IAVI’S WORLDWIDE PARTNERS AND PROGRAMS

Countries where IAVI has scientific collaborators

Belgium
Canada
China
Finland
France
Germany
India
Kenya
Netherlands

Rwanda
South Africa
Sweden
Switzerland
Uganda
UK
US
Zambia

Governments that are financial donors to IAVI

Canada
Denmark
Europe Union
Ireland
Netherlands
Norway
Sweden
UK
US

Belgium
Brazil
Canada
Denmark
Finland
France
Germany
India
Ireland
Japan
Kenya

Netherlands
Norway
Rwanda
South Africa
Spain
Sweden
Switzerland
Uganda
UK
US

Countries in which IAVI has advocacy or policy programs

Belgium
Brazil
Canada
Denmark
Finland
France
Germany
India
Ireland
Japan
Kenya

Netherlands
Norway
Rwanda
South Africa
Spain
Sweden
Switzerland
Uganda
UK
US

Front Cover: (Left) Lab technician Moses Kwizera working on samples from a feasibility site at the MRC/IAVI laboratory in Masaka (Photo IAVI). (Middle) IAVI President and CEO Dr. Seth Berkley meets with Indian Prime Minister Dr. Manmohan Singh in New Delhi on 7 December, 2004. (Photo India Prime Minister’s office). (Right) Part-Time Study Physician Dr. Immaculee Mukatete (left) and Study Nurse Kephas Kafwimbi (right) joined other participants at a GCP (Good Clinical Practices) training workshop hosted by IAVI in Entebbe, Uganda in November (Photo Vanessa Vick/IAVI).

Back Cover: (Left) HIV rapid testing at an IAVI vaccine research site in Kigali, Rwanda (Photo IAVI). (Middle) An HIV voluntary counseling and testing (VCT) session at the CGMRC center in Kilifi, Kenya (Photo IAVI). (Right) Fred Oyugi, Quality Control Manager for the Kenya AIDS Vaccine Initiative at an IAVI-sponsored GCP training workshop in Entebbe (Photo Vanessa Vick/IAVI).
### IAVI 2004 Annual Progress Report

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IAVI’s mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world.
I am pleased to present IAVI’s 2004 Annual Progress Report, which details the work that our international team and partners accomplished this past year toward the goal of a safe, effective and accessible preventive AIDS vaccine. The Report also highlights how we intend to build upon this work in the coming years, given the new realities that we face as an organization and in the field.

Throughout 2004, IAVI devoted significant resources to long-term strategic planning. We began with management and staff across departments taking a critical look at the state of global vaccine efforts, including where there has been meaningful progress, and the many places where efforts have lagged and must be redoubled or refined. This formed the basis for developing detailed programmatic objectives for the next three years, 2005 to 2007, and the indicators by which we will measure our achievements.

Two key themes emerged early on and guided strategic planning through its conclusion. First, we believe that the core principles on which IAVI was founded nine years ago remain relevant today—these include the need for an integrated approach to research and development, advocacy and policy, and the need for partnership between the public and private sectors of industrialized and developing countries. Second, we recognize that a vaccine is revealing itself to be even more scientifically challenging than initially thought, and this necessitates some course correction.

As you know, in our early years we operated from the premise that a safe and effective AIDS vaccine is scientifically feasible, and could be achieved if the world would commit to advancing the many concepts and candidates that were then considered promising but had languished for want of attention and resources. Today, we remain confident that a vaccine is feasible—in fact, the field has amassed more evidence that this is the case—although we expect that realizing this possibility will mean mounting new efforts, on a scale much larger than anticipated.

IAVI’s pledge is to do more of what we have been doing, and do it even better. We are continuing our work to construct candidates and test them in trials given what is known today, while in parallel expanding our work to discover and pursue entirely new directions. We are increasing the rigor by which we put ideas to the test of the scientific method and make decisions on priorities accordingly. We are committed to finding smarter ways of catalyzing creativity and new collaborative arrangements to pool expertise and resources; in this regard we are working closely with the new Global HIV Vaccine Enterprise.

Our new strategic plan calls for shaping and equipping the organization for the long haul. By far the most common question IAVI gets asked is when will a vaccine be available—the truth is that we simply do not know, because good science cannot be corralled into time estimates. What we do know is that we need a global movement that marshals attention and sustains commitment and resources for whatever timeline is required. At the same time, the urgency of the epidemic demands that we do all that we can to place a premium on speed, flexibility and informed risk taking.

Significant components of the 2005-2007 strategic plan had already begun to be implemented in 2004, and it is in this context that this Report explains our programs in research and development, advocacy and policy. I take this opportunity to thank you again for your generous contributions to our work, which are more critical than ever as we scale up to a new level, as well as your steadfast support for all aspects of the global response to HIV and AIDS.

Sincerely,

Seth F. Berkley, MD
President and Chief Executive Officer
EXECUTIVE SUMMARY OF 2004
ACTIVITIES AND KEY MILESTONES

IAVI’s ninth year marked a pivotal period in the organization’s evolution and growth. The year brought vital changes in IAVI’s R&D strategy and vaccine product portfolio, expansion of global policy and advocacy efforts, and increased commitment to engage and support developing country partners in the development and testing of a preventive AIDS vaccine.

STRATEGIC PLAN FOR 2005-2007. An intensive, 18-month strategic planning process culminated with approval of the new plan by IAVI’s Board of Directors in June. The 3-year plan underscores the need to continue accelerating AIDS vaccine product development and testing, and calls for expansion of applied vaccine research to answer key questions about HIV and the human immune system. The plan’s other objectives include an increased focus on public policy and AIDS vaccine advocacy, and a renewed commitment to actively involve a broad range of developing country partners—including scientists, government officials and affected communities—in the vaccine R&D process.

AIDS VACCINE RESEARCH & DEVELOPMENT (R&D)

Scientific Blueprint 2004. In July, IAVI released its Scientific Blueprint 2004: Accelerating Global Efforts in AIDS Vaccine Research and Development. The Blueprint analyzes progress in the field, identifies key challenges to vaccine R&D at this stage of the epidemic, and makes recommendations to strengthen and accelerate the global search for a preventive vaccine. The Blueprint calls for a significant increase in spending on AIDS vaccine R&D and envisions that IAVI, its partners in the Global HIV Vaccine Enterprise, and others will collaborate in regional efforts to build capacity to conduct multiple large-scale vaccine efficacy trials in high-incidence areas.

Global HIV Vaccine Enterprise. IAVI has continued its participation in the Global HIV Vaccine Enterprise, an alliance of independent agencies working toward an AIDS vaccine. Designed to foster collaboration and cooperation across R&D programs, the Vaccine Enterprise was proposed by the Bill & Melinda Gates Foundation and others in a June 2003 paper in the journal Science, and endorsed by the heads of the G8 nations at their summit in June 2004. IAVI is a founding member of the Enterprise and is fully committed to helping shape its direction and contributing to its implementation. Dr. Seth Berkley was a co-author of the 2003 Science article and is a member of the Enterprise’s Coordinating Committee.

ANNUAL MEETING OF IAVI’S SCIENTIFIC ADVISORY COMMITTEE. At its annual meeting in August 2004, IAVI’s Scientific Advisory Committee (SAC) endorsed the key R&D elements of IAVI’s strategic plan for 2005-2007. The SAC also: endorsed IAVI’s proposed criteria for advancing a vaccine candidate to efficacy trials; agreed with IAVI’s plans to address the key scientific challenges impeding AIDS vaccine development; and commended IAVI for the professionalism of its effort, and for being data-driven in terminating less promising candidates.

ADVANCING CLINICAL TESTING OF AIDS VACCINE CANDIDATES. In 2004, IAVI continued testing four AIDS vaccine candidates in human trials in eight countries:

▪ rAAV-HIV Vaccine. The Phase I trial of the rAAV-HIV vaccine completed recruiting volunteers in Germany and Belgium. Plans were made to expand this trial to an additional site in India in 2005, and to initiate a Phase II trial in Africa. Work also progressed in developing a second rAAV-HIV vaccine candidate that may be immunogenic at a lower dose.

▪ ADVAX (Multigenic DNA) Vaccine. Phase I trials of the ADVAX multigenic DNA vaccine were fully enrolled and continued at two sites in the US. This study will assess whether using a dual promoter system with two different plasmids offers advantages over other DNA vaccines. In addition, extensive work was completed on ADMVA (a multigenic MVA-based vaccine), including preclinical safety studies, quality control and immune response testing. Clinical lots of ADMVA were manufactured and passed their final tests. The first human trial with ADMVA will start in early 2005.

▪ DNA.HIVA and MVA.HIVA AIDS Vaccines. Phase I and II studies of the DNA.HIVA and MVA.HIVA vaccine candidates—tested alone and as a prime-boost combination—nearly completed in the UK, Kenya, Uganda, Switzerland and South Africa. Early immunogenicity data were presented by IAVI and its research partners at the 2004 AIDS Vaccine Conference in Lausanne, Switzerland. The data indicate that the anti-HIV cellular immune response elicited by these candidates falls short of expectations. Additional data will be available in the first half of 2005, at which time a final decision will be made regarding further development of this candidate.

IAVI also is working closely with the NIH Vaccine Research Center (VRC), the US Military HIV
Executive Summary

Based on DNA and adenovirus type 5 platforms, three closely coordinated Phase I and Phase II trials in East Africa to test the VRC candidate vaccines based on DNA and adenovirus type 5 platforms.

IAVI-Sponsored AIDS Vaccine Candidates in Preclinical Development. IAVI also continued its preclinical assessment of other vaccine candidates:

- **Human Adenovirus (Ad) Particle Vaccines.** IAVI launched this partnership with the Dutch biotechnology company Crucell N.V. to develop an AIDS vaccine based on Crucell’s AdVac® technology. The AdVac® vectors, derived from adenovirus serotypes 11 and 35, have shown promising results in preclinical studies unrelated to AIDS vaccines. It is hoped that the promise of the technology will translate to AIDS vaccine development.

- **Multigenic MVA Vaccine.** Work continued on this project, which is evaluating the potential advantage of a multigenic MVA vaccine. Preclinical safety and tolerability studies in animals were completed and clinical lots of the vaccine have been produced. The application process for regulatory approval to begin a Phase I study in India has been initiated and the clinical trial is expected to start in mid-2005.

