluations of multiple vaccine candidates and it is also likely to be difficult to obtain multiple vaccine candidates ready at the same time for parallel trials. Additionally, there will be major challenges in enrolling and retaining very high-risk populations in developing countries and the ultimate feasibility of doing this was not discussed in detail at the meeting. STOC trial design assumes that there
is no selection bias, which would be an issue only if the vaccine also reduces the rate of infection. The design has little power to detect associations between VL and tertiary endpoints, such as CD4+ T cell counts, but it will nevertheless collect data on this and other parameters such as influence of host genetics, immune response to vaccination, and genotype of infecting virus on vaccine efficacy. The STOC design would primarily be used to eliminate vaccine candidates that afford no efficacy and for ranking similar products. Consequently, significant concerns were expressed about the possibility of discarding a vaccine that might have an impact on HIV acquisition or discarding a product using a specific risk group that could be efficacious in another risk group that has not been evaluated. In comparison to phase IIB-TOC trials, STOC trials do not attempt to examine if any impact on VL could be associated with clinical benefit. This accelerated pathway also limits opportunities to optimize vaccine regimens and collect large safety data-sets prior to the conduct of a pivotal trial.

There is currently no evidence that any vaccine can reduce either HIV acquisition or VL—a crucial question for licensing—and no evidence that the targeted reductions in VL would be clinically significant in the long term. Furthermore, if reductions in VL are clinically significant, the level of VL reduction necessary for clinical benefit is also not known. The level of VL reduction and persistence of such a reduction that will be sufficient for licensure has not yet been determined. It is also unclear whether regulatory agencies will require sterilizing immunity as an outcome. In addition, VL is not yet a validated endpoint, and most accelerated efficacy trials (TOC or STOC) are not designed to definitively establish the effect of VL decrease on clinical outcomes.

According to the accelerated approval regulations, US FDA may grant marketing approval for a biological product (or drug) on the basis of adequate and well-controlled clinical trials establishing that a product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. (For biological products, see 21 CFR 601.40-46. Also, see Final Rule: New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, December 11, 1992: 57 FR 58942-60). Concurrence from the US FDA for this pathway, including the acceptable magnitude and duration of response for a particular surrogate endpoint, should be obtained in advance. One of the substantial challenges if regulatory approval is sought through the accelerated approval pathway (e.g., based on a VL endpoint) will be the design and implementation of the confirmatory trial to demonstrate clinical benefit. The US FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) input on these issues would be useful.

There was broad agreement that STOC and TOC trials represent a narrow spectrum of design and that the biggest difference between them is that the STOC design drops the primary acquisition endpoint and relies on populations with extremely high HIV incidence rates in order to achieve the smaller sample sizes, while allowing for the possible elimination of phase II immunogenicity trials from the product development path.

PARTICIPANTS IN THE WORKSHOP MADE THE FOLLOWING RECOMMENDATIONS:

+ For expedited efficacy trials (phase IIB-TOC or STOC) to provide an effective alternative pathway, there must be a clearly defined roadmap to advance to phase III trials or termination, with coordination between protocols, and a group to coordinate and expedite funding, execution, analyses, and advancement of products in an industry-like manner. Additionally, conduct of accelerated trials should probably be limited to countries with experience in HIV vaccine trials.
A high-level decision tree, or algorithm, should be developed that describes the potential different accelerated product development pathways. There was general agreement that early phase IA trials (safety, dose escalation, etc.) should be conducted in both low- and high-risk populations. For vaccine candidates that fall within the current paradigms, the following general decision path could apply: If initial immunogenicity in phase IA trials is low, the candidate is unlikely to represent an improvement upon more advanced candidates and clinical evaluation should stop. If phase IA immune responses are moderate, the candidate should advance to phase IB for optimization and, subsequently, to phase II evaluation if the results remain encouraging. On the other hand, if the candidate demonstrates very high immunogenicity in phase IA, or after optimization in IB, then it should be considered for an accelerated clinical pathway that might include a phase IIB-TOC trial or STOC trial, in addition to a downstream development plan. The immunogenicity-based qualification criteria to use for moving a given vaccine candidate from phase I directly to a STOC trial were not specifically defined by the workshop.

A modular approach to protocol design should be considered, with standardized phase II TOC or STOC type trials and pre-established decision rules to support the rapid testing of products in high-risk volunteers, and it was agreed that the definition of efficacy endpoints would be a topic of a separate Enterprise-sponsored workshop in the near future, with a particular focus on defining a ‘significant’ reduction in VL set point.

2. Humoral responses to HIV and approaches to the design of antigens that induce neutralizing and other potentially protective antibodies

The workshop on "Humoral Response to HIV and Approaches to the Design of Antigens that Induce Neutralizing and other Potentially Protective Antibodies" was held in May 2007 in Reston, Virginia, with the goal of identifying key scientific issues, gaps, and opportunities that have emerged in this important area since the Enterprise SSP was first published in 2005. The meeting, which was attended by 25 scientists, was organized by David Montefiori (Chair), Quentin Sattentau, John Mascola, Jorge Flores, and José Esparza.

The induction of broadly cross-reactive neutralizing antibodies continues to be a major priority for HIV-1 vaccines, although a clear path to achieving this goal remains elusive. In general, progress is gauged by an ability to generate antibodies that neutralize a broad spectrum of primary isolates in vitro representative of all major genetic subtypes of the virus. Although it is not known what magnitude and breadth of in vitro neutralization will predict protection in vaccine recipients, it is clear that very few if any primary isolates are neutralized by the antibodies that are generated by current vaccine immunogens. Thus, much progress needs to be made in this area. Though primary isolate neutralization is considered a critical benchmark, this may not be the only benchmark for predicting success with antibody-based HIV-1 vaccine immunogens.

The main targets for neutralizing antibodies are the surface gp120 and trans-membrane gp41 envelope glycoproteins (Env) on the virus surface that mediate receptor and co-receptor binding and the subsequent membrane fusion events that allow the virus to gain entry into cells. In order to ensure its survival, the virus exploits several mechanisms to shield itself against antibody recognition (including a dense outer coating of N-linked glycans and the strategic posi-
tioning of cysteine-cysteine loop structures on the gp120 molecule). These shielding mechanisms, although highly effective, have vulnerabilities imposed by fitness constraints. Information on the precise location and molecular structure of these vulnerable regions could be extremely valuable for the rational design of improved vaccine immunogens.

This workshop identified six areas that if given proper attention could provide key information that will bring the field closer to an effective antibody-based HIV-1 vaccine:

+ Epitope-assisted immunogen design,
+ Structure-assisted immunogen design,
+ Role of Fc receptors and complement,
+ Assay standardization and validation,
+ Assay validation using in vivo models, and,
+ Immunoregulation.

For practical reasons, epitopes are sought that are either highly conserved or only moderately variable. In this regard, rigorous efforts have focused on a small number of human MAbs that possess broadly cross-reactive neutralizing activity and the cognate epitopes for these MAbs have been well-characterized. Although each epitope is clearly a target for neutralization on many primary isolates, their poor immunogenicity in infected individuals and in immunized animals has so far precluded their utility for vaccination. Improvements are being sought by introducing specific structural alterations and by targeting autoreactive B cell pathways. These and other efforts to improve the immunogenicity of conserved neutralization epitopes should remain a high priority.

Participants recognized the need to expend greater efforts identifying and characterizing new MAbs, with special attention to MAbs from non-clade B infected individuals. Moreover, new technologies are now available that might afford an advantage for identifying novel and/or rare antibody specificities that went undetected before. Recent years also saw the development of new technologies to probe neutralizing antibodies at the epitope level. These technologies are applicable to MAbs and polyclonal antiserum and are able to circumvent technical challenges encountered when dealing with discontinuous conformation-dependent epitopes, and they have potential to yield new information on the relevant epitopes to target for vaccine design.

