A NEW COLLABORATIVE ERA IN HIV VACCINE RESEARCH

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Welcome to this report of activities of the Global HIV Vaccine Enterprise — a unique collaboration of more than 30 of the world’s leading HIV vaccine research, funding, policy-making, advocacy and stakeholder organizations, dedicated to working together to accelerate the development of a safe and effective HIV vaccine.

The HIV pandemic is among the greatest health challenges of our time. Worldwide, more than 33 million people are living with HIV, and 2.6 million people became newly infected with the virus in 2009 alone. The vast majority of these new infections — about 97 percent — occur in low- and middle-income countries. Each infection is a tragedy that forever changes individual lives and families and destabilizes nations.

Today, the growth in new HIV infections continues to outpace the global capacity to provide treatment to all who need it. For every individual who starts antiretroviral treatment today, two additional people are newly infected with HIV. Access to treatment deserves continued and increased support — but it is also becoming increasingly clear that ending this pandemic will require preventing new infections before they happen.

Fortunately, we have entered a new and highly promising era in HIV prevention. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reports that increased use of condoms and HIV testing are helping to reduce new infections in some of the most severely affected parts of the world. The RV144 trial, which provided the first evidence of safety and modest effectiveness for an HIV vaccine, has brought a renewed energy and scientific focus to the field. Antiretroviral-containing microbicides and pre-exposure prophylaxis, two new technologies to prevent HIV infection, are advancing in laboratory and clinical studies, and we are learning more about the prevention benefits of broader access to HIV treatment following the impressive results of the HPTN 052 study. If these HIV prevention approaches can be improved and made available on a large scale, the number of lives they save could be counted in the millions.

Effective HIV prevention will likely require a combination of approaches. Past experience with infectious pathogens, however, makes clear that a safe and effective HIV vaccine will be an essential component of any comprehensive global HIV prevention strategy to end this pandemic once and for all.

Vaccines are relatively inexpensive, easy to administer and yield lasting effects. Vaccines have nearly or completely eliminated global killers such as smallpox and polio. In fact, it is possible that no single product would be more powerful in saving lives, advancing development goals, reducing poverty and improving global security than an HIV vaccine.

The overwhelming need for a safe and effective HIV vaccine is matched only by the complexity of developing one. The lack of a natural, effective protective human immune response to HIV and the rapid rate of mutation and resulting antigenic diversity of the virus make this one of the greatest scientific challenges ever encountered — one that requires an unprecedented level of coordination and collaboration among researchers, funders, policy makers and advocates.

The Global HIV Vaccine Enterprise (the Enterprise) recognizes that no single organization or country can develop a safe and effective HIV vaccine in isolation. Instead, the Enterprise is an alliance of independent organizations working in collaboration to share information, develop better research tools and strategies, prioritize goals and mobilize new resources to speed the development of a safe and effective HIV vaccine through the implementation of a shared scientific strategic plan.

The idea of a Global HIV Vaccine Enterprise was first proposed by two-dozen leading scientists and funders in June 2003, and was enthusiastically endorsed by the leaders of the G8 nations the following year.

By 2005, Enterprise partners had developed the first shared Scientific Strategic Plan for HIV vaccine research.
It is possible that no single product would be more powerful in saving lives, advancing development goals, reducing poverty and improving global security than an HIV vaccine.

Building on the Plan recommendations, Enterprise stakeholders developed new collaborations to address some of the greatest research challenges facing the field: the National Institute for Allergy and Infectious Diseases’ (NIAID) Center for HIV-AIDS Vaccine Immunology (CHAVI), which focuses on understanding the critical early events that follow HIV infection; and the Bill & Melinda Gates Foundation’s Collaboration for AIDS Vaccine Discovery (CAVD), which works to deepen our understanding of immune responses and to standardize the assays and research methodologies used in HIV vaccine research worldwide. Many other advances inspired by the original Scientific Strategic Plan of the Global HIV Vaccine Enterprise, as well as the recommendations of the completely updated plan released in 2010, are detailed in this report.

Today, more than 30 stakeholder organizations from around the world have joined forces through the Global HIV Vaccine Enterprise to develop and implement a coordinated program of independently executed scientific and clinical research; catalyze fresh thinking; and support new approaches to advance HIV vaccine research. As the stories in this report show, research conducted and funded by Enterprise partners is bringing us closer to our shared goal of a safe and effective HIV vaccine.

HIV vaccine research has progressed further and faster in the past five years than at any time since the epidemic began. This new and highly promising era in research is reflected in and guided by the completely updated and revised Scientific Strategic Plan of the Global HIV Vaccine Enterprise (Nature Medicine 16, 981–989; [2010]). The Plan, informed by the input of hundreds of experts worldwide and developed in consultation with the Council of the Global HIV Vaccine Enterprise, which comprises the senior representatives of the world’s major HIV vaccine research, funding, policy and advocacy organizations, contains recommendations and strategies to address the most pressing challenges we face today. These challenges include the need to maximize the scientific knowledge gained from vaccine clinical trials, improve preclinical models for vaccine research, improve data access and analysis and better utilize the latest scientific technologies from other fields.

The Secretariat of the Enterprise helps to catalyze the activities of this diverse global network and shared scientific effort. The Secretariat’s staff works to maximize the collaborative efforts of Enterprise stakeholders to implement the Scientific Strategic Plan, support timely discussions in the field, mobilize new resources for HIV vaccine research and bring new organizations and expertise to the challenge. The Secretariat also organizes the annual AIDS Vaccine conference, the leading global forum for scientific exchange on HIV vaccine research, and facilitates stakeholder consultations on the most pressing and challenging issues in the field, such as expediting vaccine efficacy evaluation, exploring humoral responses and approaches to antigen design and developing new strategies to attract the best minds to HIV vaccine research and nurture their efforts.

This report presents moving testimony to the outstanding achievements of Enterprise stakeholders. I have had the great privilege to serve as Executive Director of the Global HIV Vaccine Enterprise during a period of remarkable progress, marked by the collective effort of the Enterprise Board of Directors and Council, the Enterprise Secretariat team and hundreds of scientists around the world, all of whom I consider friends and colleagues. Through their determined efforts, the 2010 Scientific Strategic Plan for HIV vaccine research and development was published; important consultations were held on the implications of the first trial of an HIV vaccine to show partial protection against HIV (RV144); the African AIDS Vaccine Partnership (AAVP) was established in Africa and the AIDS Vaccine for Asia Network (AVAN) was founded; the central role of young and early-career investigators and the need for new scientific technologies in the search for an HIV vaccine were recognized by the field; and new funding from the French government was secured to build a new Vaccine Research Institute.

As we reflect on our progress to date, we must also recognize that challenges lie ahead. Transforming scientific advances into a safe and effective vaccine that can help end the HIV pandemic will require the very best science, new ways of integrating that science into clinical trials and increased and sustained global support. I am confident that the Enterprise Board of Directors, the highly professional and talented team at the Secretariat and all of you reading this report will continue to move HIV vaccine research and development forward.

All the best,

Alan Bernstein, O.C., Ph.D., F.R.S.C., F.C.A.H.S.,
Executive Director,
Global HIV Vaccine Enterprise
ABOUT THE GLOBAL HIV VACCINE ENTERPRISE

Global HIV Vaccine Enterprise

Canadian HIV Vaccine Initiative (CHVI)
Centers for Disease Control and Prevention (CDC)
China AIDS Vaccine Initiative (CAVI)
European Commission
Europrise
GlaxoSmithKline
International AIDS Vaccine Initiative (IAVI)
Merck & Co. Inc.
National Agency for Research on AIDS and Viral Hepatitis in France (ANRS)
Novartis Vaccines
National Institutes of Health, U.S. Department of Health and Human Services (NIH/NIAID)
Sanofi Pasteur
South African AIDS Vaccine Initiative (SAAVI)
UNAIDS
U.S. Agency for International Development (USAID)
U.S. Military HIV Research Program (MHRP)
Wellcome Trust
World Health Organization (WHO)
History and Mission

An effective, affordable and available HIV vaccine will be central to any global strategy to slow and one day end the HIV pandemic. Yet the obstacles to developing that vaccine represent some of the greatest scientific challenges ever addressed in biomedical research.

HIV has evolved in sophisticated ways to evade and escape our immune system. HIV’s extraordinarily high degree of genetic diversity creates the unique challenge of designing a vaccine that is effective against strains circulating in different parts of the world. Moreover, HIV wipes out some of the very cells needed to mount an effective immune response. The extensive global variability of HIV, the lack of a predictive animal model for HIV vaccine development and a number of other obstacles make the development of a highly effective HIV vaccine one of the greatest scientific challenges of all time.

Recognizing the unprecedented scope of this challenge, as well as the promise that increased cooperation among HIV vaccine researchers could provide, two-dozen leading scientists and funders joined together in June 2003 to propose the Global HIV Vaccine Enterprise. This unique collaboration of independent organizations was created to identify the greatest scientific challenges facing the field, promote the best and most productive research and increase global scientific collaboration to develop an HIV vaccine.