- **Orally-Administered Bacterial Vector.** After a thorough review of the design of the *Salmonella* and *Shigella* delivery systems, disappointing immunogenicity data from preclinical studies, and an assessment of the cost and time of a required reconstruction of the HIV plasmid, IAVI decided to discontinue the development of these vaccine candidates. IAVI has recommended that this platform be further evaluated at a more basic research level.

- **Semliki Forest Virus (SFV) Replicon DNA and Replicon Particle Vaccines.** In April 2004, a non-human primate study indicated that the SFV replicon DNA.HIV clade A plasmid was not performing as it had in earlier mouse studies. In addition, observations from a mouse biodistribution study indicated that extensive toxicity studies also would be required. As a result, further development of the SFV replicon DNA vector was terminated. In parallel, construction of the SFV particle candidate was completed. However, the uncertain technical considerations facing the SFV program, and its prolonged development timeline, were the basis for IAVI’s decision not to continue development of this platform.

Throughout the year, IAVI continued active surveillance of global efforts in AIDS vaccine R&D to identify promising new technologies and evaluate their potential for further development.

IAVI’s Human Core Immunology Laboratory. Based at the Imperial College of Science, Technology, and Medicine in London, the Core Lab continued to facilitate the evaluation of IAVI-sponsored AIDS vaccine candidates. The Core Lab functions as a central base providing standard operating procedures, standardized reagents and equipment, and training and technical assistance to as many as 14 field laboratory sites. The Core Lab also served as a primary laboratory for IAVI-sponsored trials underway in London, and provided quality assurance by testing samples from all IAVI trial sites. Key activities for 2004 included:

- IAVI’s Core Laboratory became the first in the world to be accredited in GCLP, or Good Clinical Laboratory Practices, a new standard for labs conducting tests on samples from clinical trials.

- More than 20 developing country scientists and clinicians received instruction in GCLP during a series of trainings for staff of current and future IAVI-sponsored research sites in Africa and India. The Core Lab also assisted the field labs at IAVI’s Kenyan, Ugandan and South Africa trial sites as they worked towards GCLP accreditation.

- Standard operating procedures were developed and distributed to labs working on IAVI trials in Kenya, Uganda, Belgium, Germany, Switzerland, South Africa, the UK and US, and to sites of upcoming trials in Rwanda, India and Zambia.

- The Core Lab team developed a standard tool to assess laboratory capacity and gauge the need for additional infrastructure; the Lab team also conducted site assessments in India, Zambia, South Africa, Kenya and Uganda.

Applied Research to Address AIDS Vaccine Challenges. Work is underway on several research projects aimed at filling critical gaps in scientific knowledge related to AIDS vaccine development:

- **IAVI Vaccine Research & Design Laboratory.** In 2004, IAVI decided to establish its own Vaccine Research and Design Laboratory to help drive the creation and development of next-generation HIV vaccine candidates, and to support the organization’s overall scientific effort. The Lab will improve the genetic stability and level of expression of candidate vaccines; develop assays to evaluate candidates; provide laboratory backup to IAVI-funded vaccine feasibility studies; and initiate work on new candidate vaccines.

- **The Neutralizing Antibody Consortium (NAC).** Established by IAVI in collaboration with the NIH Vaccine Research Center, the NAC is a group of scientists from leading laboratories working on designing vaccine candidates that will elicit broadly effective neutralizing antibodies against HIV. In 2004, NAC researchers constructed a first-
generation carbohydrate-based immunogen that is now being tested for immune responses in small animals, and initiated the first of a series of comparative studies of novel adjuvants designed to boost the antibody response.

- **AIDS Vaccine Consortium (AVC).** IAVI has launched a new research initiative to accelerate the development of vaccine candidates that will confer the same level of protection as mutated live-attenuated SIV in non-human primates. IAVI has recruited leading AIDS vaccine researchers focused in this area and plans are underway for a comprehensive non-human primate study that will evaluate the type of immune responses that mutated live-attenuated SIV produces, where in the body those responses occur, their breadth and magnitude, and how they confer protection.

- **Non-Human Primate (NHP) Studies.** IAVI’s NHP studies have continued to generate vital supporting data as part of the organization’s program to evaluate and prioritize IAVI’s vaccine portfolio. During 2004, a total of seven comparative HIV vaccine studies were either completed or underway.

**SITE DEVELOPMENT AND PREPARATORY STUDIES FOR POSSIBLE FUTURE EFFICACY TRIALS IN AFRICA.** Work is progressing well at six sites—two in Kenya, two in Uganda, one in Rwanda and one in Zambia—that may be suitable for future efficacy trials of preventive HIV vaccines. Efforts are underway to augment the sites’ capability and capacity for conducting large-scale trials. This program includes constructing state-of-the-art laboratory and clinical facilities, and training local researchers in international clinical trial standards.

Preparatory studies (consisting of six research protocols) are planned or underway at these sites. These studies are designed to strengthen voluntary counseling and testing (VCT) using rapid HIV tests, and to gather crucial information on at-risk populations, including the prevalence of HIV (percentage of people who are infected) and the incidence of new infections. The early immune response in recently infected individuals will be studied together with changes in the virus those individuals carry. Clinical laboratory reference ranges will be defined in several African populations—a crucial and largely missing piece of information needed to interpret data from clinical trials of HIV vaccines or other vaccines and treatments. A small study will define specific cellular immune response to the strain(s) of HIV in infected volunteers, in preparation for HIV vaccine trials. Finally, pre-existing immunity to specific viral vectors will be studied in representative populations that potentially may participate in future HIV vaccine efficacy trials, since pre-existing immunity may change the effectiveness of a vector.

The HIV prevalence study (Protocol A) was completed at four sites in Kenya and Uganda after enrolling 6,300 volunteers. Sites in Kenya, Rwanda and Zambia are continuing to recruit, counsel and test couples and obtain data on prevalence and incidence. Staff at the Kigali site have identified over 800 HIV discordant couples (where one partner has HIV and the other does not), and are continuing to expand their cohort and provide VCT to couples in the greater Kigali area. The Lusaka site has identified over 1,000 HIV discordant couples.

In addition, IAVI funded the improvement of clinical and laboratory capacity at all sites:

- In Kangemi (Nairobi, Kenya), the clinic was renovated to enhance its capacity to conduct research protocols.

- In Kilifi (Kenya), a new community VCT center is being constructed, as well as a new clinical research center that will include a family medicine clinic. The clinical research lab within the new center will provide laboratory tests for the staging and management of people with HIV who are receiving antiretroviral treatment.

- In Uganda’s Masaka district, three research clinics were established adjacent to the district clinics. The research clinics are conducting preparatory studies and providing basic medical care and VCT. The laboratory at the Masaka field office was completed and upgraded to perform all assays associated with the protocols, and the field lab in Kyamulibwa also is being upgraded.

- In Lusaka, preparations for clinical trials include enlarging the clinical space and upgrading the electrical backup system, the information technology and freezers for storing vaccine and specimens. Renovations of the clinical buildings were completed and a clinical laboratory and a lab to separate and freeze immune cells were established. Two preparatory studies will be conducted in addition to counseling and testing over 800 discordant couples. The staff have completed all training to initiate a Phase I AIDS vaccine trial.

- In Kilifi, in addition to counseling and testing over 800 discordant couples, the clinic was completed all training to initiate a Phase I AIDS vaccine trial.

IAVI’s AIDS Vaccine Activities in India. Two vaccine candidates currently in the pipeline are poised for testing in India—the Modified Vaccinia Ankara (MVA) and the Adeno Associated Virus
(AAV). The Vaccine Trial Centre at the National AIDS Research Institute (NARI) in Pune is fully operational and clinical trials will begin in the first quarter of 2005. Major activities in 2004 included:

- **Preparations for Phase I Trials.** The NARI staff involved in the upcoming Phase I trial were trained in Good Clinical Practice in AIDS vaccine trials and in data management.

- **Clinical Trials Site Development.** The Indian Council of Medical Research (ICMR) endorsed the development of the second trial site at the Tuberculosis Research Centre (TRC) in Chennai. This will include extensive renovation, equipping a laboratory and providing training for clinical and laboratory staff.

- **Assessment of Willingness to Participate in Phase I Trials.** A research study was begun to understand the willingness of potential volunteers to participate in AIDS vaccine trials. A communications and advocacy plan also was developed for recruiting Phase I trial volunteers.

- **Site Assessments.** Assessments for community and site preparedness studies were conducted by IAVI together with a team of national and international experts. The team assessed clinical and laboratory infrastructure, logistics, access, community interaction, and the feasibility of conducting cohort studies. Existing VCT services and care and support systems also were studied.

### PREPARATIONS AND SUPPORT FOR AIDS VACCINE R&D

IAVI’s field offices strengthened coordination and communication among sites. Some of the key activities undertaken by IAVI’s country programs during this period are highlighted below.

- **AIDS Vaccine Literacy.** IAVI’s AIDS Vaccine Literacy project promotes the development of educational tools by providing information that can be adapted to various languages and audiences. The initial component, a reference book on AIDS entitled the *Core Content*, contains basic information on AIDS vaccines and will be distributed to country offices and partners. Supporting materials, including a curriculum and prototype educational resources, are being developed.

- **Ensuring Treatment and Care for AIDS Vaccine Trial Participants.** A national consultation on treatment and care was held in India in March and the provisions of the policy were agreed upon and incorporated within the informed consent documents for the upcoming Phase I trial in Pune. IAVI also facilitated an initial Treatment and Care Consultation in Kenya that sought to define the appropriate care and treatment for clinical trial participants and host communities, and sustainable approaches to shared responsibility for that care. Uganda has taken a leadership role by identifying participants in HIV/AIDS research as a priority group in its scale up strategy for ARV treatment.

- **Gender Concerns in HIV Vaccine Trials.** In 2004, IAVI published a paper addressing gender challenges in AIDS vaccine trials in developing countries, and presented its work on gender at a WHO-UNAIDS consultation in Lausanne, Switzerland, and at a technical seminar in Washington, DC organized by the International Center for Research on Women, The Global Coalition on Women and AIDS, and Horizons. A training curriculum on gender also was developed for AIDS vaccine trials in consultation with IAVI’s Gender Advisory Board in India. A preliminary gender consultation was held in Nairobi with KAVI and other IAVI partners to better understand the barriers to women’s participation in Kenya; a similar meeting is planned in Uganda.