While there has been considerable interest in conserved epitopes as minimal immunogens to generate a broadly neutralizing antibody response, little attention has been paid to other epitopes that might have equal or greater value if administered in the form of a polyvalent vaccine. Of particular interest are the epitopes that drive the autologous neutralizing antibody response in infected individuals. These epitopes have been largely ignored out of concern that they are too variable to be practical as vaccine immunogens; however, recent evidence suggests there are constraints on the extent of variation the virus can tolerate in these regions. Detailed molecular and immunologic studies of the autologous neutralization response would enhance our understanding of viral determinants that are vulnerable to antibody attack.
Another issue that has been largely ignored is the possibility that two or more epitopes, when bound by antibody, will yield a synergistic effect for neutralization. Synergistic combinations of neutralizing and non-neutralizing antibodies might be discovered by applying high throughput screening methods to the plethora of existing MAbs as well as new MAbs that become available in the future.

X-ray crystal structures have been determined for a few gp120 molecules and these studies have revealed important features. Of great interest is the recent crystal resolution of the MAb b12 binding site on the gp120 molecule. Because of the flexibility of the gp120, several mutations had to be introduced to allow for the formation of a stable crystal. In itself the approach employed to stabilize the envelope protein may lead to a better presentation of the b12 epitope, but also scaffolding the resolved structure onto other proteins might result in new immunogens with the desirable cross-neutralization properties of b12. Additional efforts are needed to obtain crystal structures of non-clade B envelope glycoproteins, and to bridge the gap between partial crystal structures and complete topology with the use of electron tomography studies of the envelope trimers.

Recent findings have generated renewed interest in so-called “non-neutralizing” antibodies that are unable to block virus entry inhibition but nonetheless exhibit antiviral activity through antibody effector mechanisms involving either Fc receptors (FcR) or the complement system. These antibodies do not necessarily have to bind functional spikes as is required for conventional neutralizing antibodies. Rather, they could bind cryptic epitopes that are only exposed on defective envelope spikes, where the Fc portion of the antibody would be available to mediate FcR- and complement-mediated effector functions.

Recent studies have demonstrated FcR-dependent antiviral effects of HIV-1-positive serum samples and MAbs in macrophages and immature DCs in cases where the antibodies had little or no detectable activity in a conventional neutralization assay. Other recent studies have shown an antiviral effect of non-neutralizing antibodies in an assay termed “antibody-dependent cell-mediated virus inhibition” (ADCVI) that measures cytolytic and noncytolytic killing of infected cells by FcR-bearing effector cells. Two independent groups also reported antibody-dependent complement-mediated virus lysis and inactivation activity in serum from early HIV-1 seroconverters. These combined observations provide strong rationale to screen sera for these activities in greater detail even if neutralizing activity is absent.

As new immunogens are designed and tested, it will be important to compare them to each other and to earlier prototypes with respect to the magnitude and breadth of the neutralizing antibody responses each generates. In order to adequately monitor neutralization breadth and potency and to compare and prioritize immunogens, assays are needed that are sensitive, quantitative, high throughput and have correlative value. Substantial improvements were made in the past several years in assay technology and in available reference reagents. Thus, cumbersome and expensive assays using PBMC and uncloned viruses are being replaced with a new technology that utilizes molecularly cloned Env-pseudotyped viruses and Tat-induced luciferase reporter gene expression in genetically engineered cells lines. This new technology affords greater sensitivity, reproducibility, high throughput, cost-effectiveness and scientific value compared to PBMC assays and, as a result, it has been responsible for an explosion of new data that was not possible before. Steps are being taken by the CAVD to transfer this new technology to multiple laboratories around the world and to implement a validated proficiency testing program to assure inter-laboratory equivalency in assay performance.
The new assay technology gained momentum after early validation studies showed an acceptable level of agreement with the results obtained in PBMC assays. These early validation studies, which employed a relatively small number of human MAbs and HIV-1-positive serum samples for comparisons between assays, found no cases where the new assay technology was considerably less sensitive than PBMC-based assays. In fact, in general the new technology was more sensitive. However, as the number and types of different antibodies tested in both assays grew over time, several cases were identified where neutralization was considerably more potent or only detected in the PBMC assay, including some cases involving anti-lipid antibodies derived from immunization of mice with lipids, anti-lipid antibodies derived from a patient with autoimmune disease, as well as some cases involving gp120- and gp41-specific MAbs.

Thus, the recent recognition that new assay technologies lack sensitivity for certain neutralizing antibodies raises important questions about current plans to globalize a single assay for routine use and points to the need for a better understanding of the mechanisms of neutralization. It may be necessary to use more than one assay to assure that all neutralizing antibodies are detected. Efforts are needed to:

- Study the biologic basis of differential neutralization in the two assay systems and to determine how the new assay technology might be modified to detect all neutralizing antibodies,
- Run parallel assays in PBMC with large numbers of serum samples from HIV-1-infected individuals and multiple preclinical and clinical trials to determine how often and why neutralization is missed in the new assay, and
- Develop and explore additional assays for neutralizing antibodies. Progress in this area will greatly depend on an effort to develop a more standardized approach to the PBMC assay.

Meeting participants also expressed interest in assays that measure neutralizing antibodies that block cell-cell spread of the virus. HIV-1 can spread by cell-cell contact either though direct synaptic transfer or by transfer to susceptible cells of exogenous virus that is captured by adhesion molecules (e.g., DC-SIGN, complement receptors) on the surface of either DCs or B lymphocytes. Neutralization assays based on these distinct modes of cell-cell spread have been described but have not been properly standardized or validated. It is recommended that these and similar types of assays be explored in greater detail for their biologic relevance, and that they be standardized and validated for possible use as endpoint assays in preclinical and clinical vaccine trials.

Important decisions need to be made about the type(s) of antibodies and assays that have greatest relevance to HIV-1 vaccines. Simply using highly standardized assays that reliably measure antiviral activities in vitro may not be sufficient if they do not predict a corresponding outcome in vivo. The preferred way to make informed decisions would be to employ a variety of different assays to study the antibody response in a clinical trial in which the vaccine was at least partially protective. Because no such vaccine is currently available for HIV-1, studies in animal models are the next best choice. In this regard, two animal models are widely used for HIV vaccine development: SIV and chimeric simian-human immunodeficiency virus (SHIV) infection in monkeys. Highly quantitative passive transfer experiments in either model with antibodies that exhibit different functions could be used to address the biologic relevance of in vitro assays. Because most MAbs and polyclonal antisera that need to be characterized would be derived from HIV-1-infected subjects, chimeric SHIVs containing HIV-1 envelope glycoproteins would offer greatest value. Unfortunately,
very few SHIVs are currently available and, among these, most are derived from a single genetic subtype (clade B) and exhibit properties that may not be well-suited to assay validation. The creation of new and better SHIVs from non-clade B viruses would facilitate assay standardization as well as vaccine challenge models.

This workshop identified several critical gaps in the current understanding of B cell regulatory pathways that impede a more rational development of an effective antibody-based HIV-1 vaccine. Closing these gaps may lead to a better understanding of the poor immunogenicity of Env and ways to elicit desirable neutralizing antibody responses. For example, broadly neutralizing antibodies in patient serum bind epitopes that are present on monomeric gp120, yet this is a poor immunogen for neutralizing antibody induction in vaccine recipients. Moreover, as mentioned above, epitopes for the known broadly neutralizing MAbs are poorly immunogenic in infected individuals and as vaccine candidates. Thus, Env as an immunogen appears to either bypass one or more key steps in the B cell inductive pathway for which little is known, or may actively induce negative or down-regulation of production of some broadly neutralizing specificities. Similar negative regulatory pathways do not explain the poor immunogenicity of other Env epitopes, as many show no clear evidence of autoreactivity.

In general, antibody responses are initiated when mature naive B lymphocytes encounter antigen via their B cell receptor (BCR) and subsequently engage antigen-specific activated CD4+ T helper cells. Through cognate interactions between multiple co-stimulatory molecules on specific B and T cell subsets, and in the presence of a suitable cytokine environment, a germinal center reaction ensues in which the naive B cells proliferate and undergo clonal expansion, Ig class switch recombination and somatic hypermutation to differentiate into memory B cells. Subsequent co-stimulatory signals delivered by CD4+ T helper cells induce terminal differentiation of memory B cells into plasma cells that then migrate to the bone marrow to complete their differentiation process and secrete antibody. Other mature B lymphocytes that normally reside in the marginal zone (MZ) undergo rapid differentiation into antibody secreting plasma cells, including the production of both antigen-specific and polyreactive antibodies in the absence of T cell help, but these responses tend to be short-lived.