Today, the Global HIV Vaccine Enterprise is a unique, international alliance of more than 30 independent research, funding, advocacy and stakeholder organizations and governments, engaged in unprecedented collaboration to speed the development of a safe and effective HIV vaccine.

The Global HIV Vaccine Enterprise:

- Convenes top researchers, funders, advocacy groups and stakeholders to catalyze fresh thinking, set new directions and advance global cooperation to develop a preventive HIV vaccine.
- Develops rigorous, unbiased scientific assessments of the state of HIV vaccine research and the most pressing scientific, organizational and policy issues to be addressed in the field.
- Develops and implements a shared Scientific Strategic Plan for HIV vaccine research that reflects the input and guides the work of the world’s leading scientists and vaccine research supporters.
- Facilitates faster, more efficient information sharing among partners to speed and enhance research and avoid duplication of efforts.
- Mobilizes new funding for HIV vaccine research and development, in alignment with the goals and strategies of the Scientific Strategic Plan.
- Brings new researchers and organizations to the challenge, and supports and strengthens HIV vaccine research capacity in the Global South.
G8 Support for the Global HIV Vaccine Enterprise

G8 endorsements in 2004, 2006 and 2010 have been central to making the Global HIV Vaccine Enterprise and its mission a reality.

2004 G8 Leaders delivered a critical endorsement for the establishment of the Global HIV Vaccine Enterprise at the Sea Island Summit in Georgia, USA.

2006 In their declaration, G8 Leaders reaffirmed that support and praised collaboration between the Enterprise and regional HIV vaccine coordination mechanisms in Eastern Europe and Central Asia, as well as other North/South collaborations in the field such as the European and Developing Countries Clinical Trials Partnership (EDCTP).

2010 In its assessment of action and results against development-related commitments, the G8 Muskoka Accountability Report recognized the valuable contributions of the Global HIV Vaccine Enterprise as a complement to worldwide efforts to develop vaccines, microbicides and treatments for AIDS and other neglected diseases.

Stakeholders of the Global HIV Vaccine Enterprise

- African AIDS Vaccine Partnership (AAVP)
- AIDS Vaccine for Asia Network (AVAN)
- AVAC: Global Advocacy for HIV Prevention (AVAC)
- The Bill & Melinda Gates Foundation
- Centers for Disease Control and Prevention (CDC)
- China AIDS Vaccine Initiative (CAVI)
- Canadian HIV Vaccine Initiative (CHVI)
- European Commission
- GlaxoSmithKline
- International AIDS Vaccine Initiative (IAVI)
- Merck & Co. Inc.
- National Agency for Research on AIDS and Viral Hepatitis in France (ANRS)
- National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health and Human Services (NIAID/NIH/DHHS)
- Novartis Vaccines
- Sanofi Pasteur
- South African AIDS Vaccine Initiative (SAAVI)
- UNAIDS
- U.S. Agency for International Development (USAID)
- U.S. Military HIV Research Program (MHRP)
- Wellcome Trust
- World Health Organization (WHO)
Governance

The Global HIV Vaccine Enterprise is an alliance of leading, independent HIV vaccine research, policy, funding and advocacy organizations. The Enterprise is a U.S. corporation with 501(c)(3) tax status.

The Enterprise is governed by a Board of Directors (members listed on page 30), which is charged with oversight of its assets in furtherance of its charitable, educational and scientific objectives.

Members of the Enterprise Board of Directors are drawn from the Enterprise Council, (members listed on page 30) which, together with the Secretariat, sets the strategic direction of the Enterprise. Council members include representatives of key Enterprise stakeholder organizations from academia, government, foundations, advocacy organizations and civil society, and comprise some of the most respected thought leaders in the HIV vaccine field.

The Enterprise Science Committee (members listed on p. 31) advises the Enterprise Secretariat and Council on the collaborative scientific agenda.

Secretariat of the Global HIV Vaccine Enterprise

In January 2008, Dr. Alan Bernstein became the inaugural Executive Director of the Global HIV Vaccine Enterprise, and a permanent Secretariat was established in New York City. The Secretariat is charged with overseeing the implementation of and updates to the Scientific Strategic Plan; convening stakeholders; advocating for new resources for HIV vaccine research; and managing the day-to-day strategy and advocacy activities of the Enterprise. The Secretariat is led by the Executive Director and the Enterprise Board of Directors and is advised by the Enterprise Council.

Among its responsibilities, the Secretariat of the Global HIV Vaccine Enterprise:

- Oversees implementation of and updates to, and promotes the priorities of the Scientific Strategic Plan.
- Advocates for new resources for HIV vaccine research.
- Organizes the annual AIDS Vaccine conference, the leading global scientific forum for HIV vaccine research (see page 27 for more on the annual AIDS Vaccine Conference and its impact).
- Convenes Enterprise stakeholders and organizes timely scientific workshops and meetings, including:
  - Satellite and roundtable sessions at leading international scientific conferences such as the International AIDS Conferences and International AIDS Society Pathogenesis, Treatment and Prevention conferences.
  - Stakeholder fora on key issues and challenges in the field such as expediting vaccine efficacy evaluation, humoral responses and approaches to immunogen design and innate and mucosal immunity, among others.

At the time of publication, the Enterprise governance structure is under review.
Moving forward, the Secretariat is focused on fostering the global dissemination of the updated Scientific Strategic Plan and the implementation of its recommendations — particularly those related to enhancing the clinical trials endeavor, information dissemination, resource mobilization and measuring the impact of funders’ investments.

AVAC: Global Advocacy for HIV Prevention

Global HIV Vaccine Enterprise member AVAC is an international non-profit that uses education, policy analysis, advocacy and community mobilization to accelerate the ethical development and eventual global delivery of AIDS vaccines and other HIV prevention options. Through programs such as its Good Participatory Practice (GPP) Initiative, Vaccine Communications Working Group and Advocacy Fellowship program, AVAC addresses policy, advocacy, communications and community involvement activities in order to accelerate HIV vaccine and prevention research.

Since 2008, AVAC has collaborated with UNAIDS and other partners on the revision of the Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials (GPP). The GPP Guidelines are designed to provide guidance on the roles and responsibilities of trial sponsors and trial implementers towards participants and their communities. Programs to implement the guidelines are already underway at several AIDS vaccine trial sites.

AVAC convenes the Vaccine Communications Working Group, which focuses on the development and implementation of comprehensive strategies to improve communications, stakeholder outreach, media relations, training and preparedness related to the global HIV vaccine research and development agenda. This group was especially important in the global dissemination of the RV144 vaccine trial results. The group also liaises with similar entities coordinating communications strategies in the PrEP and microbicide fields.

In 2009, AVAC launched the HIV Prevention Research Advocacy Fellowship to expand the capacity of civil society advocates in Africa and their host organizations to monitor, support and help shape HIV prevention research worldwide. Projects focus on a variety of issues related to vaccine research, including journalist and media engagement around prevention research; research literacy; and building civil society engagement in the research process, among others. Nine Fellows were selected in 2010, and seven additional Fellows were selected for 2011.

AVAC publishes an annual report of the biomedical prevention field, and in 2010 published Turning the Page, which focused on recent positive research results including the RV144 vaccine study and addressed critical questions facing the field as it writes the next chapter in HIV prevention research.

Highlights of AVAC’s support of HIV prevention research include:

- Continuous engagement of the Vaccine Communications Working Group, established as an independent entity in 2007, to track vaccine-related media, draft messages for the field and conduct trainings around reporting on AIDS vaccine research.
- The launch of the GPP Initiative in 2008 and grants awarded to a dozen groups across the globe.
- Revision of GPP guidelines in 2010, and the development of plans to implement the guidelines at clinical trial sites around the world.
- AVAC’s regular convening of meetings to discuss the possible impact of other prevention research results on AIDS vaccine research and trial design.
- In-depth analyses, via our policy program, of critical issues in vaccine research and development.
- Continued tracking and publication of annual investment and expenditure data for vaccines and microbicides for the HIV Vaccine and Microbicide Resource Tracking Working Group.

“The greatest advances in the fight against AIDS have come when people and institutions refused to accept conventional wisdom about what was possible. There have been many moments when an AIDS vaccine was deemed a scientific impossibility. Yet, we now have proof that a preventive AIDS vaccine is possible. This is the best and most important time to invest in vaccine research.”

— Mitchell Warren, executive director, AVAC
The cornerstone of the Global HIV Vaccine Enterprise is its Scientific Strategic Plan, a collaboratively developed and implemented framework to accelerate HIV vaccine research. The Scientific Strategic Plan represents the collective vision of Enterprise partners, and helps to align their strategies and activities to speed and enhance HIV vaccine research and development.

In 2005, the newly formed Global HIV Vaccine Enterprise produced the first coordinated vision for the global HIV vaccine research endeavor. That groundbreaking plan laid out a framework to improve dialogue and coordination among funders and scientists, and led to the establishment of new initiatives designed to:

- Increase global investment in HIV vaccine research, and the quantity and quality of sustainable HIV vaccine clinical research facilities.
- Standardize key assays used in HIV vaccine research worldwide, to allow for comparability of research results and increased information and knowledge sharing.
- Expand regulatory capacity to make more clinical research possible, and to ensure its safe and ethical conduct.
- Promote new principles for community engagement and update ethical guidelines for HIV vaccine clinical research.
- Expand collaboration between northern and southern world researchers.
- Create an intellectual-property framework to stimulate early-stage HIV vaccine research.