- **Partnerships for Preparedness.** The European Union is funding this IAVI project in East Africa to build capacity and partnerships with key stakeholders in trial site communities and in the region as a whole. The project includes technical support and training for NGOs in AIDS vaccine education; strengthening health care and VCT services in communities surrounding vaccine research sites; promoting best practices among vaccine researchers and researchers working on other prevention technologies; and outreach to the medical community, NGOs, the media and policymakers at the national level.

### Country Programs

**Kenya.** IAVI’s East Africa Regional Office in Nairobi is implementing an expanded country program in Kenya and supporting work in Uganda and Rwanda. To facilitate the research projects underway in Kangemi, the team has trained 180 peer leaders to disseminate HIV vaccine and prevention messages to the community, and has conducted an in-depth mapping exercise to better understand Kangemi residents’ attitudes and knowledge regarding HIV/AIDS vaccines.

- **National AIDS Vaccine Plan for Kenya.** As a result of the meeting that the Ministry of Health (MOH) convened last year bringing together key stakeholders in the field of AIDS vaccine research, an HIV/AIDS vaccine sub-committee was formed to develop a national AIDS vaccine plan for Kenya. IAVI provided financial and logistical support for the development of the document and after three months of committee work to build consensus, the *Kenya National Guidelines for the Development of HIV/AIDS Vaccines* was presented to the MOH in May 2004.
-V-
Executive Summary

- Monitoring Global Investment in R&D. Findings from a research project to estimate global investment in and spending on AIDS vaccine R&D were presented at the XV International AIDS Conference in Thailand. The working paper provides data from which to monitor future global spending and inform research on the level, adequacy, and distribution of expenditures for AIDS vaccine R&D.

- Manufacturing Challenges to Vaccine Development and Use. An IAVI Policy Discussion Paper on manufacturing issues in AIDS vaccine development and future use was completed in December. The paper identifies public policy options to address needs in the manufacture of clinical trials materials, bioprocess development, and the eventual large-scale production of future vaccines for use by developing countries.

- Ensuring Vaccines Are Accessible. At the annual meeting of the Global Forum for Health Research, IAVI staff presented a paper, co-authored with the World Bank, on assessing public and private sector demand for a preventive HIV vaccine in developing countries.

RESOURCE DEVELOPMENT

Broad-based financial support is essential to IAVI’s goal of accelerating the development of AIDS vaccines and making them available to the world. To date, IAVI has received funding and commitments totaling more than US $380 million, which includes the US $100 million from the Bill & Melinda Gates Foundation. However, funding IAVI’s programs through 2009 is currently projected to cost nearly US $654 million. IAVI must raise more than US $270 million in new commitments to support this critical, ongoing work. Moreover, in June IAVI’s Board of Directors endorsed a new strategic plan that calls for even greater resources as IAVI’s AIDS vaccine efforts continue to intensify.

PUBLIC SECTOR SUPPORT

Denmark. In July, Denmark reconfirmed its commitment to IAVI by awarding DKK 10 million (US $1.5 million) in support through mid-2005.

European Union. In January, IAVI received the first installment of a three-year matching grant of €3 million from the European Commission’s Directorate General for Development. The grant is funding an IAVI program in East Africa to build local clinical and social research capacity and community support in preparation for AIDS vaccine trials.

Norway. The Norwegian government has made an increased commitment to IAVI of NOK 15 million (US $2.4 million) for 2005.

Basque Autonomous Government of Spain. IAVI submitted a proposal to the Basque Autonomous Government to support trial site development in Chennai, India, and as well as a public awareness campaign on AIDS vaccines in the Basque Country.

Sweden. In December, IAVI received a contribution of SEK 4 million (US $594,000) from the Swedish Ministry of Foreign Affairs for 2005, which represents IAVI’s first funding from the Ministry. This augments the support previously received from the Swedish International Development Cooperation Agency/Department of Research Cooperation.

United Kingdom. The UK Department for International Development (DFID) extended its funding for IAVI with a contribution of GBP 4 million (US $7.7 million) for 2004-2005.


World Bank. In June, IAVI received US $700,000 in renewed funding from the World Bank’s Development Grant Facility through the Global Forum for Health Research. In December, the Bank announced that it would increase its support to $1 million in 2005.

PRIVATE SUPPORT

DHL. IAVI’s partnership with DHL, the world’s leading express delivery and logistics company, continues to grow. Since late 2003, DHL has been providing free shipping services for documents and non-perishable laboratory supplies to and from IAVI’s Core Lab in London. DHL also provided free shipping of IAVI materials from New York to the XV International AIDS Conference in Bangkok.

BD. Senior executives from BD, IAVI’s largest corporate supporter, visited IAVI in May for discussion and updates about how BD’s generous cash and in-kind contributions have been used, as well as IAVI’s plans for clinical trials and how BD’s technologies might support those studies.

Continental Airlines. Continental and IAVI concluded an in-kind sponsorship agreement for 2005 that included donated air travel and significantly discounted fares for group travel.

Rockefeller Foundation. In October, The Rockefeller Foundation, one of IAVI’s founding donors, announced renewed support in the form of a two-year grant of US $500,000.
Introduction

IAVI’s mission is to ensure the development and global delivery of a vaccine that prevents HIV infection and AIDS—the best hope to stop the spread of an epidemic that every day infects 14,000 people and each year claims 3 million lives. IAVI is the world’s largest organization focused solely on an AIDS vaccine, and its unique approach is to integrate research and development with advocacy and policy, working with both the public and private sectors in industrialized and developing countries.

IAVI 2005-2007 STRATEGIC PLAN

In 2004, IAVI management and staff comprehensively assessed the state of global efforts to develop a vaccine—including IAVI’s own efforts over the past nine years. Within this context, a new strategic plan was developed for 2005-2007. The plan, approved by the Board of Directors, reaffirms the organization’s mission and integrated approach of vaccine R&D with advocacy and policy efforts, and calls for expansion in these and other programs areas. It also endorses enhancements in IAVI’s operational structure and business model. Much of this work began to be implemented in 2004. The new Plan includes four major strategies:

1. Research & Development

IAVI operates a research and development program that translates basic research about HIV and the immune system into concepts for vaccine candidates that are evaluated in preclinical studies and human clinical trials. IAVI’s R&D staff, recruited in large part from industry, collaborates with an international network of partners, including biotechnology companies, academic and government research institutes, contract laboratories and manufacturers, and clinical trial sites. The sum of IAVI’s in-house and virtual capacity in R&D covers all of the major functions of a biopharmaceutical product developer.

IAVI’s R&D projects are focused on five principal areas:

- Clinical development: IAVI is testing vaccine candidates in small-scale Phase I and II human clinical trials to assess their safety and immunogenicity (ability to elicit immune responses). Today, these trials are testing only candidates that IAVI played a role in designing and manufacturing; in the future, IAVI plans to also test other developers’ candidates.
- Preclinical development: IAVI and its partners are constructing new vaccine candidates and screening them in animals for safety and immunogenicity as well as manufacturing feasibility. This will determine the candidates’ suitability for clinical trials.
- Applied research: IAVI is expanding its research consortia to identify new vaccine approaches that address potential shortcomings of the candidates currently in clinical and preclinical development. Practically all of these candidates are designed to stimulate only one of the immune system’s two arms—cell-mediated immunity and not neutralizing antibodies.
- Core laboratories: IAVI is helping to standardize and improve the laboratory assays that are used by the vaccine field to assess and compare the immunogenicity of different candidates. These assays are vital to determine whether the early test results of a candidate justify its further development compared to other candidates.
- Preparations for efficacy trials: IAVI has begun establishing clinical sites in developing countries that will be capable of conducting
efficacy trials within the next few years—trials that will require thousands of volunteers.

IAVI manages a portfolio of R&D projects, regularly prioritizing them given the latest data, scientific knowledge and priorities in the field. In consultation with an internationally recognized Scientific Advisory Committee, IAVI makes decisions to add, modify and terminate projects.

IAVI is a founding member of the Global HIV Vaccine Enterprise, an alliance of organizations that are involved in researching and developing an AIDS vaccine. Enterprise members are committed to promoting scientific cooperation and collaboration by reaching consensus on priorities, establishing joint ventures and iteratively applying each other’s advances so that the best science emerges as quickly as possible and unnecessary duplication is avoided. The Enterprise is in the initial stages of taking shape, and IAVI is actively involved.

2. Securing & Sustaining Global Commitment

IAVI collaborates with an international network of advocacy partners—largely nongovernmental organizations involved in other aspects of AIDS, health and development—to build a global movement for an AIDS vaccine. This means positioning new HIV/AIDS prevention technologies—a vaccine as well as other technologies such as microbicides—as a critical component of a comprehensive response to the epidemic. IAVI’s goal is to establish long-term high-level political and financial commitments for accelerating R&D as well as for planning ahead for future access to effective products. These commitments must not siphon away resources from treatment, care and current prevention efforts.

In order to be able to present the most credible case for a vaccine, IAVI has begun modeling the benefits of an effective vaccine and analyzing resource needs against actual commitments. In turn, IAVI and its partners are compellingly communicating these data to political and financial decision makers and influencers in industrialized and developing countries. A new initiative will bring together leaders from developing countries to serve as global spokespeople for a vaccine.

3. Promoting Supportive Public Policies

IAVI has begun to research, design and argue for public policies that will facilitate accelerated R&D. Beyond direct financing, these policies may include measures such as tax and intellectual property incentives to increase the involvement of pharmaceutical and biotechnology companies, and measures to support not-for-profit researchers and product developers. They may also include measures for strengthening and streamlining regulatory processes for clinical trials, particularly in developing countries.

New public policies are required to help assure that as soon as an effective vaccine is developed, it will be available and put to use where it is needed most. IAVI is expanding its activities to promote these access policies.

Ultimately the world needs an AIDS vaccine to control this epidemic just as we have controlled smallpox and polio.

Yoweri K. Museveni
President of Uganda
at the International AIDS Conference
July 2004

4. Engaging Countries and Communities Where the Epidemic is Most Severe

Since its inception, IAVI has pursued its efforts in R&D, advocacy and policy globally, and today has programs and partnerships in 23 countries in Africa, Asia, Europe and North and South America. This reflects a philosophy that international operations are essential from a practical standpoint. The success of all aspects of developing and delivering a vaccine depends on the active support of national governments and affected communities worldwide. IAVI’s headquarters is in New York, and three field offices serve the major regions of programs and partnerships. IAVI operates on a decentralized structure, with multidisciplinary staff in each field office.