Receptor-ligand interactions and intracellular signaling pathways that govern the production of antibody-producing plasma cells and the persistence of plasma and memory B cells are poorly understood. Additional information on the mechanisms responsible for B cell migration, selection and differentiation within and between specialized anatomical sites, particularly within lymphoid follicles, might be used to target suitable Env epitopes to appropriate B cell inductive pathways.

In parallel to these efforts, genetic studies at the population level could provide critical information on the most promising paths to follow. In particular, the recent completion of the International HapMap project now permits whole genome associated studies to be conducted with a minimum number of single nucleotide polymorphism (SNP) tags. This powerful new technology could be used to identify genes that are associated with the wide variation in neutralizing antibody responses in HIV-1-infected individuals and in vaccine recipients. A critical question to ask is whether the potent neutralizing antibody response in a small subset of infected individuals is due to unique viral epitopes or to host genetic polymorphisms. Current evidence suggests that both might make a substantial contribution in the context of combined epitope and allelic representations.
Other means to improve the B cell response to Env might reside in the Env molecule itself. Results of a recent study suggest that Env exerts a suppressive effect on CD4⁺ T cells that is mediated by CD4 binding and might explain why Env is a poor immunogen. The fact that Gag-specific but not Env-specific antibody responses decline in parallel with CD4⁺ T cell loss suggests that Env is mostly a T cell-independent immunogen in infected individuals. Chronic activation of B cells through a CD40-independent pathway involving the up regulation of a B cell activating factor of the TNF family (BAFF) was recently proposed as a mechanism that contributes to the impairment of T cell-dependent antibody responses to Env. Continued investigations along similar lines, when combined with new information about B cell regulatory pathways, could give rise to a new blueprint for improved vaccine design and delivery strategies (e.g., adjuvants, vectors, routes of administration).

To date most studies of the humoral responses in AIDS virus infections have investigated immunoglobulins, the final product of B cells responses. Relatively few studies have examined B cell immunopathogenesis. A number of basic questions are still unanswered (e.g. extent and reason for perturbation of B cell subset changes, including memory B cells and plasma cells in peripheral blood and tissues). Questions also remain about other potential functional contributions of B cells to AIDS virus infections (e.g. role as antigen presenting cells). *In vivo* studies should be performed in the non-human primate animal model to determine the emergence of pathologic events in the B cell compartment, in particular in lymphatic and gastrointestinal tissues of naïve and vaccinated animals that get challenged with pathogenic SIV or SHIV. These investigations should be done in parallel to detailed analyses of the magnitude and function of AIDS virus-specific immunoglobulin responses determined in plasma and tissue secretions, and of AIDS virus-specific B cells on a single cell basis.

**PARTICIPANTS IN THE MEETING MADE THE FOLLOWING RECOMMENDATIONS:**

- New information is needed to identify relevant epitopes to target with vaccines. Epitopes responsible for generating potent autologous virus neutralization as well as broadly neutralizing activity in sera from infected individuals appear to be suitably immunogenic and antigenic for this purpose. These epitopes need to be identified and characterized for possible use as monovalent and polyvalent vaccine immunogens. Increased effort is needed to develop sophisticated, high-throughput methods for screening epitopes and antibodies using the latest technologies,

- Crystal structures of monomeric gp120 and gp120-gp41 trimer complexes in their native unliganded form need to be elucidated as the natural targets for neutralizing antibodies. This information is needed for multiple genetic subtypes of the virus and for transmitted strains of the virus. Coupled with this effort should be a program to make necessary improvements in electron tomography technology to gain a higher resolution of native Env spikes as they exist on virus particles.

- Antibody effector functions that mediate complement activation and FcR engagement on macrophages, DCs, NK cells, and other cell types need to be evaluated to determine their relevance to HIV-1 vaccines. Assays that measure these antiviral antibodies should be standardized and used to assess biologic relevance in passive protection experiments in animal models using antibodies that exhibit the different effector functions *in vitro*,

- Additional effort is needed to standardize and compare neutralizing antibody assays and to decide which assay or combination of assays should be used for standardized assessments of vaccine-elicited
neutralizing antibody responses. A major priority is to strengthen the standardization of the PBMC assay as the only assay that has been at least partially validated in passive antibody experiments in animal challenge models. Similar validation experiments in animal models are needed to determine the potential correlative value of new assay technologies that rely on the use of genetically engineered cell lines and Env-pseudotyped viruses.

+ New and better SHIVs are needed that contain non-clade B envelope glycoproteins and that more closely approximate the neutralization phenotype, cellular tropism and pathology of HIV-1. These SHIVs are needed for studies of the biologic relevance of in vitro assays and to decide which antibodies and assays are most relevant for HIV-1 vaccine design and testing.

+ Additional efforts are needed to support studies in fundamental B cell biology as it relates to HIV-1 vaccines. A program could be structured in a way that asks key scientific questions about B cell regulatory pathways that modulate Env immunogenicity, including new adjuvant development.

+ More detailed B cell immunopathogenesis studies are needed to correlate pathologic changes in the B cell compartment in peripheral blood and organs including lymphatic and gastrointestinal tissues to AIDS virus-specific immunoglobulin responses. In particular, the non-human primate animal model should be utilized to study B cell immunopathogenesis in naïve and vaccinated monkeys that get challenged with pathogenic AIDS viruses.

+ Ultimately, the design of new immunogens either with stabilizing mutations in gp120, scaffolds of conserved neutralization epitopes on other proteins, or other structurally-based approaches (e.g., Env-CD4 chimeras or mimics of them) may lead to more promising products. Unmistakably, significantly improving HIV vaccine design is still of the highest priority.

While each of the above research objectives needs to be better supported, structuring the support in a manner that fosters collaboration, coordination, and results sharing would be equally important.

3. Improving defenses at the portals of entry: innate and mucosal immunity

The workshop on “Improving Defenses at the Portals of Entry: Innate and Mucosal Immunity” was held in June 2007 in Durham, North Carolina, to discuss innate responses to HIV in general and mucosal innate and adaptive responses against HIV at the portals of entry. The meeting, which was attended by 26 scientists, was organized by Barton Haynes, Bali Pulendran, Robin Shattock, Jorge Flores, and José Esparza.

ROADBLOCKS TO INDUCING PROTECTIVE IMMUNITY AT MUCOSAL SURFACES

Defining the earliest events in mucosally transmitted HIV-1 infection is of central importance for characterizing the precise virus-host interactions that must be altered by vaccine-induced immune responses. While sexual transmission accounts for over 90% of all instances of HIV-1 infection, the immediate events between exposure to infectious virus and establishment of infection are poorly understood. Mucosal transmission of HIV-1 infection is mediated by exposure to infectious virus and/or cells within mucosal secretions. While the risk of transmission is influenced by factors relating to the infected partner, transmission is critically dependent upon transfer of infectious virus across the mucosal
epithelium providing access to sub-epithelial DCs, macrophages and/or T cells that express both CD4 and co-receptors CCR5 and CXCR4. Multiple mechanisms for mucosal HIV-1 transmission have been proposed including: direct HIV-1 infection of epithelial cells, transcytosis of HIV-1 through epithelial cells and/or specialized M cells, epithelial transmigration of HIV-1-infected donor cells, uptake of HIV-1 by intra-epithelial Langerhans and DCs, or entry via epithelial micro-abrasions or ulceration. These events may be critically influenced by viral genotype, incorporation of host cell proteins, cell-free/associated virus, and the presence of genital secretions. However, none of these mechanisms, the receptors involved, or their modulation by immune responses (adaptive and/or innate) has been fully defined in tissue and/or NHP studies. A broad consensus from the meeting was that a preventive vaccine must effectively target the earliest events in the establishment HIV infection right after transmission (hours-days).