Developed with input from 140 scientists in 15 countries, the 2005 Scientific Strategic Plan of the Global HIV Vaccine Enterprise transformed HIV vaccine research. A field that had been led previously by the initiative of individual investigators and research institutions now had the additional force of a shared global strategy behind it.

Collaborative approaches to vaccine development in response to the Scientific Strategic Plan, including the creation of HIV vaccine research centers and consortia, continue to transform the field today. The Center for HIV/AIDS

“...It is feasible to block acquisition of HIV infection. We know from the Thai trial that it can be done. The proof of concept here is huge. I don’t think there’s any question we’re going to get there. We have a light at the end of the tunnel. All we need to do is follow the light, follow the science.”

Anthony S. Fauci, director, National Institute of Allergy and Infectious Diseases, at AIDS Vaccine 2010, Atlanta, Georgia
Vaccine Immunology (CHAVI), funded by the U.S. National Institutes of Allergy and Infectious Diseases (NIAID), is a consortium of scientists in universities and academic centers that focuses on understanding the critical early events that follow HIV infection and works to solve major problems in HIV vaccine development and design through the efforts of highly collaborative Discovery Teams. The Collaboration for AIDS Vaccine Discovery (CAVD), funded by the Bill & Melinda Gates Foundation, is an international network of scientists and experts working to improve understanding of immune responses, develop standardized assays and research methodologies for use in HIV vaccine research worldwide and design and test novel HIV vaccine candidates.

**Stakeholder Achievements**

Working independently and in collaboration, Enterprise stakeholders, the global leaders in HIV vaccine research, have produced major discoveries that have made the last five years the richest period in HIV vaccine research since the epidemic began. Among the recent advances that Enterprise partners have led and are building upon are:

- The landmark results of the RV144 clinical trial in Thailand, the first evidence that a vaccine regimen can confer protection against HIV acquisition.
- New insights into the potential of mosaic sequences to elicit broader immune responses in non-human primates.
- New understanding of the immunological events following HIV infection, which provide important insights into potential strategies for HIV vaccine development.
- The discovery of antibodies capable of neutralizing a broad array of HIV isolates, and the development of new technology that allows for the faster and more detailed identification of these antibodies.
- A deepening understanding of the mechanisms of viral control in both nonhuman primates and in humans, and new insights into the immunological and genetic basis by which some individuals (elite controllers or long-term non-progressors) control HIV infection.
- Increased appreciation and study of the mucosa as a barrier to HIV infection and the site of early host responses following acute infection.
- Multiple non-human primate (NHP) models showing protection against infection with SIV with rectal or vaginal challenge.
- The demonstration of vaccine-induced control of SIV by CD8+ effector memory T cells.
- New insights into vaccine design through the ongoing analysis of four efficacy trials: VaxGen 003, VaxGen 004, STEP and Phambili.

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“The together we can succeed in overcoming what some have called the greatest scientific challenge of our time — finding an HIV vaccine.”

— Michel Sidibé, executive director, UNAIDS

The Enterprise was instrumental in expanding the scientific and communications response to one of the most important events to date in the HIV vaccine research endeavor: the announcement of positive results from the RV144 HIV vaccine trial in Thailand. In June 2009, the Enterprise Coordinating Group to Prepare for the Release of Results from Large Scale Efficacy Trials, consisting of 40 representatives from basic science and clinical research and representing industry, regulators, the trial sponsors and five major funding agencies, met to discuss the possible scientific and communication challenges related to the imminent release of results from this historic trial involving more than 16,000 volunteers in Thailand. The Enterprise Secretariat hosted a follow-up meeting approximately one week after the Thai trial results became available, on October 1, 2009, to review and help coordinate the initial field-wide response to the trial, and plan how best to communicate to various audiences the results and their implications for the future of HIV vaccine research and development.
Center for HIV/AIDS Vaccine Immunology (CHAVI)

Since 2008, the National Institute of Allergy and Infectious Diseases (NIAID) at the U.S. National Institutes of Health (NIH) has funded a number of initiatives that have furthered HIV vaccine discovery and preclinical research. Highlights include:

- The discovery of two potent human antibodies (VRC01 and VRC02) by NIAID’s Vaccine Research Center (VRC), which inactivated more than 90 percent of a panel of global HIV-1 strains in the laboratory.1,2
- The study of a vaccine regimen employing two distinct adenovirus vectors (rAd26, rAd5) at NIAID’s Integrated Preclinical/Clinical AIDS Vaccine Development Program (IPCAVD), which reduced viral set point and decreased AIDS-related mortality in non-human primates better than a regimen employing a single vector.3
- The use of a vaccine insert with a “mosaic” design, which expanded the breadth and depth of immune responses in mice and rhesus monkeys. In theory, these immunogens could provide nearly optimal coverage of the diverse variants of HIV circulating globally.4,5,6
- A new “scaffold” strategy to teach the immune system to recognize certain protein structures on the viral surface and produce antibodies that bind to those structures. Efforts will continue to refine this technique and apply it to vaccine design.7

In addition, NIAID has facilitated important progress in clinical research including:

- The Thai HIV Vaccine Trial (RV 144), sponsored by the U.S. Military HIV Research Program (MHRP) with major funding and support from NIAID, showed that a candidate vaccine (ALVAC-HIV and AIDSVAX B/E) was 31 percent effective at preventing HIV infection. Though modest, the protective effect showed for the first time that an HIV vaccine can prevent infection in people.8
- The evaluation of HIV immune responses of the STEP study volunteers who became infected during the study by the HIV Vaccine Trials Network (HVTN) laboratory program. This research, which seeks to gain insight into the lack of efficacy of this particular vaccine approach, indicates that broader Gag responses may be associated with increased control of viral replication in STEP study vaccinees.9

NIAID is also actively involved in encouraging other valuable collaborations across organizations working in HIV vaccine research, such as the IAVI/HVTN collaboration.

National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH)

Since 2008, the National Institute of Allergy and Infectious Diseases (NIAID) at the U.S. National Institutes of Health has funded a number of initiatives that have furthered HIV vaccine discovery and preclinical research. Highlights include:

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NIAID is also actively involved in encouraging other valuable collaborations across organizations working in HIV vaccine research, such as the IAVI/HVTN collaboration.
The Bill & Melinda Gates Foundation

HIV vaccine development is a top priority for the Bill & Melinda Gates Foundation, one of the founding members of the Global HIV Vaccine Enterprise. The foundation focuses its funding primarily on advancing novel HIV vaccine concepts to early clinical evaluation, and on moving more advanced vaccine candidates towards efficacy testing.

In 2006, the Gates Foundation launched the Collaboration for AIDS Vaccine Discovery (CAVD) in support of the original Enterprise Scientific Strategic Plan and its emphasis on the need for increased scientific collaboration in the field. CAVD brings together HIV vaccine researchers focused on different aspects of HIV vaccine discovery and development, in order to promote the use of standardized reagents and the prompt sharing and evaluation of ideas and data. The foundation has provided over $355M to the effort since 2006.

By 2010, CAVD had grown to include more than 700 investigators from more than 100 different institutions in 19 countries. CAVD’s progress in advancing HIV science and collaboration in the field has accelerated rapidly in the past two years, as the consortium has matured and collaborations increased.

Today, important scientific progress is being made on antibody and T cell vaccine approaches, and with other novel concepts. CAVD investigators have discovered new neutralizing and broadly neutralizing antibodies; identified novel CD4i antibodies; discovered novel immunogens; and have facilitated a greater understanding of the mechanisms of neutralization. CAVD investigators focused on T cell approaches have advanced the development of replication competent vectors, the optimization of novel poxvirus vectors, and our understanding of the role of epitope processing to improve immunogenicity.

The CAVD centralized service facilities have made significant progress in optimizing and standardizing reagents and methods to ensure that studies from different laboratories can be compared and combined. Approaches for data and material sharing have improved, with 154 Material Transfer Agreements executed to date. CAVD consortia have registered 83 studies on the CAVD portal, with data from 32 studies being shared with the CAVD community within one month of study completion, and data from an additional 17 studies shared with the broader scientific community within three months of study completion. Publications and abstracts provide an additional avenue for sharing data from CAVD research consortia. CAVD consortia have published 253 scientific articles, 40 of which were authored collaboratively by two or more consortia, and 327 abstracts have been presented at 71 different conferences.

The foundation also funded a handful of HIV vaccine initiatives outside of the CAVD. These include:

- Four research grants through the Grand Challenges in Global Health and several through the Grand Challenges Explorations (GCE) efforts.
- Funding to the AIDS Vaccine conference to ensure data sharing and collaboration beyond the CAVD.
- Foundation support for policy and advocacy efforts through grants to IAVI, AVAC, the Global HIV Vaccine Enterprise and WHO.
- Support for six clinical trials capacity building efforts in Sub-Saharan Africa through a grant to EDCTP.