From an R&D perspective, IAVI is sensitive to the possibility that a vaccine that is appropriate for some countries may not be for others, for any number of reasons, including that the genetic makeups of HIV and the human immune system vary geographically. IAVI prioritizes projects to develop a vaccine that will be appropriate for developing countries where most new HIV infections are occurring. Many of IAVI’s vaccine development projects include principal investigators from developing countries, and IAVI is investing significantly in establishing capacity for clinical trials in Africa and India.
Conducting vaccine R&D successfully in any area entails addressing a number of non-scientific issues; many of these are particularly challenging in developing countries. They include assuring the involvement of local leaders and community groups; assuring adherence to the highest standards for ethics and human rights in trials; assuring that the general health care infrastructure can support the needs of trials, for example by providing HIV counseling and testing; and assuring the equitable participation of men and women in trials.

(For more information regarding IAVI’s strategic planning process, please see p. 54. To obtain a copy of IAVI’s 2005-2007 Strategic Plan, please send a request via email to info@iavi.org. The Plan also is available on IAVI’s web site and may be downloaded by visiting www.iavi.org/strategicplan2005.)

AIDS Vaccine Research & Development

In the midst of an expanding and rapidly changing AIDS vaccine field, 2004 was a pivotal year for IAVI’s Research and Development (R&D) program. As reported below, the organization increased its senior R&D leadership, made key decisions regarding its product development portfolio, published a 2004 edition of its Scientific Blueprint, and continued to refine and focus its AIDS vaccine R&D strategy, including the expansion of applied research efforts to overcome daunting scientific obstacles that have impeded AIDS vaccine development.

Dr. Emilio Emini Joins IAVI

As reported in IAVI’s Mid-Year Progress Report, in February 2004, IAVI welcomed Dr. Emilio A. Emini to help lead its R&D effort. Dr. Emini joined the IAVI senior management team as Senior Vice President and Chief of Vaccine Development, and is working alongside Dr. Wayne Koff, IAVI’s Senior Vice President and Chief of Vaccine Research.

Prior to joining IAVI, Dr. Emini spent 20 years at Merck & Co., Inc., where he gained recognition as one of the world’s preeminent AIDS vaccine scientists. As Merck’s Senior Vice President of Vaccine Research, Dr. Emini was responsible for Merck’s overall basic vaccine research program. During his tenure, he led the company’s AIDS vaccine efforts, advancing five different vaccine candidates to human trials. In addition, Dr. Emini led the Merck team that developed one of the first highly effective antiretroviral agents for the treatment of people living with HIV.

Dr. Koff is leading IAVI’s research efforts to address major scientific challenges and to identify the next generation of promising vaccine concepts. Dr. Emini will focus on accelerating the development of these concepts into vaccine candidates that can be tested in human trials, and advancing the most promising into large-scale efficacy testing and eventual licensure. Together they will assure scientific leadership and seamless integration of IAVI’s R&D program.

Scientific Blueprint 2004

At the International AIDS Conference in Bangkok in July, IAVI released its Scientific Blueprint 2004: Accelerating Global Efforts in AIDS Vaccine Research and Development. The 2004 edition of the IAVI Blueprint analyzes progress in the AIDS vaccine field, identifies key challenges to vaccine R&D at this stage of the epidemic, and makes recommendations to strengthen and accelerate the global search for a preventive vaccine.

The Blueprint notes major progress since the last review: a wider pipeline of vaccine candidates, completion of the first efficacy trial, and engagement in the field by a greater number of research groups. However, it also points to a number of shortcomings. At present, clinical trial capacity in developing countries would permit only a limited number of additional large-scale HIV vaccine trials, even though the urgency of the AIDS epidemic will demand simultaneous development and testing of multiple promising vaccine candidates. Overall, the global vaccine R&D effort continues to be severely limited, having attracted significant investments from relatively few private sector companies.

To speed the day when a preventive vaccine will be available, the Scientific Blueprint 2004 calls for a significant increase of current spending on AIDS vaccine R&D. The candidates currently in development, which are mostly designed to induce ‘cellular immunity’ (see Glossary), should continue to be aggressively pursued, with key stakeholders in the field collaborating to prioritize the most promising for expedited efficacy testing. Intensified scientific focus is needed to develop improved products, including candidates that elicit broadly neutralizing antibody responses, as well as those that will confer the same level of protection as mutated live-attenuated SIV in non-human primates. The Blueprint also envisions that IAVI and other stakeholders will collaborate in the creation of regional vaccine efforts in high-incidence areas, each with the capacity to conduct multiple large-scale human trials.
GLOBAL HIV VACCINE ENTERPRISE

Patterned after the Human Genome Project, the Global HIV Vaccine Enterprise is a new alliance of agencies working toward an AIDS vaccine. The Vaccine Enterprise is intended to foster collaboration and cooperation across research and development programs. It was proposed by the Bill & Melinda Gates Foundation and others in a June 2003 paper in the journal *Science*, and endorsed by the heads of the G8 nations at their summit in June 2004. As a founding member of the Enterprise, IAVI believes that it should serve as a forum for the best vaccine concepts and candidates to be prioritized, regardless of where they originate.

IAVI remains committed to helping shape the direction of the Enterprise and to contributing to its implementation. Dr. Seth Berkley was a co-author of the 2003 *Science* article. Both he and Dr. Emilio Emini, IAVI’s Senior Vice President and Chief of Vaccine Development, served on the initial Steering Committee of the Enterprise. Dr. Berkley is currently a member of the Coordinating Committee and IAVI R&D staff have led or participated in nearly all of the Enterprise working groups for the six priority areas (Vaccine Discovery, Laboratory Standardization, Clinical Trials Capacity, Product Development and Manufacturing, Regulatory Issues, and Intellectual Property). As IAVI works with its Enterprise partners, it also will remain focused on continuing to strengthen its areas of core competence and carrying out the activities laid out in IAVI’s 2005-2007 Strategic Plan.

UPDATE ON IAVI-SPONSORED AIDS VACCINE CANDIDATES IN CLINICAL DEVELOPMENT

At the end of 2004, there were three IAVI-sponsored HIV vaccine projects testing four different candidate vaccines in clinical trials:

1. DNA.HIVA + MVA.HIVA (Modified Vaccinia Ankara) Vaccine;
2. tgAAC09 Vaccine (*Recombinant* Adeno-Associated Viral Vector Vaccine, AAV); and

**DNA+MVA (MODIFIED VACCINIA ANKARA) VACCINE**

Project Background Summary. Launched at the end of 1998, the DNA+MVA (Modified Vaccinia virus Ankara) Vaccine Development Partnership (VDP) has linked vaccine designers in the UK with clinical research scientists in Kenya. Led by Dr. Andrew McMichael of the University of Oxford and the UK Medical Research Council (MRC) and Dr. J.J. Bwayo of the University of Nairobi and the Kenya AIDS Vaccine Initiative (KAVI), the project has been working to develop vaccine candidates designed to stimulate HIV-specific cellular immune responses.

The Vaccine Constructs. This AIDS vaccine approach is based on using four constructs in combination:

- **DNA.HIVA**: the gag gene of HIV-1 subtype A p24 and p17, plus a series of mini-genes representing CTL epitopes from HIV-1 env, gag, pol and nef, are delivered via naked DNA.
- **MVA.HIVA**: the same gag-CTL epitope genetic material is delivered by Modified Vaccinia virus Ankara (MVA) vector.
- **DNA.RENTA**: naked DNA delivers HIV clade A reverse transcriptase gene (RT, tat and nef genes all biologically inactivated) and two regions of env.
- **MVA.RENTA**: the same RT-tat-nef-env genes delivered by MVA vector.

The vaccine field identified DNA and MVA technologies as promising in the early 1990s. The IAVI-Oxford-Nairobi partnership was the first to complete design and manufacture of candidates to prevent HIV/AIDS based on the combination of these technologies and to accelerate them into human trials, which have been evaluating their safety and seeking to determine whether they elicit an anti-HIV cell-mediated immune response.

**Manufacturing.** Clinical Good Manufacturing Practice (cGMP) contracts were signed with Cobra Biomanufacturing plc (UK), which manufactured the DNA.HIVA and the DNA.RENTA, and with Impfstoffwerk Dessau-Tornau GmbH (IDT) (Germany), which manufactured the MVA.HIVA.

**Clinical Testing.** Since clinical trials were initiated in 2000, the DNA.HIVA and MVA.HIVA vaccine candidates have been extensively tested in an accelerated clinical trial program in over 400 volunteers in five countries: the UK (MRC-Oxford; St. Mary’s and St. Thomas’s Hospitals, London; and SIMBEC, Wales), Kenya (KAVI/University of Nairobi), Uganda (UVRI, Entebbe), Switzerland (University of Lausanne) and South Africa (Chris Hani Baragwanath Hospital, University of Witwatersrand, Johannesburg, and Medical Research Council, Durban). The candidates were tested alone and as a prime-boost combination. The DNA.RENTA and MVA.RENTA constructs have not entered clinical trials.
As noted above, the objectives of these trials were to assess safety and immunogenicity of the vaccine candidates in healthy individuals who are not infected with HIV. Upon completion of these studies, a final decision will be made as to whether the data warrant continuation of the program (see Preliminary Safety and Immunogenicity Data below).

Progress in 2004

Manufacturing. The manufacture of MVA.RENTA was put on hold in August, following a review of the latest interim data from HIVA clinical trials.

Clinical Trials of the DNA.HIVA and MVA.HIVA Vaccine Constructs

During 2004, clinical testing of the DNA.HIVA and MVA.HIVA vaccine constructs as prototype vaccines continued:

- Trial #004 (Phase I safety and immunogenicity study): The study protocol was amended (#004A) to boost volunteers with a third dose of MVA.HIVA or placebo at least 12 months after receipt of two doses of MVA.HIVA or placebo. Regulatory approval was obtained. All vaccinations were completed in November 2004.

- Trial #006 (Phase I/II DNA+MVA prime-boost): This prime-boost study conducted at two UK sites (MRC-Oxford and St. Mary’s Hospital, London) enrolled 119 healthy volunteers and examined the need for a DNA prime, the optimal dosage level of the DNA.HIVA vaccine and the best interval between the DNA.HIVA prime and MVA.HIVA boost injections. Safety and immunogenicity data were presented at the AIDS Vaccine 2004 Conference in Lausanne, Switzerland (Aug 30-Sept 1, 2004). Twelve-month follow up was completed in August 2004 and the study was unblinded. A manuscript of safety and immunogenicity data is in preparation.