The following scientific priorities were identified that will bring the field closer to defining the correlates of mucosal protection against HIV and developing the enabling technology for an effective HIV-1 vaccine:

+ Definition of the sequence of events required to establish infection following exposure to HIV,
+ Elucidation of acute mucosal sequela that need to be prevented or subverted by HIV vaccines,
+ Development of better tools for measuring mucosal immune responses (assay development, standardization, and validation),
+ Defining the role of the common mucosal system in protection,
+ Characterization of protective mucosal antibody responses,
+ Definition of the role of T cell responses in eliciting mucosal protection.

As argued above, understanding the mechanisms of HIV infection across mucosal surfaces and the ability of immune responses to modulate these events is likely to be important for effective vaccine design and development. For a preventive vaccine to work, it must be able to target these very early events. One critical unanswered question is the relative role of cell free vs. infected cells in mucosal transmission, whether the relative importance of these varies by mucosal route, and the relative impact of mucosal responses on these different pathways. A second knowledge gap relates to the different potential mechanisms of viral transport across mucosal surfaces and their potential modulation by different aspects of the immune response. Furthermore, there is still debate as to the identity, frequency, location, and role of the primary targets of infection. Attention should be paid to the difference in infectivity and protection between the stratified squamous epithelium of the ecto-cervico vaginal and foreskin epithelia in contrast to the columnar nature of the rectal and endo-cervical epithelium. In this regard, several specific recommendations were made:

+ Develop tools for tracking virus and/or infected cell interaction with mucosal surfaces and subsequent spreading of infection within mucosal sites and dissemination to lymphoid tissue/determine the role of DC in the mucosa for dissemination of HIV,
+ Cross reference and standardize cellular, tissue and NHP models of mucosal transmission,
+ Develop better and more relevant panels of HIV and SHIVs from transmitted sequences for human explant tissue and NHP studies, and
Evaluate the impact of protective vaccines on initial events of transmission to determine the point at which the chain of events required to establish infection may be aborted.

Parallel studies of pathological events in acute infection in NHP and humans have generated important insights into the subversion and/or destruction of the mucosal immune system. This is most evident by the rapid depletion of CD4 T cells within the gut-associated lymphoid tissues (GALT). It has become abundantly clear that once mucosal infection has occurred, mucosal immune responses to infection are insufficient to prevent these events. What is less clear is whether they have any role in controlling mucosal replication and or immune cell depletion. While important work has been carried out to identify pathogenic sequelae in acute infection, the underlying mechanisms driving these events are not fully understood. Less still is known about the impact of immune response (innate and adaptive) in their modulation. Perhaps most critically for vaccine design, it is unclear whether infection can be prevented or aborted after the initiation of these events or merely controlled. Several specific recommendations were made:

- Define why HIV fails to induce robust HIV-specific mucosal IgA and IgG responses,
- Determine whether immunosuppressive mechanisms mediated by Treg and apoptotic pathways at mucosal surfaces prevent robust immune responses and/or promote viral replication,
- Develop a focused approach of parallel human and NHP studies of acute infection to further delineate common pathology of acute infection,
- Define key differences in specific mucosal IgA and IgG responses and regulatory cytokines in acute infection and following vaccination with HIV antigens and control antigens,
- Monitor mucosal immune depletion in multiple mucosal sites—GALT, bronchus-associated lymphoid tissue (BALT), genito-urinary (GU) tract,
- Characterize the relationship between immune depletion, bacterial permeability, cytokine environment, activation status, and viral quasispecies within different mucosal compartments,
- Determine the mechanistic features that render the GI tract in acute HIV/SIV infection permeable to bacterial products, and
- Monitor mucosal immune responses, T cell depletion, and gut permeability in naïve NHP and vaccinated animals in response to rectal challenge.

As already discussed, understanding the role of mucosal immunity in HIV transmission and prevention is likely to be key to the rational development of HIV vaccines. However, to date techniques for evaluating mucosal immune responses (in humans and NHP) have been primarily based on assays established for the evaluation of systemic responses where sample volume and cell numbers are not rate limiting. The technological hurdles are different for mucosal humoral and T cell assays and these will be discussed separately below. However, one common research issue was the need to identify novel mucosal specific homing markers (GALT, BALT, GU).

Recently much has been done to increase the sensitivity of antibody binding assays using high sensitivity ELISA technology. Additional advances are being realized with multiparameter luminex assays able to evaluate responses
to a wide range of antigens using small sample volumes, the use of Surface Plasmon Resonance (SPR) to evaluate kinetics and avidity of binding, and Resonant Acoustic Profiling able to detect antibody binding to whole virions. However these gains in technology have not been matched with optimization of mucosal sampling techniques to detect vaccine induced responses, and specific recommendations were made, including:

+ Define the optimal methods to acquire mucosal samples and to detect vaccine-induced mucosal humoral immune responses,
+ Establish validated biomarkers for sample standardization and assay controls that will facilitate cross comparison between trials,
+ Encourage standardized measurement of humoral mucosal responses as a standard parameter for NHP and human vaccine studies, and
+ Determine at what age the macaque mucosal immune system becomes fully developed in NHP models.

While there is a substantial body of literature describing antigen specific T cells responses to HIV in peripheral blood, far less is known about mucosal T cell responses. This reflects the lack of an accessible, reliable, and sensitive method for assessing mucosal cellular responses and represents a significant bottleneck in the ability to determine the mucosal correlates of protection and or viral control. As a consequence little is known about the quality, quantity, and duration of mucosal T cell responses following infection or vaccination and their relation to systemic T cell responses. Analysis of mucosal T cell responses (both vaginal and rectal) faces a number challenges. Firstly the number of cells for analysis is rate limiting when compared to established PBMC assays. Mucosal assays need to be performed on $10^4$ T cells of which >1% may be responsive to HIV antigens. The following specific recommendations were made:

+ Establish transport and storage conditions for mucosal T cell samples,
+ Maximize the efficiency of polyclonal expansion of mucosal T cells to facilitate mucosal assessment,
+ Identify and validate surrogate biomarkers in blood for mucosal response, such as mucosal homing receptors,
+ Establish a novel platform technology for single-cell evaluation of mucosal T cell responses, and
+ Determine the role of soluble T cell factors in infection-induced and vaccine-induced control of HIV-1.

The Working Group had a robust discussion over the role of the common mucosal system in evoking protective immune responses. The central dogma that protection is best primed by mucosal vaccination has not been fully validated. Protection against mucosal challenge has been demonstrated in NHP studies with parenteral vaccines (at least with homologous virus) and live attenuated vaccines. It is unclear whether systemic immunization induces protection at mucosal surfaces, or whether more robust protection might be achieved with mucosal priming and/or boosting. New tools for tracking virus and infected cells may now allow studies to determine the point of protection in vaccinated animals. The unique contribution of NHP studies to addressing these questions was clearly recognized, but this was underscored with an emphasis for parallel immunogenicity studies in humans. Again the requirement for cross comparison between trials (and the tools to facilitate this) was seen as paramount. The following specific recommendations were made:
+ Establish a broad paradigm of the commonalities of the mucosal immune system through parallel studies in humans and NHP (BALT, GALT, genito-rectal associated lymphoid tissues),
+ Define the potential of mucosal immunization in different prime boost strategies to optimize protective mucosal responses,
+ Determine the role of mucosal immunity in protection afforded by parenteral vaccines (tracking of infectious events, determine differences by route of challenge),
+ Determine whether protection afforded by parenteral vaccines can be boosted by mucosal immunization, and
+ Establish the role of mucosal antibodies (passive infusion studies, topical application of IgG, sIgA, etc, neutralizing/non-neutralizing) in prevention of mucosal transmission.