Global HIV Vaccine Enterprise partners are also building on advances in other areas of biomedical research with important implications for HIV vaccine development — many of which span both basic and clinical research. These advances include the development of faster, cheaper DNA sequencing technologies; high-throughput technologies; and new computational and database methodologies. New technologies in structural and computations biology are providing novel approaches for designing immunogens that might elicit broadly reactive neutralizing antibodies, and fresh insights into innate and mucosal immunity are expanding HIV vaccine design strategies.

“The Bill & Melinda Gates Foundation has been committed from day one to the vision and mission of the Global HIV Vaccine Enterprise and to fostering greater collaboration in the field. The Collaboration for AIDS Vaccine Discovery has made collaboration among researchers a valued opportunity.”

— José Esparza, deputy director, HIV, senior advisor, HIV Vaccines, The Bill & Melinda Gates Foundation
The U.S. Military HIV Research Program (MHRP) seeks to reduce the risk of HIV infection worldwide. MHRP is focused on a number of key targets outlined in the Global HIV Vaccine Enterprise Scientific Strategic Plan, including accelerating the testing of diverse vaccine candidates in at-risk populations; strengthening operational and regulatory capacity; fostering new collaborations; improving data access and analysis; developing, standardizing and sharing new tools for preclinical models; and expanding and improving platforms and assays.

In 2009, MHRP announced results of RV144, an Army-sponsored clinical trial in Thailand that demonstrated for the first time a modest ability to protect against HIV infection, reducing the number of infections by 31.2 percent. MHRP researchers are now working with scientists around the world, with support from the U.S. National Institutes of Health (NIH), to dissect the results of RV144 in order to inform basic research and design future clinical trials to translate this scientific milestone into a deployable vaccine.

MHRP is also planning follow-on studies to RV144, including two smaller clinical trials slated to begin in 2011 in Thailand and a larger trial in men who have sex with men planned for 2014. These studies will build on the early effect seen in RV144 — in which protection against HIV infection appeared as high as 60% between 6-12 months. These trials are being designed to determine whether a new, additional boost can prolong this level of protection and whether this protection will extend to groups at higher risk of acquiring HIV infection.

MHRP also began two Phase I studies that include a promising new modified vaccinia virus Ankara (MVA) vaccine in combination with a DNA vaccine candidate, with the goal of achieving broad protection against a variety of HIV strains. The MVA vaccine was developed collaboratively with researchers from MHRP and the U.S. National Institute of Allergy and Infectious Diseases (NIAID). MHRP researchers are developing another vaccine candidate in collaboration with Harvard University that will employ mosaic inserts carried by Ad26 and MVA vectors. Early studies of this candidate prime boost vaccine regimen have shown unprecedented immune responses and protection from SIV infection in non-human primates.

These studies are the result of extensive partnerships with U.S. and international governments, research institutions and academia. The RV144 laboratory studies represent one of the broadest collaborative efforts in the field, encompassing more than 30 research organizations. RV144 also showed the value of empirical clinical trials and has prompted other research groups to plan clinical trials using a vaccine combination similar to the one used in the RV144 prime-boost trial.

Other MHRP HIV vaccine research initiatives include:

- A Phase I - HIVIS 02 DNA/MVA-CMDR study, conducted at the Karolinska Institute in Sweden. Results of the study were published in the *Journal of Infectious Diseases* 15 Nov 2008. The phase I/II–HIVIS 03 study is ongoing in Tanzania and has shown a very high level of immunogenicity.

- A Phase I study of PENNVAX-G/MVA-CMDR began in the U.S. in September 2010. The study will assess safety and immune responses in HIV-uninfected volunteers in the U.S., Thailand and four sites in Africa. This combination prime boost vaccine regimen was designed to deliver a diverse mixture of antigens for HIV-1 subtypes A, B, C, D and E including an arm where DNA will be given by electroporation.

- HVTN and other researchers are planning to conduct adaptive clinical trials of vaccine regimens similar to RV144 and conventional trials of a subtype C ALVAC + gp120 prime boost regimen in high-risk heterosexuals in South Africa in 2012 and 2014, respectively.

“RV144 marked a ‘yes we can’ moment in the search for an effective HIV vaccine. The study raised several interesting hypotheses — and questions — about the types of immune responses that may control acquisition and how to measure them that will inform new clinical trials.”

— Colonel Nelson Michael, director, U.S. Military HIV Research Program
European Commission

The European Commission (EC), a founding member of the Enterprise, works to structure and integrate European research on HIV/AIDS into a pipeline of projects ranging from basic science to preclinical and early-clinical testing of new drugs and therapeutic approaches, microbicides and vaccine candidates.

To achieve its mission, the EC supports close partnerships between European scientists and research teams in non-European countries, as well as between industrial and public sector research. Any country is able to participate in the EC’s Framework Programme (FP), which funded seventeen collaborative multidisciplinary projects on HIV/AIDS research from 2007–2010. About €32 million was allocated to HIV vaccines of a total EU contribution to HIV/AIDS research of €82 million during this period.

In addition, the EC continues to fund the EUROPRISE Network of Excellence, which is designed to integrate and coordinate activities among top European research centers working on new prevention strategies against HIV, including microbicides and vaccine research. The network of 40 partners and 26 affiliated partners from 13 European countries directly supports three clinical trials. Europrise partners are also involved in 31 separate clinical trials, including approximately 15 research projects funded by both the EC and The Bill & Melinda Gates Foundation.

The EC also finances the European and Developing Countries Clinical Trials Partnership, an initiative launched in 2003 to promote European research integration and strong partnerships with African scientists to support capacity-building and advanced clinical trials for HIV/AIDS, malaria and tuberculosis.

Among its key accomplishments, the EDCTP has established four networks of excellence to prepare African sites for clinical trials on HIV, TB and malaria. EDCTP’s Framework Program 5 “HIVIS” project has completed a phase I trial and is in early phase I/II to assess the safety and immunogenicity of a DNA prime and MVA boost in Tanzania and Mozambique (TOMAVAC I). Two infant HIV vaccine trials have also been initiated to assess the safety of new vaccine candidates.

Since 2007, the EC has also financed a number of collaborative multiyear HIV vaccine projects involving European, non-European and developing world research organizations. Among these are:

- “Next generation HIV-1 Immunogens inducing broadly reactive neutralizing antibodies (Nab),” or NGIN (http://ngin.eu). NGIN seeks to develop a variety of ‘next-generation’ HIV-1 envelope-based immunogens that are capable, in combination with new adjuvant formulations, of eliciting high-titer broadly Nab responses.

- “EUROpean consortium on NEUTralising antibodies using gp41” or EuroNeut-41 (http://www.euroneut-41.eu) coordinated by Dr Raphaelle El-Habib from Sanofi-Pasteur. The project is establishing a platform where gp41-derived vaccine candidates can be designed for eliciting neutralizing antibodies.

- “Cutaneous and mucosal HV vaccination” or CUTHIVAC (http://www.upmc.fr/fr/recherche/europe/7e_pcrd/cut_hivac.html) coordinated by Prof Behazine Combadière from the Université’ Pierre et Marie Curie in France.

CUTHIVAC will assess a new HIV vaccine strategy to prevent and control HIV infection based on transcutaneous and/or mucosal routes and immunogen delivery systems.

- “Optimisation of the development of Poverty-Related-Diseases (PRD) vaccines by a transversal approach, addressing common gaps and challenges” or INYVAX (http://www.inyvax.eu/), coordinated by Dr Odile Leroy from the European Vaccine Initiative (EVI) in Heidelberg. INYVAX aims to i) establish a comprehensive database of marketed vaccine technologies; ii) optimise knowledge and resources for the formulation of PRD vaccines; and iii) implement safety standards in clinical trials of PRD vaccines. INYVAX is also sponsoring training programs such as the Advanced Training Course in Vaccinology (ADVAC) for young investigators.

- “Platform for the Harmonization of Vaccine Adjuvant Testing” or PHARVAT (http://www.pharvat.eu/), coordinated by from the European Vaccine Initiative (EVI) in Heidelberg, aims to establish laboratory assays that can be used to harmonise pre-clinical determination of vaccine adjuvant activity.
The new collaborative approach to HIV vaccine research outlined in the first Scientific Strategic Plan for HIV vaccine research and embodied by the Global HIV Vaccine Enterprise helped to ensure that the years 2008–2010 were among the richest and most scientifically productive in HIV vaccine research since the epidemic began. During this period, landmark discoveries such as the isolation of broadly neutralizing antibodies were informing new strategies for vaccine design, and powerful new technologies advanced our understanding of HIV infection and the human immune system. In September, 2009, results from the RV 144 vaccine trial in Thailand provided the first proof of concept that a vaccine could reduce the risk of HIV infection in humans.