- Trial #008 (Phase I rollover-boost): This small Phase I study at the KAVI site in Kenya was a rollover trial to boost volunteers who had received the DNA.HIVA vaccine in trial #002 with two doses of MVA.HIVA. The study was completed in 2004. Preliminary safety and immunogenicity data were presented at the AIDS Vaccine 2004 Conference in Lausanne.

- Trial #009 (Phase I/II DNA+MVA prime-boost): A DNA+MVA prime-boost study conducted at the Uganda Virus Research Institute (UVRI) in Entebbe enrolled 50 volunteers. This trial compared one versus two priming injections of DNA.HIVA versus placebo followed by two doses of MVA.HIVA or placebo. All vaccinations and 12-month follow-up visits were completed.

Temporary Interruption of Vaccinations. On 30 March 2004, IAVI temporarily interrupted all vaccinations in this program as a result of observations made in a pre-clinical mouse study. After careful review of the data, it was concluded that the observations were not caused by the vaccine. A meeting was convened in London on 30 July 2004 to inform the partners and investigators and discuss how to proceed with the clinical trials. It was agreed that trials #004A, #010 and #016 would resume vaccinations in order to complete the data set, while vaccinations would not resume for trial #011 because study #010 would provide sufficient information on the routes and doses for MVA.HIVA at a much earlier timepoint. The decisions taken at this meeting were communicated to clinical investigators, regulatory agencies, ethics committees, volunteers, Data...
Monitoring and Ethics Committees (DMECs), Trial Steering Committees (TSCs) and other stakeholders.

The regulatory agencies in the UK and in Kenya, where vaccinations were temporarily interrupted, agreed with the conclusion regarding the findings in the mouse study and gave permission to resume vaccinations in studies #004A, #010 and #016.

Interim Safety and Immunogenicity Data. IAVI’s partners and Scientific Advisory Committee met in early August to review the latest interim data from clinical trials on these products. These interim data were presented by the Oxford, Kenyan and Ugandan investigators at the AIDS Vaccine 2004 International Conference in Lausanne, Switzerland, 30 August - 1 September. The data showed that the vaccines are in general safe and well tolerated. However, as measured using currently accepted techniques, the anti-HIV cellular immune response elicited by these candidates (ranging between 9-18% CD8 T cell responses) fell short of expectations and did not reach the minimum level IAVI has stipulated to move them forward in clinical testing.

During the first half of 2005, IAVI and its partners will complete ongoing trials, administering a higher dose of MVA.HIVA (#010 and #016) and a third dose of MVA.HIVA (#004A). If observations from the interim data are not significantly improved by the conclusion of these trials, IAVI and its partners have concluded that further development of these particular DNA and MVA candidates for the prevention of HIV/AIDS would not be warranted. In such case, IAVI will reallocate organizational resources to its other priority research and development projects.

It should be emphasized that a potential termination of the Oxford-Nairobi DNA+MVA program would not represent a failure of the DNA+MVA platform in general. IAVI is investigating another DNA+MVA platform and another MVA candidate—all molecularly distinct from the Oxford-Nairobi constructs—to determine the overall viability of the DNA and MVA technologies.

Independent of the final decision, the extensive research infrastructure that was created—primarily in Africa—to enable the conduct of clinical trials will continue to be supported by IAVI to facilitate the assessment of other candidates, including both IAVI-sponsored vaccines and products developed by other research institutions.

HIV VACCINE BASED ON RECOMBINANT ADENO-ASSOCIATED VIRAL VECTOR (rAAV-HIV)

Project Background Summary. Initiated in February 2000, this VDP is led by Principal Investigator Dr. Phil Johnson of the Children’s Hospital of Philadelphia (Pennsylvania, US), formerly of Columbus Children’s Research Institute (Ohio, US). This program uses recombinant adeno-associated virus (rAAV) as a vector. In the recombinant AAV vector, the rAAV genes have been replaced by a selected number of HIV genes. Currently, three vaccine constructs based on AAV technology are being developed by Targeted Genetics Corporation (Washington, US): 2

1. **tgAAC09**: The first vaccine construct, designated tgAAC09, is based on AAV type 2 and contains the gag-pro genes and a portion of the reverse transcriptase gene (Gag-Pro-\(\Delta\)RT) from HIV-1 subtype C, the most common strain of HIV in the world today. Proof of concept in Phase I trials will be to demonstrate safety and confirm in humans the immunogenicity of rAAV Gag-Pro-\(\Delta\)RT previously observed in monkeys.

2. **tgABF66**: The second candidate, designated tgABF66, contains the HIV gag-pro and reverse transcriptase gene (Gag-Pro-RT) from subtype C, but the HIV DNA is enclosed in an AAV type 1 capsid (or protein coat). In non-human primates this vaccine has been shown to elicit similar immune response but at lower doses than the AAV2-based vaccine. The second candidate is currently in preclinical studies and proof of concept in Phase I trials are planned to demonstrate safety and confirm that AAV1 may be a superior vaccine platform compared to AAV2.

3. **tgAXF90**: Early development continues on a multi-component vaccine, also made from AAV1 and designated tgAXF90. These constructs would contain additional genes of HIV-1 subtypes C and A, including env, and the gag pro-RT construct, potentially to broaden the immune response.

Use of rAAV as a vector for HIV genes is desirable as a vaccine approach because AAV is not associated with disease in humans. New data from macaques indicate that AAV1 may be a better vaccine platform than AAV2 and additional data suggests that a second administration of the vaccine may lead to a boosting of the immune response. This potential to boost immune response

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2 This project has vaccine candidates in several stages of development, including clinical, preclinical and early development.
responses will also be evaluated in human clinical trials.

**Progress in 2004**

**rAAV-HIV Preclinical Studies.** Additional preclinical studies were initiated to better characterize the platform and provide data that may benefit the clinical program. Additional ‘boost’ configuration studies were initiated after data showed improved responses following vaccination with rAAV-HIV vaccines followed by either an additional vaccination of rAAV-HIV or other vaccine candidates.

**tgABF66 Biodistribution Study.** A biodistribution study with tgABF66 was completed to evaluate the use of the AAV1 platform.

**Manufacturing.** Additional vaccine is in production for the Phase II study of tgAAC09 to be conducted in several African countries. Process development also is ongoing for manufacture of the tgABF66 vaccine candidate. The cell line—which is utilized to prepare a component of the manufacturing process used to make the vaccine—has been identified and is being characterized. Quality Control testing is ongoing.

**Clinical Trials.** A Phase I dose-escalation study (#A001) was conducted at two sites in Belgium (Brussels and Antwerp) and two sites in Germany (Hamburg and Bonn). Fifty healthy volunteers not infected with HIV were randomized to receive a single injection of tgAAC09 (three dosage levels) or placebo. Preliminary safety data show that the tgAAC09 vaccine is well tolerated. Preliminary immunogenicity data is expected to be available in 2005. This study was recently amended to offer the volunteers a late boost inoculation of tgAAC09 (six months or more after the initial vaccination). As of 31 December 2004, approvals were pending.

The #A001 trial protocol was also amended to include 30 volunteers in a dose escalation study at the National AIDS Research Institute (NARI) in Pune, India. All necessary ethical and regulatory approvals were obtained—from the NARI and National Ethics Committees, the Drugs Controller General of India (DCGI), the Health Ministry Steering Committee (HMSC) and the Genetic Engineering Approval Committee (GEAC)—and the first HIV vaccine study in India began in the first quarter of 2005.

A Phase II protocol (#A002) was developed to evaluate the safety and immunogenicity of two doses of tgAAC09 at a total of six clinical trial sites in South Africa, Zambia and Uganda. In this planned trial, volunteers will be receive tgAAC09 or placebo; half will receive a second vaccination of the same vaccine at six months while the other half will receive their second vaccination at 12 months. Ethical and regulatory approvals are pending in Zambia and have been obtained in South Africa for two dosage levels. A proposal to add a site in Uganda, as well as a third dose level in all countries, is pending. The #A002 trial is expected to start in mid-2005.

Drs. Pat Fast and Chrispin Kambili meet with the Zambian Minister of Health, Dr. Brian Chituwo, to discuss initiation of the planned Phase II trial A002.

**MULTIGENIC DNA+MVA PRIME-BOOST VACCINE USING INACTIVATED FULL-LENGTH HIV GENES**

**Project Background Summary.** This project is a partnership between IAVI and the Aaron Diamond AIDS Research Center (ADARC) in New York. The vaccine candidates are a DNA prime (ADVAX) and MVA (ADMVA) vector booster vaccine expressing HIV genes env, gag, pol, nef, and tat based on HIV clade C circulating in China.

This multigenic DNA+MVA vaccine combination offers potential advantages, namely enhanced expression by codon-optimization of the genes and by the capacity to immunize against five different genes. Full-length HIV genes have been mutated to prevent potentially harmful biological activities. A dual promoter system with two different plasmids was used for the design of the DNA prime: ADVAX EG-1 expressing HIV env and gag, and ADVAX NTP-2 expressing Pol-Nef-Tat. These two DNA plasmids were combined and evaluated for safety in preclinical studies in small animals. Construction of the MVA boost component, ADMVA, containing all five HIV genes, was completed in 2002, and immunogenicity for all genes has been demonstrated in small animals.

**Progress in 2004**

**Preclinical Studies.** Safety and immunogenicity studies of ADMVA in small animals are complete. The repeat toxicology study in mice and local
tolerance study in rabbits were completed and no safety issues were identified.

**Manufacturing.** Extensive analysis has been completed—including quality control (QC) testing at IDT in Germany; characterization of the recombinant at Transgene (France), Micromun (Germany) and the Aaron Diamond AIDS Research Center in New York; and immunogenicity testing at BD Pharmingen (US)—and clinical lots of the ADMVA have been released.

**Regulatory.** An IND application for ADMVA was submitted to the FDA on Nov 16, 2004. Ethics approvals from the Institutional Review Boards at Rockefeller University and Rochester University for the study with ADMVA are pending.

**Clinical Testing.** The first Phase I double blind, randomized, placebo controlled, dose escalation trial with ADVAX, conducted at the Rockefeller University and the Rochester University, is in the follow up phase. All vaccinations have been given. Preliminary safety data show that the vaccine is safe and well tolerated at the dosage levels and regimens tested.

The first clinical trial with ADMVA is a double blind, randomized, placebo-controlled, dose escalation study enrolling 45 healthy, HIV sero-negative volunteers. The trial is expected to start in early 2005.