While there is general agreement that a protective vaccine will require the induction of a humoral response, a large number of questions remain about the characteristics of such a response that will provide protection. It is unclear whether the induction of neutralizing antibodies is the only response contributing to robust protection or whether other functional characteristics of non-neutralizing antibodies may have equal or additional importance. This question may be key in focusing vaccine development. There was a strong sense in the group that additional functional activities of antibodies should be considered, including: complement fixation, inhibition of epithelial transcytosis, blockades of cell-cell transmission across infectious synapses (in particular those between DCs and T cells), antibody-dependent cell-mediated cytotoxicity (ADCC), and mucosal tissue studies. At present, there is no certainty as to which of the many different functional antibody assays might correlate with mucosal protection, and thus these must be tested in parallel with NHP and human studies, proving a way forward to understanding the humoral correlates of protection. How much spill over of systemic antibodies is there into mucosal compartments, could this be changed by sexual arousal, are luminal antibodies important? It was agreed that many of these issues could now be addressed experimentally in NHP and human studies. The following specific recommendations were made:

+ Determine the correlates of protective antibody responses. Are mucosal antibodies necessary for protection or will antibodies of systemic origin suffice?,
+ Define the role of antibody isotype in mucosal protection (combination of passive infusion NHP studies and in vitro functional assays),
+ Define the kinetics of protective antibodies—what is the time frame in which they have to work—hours, days? Can this be elicited by memory responses?,
+ Determine the concentration of antibodies needed at mucosal sites for an effective initial response, and
+ Characterize the different protective humoral responses against HIV transmission mediated by cell free virus and infected cells, and
+ Characterize the role of immune complexes in viral transmission and their impact on vaccine induced responses.
As discussed above, there are several technological hurdles to studying mucosal T cell responses. Should these hurdles be overcome, there are a number of strategically important questions about the role of mucosal T cell responses. Answers to these questions could enhance the design of protective vaccines against mucosal HIV transmission. Comparison of systemic and mucosal responses in infected individuals would define whether there was any compartmentalization of T cell responses that would require differences in prime/boosting by vaccines. Definition of the correlates of protection and/or non-progression in elite controllers (NHP and humans), using broad systems approaches that includes multiparametric cytokine analysis and genomics may provide new insight into the role of T cell responses in protection/control of HIV infection and may explain why elite controllers have virus in their semen but not in their blood. Furthermore, NHP studies could assess the relative contribution of specific mucosal memory vs. effector cell numbers and the duration of protection. Ex-vivo challenge studies of mucosal tissue might be developed as a tool for bridging studies between NHP and human studies. The following specific recommendations were made:

- In depth comparison of mucosal and systemic T cell responses in acute and chronic infection of humans (frequency and functionality),
- Comparison of mucosal and systemic T cell responses in protected NHP studies (frequency and functionality),
- Define the correlates of non-progression in elite controllers (NHP and human studies),
- Define any correlation between mucosal versus systemic T cell responses (effector/memory ratio, specificity, functionality) with protection in NHP studies and their potential role in duration of protection/viral control,
- Characterize the role of durable low-level infection (replication competent vectors, attenuated virus) in inducing T cell response, and determine if it induces compartmentalized mucosal immunity at the site of exposure, and
- Explore the use of ex-vivo mucosal tissue challenge model as a tool for bridging studies between NHP and human immunogenicity studies.

ROADBLOCKS TO INDUCING PROTECTIVE INNATE IMMUNITY TO HIV-1

Research done over the past decade has placed innate immunity at the center of immune regulation. The “innate” immune response is an evolutionarily ancient system of host defense, which occurs within minutes or hours of pathogen entry, or vaccination. A critical cell type in the innate system is the DC, which has evolved to “sense” components of bacteria or viruses, to process this information, and then to convey instructive signals to antigen-specific T and B lymphocytes in the adaptive immune system. There are several different sub-populations of DCs that differ in their surface phenotype, function, and immune stimulatory potentials. DCs, as do most types of immune cells, express so-called pattern recognition receptors (PRRs), which enable them to sense components of viruses, bacteria, parasites and fungi. Toll-like receptors (TLRs-) represent one such family of PRRs. Emerging evidence suggests that DCs and TLRs play critical roles in modulating the strength, quality and persistence of adaptive immune responses. Therefore DCs and TLRs represent attractive targets for enhancing HIV-specific immunity in vaccination. However TLRs are not the only innate immune receptors. Growing evidence suggests that other families of innate receptors such as C-type lectin like receptors (CLRs), NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs) also play critical roles in innate
sensing of pathogens, and induction of inflammatory responses. CCR5 chemokine receptor is an emerging non-TLR PRR as CCR5 binds HIV, M. tuberculosis, Toxoplasma gondii and microbial HSP70 stimulating maturation of DCs and eliciting TH1 cytokines and CC chemokines. However the importance of such non-TLRs in regulation of adaptive immunity is only beginning to be understood.

Importantly, there is a growing realization that many of our best empirically derived vaccines mediate their efficacy by activating specific innate immune receptors. For example, the highly effective yellow fever vaccine-17D, one of the most successful vaccines which has been administered to over half a billion people globally, signals via at least four different TLRs, as well as RIG-I like receptors, to elicit a broad spectrum of T cell responses. This work suggests that the immune response generated by a live attenuated vaccine can be effectively mimicked by adjuvants composed of the appropriate TLR and/or non-TLR ligands. Furthermore, the efficacy of recombinant vaccines can also be enhanced by non-TLR signaling pathways. For example, recent work suggests that some adjuvants can induce robust adaptive immunity in a TLR-independent manner, perhaps through other receptors in the innate immune system. Therefore, understanding the precise roles played by TLRs and other non TLRs, in the induction and regulation of adaptive immune responses, is critical for the design of optimally effective vaccines against HIV.

The Working Group focused its innate immunity discussion in three areas:

1. Harnessing TLRs and non-TLRs in HIV vaccine development,
2. Understanding the role of natural anti-HIV factors and innate immune cells (e.g., NK cells, NK-T cells, gamma-delta T cells, B-1 B cells, marginal zone B cells) in mediating the interface between innate and adaptive immunity in HIV, and
3. Understanding the role of innate immunity in early HIV infection.

There should be enhanced efforts to understand how DC subsets, TLRs, and other innate immune receptors (non-TLRs) all represent potential targets, which can be manipulated to induce effective HIV-specific immunity.

The working group made the following specific recommendations:

1. Determine how to use TLRs, non-TLRs and antigen presenting cells (APCs) to induce robust, persistent and protective immune responses, systemically and at mucosal surfaces,
2. Determine how innate immune activation controls the quality of adaptive immune response,
3. Develop novel adjuvants that safely yet potently stimulate TLRs and/or non-TLRs,
4. Develop delivery systems, formulations, nanoparticles that facilitate the local or mucosal delivery of specific ligands for TLRs and non-TLRs. There is a growing belief that delivery of multiple TLR ligands might result in synergistic activation of DCs and a consequent enhancement of the adaptive immune response,
5. Determine how successful vaccines and adjuvants activate the innate immune system, with a view to exploiting such knowledge in the generation of new vaccines against HIV, and
6. Use systems biology approaches to identify signatures of early innate immune activation that can predict the immunogenicity of vaccines.
Although much attention has focused on antigen-presenting cells, it is now clear that other innate activities including antiviral cytokines and cells such as NK cells, BK T cells, gamma-delta T cells play fundamental roles in mediating innate immune responses. Their function in inducing and in regulating adaptive immunity against HIV is important but poorly understood. Furthermore, the potential activity of innate B-1 and marginal zone B cells in mediating rapid induction of neutralizing antibodies against HIV remains unexplored. These issues were identified as important knowledge gaps in our current understanding, and it was recognized that advances in this area might facilitate the effective manipulation of innate immunity to induce optimally effective adaptive immunity against HIV. The group made the following specific recommendations:

+ Determine if NK, NK-T, gamma/delta T cells have biologically relevant roles in control of HIV-1 during the transmission event, and
+ Determine if innate B cells can be induced to rapidly produce protective antibodies in response to AHl by previous vaccination.