By 2009, collaborative efforts such as the Enterprise, the African AIDS Vaccine Partnership (AAVP), Chinese AIDS Vaccine Initiative (CAVI), CHAVI, CAVD, South African AIDS Vaccine Initiative (SAAVI) and other initiatives had brought about a new era of global collaboration in the field. While HIV vaccine research was progressing as never before, however, new challenges were also emerging that required a fresh and thorough reevaluation of the vaccine research endeavor.

Development of the 2010 Plan
Enterprise partners agreed that continuing and speeding the forward momentum in HIV vaccine research would require an updated plan for the field. The Enterprise Council called for the development of an updated Scientific Strategic Plan, to incorporate the input of leading HIV vaccine researchers worldwide. The Enterprise Science Committee created the framework for the updated Plan, establishing five expert Working Groups to develop detailed reports on specific challenges in key areas of HIV vaccine research, including:

- Immunogens and antigen processing.
- Host genetics and HIV diversity.
- Novel approaches to HIV vaccine research and development.
- Bridging the gaps between fundamental, preclinical and clinical research.
- Attracting and retaining young and early-career investigators to HIV vaccine research.

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Working Group focus areas were chosen in part to encourage interaction and problem solving between groups that often do not have the opportunity to collaborate in the normal process of HIV vaccine research, discovery and testing. Members of the Enterprise Science Committee identified potential Working Group participants, and the committee chairs selected Working Group members with an eye toward diversifying Working Group membership by country, region, gender and expertise, and to ensuring the inclusion of participants from academia, industry, government and stakeholder organizations (see page 32 for a list of Working Group members).

Across an 18-month process, a diverse group of scientists, policymakers, funders and advocates worldwide collaborated to develop the Working Group reports. Those expert reports were then incorporated through the efforts of the Enterprise Science Committee and Council in the final version of the Global HIV Vaccine Enterprise Scientific Strategic Plan.

The resulting Plan, which was published in *Nature Medicine* in October 2010, is a forward-looking framework to speed the development, execution and analysis of HIV vaccine trials; better integrate pre-clinical and clinical research; more effectively capitalize on scientific advances from other fields; and bring new researchers and new funders to the global effort to develop a safe and effective HIV vaccine. The Enterprise Plan seeks to take the field forward in the fastest, most efficient way possible, toward the goal of developing a safe and effective HIV vaccine.
Supporting and Implementing the Scientific Strategic Plan

Dozens of research priorities emerged from the collaborative process of developing the new Scientific Strategic Plan. Following extensive deliberation and review, these priorities were synthesized by the Enterprise Council into two overarching scientific priorities for the future of HIV vaccine research:

**Priority 1: Optimize the clinical trials endeavor by fully integrating iterative scientific inquiry with product development.**

**Priority 2. Harness the full potential of preclinical models and the revolution in biomedical science.**

In addition, the new Scientific Strategic Plan identified three key issues that cut across the Plan priorities: the need to increase the engagement of the pharmaceutical and biotech industries in HIV vaccine research and development; the need to attract new researchers, including young and early-career investigators, to the HIV vaccine challenge; and the need to increase and diversify funding for HIV vaccine research.

**Plan Priority 1**

HIV prevention trials take many years to plan, fund, approve, conduct and analyze. Priority 1 focuses on the importance of clinical efficacy trials and the unequalled opportunity they present to obtain critical information about signatures of protection and the human immune system’s response to vaccine candidates. Priority 1 emphasizes the importance of integrating fundamental laboratory science with the conduct and analysis of clinical trials and strategies, in order to develop and implement clinical trials that test more HIV vaccine concepts in less time, while preserving appropriate safety, community engagement and ethical guidelines.

Among the strategies to fulfill Priority 1, the Plan proposes new approaches to expand the pipeline of promising HIV vaccine candidates, speed the testing of new vaccines and improve the efficiency with which the results of those studies are shared and analyzed. Specifically, the Plan recommends stakeholder action to:

- Accelerate the clinical testing of promising vaccine candidates, while simultaneously maximizing opportunities to advance scientific discovery.
- Support a diversity of approaches to vaccine research and trial design.
- Strengthen regulatory and clinical trial capacity to expedite the review, approval and execution of trials.
● Engage concerned communities, including volunteers, advocates and community leaders, in the design and implementation of scientifically robust and ethically sound trials.
● Expand and improve laboratory platforms and assays to analyze immunological responses to vaccination.

Plan Priority 2

Priority 2 acknowledges that fundamental questions about how to achieve immune protection against HIV infection remain unanswered. More basic research is needed to better understand key issues such as the window of opportunity for protection that exists at the beginning of the infection process, and the interplay between host defenses and viral evolution. Recognizing this, the Plan recommends a series of actions to facilitate the incorporation of new tools and ideas from other areas of biomedical research into HIV vaccine research. Among the promising developments in other fields with the potential to advance HIV vaccine research are the development of advanced imaging technologies for studying mucosal immunity and the trafficking of viral/vaccine antigens and immune effectors; genomic technologies to better understand the complex interplay between the host and HIV; high-throughput methodologies for optimizing vaccine design; and promising new immunogen design and gene-delivery technologies.

“Being a product development partnership, IAVI has always sought to explore neglected avenues of research and build bridges between sectors. These strategies are essential to bring together all the expertise needed to speed progress toward a broadly effective AIDS vaccine.”

Seth Berkley, M.D., CEO and founder, International AIDS Vaccine Initiative

The 2010 Scientific Strategic Plan also recommends strategies to increase collaboration with researchers from other disciplines, whose insights could help to transform current approaches to HIV vaccine discovery and development. Notable among these is systems biology, which provides a promising approach to understanding the complex architecture of the host immune response to HIV and for the integrative analysis and modeling of large datasets that could drive improvements in vaccine design and delivery strategies.

Maximizing the value of the growing data sets generated by today’s “omics” science and complex vaccine trials requires increasingly sophisticated computational technologies and an unprecedented global commitment to rapid data access. To address this challenge, the 2010 Plan calls for a new consensus on the principle of rapid access to data and the development of infrastructure required to annotate, deposit and analyze the increasingly large amounts of data being generated by HIV vaccine research and clinical trials today and those expected in the future.

International AIDS Vaccine Initiative (IAVI)

The International AIDS Vaccine Initiative (IAVI) is a founding member of the Enterprise and has continued its work to ensure the development of safe and effective HIV vaccines for use throughout the world. IAVI’s antibody project, a global hunt for new broadly neutralizing antibodies (bNAbS) to HIV and an effort to develop immunogens informed by them, has provided a significant return on investment for the field. The project is led by IAVI-affiliated researchers who worked closely with two biotechnology companies to screen serum samples collected from more than 1,800 volunteers at research centers in 11 countries on four continents. To date, the antibody project has led to the isolation of more than a dozen new bNAbS, including a number that are highly potent and that have led to identification of vaccine targets on the virus. The most promising of these newly uncovered bNAbS are informing immunogen design efforts by researchers working within IAVI’s Neutralizing Antibody Consortium and in companies recruited to the effort through IAVI’s Innovation Fund.

IAVI’s vector design and vaccine development efforts have proceeded apace as well, through a number of early-stage clinical trials in the U.S., U.K., India and several countries in sub-Saharan Africa. IAVI is supporting the first study of DNA vaccine candidate delivery by electroporation, involving a prime-boost strategy and a novel adenovirus 35 candidate that has been shown to be safe and immunogenic. IAVI and its partners are also advancing four replicating vector candidates, designed to better activate immune defenses at mucosal surfaces, with the aim of putting two of these into Phase I trials beginning in 2012.

In keeping with its longstanding commitment to community engagement and ethical vaccine research, IAVI has maintained its community outreach and mobilization programs, including training community advisory boards and advocating for HIV vaccine R&D. The organization has developed a program to train staff to take gender issues into account in the conduct of clinical trials at collaborating research centers. It has continued to train staff in the clinical trials network it supports in sub-Saharan Africa and India, adding competence in sophisticated immunologic assays, such as epitope mapping, to a training program that already covers Good Clinical Practice, Good Clinical Laboratory Practice and Good Participatory Practices.
Improving the relevance of preclinical models, including humanized mouse models and non-human primates (NHP), is another major focus of Priority 2. To date, the utility of the NHP model has been limited by challenges including high costs, which have underpowered many studies; the lack of standardized methodologies and challenge models; and the lack of shared reagents, tools, technologies and infrastructure to optimize the model. To address these challenges, the 2010 Plan recommends a number of strategies to standardize protocols, assays and reagents in NHP research, and to establish consortia designed to reduce the costs and maximize the impact of existing NHP resources.

To advance Priority 2, the Plan recommends stakeholder action to:

- Continue and expand efforts to open the HIV vaccine research endeavor to the use of novel scientific approaches and technologies.
- Foster collaboration with researchers from disciplines that have the potential to transform current approaches to HIV vaccine discovery and development.
- Build consensus on the principle of rapid access to data and develop the infrastructure to annotate, deposit and analyze large amounts of data.
- Make better use of global NHP infrastructure and enhance current capacity to support appropriately powered experiments.
- Develop, standardize and share tools and technologies to support NHP studies.