**IAVI-NIH COLLABORATION ON HIV VACCINE TRIALS**

IAVI also is working closely with the NIH Vaccine Research Center (VRC), the US Military HIV Research Program (USMHRP), the HIV Vaccine Trials Network and the NIH Division of AIDS to plan for a series of three closely coordinated Phase I and Phase II trials to test the VRC candidate vaccines based on DNA and adenovirus type 5 platforms. These vaccines contain sequences from multiple genes representing clades A, B and C. According to the plans, IAVI and the USMHRP would test the vaccines in East Africa. The protocols have not yet been submitted for regulatory review.
## OVERVIEW OF IAVI-SPONSORED CLINICAL TRIALS

*(Please note that the status of trials given in the Comments section below is as of 31 December 2004.)*

### DNA.HIVA + MVA.HIVA Prime-Boost Vaccine Constructs

<table>
<thead>
<tr>
<th>IAVI Trial Protocol Number</th>
<th>Country (Sites)</th>
<th>First Participant Enrolled</th>
<th>Total # of Volunteers Enrolled</th>
<th>Vaccines</th>
<th>Comments / Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>UK (Oxford)</td>
<td>Aug-00</td>
<td>18</td>
<td>DNA.HIVA</td>
<td>Initial safety, DNA.HIVA dose escalation; study completed.</td>
</tr>
<tr>
<td>002</td>
<td>Kenya (Nairobi)</td>
<td>Feb-01</td>
<td>18</td>
<td>DNA.HIVA</td>
<td>DNA.HIVA versus placebo; study completed.</td>
</tr>
<tr>
<td>003</td>
<td>UK (Oxford)</td>
<td>Mar-01</td>
<td>8</td>
<td>MVA.HIVA</td>
<td>Initial safety, MVA.HIVA; open label; study completed.</td>
</tr>
<tr>
<td>004</td>
<td>Kenya (Nairobi)</td>
<td>Feb-02</td>
<td>18</td>
<td>MVA.HIVA</td>
<td>MVA.HIVA versus placebo; original study completed. Study amended to give a third dose of MVA.HIVA as a late boost (#004A); all vaccinations given.</td>
</tr>
<tr>
<td>005</td>
<td>UK (Oxford)</td>
<td>Oct-01</td>
<td>9</td>
<td>MVA.HIVA boost</td>
<td>MVA.HIVA boost for volunteers in trial 001; study completed.</td>
</tr>
<tr>
<td>006</td>
<td>UK (Oxford, London)</td>
<td>Apr-02</td>
<td>119</td>
<td>DNA.HIVA prime, MVA.HIVA boost</td>
<td>DNA.HIVA dose (low, medium dose) versus placebo, followed by an early interval MVA boost versus a late interval MVA boost; study completed.</td>
</tr>
<tr>
<td>008</td>
<td>Kenya (Nairobi)</td>
<td>Mar-03</td>
<td>10</td>
<td>MVA.HIVA boost</td>
<td>MVA.HIVA boost for volunteers in trial 002; study completed.</td>
</tr>
<tr>
<td>009</td>
<td>Uganda (Entebbe)</td>
<td>Feb 03</td>
<td>50</td>
<td>DNA.HIVA prime, MVA boost</td>
<td>One or two doses of DNA.HIVA followed by two doses of MVA.HIVA; vaccinations completed; last volunteer visit in February 2005.</td>
</tr>
<tr>
<td>010</td>
<td>Kenya (Nairobi), UK (London)</td>
<td>Apr 03</td>
<td>111</td>
<td>DNA.HIVA prime, MVA.HIVA boost</td>
<td>Prime-boost to evaluate three dosage levels of MVA.HIVA and three routes of administration; enrollment completed; study ongoing.</td>
</tr>
<tr>
<td>011</td>
<td>So. Africa (Durban, Johannesburg), Switzerland (Lausanne), UK (Wales)</td>
<td>Nov 03</td>
<td>81</td>
<td>MVA.HIVA</td>
<td>Dose escalation study to evaluate MVA.HIVA at three dosage levels and using three routes of administration. Low and middle dosage-level enrollment complete; study ongoing. High dose group will not be enrolled.</td>
</tr>
<tr>
<td>016</td>
<td>UK (Oxford)</td>
<td>Feb 04</td>
<td>24</td>
<td>MVA.HIVA, DNA.HIVA prime + MVA.HIVA boost</td>
<td>High dose of MVA alone or prime-boost of high dose of DNA and MVA to evaluate peak immune response. Vaccinations complete, last volunteer visit in February 2005.</td>
</tr>
</tbody>
</table>

### AAV Vaccine Construct (tgAAC09)

<table>
<thead>
<tr>
<th>IAVI Trial Protocol Number</th>
<th>Country (Sites)</th>
<th>First Participant Enrolled</th>
<th>Total # of Volunteers Enrolled</th>
<th>Vaccines</th>
<th>Comments / Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>A001</td>
<td>Belgium (Antwerp, Brussels); Germany (Bonn, Hamburg); India (Pune)</td>
<td>Dec 03</td>
<td>50</td>
<td>AAV</td>
<td>AAV-HIV vaccine dose escalation and dose optimization study (low, medium, high) versus placebo in European follow-up phase. Protocol Amendment: late boost with high dose in European volunteers, slated to begin first quarter 2005. Protocol Amendment: 30 volunteers to be enrolled in India in first half of 2005 (dosage escalation).</td>
</tr>
</tbody>
</table>

### ADVAX DNA Vaccine Construct

<table>
<thead>
<tr>
<th>IAVI Trial Protocol Number</th>
<th>Country (Sites)</th>
<th>First Participant Enrolled</th>
<th>Total # of Volunteers Enrolled</th>
<th>Vaccines</th>
<th>Comments / Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>C001</td>
<td>US (New York, Rochester)</td>
<td>Dec 03</td>
<td>45</td>
<td>DNA</td>
<td>DNA HIV vaccine dose escalation study (low, medium, high) versus placebo; enrolment completed, study ongoing.</td>
</tr>
</tbody>
</table>
IAVI-Sponsored AIDS Vaccine Candidates in Preclinical Development

IAVI has continued its preclinical assessment of additional vaccine candidates. These candidates, together with the vaccines now in clinical trials, constitute IAVI’s current AIDS vaccine product portfolio.

Human Adenovirus (Ad) Particle Vaccines: AdVac® Vectors, Adenovirus Serotypes 11 & 35

Project Background Summary. Launched by IAVI in 2004, this partnership is a collaboration with the Dutch biotechnology company Crucell N.V. (Leiden, The Netherlands) to develop AdVac® vectors for use in IAVI’s AIDS vaccine development program. Crucell and IAVI have entered into an exclusive license agreement to develop an AIDS vaccine based on Crucell’s AdVac® technology.

The AdVac® vectors, derived from adenovirus serotypes 11 and 35, have shown promising results in a series of preclinical studies unrelated to AIDS vaccines.

The four principle early phase objectives for this collaboration are as follows:

1. Expand the sero-epidemiology profile of the human adenoviruses in Africa to ascertain whether serotypes 35 and 11 have low seroprevalence.
2. Construct, characterize and produce adenovirus vectors expressing HIV genes for immunogenicity assessment in a non-human primate study.
3. Develop and characterize a production cell line for the adenovirus vectors.
4. Select vaccine candidates for preclinical development and subsequent evaluation in clinical trials.

Progress in 2004

The plans for this project have been created and the human adenovirus type 35 vector is being constructed to express HIV-1 clade A transgenes. The vector will be produced in 2005 for preclinical testing. In parallel, plans were established and work begun to derive a cell line, acceptable to regulatory authorities, for efficient production of the adenovirus vector vaccine for human trials.

Multigenic MVA Vaccine (TBC-M4)

Project Background Summary. This project is a collaboration between the Indian Council of Medical Research (ICMR), IAVI and Therion Biologics Corporation (Cambridge, Massachusetts, US), and was officially launched in March 2001 when IAVI signed a Memorandum of Understanding with the ICMR and the Government of India.

The goal of this VDP is to evaluate a multigenic MVA vaccine (TBC-M4). The potential advantage of this construct over a single gene approach is that inclusion of multiple HIV genes likely would induce broader cell-mediated immunity to various epitopes (determinants on proteins) of HIV. This HIV vaccine candidate is based on recombinant MVA expressing HIV-1 env, gag, pol, rev, nef and tat genes of an Indian Clade C HIV.

The HIV genes were identified and selected from two sources: from people infected in India (done in collaboration with scientists at the National AIDS Research Institute (NARI) in Pune) and from consensus sequences of the Indian clade C. Genes have been modified to prevent potentially harmful biological activities.

Progress in 2004

Preclinical Studies: In addition to cellular immune response to the HIV antigens, an antibody response to the MVA vector was demonstrated. A repeat dose toxicity study in mice was completed. Safety and local tolerability studies in rabbits required for the regulatory application also were completed and no safety concerns were raised.

Manufacturing: Clinical lots of TBC-M4 have been produced. The vaccine is stable at -15°C and -70°C for at least 18 months.

Regulatory: The clinical trial protocol including the Informed Consent Document (ICD) has been reviewed and approved by the Scientific Committee of the TRC (Tuberculosis Research Center) in Chennai (formerly Madras), India. The dossier for TBC-M4 has been submitted to the Clinical Site Ethics Committee for review beginning in mid-December 2004. Application for approval from national regulatory authorities to begin a Phase I study in India is planned for early 2005, after approval from the local regulatory bodies.

Clinical Testing: The first Phase I clinical trial is planned as a double-blind, randomized, placebo-controlled study. Three injections of TBC-M4 will be given at two dosage levels. The Tuberculosis Research Center (TRC) has been selected as the clinical site to conduct the TBC-M4 Phase 1 clinical trial. Renovation of the safety and immunology
laboratories began in mid-December 2004 and the clinical trial is expected to start in mid-2005.

**Orally-Administered Bacterial Vector**

**Project Background Summary.** This VDP, launched in May 2000, was a collaboration between IAVI and several research partners: the University of Maryland’s Institute of Human Virology (Drs. Robert Gallo and George Lewis) for development and evaluation of the *Salmonella* and *Shigella* vaccines; the Walter Reed Army Institute of Research (WRAIR) for evaluation and production of the *Shigella* vaccine; and Berna Biotech AG, a Swiss vaccine manufacturer, for process development and production of the *Salmonella* vaccine.