There is presently little knowledge about the early innate immune events that occur in response to mucosal HIV infection, and their potential influence on the ensuing adaptive immune response and disease progression. This issue was identified as an important gap in current understanding and it was widely recognized that advances in this area might facilitate the rational design of interventions in acute infections. Intracellular innate antiviral factors such as APOBEC3CG can be upregulated and maintained so it may play an important role in prevention of HIV infection in the first few days after exposure to the virus. The Working Group identified the need to understand the roles of:

+ DC subsets, TLRs and non-TLRs in mediating innate and adaptive responses to HIV in early infection; and
+ of other innate immune cells—NK, macrophages, marginal zone, B-1 B cells in mediating innate and adaptive immunity to HIV in early infection
+ Role of innate antiviral cytokines in curtailing early HIV infection
+ Role of innate intracellular antiviral factors

**SUMMARY**

There was general agreement that understanding the role of both innate and mucosal immunity in protection against mucosal HIV transmission was still in its infancy and may represent a significant bottleneck to development of a preventative HIV vaccine. Considerable gains could now be made with the development of new technology and the application of a focused approach to understanding the contribution of localized immune responses to preventing or aborting infection. It was recognized that acceleration of work in this area would most likely be met by a combination of a “multidisciplinary big science approach” facilitating the development of validated and standardized novel assay platforms and cross comparative NHP and animal studies, and innovative investigator driven projects facilitating the development of new vaccine strategies specifically targeted at elucidating mucosal immune responses.

Substantial effort needs to be devoted to designing and developing novel vaccine candidates that target mucosal tissues, both at the portal of entry as well as within the mesenteric lymphatic system, where the “battle” with the virus takes place. Likewise, designing TLRs and similar pattern recognition ligands to enhance and modulate protective responses and testing them in NHP and human clinical trials is of critical importance.
Section III: Enterprise Structure and Interim Secretariat Operations Update

A small Secretariat is needed to implement the Enterprise’s central priority, the SSP, as well as other Enterprise priorities. To help ensure the progress of this work, the Bill & Melinda Gates Foundation agreed to serve as the interim Secretariat until a full-time Executive Director (ED) could be hired and a permanent Secretariat established. The process of identifying and recruiting the Enterprise ED is well underway, and it is expected that the selected candidate will assume the position within the next few months.

In the two and a half years since the Enterprise SSP was published, significant progress has been made in the development of the structure of the Enterprise and in the activities of the interim Secretariat to facilitate and support stakeholder initiatives, communications, and new opportunities for collaboration.

1. Proposed structure

A simplified diagram of the proposed Enterprise structure (once a permanent Secretariat is established) is shown in Figure 3.
The core activities of the Enterprise include:

+ **Strategy**: defining areas where further scientific and capital resources are required to accelerate HIV vaccine development,

+ **Market Making**: bringing stakeholders together to coordinate their activities and build enabling capabilities (where there are currently gaps) to help stakeholders advance their work, and

+ **Advocacy**: bringing new scientific and financial resources to bear on HIV vaccine research and development and educating the general public about the Enterprise work.

The Secretariat is the central coordinating body of the Enterprise, holding primary responsibility for managing the day-to-day strategy, market-making and advocacy activities. The Secretariat plays a key integrative function, ensuring communication among stakeholders and promoting coordinated action.

The first steps in the development of the formal structure of the Enterprise were taken in mid-2005 when it was incorporated in the State of Washington, USA, and an application was filed with the US Internal Revenue Service for non-profit, tax-exempt status. As required of all US corporations, a Board of Directors was set up to govern the newly established organization. The Board members were drawn from those already serving on the Enterprise Coordinating Committee—an advisory body made up of individuals drawn from key stakeholder organizations as well as from outside the field based on their expertise and influence (members of the Enterprise Coordinating Committee are listed in Appendix 3). This Coordinating Committee, established in 2004, provides essential guidance to the overall effort and its members champion the Enterprise vision and principles.

When the Enterprise ED assumes his functions, the Coordinating Committee will be replaced by an Enterprise Council, which will be composed of approximately 14 individuals who will provide strategic guidance and advice regarding the Enterprise mission, objectives, and policies. A subset of this Council will form the new Board of Directors of the Enterprise that will oversee the ED and will have fiduciary responsibilities for managing the Enterprise’s assets in furtherance of its mission and goals.

While the roles and responsibilities of the Council and Board of Directors relate to the management of the Enterprise and its Secretariat, a Scientific Stewardship Committee (SSC) will be formed to provide scientific guidance to the effort. The SSC will continuously assess the scientific landscape and identify scientific, technological, or institutional gaps that are appropriate for Enterprise action. Members of the SSC will be drawn from a diverse set of stakeholders with relevant and outstanding scientific expertise, making the SSC another channel for dialogue between the Enterprise, its stakeholders, and the broader community.

The Enterprise will also continue to rely on Expert Working Groups as it did in the development of the SSP and in development of the Section II of this report, to identify important priority areas and gaps in the HIV vaccine research and development landscape and make recommendations for specific actions to address them. These ad hoc Working Groups...
Groups will be constituted as needed by the Secretariat, thus providing a flexible source of capacity and expertise that can be used to complement activities undertaken by the Secretariat’s permanent staff.

2. Activities to operationalize the Secretariat

The interim Secretariat, with the support of the Coordinating Committee, developed a business plan that details the activities, structure, staffing, and resources needed to achieve the goals and objectives of the Enterprise in the next five years. The business plan is used to guide the development of the Enterprise and its Secretariat and provides a benchmark for progress made in the operations of the organization.

In 2006 the Gates Foundation made a grant to the Enterprise to enable it to begin to function more independently in anticipation of the hiring of the ED. The interim Secretariat used the grant funds to contract with outside vendors to support operations, including event and travel coordination, finance and accounting, legal counsel, website and materials design and development, and conference management.

The interim Secretariat also contracted with a search firm to conduct the ED search. An initial search began in mid-2005 in which a sub-set of the Coordinating Committee (referred to as “the search committee”) worked with the search firm to identify potential candidates. A lead candidate was named in early 2006. However, before the appointment was formalized, the candidate and Board of Directors decided to not pursue the opportunity. The search for an Enterprise Executive Director was renewed in October 2006, and after the process of candidate identification and prioritization, the search committee identified a strong lead candidate. At the time of the preparation of this report the Enterprise is negotiating with the candidate who, it is anticipated, will assume the position full time in January 2008.

3. Core activities

3.1. Monitoring and updating the SSP

During the last two years, the Enterprise interim Secretariat engaged in a number of core activities, including the monitoring and updating of the SSP. While the Enterprise Coordinating Committee recommended that a full update of the SSP wait until the permanent Secretariat is established, the committee did agree that there were areas of HIV vaccine research in which more analysis and clarity were needed at this time. Thus, as described in Section II of this report, three expert Working Groups were convened in April, May, and June 2007 to develop the recommendations to update the SSP.

Altogether the three two-day workshops had a total of more than 95 participants and 58 presentations on the state-of-the-art in HIV vaccine research which resulted in rich discussions on emerging concepts and approaches, and the identification of priority areas for additional research to advance the field. It is anticipated that additional expert Working Groups will be convened in the next year to review the original six priority areas of the SSP and to tackle additional new priority areas in order to provide a comprehensive update of the SSP.
3.2. Advocacy
An important core activity of the Enterprise Secretariat relates to its role as a vehicle for communication and knowledge transfer between the many constituencies involved in research and development of an HIV vaccine. The Enterprise’s initial advocacy efforts aim to bring new scientific and financial resources to bear on HIV vaccine research and development, and to stimulate a broader interest in efforts to address the priority areas of the SSP in order to accelerate research.

At its July 2004 Sea Island summit, the Group of Eight (G8) endorsed the establishment of the Enterprise, providing important political support to the effort. The 2005 G8 summit communiqué again mentioned the importance of the Enterprise but lacked any concrete commitments in this area. To prepare for the G8 summit in Russia in 2006, the interim Secretariat organized a series of meetings between a delegation of Enterprise representatives and several Russian officials in order to raise awareness of the mission of the Enterprise and the need for increased involvement of Russian scientists, as well as the need for increased resources for Russian HIV vaccine research institutes. In conjunction with these meetings, the interim Secretariat organized a satellite session at the First Eastern European and Central Asia AIDS Conference in Moscow in May 2006. The session provided an overview of the Enterprise and the SSP and included presentations by Russian HIV vaccine scientists describing some of their ongoing research efforts. The meetings with the Russian officials and the conference satellite session were an important first step in helping to bolster financial and political support for Russia’s national HIV vaccine research programs. At the July 2006 G8 summit, the Russian Federation announced plans to commit $40M for the creation of a national HIV vaccine research center.