“Public-private cooperation and the creation of global partnerships are central to winning the battle against HIV/AIDS. The European and Developing Countries Clinical Trials Partnership (EDCTP) has invested €200 million in accelerating the clinical development of new products to address poverty related diseases including HIV/AIDS. The EU Research Framework Programme has been instrumental in generating today’s pipeline of vaccine candidates.”

— Ruxandra Draghia-Akli, director for health, directorate-general for research, European Commission
Industry Engagement

Several principles that cut across these priorities are key to achieving the vision of the Plan. Among these are the need to increase the engagement of private enterprise in the development and testing of HIV vaccine candidates, and increase collaboration between academia and the private sector. To draw industry back to this global health challenge, the Plan recommends strategies to maximize the scientific value of partnerships with industry, minimize risk for industry and allow for more open, nonexclusive arrangements, especially for precompetitive areas of research.

Specifically, the Plan recommends the establishment of more innovative partnerships with industry that allow industry to maximize the scientific value of their investments in HIV vaccine research and development efforts in the private and public sectors including academic institutions, as well as activities related to the prevention of mother-to-child transmission of HIV.

The Initiative will also support the establishment of a CHVI Research and Development Alliance (Alliance), based in Canada, to serve as the focal point for Canadian research, product development and technical expertise related to HIV vaccines. The Alliance will enable Canada to be a leading contributor to global efforts in developing a safe, effective, affordable and globally accessible HIV vaccine.

Additional achievements include: the launch of several funding competitions with a total of 38 projects supported focusing on domestic and international research, improving collaboration among researchers in Canada and around the world and enhancing capacity for vaccine trials, policy development and community engagement; stakeholder consultations; literature reviews and policy papers; and a mid-term evaluation. The CHVI has also contributed to several national and international fora and has developed meaningful relationships with global stakeholders. Additional information is available on the CHVI website http://www.chvi-icvv.gc.ca.

The Canadian HIV Vaccine Initiative (CHVI)

The Canadian HIV Vaccine Initiative (CHVI), Canada’s contribution to the Global HIV Vaccine Enterprise, is a collaborative undertaking between the Government of Canada (GoC) and The Bill & Melinda Gates Foundation (Gates Foundation).

In July 2010, the GoC and the Gates Foundation renewed their collaboration and financial commitment to implement the CHVI. The primary goal of the renewed collaboration is to accelerate the development of a safe and effective HIV vaccine by building on Canada’s scientific excellence for the benefit of those most in need in Canada and in low- and middle-income countries (LMICs), particularly in Africa. The renewed Initiative supports activities that span the continuum of HIV vaccine research and development efforts in the private and public sectors including academic institutions, as well as activities related to the prevention of mother-to-child transmission of HIV.

“Canada continues to lead the way in the global fight against HIV and AIDS. The launch of the CHVI Research and Development Alliance reflects our Government’s continuing commitment to help find a cure for this devastating virus which crosses borders, cultures, genders and backgrounds.”

— Leona Aglukkaq, minister of health, Canada

Other projects funded by the CHVI include:

- Eight catalyst grants awarded to support innovative HIV vaccine-related research activities aimed at the development of new tools, techniques, inventions or methodologies.
- Five operating grants awarded to support Canadian researchers to build future Canadian research capacity in the field.
- Six travel grants awarded to facilitate the participation of Canadian researchers in the CHVI Partnership Development Forum held in October 2008 at the AIDS Vaccine conference.
- Two Emerging Team Grants awarded to support Canadian research teams undertaking collaborative research into discovery of HIV vaccines and related HIV research.
- Launch of a large team grant funding opportunity to foster and support larger collaborative teams of Canadian and LMIC researchers through development of integrated research programs.
- Seven grants and $16 million in funding to Canada-Africa research teams to strengthen the capacity and leadership of African researchers and institutions to conduct future HIV/AIDS prevention trials in sub-Saharan Africa.
- Eight projects to support community engagement and preparedness activities related to HIV vaccines.
- Launch of a funding opportunity to establish and operate an Alliance Coordinating Office in support of a CHVI Research and Development Alliance based in Canada to develop innovative solutions in HIV vaccine research and development.
- The granting of $2 million to the World Health Organization to support capacity-building activities to improve regulatory capacity in LMICs, especially in countries where clinical trials are planned or are ongoing.
- Funding provided to the Global HIV Vaccine Enterprise to foster collaboration among stakeholders; identify the latest scientific developments and gaps in HIV vaccine research; and to further develop and support the 2010 Scientific Strategic Plan.
and strategic collaborations between pharmaceutical and biotech companies, public funders and researchers. Examples include the IAVI/Gates Innovation Fund, which identifies and finances new technologies with the potential for HIV vaccine discovery and development. Other strategies outlined in the Plan include the development of mechanisms to protect intellectual property while ensuring maximum public benefit—such as a globally accepted intellectual-property framework that would support innovation and information sharing while protecting vaccine developers—and the exploration of novel mechanisms to share the results of precompetitive research, while safeguarding the intellectual property of industry partners.

### People

People are at the heart of the HIV vaccine research. The Scientific Strategic Plan emphasizes that an innovative HIV vaccine research effort requires ongoing efforts to attract and maximize the contributions of researchers from areas most affected by the epidemic, and from early-career investigators who bring fresh perspectives, enthusiasm and creativity to research. The Plan also emphasizes that global responses to a global epidemic means strengthening and supporting researchers in the developing world and enabling these researchers to contribute as full partners in HIV vaccine research and development.

To support and sustain the best research talent in low- and middle-income countries, the Plan calls for expanding opportunities for training and mentorship; enhancing efforts to ensure protected research time, salary support and leadership opportunities for researchers; supporting career pathways for clinical trial staff; and strengthening the capacity of research institutions in the developing world.

Developing world governments are vital partners in these efforts. Their support is key to building sustainable national research capacity and ensuring that developing world institutions can fully contribute to the global effort to develop a safe and effective HIV vaccine.

Among the Enterprise stakeholders that have led efforts to strengthen developing world research capacity to date are the African AIDS Vaccine Partnership (AAVP), AIDS Vaccine for Asian Network (AVAN), the International AIDS Vaccine Initiative (IAVI), the WHO-UNAIDS HIV Vaccine Initiative, the Wellcome Trust and the NIH Fogarty International Center, among others.

### Funders and Resources

Securing adequate funding is key to speeding efforts to develop a safe and effective HIV vaccine. Current funding for HIV vaccine research (about $850 million in 2008) is a comparatively small investment of global AIDS resources. This is especially clear when the global investment in HIV vaccine R&D is compared to the global economic impact of AIDS, which is estimated to be between $20 and $50 billion per year, or the $10 billion per year direct cost of providing treatment to just one-third of people who are eligible for it today.

“The development of safe and effective HIV vaccines remains among NIAID’s highest priorities, but we recognize that we cannot reach this goal alone. Collaboration with the industry, U.S. and international government agencies, advocacy and non-profit organizations, and the community is vital to HIV vaccine research. We look forward to continuing and strengthening these important partnerships as we strive to find a vaccine that will prevent HIV globally.”

— Carl W. Dieffenbach, Ph.D., director, Division of AIDS, NIAID/NIH/DHHS

### Wellcome Trust

In Support of the Scientific Strategic Plan’s first priority, the Wellcome Trust, in partnership with the U.K. Medical Research Council and the Department for International Development, will fund global health trials to generate new knowledge about interventions that will contribute to the improvement of health in low and middle-income countries. The focus is on late-stage (Phase III/IV) efficacy and effectiveness trials. Up to £12 million per year for three years has been committed to this effort.

The Wellcome Trust also supports various organizations and initiatives working in biomedical research and medical humanities. These include:

- The U.K. HIV Vaccine Consortium, which is investigating potential HIV vaccine constructs and immunization strategies.
- The Jenner Institute, which aims to develop innovative vaccines against a range of diseases.
- Ongoing partnerships with industry and through the Trust’s Technology Transfer Division. As part of this division, the MSD-Wellcome Trust Hilleman Laboratories was created, which aims to develop affordable vaccines against a range of diseases.
- Support for outstanding individuals via the Trust’s Fellowship Investigator Award.
**AIDS Vaccine for Asia Network (AVAN)**

AVAN’s vision is to develop a safe and effective HIV vaccine and ensure its access as a part of a comprehensive public health strategy for the control of new HIV infections across Asia.

Between 2008 and 2010, the AVAN Task Force was established to foster further dialogue and develop the principles and priorities for a strategic plan for the network. A Task Force website ([www.avan.asia](http://www.avan.asia)) was also developed for team discussions and resource sharing. Soon after, China, under the direction of Dr. Yiming Shao, was selected as the site for the permanent AVAN Secretariat.

In 2010, AVAN held its 3rd annual meeting in Pattaya, Thailand. The meeting was jointly organized by the World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the Global HIV Vaccine Enterprise, International AIDS Vaccine Initiative (IAVI), U.S. National Institutes of Health (NIH) and U.S. Military HIV Research Program (MHRP) and hosted by Faculty of Tropical Medicine, Mahidol University. The meeting was designed to provide a platform to review the current HIV vaccine pipeline along with Asian country-level progress in HIV vaccine research and development. The meeting discussed challenges and opportunities in the areas of public-private partnerships, clinical trial capacity, basic and clinical research, non-human primates and animal models and young and early-career investigators.