This VDP has sought to determine whether oral administration of an attenuated (weakened) bacterial vector to deliver a DNA vaccine expressing HIV genes is more effective than injection of naked DNA vaccines. Bacterial vectors have offered the potential for induction of both systemic and mucosal immunity, with the advantage of oral administration. It has been demonstrated with non-HIV antigens that bacterial delivery of DNA is effective in eliciting protection against mucosally delivered pathogens.

This VDP has used the Oxford-Kenya prototype HIVA DNA subtype A gag plus epitope genetic sequence administered orally via the bacterial delivery system. Two different bacterial strains—*Salmonella* and *Shigella*—have been evaluated as candidate vectors in pre-clinical studies and in manufacturing.

**Progress in 2004**

**Preclinical Studies.** The *Salmonella typhi* pDNA and the *Shigella* pDNA vaccine candidates were evaluated extensively for immunogenicity in small animals. For both candidates, a weak immune response against the HIV gene product was detected under the experimental conditions used.

**Regulatory.** The FDA advised, that due to issues arising from the inclusion of certain antibiotic resistance genes in other products (not candidate HIV vaccines), that the backbone of the HIV plasmid in the *Shigella* and *Salmonella* vaccine candidates be modified for safety reasons, and more precisely the antibiotic resistance gene be removed. Berna Biotech and Cobra (UK) were approached for possible reconstruction and it appeared that to engineer a new bacterial pDNA delivery system would take approximately two years with no guarantee of success.

**Conclusion.** After a thorough review of the design of the *Salmonella* and *Shigella* delivery systems, the cost and time of reconstruction, and the disappointing immunogenicity data from preclinical studies, IAVI decided to discontinue the development of these vaccine candidates and focus on other priorities. This is in keeping with IAVI’s strategy to regularly review and prioritize its research and development portfolio. IAVI and IHV mutually agreed to end their collaboration 31 December 2003, and IAVI’s work with WRAIR and Berna ended 30 June 2004.

IAVI has recommended that this platform be further evaluated at a more basic research level. Optimal animal models for immunogenicity evaluation should be developed and adapted for such microbial-based plasmid delivery systems. Appropriate immunogenicity tests also should be further developed and enhanced for mucosal immunity assessment. In addition, a stable bacterial strain and plasmid should be genetically engineered to increase potency and safety.

**Semliki Forest Virus (SFV) Replicon DNA and SFV Replicon Particle Vaccines**

**Project Background Summary.** Launched by IAVI in 2001, this VDP was a collaboration with the Swedish biotechnology firm Bioption AB. Led by Dr. Peter Liljestrom, the VDP worked to develop AIDS vaccine candidates using Semliki Forest Virus (SFV) replicons, a technology pioneered at Sweden’s Karolinska Institute.

**Vaccine Design.** The plans for this project included two vaccine designs: SFV replicon DNA, which is aimed at producing more of the vaccine antigen and inducing a more potent immune response than conventional (naked) DNA plasmids; and SFV particles, which preferentially target cells of the immune system and were immunogenic in preclinical studies in combination with MVA.

The project’s four objectives included: (1) comparing SFV replicon DNA vectors with a conventional DNA plasmid vaccine expressing the HIVA antigen (using the Oxford-Kenya DNA.HIVA as reference); (2) designing, constructing and testing recombinant SFV replicon DNA expressing multiple antigens from an Indian HIV clade C isolate; (3) designing, constructing and testing recombinant SFV particles expressing multiple antigens from an Indian HIV clade C isolate; and (4) developing methods for production of recombinant SFV particle vaccines in cell culture.
Research Progress. Several different SFV replicon DNA.HIV clade A plasmids were constructed and their immunogenicity was assessed in mice. The objective was to compare different SFV vector designs with the conventional naked DNA plasmid expressing the HIV clade A antigen.

The mouse data indicated that SFV-replicon DNA may have an advantage compared to conventional DNA in eliciting cellular immune responses to the model HIV clade A antigen. A confirmatory mouse study using clinical material also demonstrated the advantage of the product in this model. However, a non-human primate study provided data in April 2004 indicating that the SFV replicon DNA.HIV clade A plasmid was not performing as it had in the earlier mouse studies. In addition, observations from a mouse biodistribution study indicated that extensive toxicity studies also would be required. As a result, further development of the SFV replicon DNA vector has been terminated.

In parallel, SFV particle construction was completed. Immunogenicity data from a murine study with the particles demonstrated a T-cell response after one dose, which was then boosted with second and third doses. However, the observations from the murine biodistribution studies of the related SFV replicon plasmid imposed a significant hurdle in that they required the program to conduct an extensive, multi-species toxicologic assessment of the SFV particle vaccine prior to human administration. Following these studies, the SFV particle candidate would face considerable bioprocess development issues, including the selection of an acceptable cell line for production. The uncertain technical considerations facing the SFV particle program, and the program’s prolonged development timeline, were the basis for IAVI’s decision not to continue development of this platform. Consequently, IAVI did not renew the partnership following expiration of the agreement on 31 December 2004.

Core Immunology Laboratory for Comparison of AIDS Vaccine Candidates

Project Background Summary. The IAVI Human Core Immunology Laboratory (the Core Lab) is based at Imperial College Faculty of Medicine, at the Chelsea and Westminster Hospital in London. The Core Lab’s purpose is to facilitate evaluation of IAVI-sponsored AIDS vaccine candidates. To that end, the Core Lab functions as a central base for field site laboratories, providing standard operating procedures, standardized reagents and equipment, and training and support for field staff. The Core Lab also performs a number of key testing roles:

- Serving as a primary field laboratory for IAVI-sponsored trials underway in London;
- Conducting all immunogenicity testing on samples from trial sites that do not perform such assays themselves (currently all European and US sites); and
- Providing quality assurance (QA) through testing a percentage of samples from all IAVI trials.

The IAVI Core Laboratory team in London includes three post-doctoral scientists, one administrator and six technicians, as well as field staff in Kenya, South Africa and New York.

Good Clinical Laboratory Practices. To ensure that data on immune responses and other parameters from vaccine trials is of the highest quality—and therefore acceptable to regulatory authorities, the work must be carried out in accordance with Good Clinical Laboratory Practices (GCLP), a new standard for clinical trial laboratories. In 2004, the IAVI Core Lab became the first laboratory in the world to become accredited to GCLP. This new standard was developed by Qualogy Ltd., an independent UK-based consulting agency, in association with the British Association of Research Quality Assurance (BARQA). GCLP principles are in line with European, Japanese and American regulatory agency expectations, and have been adopted as the international standard by the South African National Accreditation System (SANAS).

Standard Operating Procedures. New standard operating procedures (SOPs) were developed by the Core Lab for the use of new equipment and for the conduct of ELISPOT, flow cytometry and other assays. All of the scientific SOPs used at the Core Lab are routinely reviewed and updated to ensure GCLP compliance. To standardize procedures across all sites, new and modified SOPs are distributed to the labs working on IAVI trials (Kenya, Uganda, Belgium, Germany, Oxford, Switzerland, South Africa, US, Wales), as well as sites selected for upcoming trials (Rwanda, India and Zambia).

The Core Lab continues to provide standardized equipment, reagents and supplies to all laboratories participating in IAVI-sponsored AIDS vaccine trials.

Ongoing Laboratory Training. Members of the Core Lab team routinely provide in-depth training and troubleshooting to all laboratory staff involved
in IAVI vaccine trials. This ensures that all necessary equipment and reagents are in place, that GCLP are followed (see below) and the assays to detect immune responses are performed correctly. Initial training is provided either at the IAVI Core Lab in London, the CLS laboratory (Contract Laboratory Service) in Johannesburg, or the Uganda Virus Research Institute-IAVI lab in Entebbe, followed by on-site training at the field laboratories to ensure that staff are fully conversant in IAVI’s SOPs.

Training was provided at the Core Lab in January to members of the laboratory teams from Rwanda and the NARI site in India (see GCLP Training Workshops below), and in August to staff from the CLS laboratory in Johannesburg and the KAVI laboratory in Kenya. In October, the CLS laboratory hosted a training on the standardized Clinical Chemistry machine for staff from a number of African sites, with an additional day for selected sites to review skills on the standardized Hematology machine. In November, the laboratory team from Zambia spent two weeks training at the CLS laboratory, which included hematology, chemistry and PBMC isolation and freezing.

Core Lab staff provided on-site training at the trial sites in Rwanda, India, Bonn, Hamburg and Belgium. Training also was provided to laboratories in Amsterdam, Wales and Lausanne, and to a laboratory in Boston with whom IAVI is collaborating.

Training Manual. A comprehensive manual was developed by the Core Lab team during 2004 to aid in the training of new laboratory staff. This easy to read manual includes sections on the basics of immunology, GCLP and background on each assay. Each section contains a test for staff to complete as they work through the manual. Technicians at the Rwanda laboratory and the lab under development in Zambia were the first to complete sections of the manual, which will be distributed to all laboratories in early 2005.

Training of Trainers Course. The Core Lab team is working to develop a ‘training of trainers’ course to identify the best methods and materials for training senior laboratory staff at trial sites. This course will facilitate the training of staff at other sites and further enhance the capacity of senior staff—both in conducting the assays and in training junior staff and new members of their teams. Core Lab team members attended an initial pilot training for trainers sponsored by the World Health Organization (WHO) in Johannesburg in November. Information and tools gleaned from this pilot course will be used to further develop material for the IAVI course in 2005.

GCLP Training Workshops. The Core Lab team continues to assist IAVI clinical trial sites with implementing GCLP and working towards accreditation in 2004. GCLP training workshops facilitated by Qualogy were held in London in January and in Lusaka, Zambia in November. These trainings, which are tailored to address issues specific to vaccine trials and the sites of the current IAVI AIDS vaccine trials, covered all the theoretical aspects of GCLP, as well as how to implement these guidelines in field laboratories. Program sessions included: regulatory inspection, organization and personnel within the lab, standard operating procedures, analytical plans/methods/protocols, method and systems validation, conduct of the work, management of data, and reporting results. This program brought together technicians and laboratory managers from IAVI-sponsored trial sites in Kenya, Rwanda, South Africa, Uganda, Zambia, India, the UK and the US.

A follow-up GCLP workshop was held in Nairobi in May for trial staff that had attended a previous GCLP training. This workshop involved the trial site laboratory managers and QA officers, who are responsible for organizing and implementing GCLP, including representatives from KAVI, UVRI, Rwanda, India, South Africa, Oxford and the Core Lab. An important objective of this meeting was to examine the challenges facing the Kenyan, Ugandan and South Africa trial sites as they work towards GCLP accreditation. The Core Lab team provided additional GCLP follow-up through monthly conference calls with staff from the trial site labs.