To strengthen communications targeting key stakeholders and more general outreach efforts, the Enterprise interim Secretariat developed a website (www.hivvaccineenterprise.org) in early 2005 that contains information on the SSP, ongoing collaborative efforts, press releases of initiatives in support of the Enterprise, the annual AIDS Vaccine Conference site, and other more general information and useful links. As the Enterprise grows, the website will become an important tool for the exchange of information among collaborators and as a knowledge management resource for the field. Email updates are periodically sent to stakeholders to inform them of new Enterprise-related activities, or Enterprise-supported initiatives. Print materials such as a brochure and fact sheets have been developed to increase visibility and understanding of the Enterprise mission and goals.

3.3. Coordinating stakeholder activities
Stakeholder involvement in the Enterprise is essential to the success of the alliance and to the goal of accelerating the development of an HIV vaccine. The Enterprise Secretariat focuses much of its activities and resources on facilitating the coordination of stakeholder activities to ensure that the priority areas of the SSP are addressed through collaboration, cooperation, and transparency.

In order to coordinate the activities of key Enterprise stakeholders, the interim Secretariat has organized seven face-to-face Coordinating Committee meetings since February 2005 in the US and Europe, and organized numerous conference calls for the full committee and its ad-hoc subcommittees including the Scientific Program Development sub-committee, the Partnership Development sub-committee, the Organizational Development sub-committee, and the ED search committee.
STAKEHOLDERS FORA
The Enterprise interim Secretariat has also convened meetings of the broader group of stakeholders in order to provide a formal means for all interested parties – organizations and individuals – to learn about the activities of the Enterprise and influence these activities, consistent with the aspirations of the Enterprise to be global and inclusive. The UK Government (under the auspices of the UK Leadership of the G8) and the Enterprise jointly convened a stakeholders meeting in London in May 2005 at the headquarters of the Wellcome Trust. This first meeting of stakeholders brought together over 50 representatives of developing and developed country advocates, social scientists, researchers, and others who have important roles to play advancing HIV vaccine research. Participants at the meeting, which was led by the UK Department for International Development, suggested mechanisms for engaging a wider range of stakeholders in the work of the Enterprise. Smaller stakeholder engagement opportunities were created through an Enterprise satellite session at the International AIDS Society pathogenesis meeting in Rio de Janeiro in 2005, as well as a roundtable session at the AIDS Vaccine 2005 conference in Montreal and presentations at the 2006 International AIDS Conference in Toronto and at the AIDS Vaccine 2006 in Amsterdam. Collectively, these meetings provide a formal venue for ongoing dialogue with stakeholders, promoting transparency of Enterprise activities and accountability of the Enterprise to the stakeholder community.

FUNDERS FORA
The Funders Forum is an event organized by the Enterprise Secretariat to provide efficient multi-way communication to address individual funders’ questions and report on progress made towards the implementation of the Enterprise SSP. This networking forum seeks to ensure that necessary activities are undertaken in a collaborative, high quality, and timely manner for the purpose of accelerating HIV vaccine development.

In its role as a neutral broker, the Enterprise encourages funders to utilize the evolving SSP to help guide their proposal requests and granting decisions, and to collaborate with other funder to minimize unnecessary redundancy of research funding.

The interim Secretariat organized the first Funders’ Forum October 31-November 1, 2005, at the Wellcome Trust in London. Approximately 60 participants, representing research and development funding agencies from around the world, attended the forum. The goals of the forum included: to brief funding agencies on current HIV vaccine efforts in the context of the overall response to the HIV pandemic; to describe the overall mission of the Enterprise and activities that need to be implemented in order to address key issues identified in its SSP; and; to discuss financial needs, as well as opportunities and mechanisms, to implement the SSP. The first Funders’ Forum successfully introduced the goals and activities of the Enterprise to funding agencies from around the world and a subsequent forum will provide donor agencies with the opportunity to make specific pledges to contribute funds to the effort. The Funders Forum will become an annual event organized by the Secretariat in order to fully engage a broad spectrum of funders in HIV vaccine research and development efforts.

In preparation for the first Funders Forum, the interim Secretariat convened the chairs of the original expert Working Groups of the SSP for a one day workshop to develop the case for the investment needed in HIV vaccine R&D, as called for in the SSP. This investment “menu” will be updated within the next year in preparation for a second Funders’ Forum.
FORA FOR SCIENTIFIC COLLABORATION

Beginning with the AIDS Vaccine 2007 conference (to be held in Seattle in August 2007), the Enterprise now plays a central role in facilitating the organization of this important annual conference. The conference began as a small meeting of HIV vaccine researchers in Paris in 2000 and has grown to a large annual event that attracts nearly 1000 people. Part of the Enterprise interim Secretariat’s role for the conference includes supporting the AIDS Vaccine Conference Steering Group which provides general guidance for the organization and funding of the annual conference. Members of the Steering Group include the chairs and major funders of previous conferences, as well as at-large members and Enterprise key stakeholders (members of the Steering Group are listed in Appendix 4). In 2007, the conference website was integrated into the Enterprise website, and beginning in 2008, the Enterprise Secretariat will provide conference management support to each year’s host through a contract with a conference management company. By centralizing some of the processes, the Enterprise will ensure a more fluid transition from one year’s conference host to the next and allow the host to focus on the scientific areas of the conference, rather than on the development and maintenance of a website, registration processes, and abstract management pieces.

DEVELOPING NEW COLLABORATIONS

The Enterprise Secretariat, in collaboration with WHO/UNAIDS and other stakeholders, is leading an effort to develop a strategic framework to prepare for decision-making and communications concerning the interim analyses and final results of ongoing efficacy trials of HIV vaccines. As mentioned in Section I of this report, in March 2007, the WHO/UNAIDS and the Enterprise organized a consultation at the WHO’s headquarters in Geneva on “Preparing for vaccine efficacy results.” The participants were drawn from key stakeholder organizations, including regulatory agencies, UN agencies, HIV vaccine funders, vaccine developers, representatives from trial sites in developing countries, and policy and advocacy organizations who have been directly or indirectly involved in the preparation and conduct of those trials. The trials are a phase III trial in Thailand testing a Sanofi Pasteur canarypox vaccine candidate with a VaxGen rgp120 subunit boost, and two test-of-concept (phase IIB-TOC) trials of Merck’s candidate Ad5 vaccine candidate.

The trials are currently expected to be completed between 2009 and 2011, but there will be multiple interim analyses of the results, and some data may become available as early as 2007 or 2008. The purpose of the consultation was to consider multiple scenarios for the different potential trial results, identify the critical information needed for rational decision making, and map the next steps needed to obtain that information. The recommendations from this consultation included a series of follow-up workshops/consultations and position papers and, as described earlier, the establishment of an Enterprise Coordinating Group on Preparation for Release of HIV Vaccine Efficacy Trial Results, and the creation of a sub-group focused on related communication issues which will be led by AVAC, as discussed in Section I.

In order to respond to one of the specific recommendations from the March 2007 consultation, the WHO/UNAIDS in collaboration with the Enterprise organized a consultation in early June 2007 in Thailand bringing together Thai and international researchers, regulatory experts, community leaders, and politicians to support decision-making and communications in preparation for the interim analysis of the Phase III Thai Prime-Boost trial which took place in July 2007. The two-day consultation discussed potential outcomes of the upcoming interim analysis and next steps to prepare the volunteers, media, and others for the different possible scenarios.
Likewise, an Enterprise consultation to better define the potential endpoints for efficacy in future HIV vaccine trials is being organized by WHO/UNAIDS in collaboration with the ANRS to take place in early September 2007 in Paris. The goal of this consultation will be to build consensus among key stakeholders regarding the interpretation of VL as an endpoint in preventive HIV vaccine trials, and to outline additional research that will likely be required to inform regulatory decisions regarding licensure and delivery of vaccines that do not prevent HIV acquisition but reduce VL.