These discussions led to an established organizational structure for the permanent Secretariat and the development of prioritized action plans for AVAN for next five years. This includes the establishment of Collaborating Centers in various countries focusing on training (Japan, Thailand, Australia), resources (China, Thailand, India, and Japan), clinical trial and ethical centers (Thailand), regional laboratories (Australia, Thailand) and Primate centers (China, India, Malaysia).

**African AIDS Vaccine Partnership (AAVP)**

The African AIDS Vaccine Partnership (AAVP) advocates for and supports a coordinated international effort to promote the development of and future access to HIV vaccines suitable for use in Africa. To meet the vision of an AIDS-free Africa through an effective vaccine, AAVP has strengthened the network of African HIV vaccine stakeholders through research, advocacy, partnership, and contribution to capacity strengthening and policy development. AAVP aims to ensure that African communities and Africans participating in the HIV vaccine development process are adequately supported, are well represented globally and are equal partners playing a critical role in HIV vaccine development efforts. AAVP is a partnership-based network, committed to working closely with all HIV vaccine partners and sharing its resources and capacity consistent with the Global HIV Vaccine Enterprise.

In 2009, the Uganda Virus Research Institute (UVRI) was selected to host the AAVP Secretariat, previously hosted under the World Health Organization and UNAIDS. Following the public announcement at the 5th AAVP Forum in 2010, the Government of the Republic of Uganda and WHO signed a Memorandum of Understanding (MOU) for the hosting modalities of the AAVP secretariat at the UVRI. The Secretariat will transition to Uganda in 2011 and establish a permanent secretariat led by an Executive Director.

The AAVP Secretariat’s move to Uganda will bring AAVP closer to its partners working in Africa and to African leadership, and will increase African ownership. The collaborating centers will be key to AAVP’s activities, bringing together partners to address a shared plan. AAVP is entering a new phase of increased activities and exposure and is firmly positioned to play a significant leadership role on the African continent as the voice of African stakeholders involved in HIV vaccine development. AAVP’s plans are responding to the changing HIV vaccine environment, and offer substantial added value to those working in Africa by focusing on areas where AAVP has a comparative advantage. AAVP looks forward to the next five years of enhanced activities and greater impact towards its vision of “an AIDS-free Africa through an effective vaccine.”
A strengthened clinical trials endeavor, as recommended by the 2010 Plan, will require a major increase in financial support. While emphasizing the need for new investments in HIV vaccine research from a larger and more diverse pool of funders, the Plan also proposes a number of strategies to ensure that existing resources are sustained and optimized — for example through increased coordination and sharing of global clinical trial site capacities and expertise.

Secretariat Activities to Advance the Plan Priorities

The 2010 Scientific Strategic Plan articulates the views of Enterprise Council members to work toward aligning their strategies and activities to transform the Plan recommendations into concrete and tangible action. The Enterprise Secretariat also supports a number of stakeholder activities to identify smarter, more efficient and more comprehensive avenues of collaboration to speed and enhance HIV vaccine research.

Priority 1

Plan Priority 1 addresses the consensus that HIV vaccine clinical efficacy trials must be designed and implemented as an integral part of the discovery process. The need to improve clinical trial planning to anticipate possible outcomes and allow for the rapid modification of trial protocols is essential to speeding data analyses and informing the development of future vaccine candidates.

To transform this commitment into action, the Enterprise Secretariat, the HVTN, IAVI and WHO-UNAIDS are working together to identify opportunities and challenges in adaptive trial design. On another front, the Canadian HIV Vaccine Initiative and WHO-UNAIDS, with support from the Enterprise Secretariat, will lead an international discussion to identify how best to address critical challenges in HIV vaccine development related to global, ethical, legal and regulatory frameworks and approval processes.

Priority 2

Plan Priority 2 emphasizes the need to strengthen support for basic and preclinical HIV vaccine research. Central to this effort are activities to more effectively integrate the latest achievements in other areas of biomedical investigation into HIV vaccine research, and to expand and enhance knowledge-dissemination and data sharing among researchers and research organizations. These efforts become critical as high-throughput data-rich technologies become widely adopted, more trials are conducted and more extensive scientific inquires are incorporated into trial design.

To advance Priority 2, the Enterprise Secretariat is working with stakeholders on an initiative to improve the annotation, deposition, sharing, analysis and stewardship of laboratory and clinical research data. The initiative is designed to develop a harmonized global approach to promote and facilitate data sharing, along with the guidelines to do so.

Industry Engagement

The current absence of many major pharmaceutical companies from HIV prevention research is unsustainable. As it becomes increasingly clear that a combination of vaccines, microbicides or PrEP may hold the key to large-scale HIV prevention strategies, the pharmaceutical industry and other key stakeholders must participate in the development of
systematic, strategic approaches that maximize the scientific value of public-private partnerships, minimize risk for industry and allow for more open, nonexclusive arrangements that support the sharing of research findings and data.

Enterprise stakeholders are focused on increasing the engagement of the biotech and pharmaceutical industry, particularly in efforts to take early stage HIV vaccine candidates efficiently through to the latter stages of the development pipeline. In 2010, a novel collaborative effort known as the Pox-Protein Public Private Partnership (P5) formed to carry forward a coordinated, multi-country effort to follow-up on the RV144 result. P5, comprising Sanofi Pasteur, Novartis Vaccines & Diagnostics, Inc., the U.S. National Institutes of Health, the Bill & Melinda Gates Foundation, the U.S. Military HIV Research Program and the HIV Vaccine Trials Network, is developing an overarching development strategy to move the RV144 result to a potentially licensable product for Thailand and elsewhere in the world.

People
Young and early-career investigators face challenges in establishing a career in every field of scientific research; the collaborative nature of HIV vaccine research, however, can make the hurdles in our field particularly high. Collaborative research can make recognition of individual researchers more difficult, and may complicate the efforts of young and early-career investigators to secure initial funding and develop their individual career pathways.

Enterprise stakeholders are helping to overcome these obstacles and to develop and sustain the careers of young and early-career investigators. The Collaboration for AIDS Vaccine Discovery (CAVD) is recognizing young or early career investigators who have made significant contributions to research conducted within the CAVD; the Wellcome Trust provides a variety of junior fellowships for scientists in the United Kingdom and in low-income countries; and the Enterprise Secretariat is also assisting stakeholders in their efforts. The ongoing collaboration between the Enterprise and the OCTAVE Project increases training opportunities on topics critical to career development including immunology, virology and clinical trial design. A new online portal, the HIV Vaccine Electronic (e) Resource (HIVe) (http://www.hivvaccineenterprise.org/hive), developed with funding from the Canadian HIV Vaccine Initiative, facilitates the exchange of career-supporting information among the entire HIV vaccine research community.

Funding
Mobilizing new resources, helping funders more efficiently channel their support for HIV vaccine research and identifying new opportunities to advance the field are the objectives of the Enterprise Resource Mobilization Working Group. Comprised of individuals representing The Bill & Melinda Gates Foundation, the National Agency for AIDS Research in France, the International AIDS Vaccine Initiative and the Wellcome Trust, a key focus of the Working Group is mobilizing increased contributions from those countries that possess the scientific, financial and social resources to invest in prevention research, but which are not doing so today.
WHO and UNAIDS, founding members of the Global HIV Vaccine Enterprise, are strongly committed to promoting the development of safe, globally effective and accessible HIV vaccines. Through its joint HIV Vaccine Initiative, WHO and UNAIDS work to: (1) support HIV vaccine R&D through advocacy, promotion of collaboration and regional networking; (2) promote the creation and implementation of internationally agreed policies, norms and standards for the development, evaluation and future accessibility of HIV vaccines; and (3) support sustainable capacity strengthening of trial sites in low- and middle-income countries, integrated into prevention R&D efforts for other diseases of public health importance such as malaria and tuberculosis.

In alignment with the first priority of the Scientific Strategic Plan of the Enterprise, WHO and UNAIDS provide guidance and technical advice to Member States on clinical trial protocols and design, regulatory and ethical decision making, the utility of efficacy trial results and the potential for licensing through the existing WHO-UNAIDS Advisory Committee (VAC); provide guidance and capacity building on ethical, legal and community participation in biomedical prevention trials, including publication and dissemination of guidance documents such as the UNAIDS/WHO Ethical Considerations in Biomedical HIV Prevention Trials and the UNAIDS/AVAC Good Participatory Practice guidelines; promote advocacy, collaboration and capacity strengthening on a regional level for Africa (e.g., African AIDS Vaccine Partnership) and Asia (e.g., AIDS Vaccine for Asia Network); support research and training in regulatory research, molecular epidemiology and assay standardization; and promote collaboration and integration of HIV vaccine-related activities with other vaccine research and with research into biomedical prevention tools.

From 2008–2010, WHO-UNAIDS
- Conducted annual meetings of the WHO-UNAIDS HIV Vaccine Advisory Committee.
- Led international expert group meetings and consultations on the utility of the RV144 trial results, in collaboration with the Enterprise.
- Published technical recommendations on the “Use of surrogate markers in HIV vaccine prevention trials.”
- Developed and conducted trainings on the application of the WHO-UNAIDS Ethics Guidance Document for researchers, ethics committees and regulatory authorities from Francophone, Anglophone and Russian speaking countries.
- Developed guidance and conducted regional consultations in Eastern Europe & Central Asia and Asia on the “Ethical involvement of people who inject drugs (PWID) in HIV biomedical prevention trials.”
- Collaborated with other key partners to finalize plans for the AAVP Secretariat transition to the Uganda Virus Research Institute in Entebbe.
- Published detailed technical and strategic planning reports to support the national AIDS Vaccine Programmes in China and Thailand.
- Published WHO-UNAIDS estimates on global distribution of HIV subtypes and CRFs (AIDS 2010), funding a project on molecular epidemiology in Eastern Europe, which resulted in three key scientific publications in peer reviewed journals.
- Trained young scientists from Eastern Europe and on sequencing and phylogenetic analysis of HIV-1.
- Convened modellers to compare the cost and impact of a partially protective vaccine with properties similar to that of the prime-boost RV144 regimen.
- Participated in and organized trainings to support the Gates Foundation CAVD Consortium on the development of cryopreservation technologies.
- Promoted collaboration and integration with other vaccine and HIV prevention programmes through the development of the WHO Initiative for Vaccine Research Strategic Plan for 2010-2011, which has integrated its priorities with other poverty-related diseases, such as tuberculosis and malaria.
- Co-lead global responses and programming on medical male circumcision, the CAPRISA 004 tenofovir gel microbicide trial and on pre-exposure prophylaxis (PrEP).

UNAIDS-WHO activities are helping to meet the targets put forward in the 2010 Scientific Strategic Plan, with efforts concentrated in the areas of multidisciplinary collaborations (Priority 2); increasing participation of researchers from affected countries; and promoting partnerships and strengthening research capacity for young investigators (cross-cutting considerations 1-3).
Colonel Jerome Kim from the MHRP discusses RV144 and follow up plans one year after the landmark announcement with journalist scholars at the 2010 conference in Atlanta.

Dr. Anthony Fauci, NIAID/NIH/DHHS, Dr. Eric Hunter, CFAR at Emory University and Dr. Alan Bernstein, Global HIV Vaccine Enterprise, prepare for the opening press conference at the 2010 conference in Atlanta. Dr. Hunter chaired the session where journalists were briefed on the scientific program.

Dr. José Esparza from the Bill & Melinda Gates Foundation discusses one of the conference posters with the presenting investigator.

Dr. Glenda Gray, Perinatal HIV Research Unit, Dr. Seth Berkley, IAVI and Dr. Catherine Hankins, UNAIDS present on future directions for HIV vaccine research and development following the 2009 results of RV144.
The annual AIDS Vaccine meeting is the largest and most important global scientific conference focused exclusively on AIDS vaccine research. Hosted by the Global HIV Vaccine Enterprise and different local HIV vaccine research partners each year, AIDS Vaccine brings together more than 1,000 scientists, community advocates, funders and policy makers from around the world to share cutting-edge scientific data, exchange new ideas and educate future leaders of the quest for an HIV vaccine.

The AIDS Vaccine 2008, 2009 and 2010 conferences included presentations of some of the most important scientific advances of the field's twenty-eight year history.

AIDS Vaccine 2008
Cape Town, South Africa

AIDS Vaccine 2008, held in Cape Town, South Africa October 13–16, was a turning point for the field. The conference marked the first time the conference was held in Africa, the epicenter of the epidemic. AIDS Vaccine 2008 also proceeded the cancellation of international trials of two of the most advanced HIV vaccine candidates at the time, STEP and Phambili.

The Cape Town conference focused on the need to identify new approaches to vaccine research to complement studies already underway and the need for collaborative efforts to incorporate the latest and most innovative ideas and technologies to move the field forward following STEP and Phambili. The conference also marked an important milestone in the history of the AIDS epidemic when South Africa’s new minister of health, in her first international appearance, dramatically reversed that country’s discredited national AIDS policies, which had denied the link between HIV and AIDS.

AIDS Vaccine 2009
Paris, France

AIDS Vaccine 2009, hosted by the Global HIV Vaccine Enterprise and the National Agency for AIDS Research in France (ANRS) was held in Paris, France October 19–22. AIDS Vaccine 2009 received a record number of abstracts and registrants, reaffirming the meeting’s role as the leading forum for the exchange of the latest information on HIV vaccine research. Much of the excitement at the Paris conference focused on the results of the RV144 trial. Among the other scientific advances reported at the Paris conference:

- Researchers reported on the discovery of three new antibodies capable of neutralizing a broad range of HIV types. These findings open new opportunities for designing vaccines that can elicit such antibodies and may ultimately block HIV infection.
- A presentation of additional results from the STEP and Phambili HIV vaccine trials revealed new HIV infections in both cohorts, with the data pointing toward lack of circumcision as the primary correlate with increased numbers of infections in male vaccinees.
- New data demonstrated that, while HIV infection involves millions of different HIV variants, only a single “founder” virus takes hold in the majority of heterosexually transmitted cases. In a related development, a non-human primate study provided important new information regarding the earliest phases of infection, prior to viral replication and diversification within the body. These important findings reaffirmed the need to develop a vaccine capable of preventing HIV infection, and of generating the immune responses needed to rapidly clear the virus before infection is established.

AIDS Vaccine 2009 included the first formal conference media program, with daily press conferences, session webcasts, a fully operational media center and a scholarship training program that provided two-days of intensive background briefings on HIV vaccine research for 17 journalists from around the world. The scholarship program, a collaboration between the Global HIV Vaccine Enterprise, the ANRS and the National Press Foundation, helped to increase and inform quality media coverage of Enterprise stakeholder efforts to develop a safe and effective HIV vaccine.

Steve Wakefield, HIV Vaccine Trials Network, briefs journalist scholars on the importance of the community in HIV vaccine clinical trials (top). Investigators share results with conference delegates during the poster receptions at the 2008, 2009 and 2010 conferences.
AIDS Vaccine 2010
Atlanta, Georgia USA

AIDS Vaccine 2010, hosted by the Global HIV Vaccine Enterprise and the Center for AIDS Research at Emory University was held in Atlanta, Georgia in September 2010. Key topics at the Atlanta conference included the mechanics of HIV infection, the interaction of the virus with the immune system and efforts to build upon the protection achieved in the RV144 Thai Trial. Other highlights included:

- The isolation of several new broadly neutralizing antibodies by the International AIDS Vaccine Initiative and The Scripps Research Institute and structural insights into how one antibody discovered by the Vaccine Research Center of the NIH binds to gp120 and neutralizes the virus. Three of the newly-discovered antibodies target a less-defined epitope that may be important in the development of future candidate vaccines.

- The presentation of data from ongoing clinical trials that suggest that both an adenovirus (Ad) serotype 35 vector-based vaccine candidate and an Ad26 serotype vector-based candidate are safe and immunogenic. This discovery led to the initiation of a Phase I trial to test the safety and immunogenicity in a prime-boost combination.

- The launch of the 2010 Scientific Strategic Plan of the Global HIV Vaccine Enterprise and a rich discussion among the world’s major HIV vaccine funders and researchers of strategies to put the Plan recommendations into action.

AIDS Vaccine 2010 also hosted the conference’s first undergraduate scholarship program. As part of this initiative, 14 Centers for AIDS Research (CFAR) from around the United States selected one undergraduate student each to attend the conference and a pre-conference training program to better prepare them for the meeting’s scientific sessions. The conference also offered a series of networking opportunities for young- and early-career investigators, including networking lunches where these investigators had the opportunity to meet with 36 senior researchers to discuss issues relevant to career advancement.

For the second year, the Global HIV Vaccine Enterprise in collaboration with the National Press Foundation and the Center for AIDS Research at Emory University, offered scholarships to 22 journalists from 17 countries to participate in briefings on key issues in HIV vaccine research in advance of the conference. The training, which is intended to help build a corps of journalists with the background necessary to cover HIV prevention research around the world, included sessions led by Linda-Gail Kripke, University of Cape Town; Catherine Hankins, UNAIDS; Jerome Kim, MHRP; Katharine Kripke, NIAID; Steve Wakefield, HVTN and others.

The establishment and first year of independent operation of the Enterprise Secretariat in 2008 increased the proportion of expenditures that year dedicated to operational expenses. An appropriate long-term balance between spending on operations and programmatic activities was achieved in 2009, as the Enterprise Secretariat became fully operational and was able to focus on programmatic activities including the development of the 2010 Scientific Strategic Plan.

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* Operations includes office space, staffing, recruitment, rental fees, consultants, etc.
† Programs includes costs associated with planning and implementation of activities in support of the Enterprise Scientific Strategic Plan.
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17 AIDS Vaccine 2010, Abstract, Analysis of the relative risk of HIV acquisition among Step study participants with extended follow-up.

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