While the identification of the Enterprise ED and thus the development of the permanent Secretariat took longer than initially anticipated, the interim Secretariat has worked with the Coordinating Committee and other Enterprise stakeholders to ensure the implementation of priority activities and the development of the Enterprise structure. The incoming Enterprise ED will find a surfeit of ongoing activities and new opportunities for the Enterprise to advance the field of HIV vaccine research and development.
Selected References


Appendices

APPENDIX 1:
Members of the Enterprise Coordinating Group to Prepare for Release of HIV Vaccine Efficacy Trial Results

Larry Corey
(HIV Vaccine Trials Network, USA)

José Esparza
(Bill & Melinda Gates Foundation, USA)

Hanna Golding
(US Food and Drug Administration, USA)

Glenda Gray
(Hani Baragwanath Hospital, South Africa)

Rob Hecht
(International AIDS Vaccine Initiative, USA)

Margaret Johnston
(National Institutes of Health, USA)

Pontiano Kaleebu
(African AIDS Vaccine Programme, Uganda)

Nelson Michael
(Walter Reed Army Institute of Research, USA)

Nathalie Morgensztejn
(European Agency for the Evaluation of Medical Products, France)

Saladin Osmanov
(World Health Organization, Switzerland)

Suppachai Recks Ngram
(Ministry of Public Health, Thailand)

Michael Robertson
(Merck & Co. Inc., USA)

Mauro Schechter
(Universidade Federal do Rio de Janeiro, Brazil)

Lucky Slamet
(Developing Countries Regulators Network)

Jim Tartaglia
(Sanofi Pasteur Ltd., USA)

Mitchell Warren
(AIDS Vaccine Advocacy Coalition, USA)

APPENDIX 2:
Participants at the Enterprise Working Group Meetings on Key Scientific Issues (2007)

Working Group: Approaches to Expediting HIV Vaccine Efficacy Evaluation

Jim Ackland
Susan Allen
Ripley Ballou*
Don Berry
Susan Buchbinder
Ann Duerr
José Esparza
Jean-Louis Excler
Pat Fast*
Alan Fix
Jorge Flores
Karen Goldenhal
Hana Golding
Barney Graham
Scott Hammer
Richard Hayes
Jerome Kim*
Wayne Koff
Michael Krams
Katharine Kripke*
Jim Kublin
Stephen Lagakos
Yves Levy
Ruth Macklin
Stobhan Malone
Bonnie Mathieson
Margaret McCluskey
Devan Mehrotra
Saladin Osmanov
Giuseppe Pantaleo
Punnee Pitisutthitum
Fran Priddy
Wasima Rida
Merlin Robb
Michael Robertson
Nina Russell*
Jerry Sadow
Steve Self*
KJ Singh
Bill Snow
Jim Tartaglia
Mitchell Warren

Working Group: Humoral Responses to HIV and Approaches to the Design of Antigens that Induce Neutralizing and other Potentially Protective Antibodies

James Bradac
Donald Burke
Emily Canow
Robert Carter
Andrea Cenutti
Raphaelle El Habib
José Esparza*
Jorge Flores*
Donald Forthal
Barton Haynes
Gunilla Karlsson Hedestam
Peter Kwong
John Mascola*
David Montefiori*
Christian Moog
Victoria Polonis
Helen Quill
Quentin Sattentau*
Gabriella Scarlatti
Jörn Schmitz
George Shaw
Sriram Subramaniam
Gerald Voss
Drew Weisman
Richard Wyatt

Working Group: Improving Defenses at the Portals of Entry: Innate and Mucosal Immunity

Alan Aderem
Lesley Bergmeir
Jason Brenchley
Heather Davis
Jorge Flores*
Bart Haynes*
Tom Hope
Pamela Kozlowski
Roger Le Grand
Thomas Lehner
Norman Letvin
Jay Levy
John Mascola
Julie McElrath
Philip Norris
Gillis Otten
Jo-Ann Passmore
Bali Pulendran*
Helen Quill
Bob Seder
Rafick-Pierre Sékaly
Barbara Shacklett
Robin Shattock*
Georgia Tomaras
Ron Veesey
Peter Wright

* Workshop Organizing Committee Members
APPENDIX 3:

Members of the Enterprise Coordinating Committee

Soon after the Enterprise was proposed an initial Steering Committee was established, which later became the Coordinating Committee of the Enterprise. The following is a list of individuals that have served, or are serving as committee members. Helene Gayle and Michel Kazatchkine served as Co-Chairs of the Coordinating Committee.

Seth Berkley (International AIDS Vaccine Initiative, USA)
M.K. Bhan (Ministry of Science and Technology, India)
Michel DelWitte (Sanofi-Pasteur, USA)
Emilio Emi (Merck Research Laboratories, USA)*
José Esparza (Bill & Melinda Gates Foundation, USA)
Anthony Fauci (National Institutes of Health, USA)
Helene Gayle (Bill & Melinda Gates Foundation*, CARE USA)
Catherine Hankins (Joint United Nations Programme on HIV/AIDS, Switzerland)
Margaret Johnston (National Institutes of Health, USA)
Pontiano Kaleebu (African AIDS Vaccine Programme, Uganda)
Edward Karamov (Ivanovski Institute of Virology, Russia)
Michel Kazatchkine (Agence Nationale de Recherches sur le Sida et les Hépatites Virales, ANRS, France)*
Richard Klausner (Bill & Melinda Gates Foundation, USA)*
Eric Lander (Broad Institute of MIT and Harvard University, USA)
Malegapuru Makgoba (University of KwaZulu-Natal, South Africa)
Pascoal Mocumbi (European and Developing Countries Clinical Trials Partnership, the Netherlands)
Peter Plot (Joint United Nations Programme on HIV/AIDS, Switzerland)
Octavi Quintana-Trias (European Commission, Belgium)
Rino Rappuoli (Novartis, Italy)
William Snow (AIDS Vaccine Advocacy Coalition, USA)
Mark Walport (Wellcome Trust, UK)
Hans Wigzell (Karolinska Institute, Sweden)

Note:
Individuals with an (*) have left the organization that they were representing when they were members of the Steering Committee and/or Coordinating Committee.

APPENDIX 4:

Members of the AIDS Vaccine Conference Steering Group

Larry Corey (HIV Vaccine Trials Network, USA)
Jean François Delfraissy (Agence Nationale de Recherches sur le Sida et les Hépatites Virales, France)
José Esparza (Bill & Melinda Gates Foundation, USA)
Catherine Hankins (Joint United Nations Programme on HIV/AIDS, Switzerland)
Bart Haynes (Duke University, USA)
Margaret Johnston (National Institutes of Health, USA)
Pontiano Kaleebu (African AIDS Vaccine Programme, Uganda)
Joep Lange (University of Amsterdam, the Netherlands)
Bonnie Mathieson (National Institutes of Health, USA)
Lynn Morris (National Institute for Communicable Diseases, South Africa)
Guisepp Pantaleo (Centre Hospitalier Universitaire Vaudois, Switzerland)
Rino Rappuoli (Novartis, Italy)
Manuel Romaris (European Commission, Belgium)
Rafick-Pierre Sekaly (University of Montreal, Canada)
Steve Wakefield (HIV Vaccine Trials Network, USA)
Acknowledgements

The Enterprise would like to acknowledge the efforts of all those in the HIV vaccine field who have embraced the mission of the Enterprise to accelerate HIV vaccine development through increased collaborations and a commitment to contributing to the implementation of the shared scientific plan.

The Enterprise Coordinating Committee members are recognized for their many hours of service in advising the interim Secretariat and guiding the development of the Enterprise.

We would also like to take this opportunity to recognize the Bill & Melinda Gates Foundation’s support for the Enterprise in agreeing to serve as the interim Secretariat, and contributing the time and effort of several of its staff members. Specific thanks to José Esparza and Siobhan Malone for their dedication to the work of the interim Secretariat. Other Gates Foundation staffs who have been a great asset to the interim Secretariat include Nina Russell, Todd Summers, and Suzanne Wrynn.
The highlighted countries are those with ongoing or completed HIV Vaccine trials.