GCLP Accreditation at African Trial Site Laboratories. Pre-audit GCLP accreditation visits were conducted by Qualogy at the Kenyan, Ugandan and South African trial site laboratories in October. These visits involved an in-depth examination of the laboratory working environment with regard to GCLP and reports were produced and shared with the respective teams. The CLS laboratory in Johannesburg underwent a formal GCLP accreditation audit in mid-December 2004, with the report and outcome due in early 2005. The Kenyan, Ugandan and other South African trial laboratories will undergo GCLP accreditation audits later in 2005.

Cold Chain System. Cells obtained from blood samples of volunteers participating in IAVI clinical trials are stored in liquid nitrogen prior to testing. This ensures the viability of samples for future immunogenicity analysis. Therefore it is crucial to make certain that storage tanks are well maintained and that a constant supply of liquid nitrogen is available to facilitate such storage. In October, a cryogenics specialist from the UK conducted a cold-chain assessment of both the
present clinical trial sites in East Africa and a number of the newer clinical research sites in Uganda and Kenya. This involved an assessment of local liquid nitrogen supply and distributors, including capacity and back-up solutions, and analysis of how site laboratories set-up and use liquid nitrogen facilities. Meetings were held with site investigators and laboratory managers to discuss the findings and recommendations.

On the road to Kyamulibwa, where IAVI set up a research site in the fall of 2004. IAVI faced a unique IT challenge in equipping this and similar facilities with state-of-the-art Internet and networking technology to allow data access and communications in remote locations.

**Trial Site Assessments.** A key component to selecting a potential clinical research or trial site is to ensure that adequate laboratory capacity exists—or can be developed—to meet the needs of the study protocol. A standard assessment tool has been developed to gauge laboratory capacity and determine what investment is necessary for the development of additional infrastructure. This assessment includes an in-depth review of: (a) the space currently occupied by the institution or vacant and available for immediate use; (b) existing laboratory capabilities (experience and equipment); (c) methods and means for shipping blood samples; (d) storage capacity (fridges, freezers, liquid nitrogen supply); and (e) computer capabilities (Internet access and e-mail). This assessment tool was successfully field-tested in Uganda and Kenya and now can easily be applied to develop additional laboratory capacity in other resource poor settings.

Using the standard template created to perform site assessments and to monitor site start-ups, members from the Core Lab conducted a site visit/assessment in Chennai, India, in January in preparation for future trials. Core Lab staff also conducted a number of clinical trial site assessments in May for possible future sites in Zambia (Lusaka) and South Africa (Pretoria and two sites in Cape Town). Additional assessments were performed in July and September for laboratories in Kenya (Kilifi) and Uganda (Entebbe, Masaka, Kyamulibwa and Kampala).

**Development of Laboratories at New Sites.** As noted above, when new sites do not have adequate infrastructure to conduct clinical trials, the Core Lab builds the local laboratory and staff capacity to ensure readiness for AIDS vaccine trials.

Following the site assessment, a design plan must be created for the laboratory to ensure that suitable space, access and storage are provided. In 2004, Core Lab staff reviewed and contributed to design plans for new laboratories for future clinical trials in India (Chennai), South Africa (Cape Town) and Zambia (Lusaka), and for a possible new laboratory in Kenya (Kilifi).

In January and February, members of IAVI’s Core Lab and efficacy trials teams, together with local site staff, fully equipped and installed a new laboratory in Kigali, Rwanda. (This site is a collaboration between IAVI and Project San Francisco, an NGO established by Dr. Susan Allen of Emory University in Atlanta.) This entailed constructing and renovating the existing space to make it suitable for laboratory use, ordering all necessary equipment and reagents, and installing and validating the equipment.

Upon completion, the local laboratory team was trained in IAVI’s SOPs and the principles of lab work and GCLP. In addition, ongoing quality assurance programs were established at the site by a team from the CLS laboratory. The Rwandan lab team subsequently conducted a successful qualifying run (see **Laboratory Qualification** below) that included isolating, counting, freezing and shipping cells from blood samples to the Core Lab in London. The group also successfully completed a cross validation study with CLS to qualify the clinical laboratory procedures used.

Between January and March 2004, a new immunology laboratory was established in India at the NARI trial site in Pune. This effort involved extensive construction and renovation, as well as the purchase and installation of new equipment, reagents and supplies, thus enabling the site to perform the ELISPOT assay using cells isolated from blood samples. In May, a member of the Core Lab visited Pune to provide on-site training in the IAVI SOPs. Following this visit, the local laboratory team successfully completed a qualifying run.
Qualification of Field Labs. Before starting trials at new sites, laboratories must demonstrate their readiness by successfully completing a qualifying test run. This consists of processing blood samples at the trial site and sending them to the Core Lab, where the viability of the sample and its performance in the ELISPOT assay is confirmed. This ensures specimen quality and that all systems are in place prior to commencing a trial. In 2004, qualifying runs were successfully completed by the IAVI trial sites in Rwanda, India (NARI), South Africa (Johannesburg and Durban), the US (New York City and Rochester), Amsterdam, Germany (Hamburg and Bonn), Switzerland (Lausanne) and Belgium (SGS). In addition, a collaborating vaccine trial site in Boston (US) successfully passed a qualifying run.

Storing and Testing Samples from Field Trial Sites. The Core Lab operates a QA program to ensure that valid comparisons can be made across vaccine trial sites and products. All sites send cell samples to be tested for immune responses. This work continued for the ongoing trials in Oxford (#006 and #016); Kenya (#004 and #008); Kenya/London (#010); Uganda (#009); South Africa, Lausanne and Wales (#011); Belgium (A001); and the US (C001).

Monitoring of Samples. A web-based laboratory inventory management system (LIMS) is used by the Core Lab to accurately track the hundreds of samples that are received during vaccine trials. This system is used by all laboratories working on IAVI-sponsored trials. A new temperature monitoring system for all cell shipments was successfully implemented in 2004.

External Quality Assurance Program (EQA). The methods for measuring immune responses elicited in trial participants must be standardized in order to make valid comparisons of different vaccine approaches. Furthermore, it is important to demonstrate that different vaccine trial sites can consistently reproduce test results. To that end, the Core Lab implemented a Proficiency Panel scheme in 2004 that consisted of sending frozen cell samples from the Lab in London to all IAVI-sponsored vaccine trial sites that perform immunogenicity assays. These included sites in Kenya, Uganda, South Africa and the UK. The samples then were tested with reagents included in the shipment—sites had to perform ELISPOT and cytokine flow cytometry (CFC) analysis—and the results were submitted to an independent statistics consultant. The results from the first proficiency panel were documented in a report showing good concordance across sites in detecting positive and negative responses and in identifying low, medium and high responders. In November, a second proficiency panel was distributed to the same sites and also to the new trial site in Pune, India. These proficiency panels will be conducted every four to six months to gauge whether trial sites are performing at an appropriate level. Such proficiency testing will be pivotal in validating head-to-head comparisons of HIV vaccine candidates.

The Core lab participated in the second NIH-organized ELISPOT Proficiency Panel during 2004. Data were submitted and a report is expected in the first half of 2005.

CFC Standardization. Two main assays are used at the Core Lab to detect immune cells responding to the vaccine—the ELISPOT assay and the cytokine flow cytometry (CFC) assay. Using these assays, responsive cells are identified by their ability to produce certain proteins known as cytokines, which form part of the immune response.

In 2004, further work was undertaken with flow cytometry specialists BD (Becton, Dickinson and Co., US) and the Canadian Network for Vaccines and Immunotherapeutics (CANVAC) in an effort to further standardize and validate the CFC technique. The Core Lab coordinated the distribution of cells and reagents for this study to the labs at KAVI, UVRI, and NICD (National Institute for Clinical Development) in South Africa, as well as to the Core Lab itself. Data were submitted to BD for evaluation and the results were comparable across the different sites. Procedures also were identified which resulted in reduced cross-site assay variation, and BD will submit a paper for publication based on these data.

New Assay Development. The HIV vaccine field is currently facing a key question: do the commonly used ELISPOT and CFC assays detect the most important cells responding to a vaccine? Definitive answers to this question will be important in determining correlates of protection induced by a vaccine. The Core Lab has evaluated a flow cytometry-based assay (CFSE) that measures cell division. This assay appears suitable for use to detect immune responses in vaccine recipients. Plans have been produced for the validation study required for implementation as a new assay. An assay of CD107 expression, which measures degranulation by T cells as a marker of cytotoxicity, also was evaluated. This flow-based assay was found to be compatible with concurrent analysis of cytokine production and will form an important tool in immunogenicity testing.

A binding antibody ELISA assay to detect HIV specific binding antibodies was implemented at the Core Lab this year and used in trials.

Clinical Safety and Diagnostic Role. In 2004, the Core Lab team assumed an additional role to
ensure that the clinical safety and diagnostic laboratory component of clinical trial laboratories is standardized and continually assessed. This is specifically for existing and newly developed IAVI sites in Africa that are conducting trial and research protocols. The clinical laboratories determine who is eligible to participate in a trial and monitor participants for possible adverse events. Standardization and cross validation are essential when working in multiple sites to ensure that data may be combined into one safety database.

For the African sites, standardization of equipment and test kits has been initiated, and existing sites (UVRI, Uganda; PSF-IAVI, Rwanda; KAVI, Kenya) have participated in cross validation panels arranged by the CLS and National Health Laboratory Service in South Africa—who run EQA programs for more than 200 laboratories across Africa. Sites with IAVI clinical safety laboratories in development (Lusaka, Zambia; Masaka, Uganda; Kilifi, Kenya) will undergo this cross validation in 2005. This process ensures that test results obtained on site—for control samples that include hematology, clinical chemistry, CD4 count, HIV ELISA and hepatitis serology—are comparable to results obtained by the reference laboratory (CLS).

To ensure that the clinical safety and diagnostic laboratories are performing well, that staff are appropriately trained, and that new sites are set-up correctly, a contract laboratory will be selected to monitor, and develop the sites, where applicable. The selection of this contract lab will be determined by a competitive bidding process in early 2005.

Core Lab Expansion. To support a growing clinical research program, the Core Lab was expanded in 2004 to create increased laboratory space and specimen storage capacity. The initial expansion work was completed, yielding new laboratories and increased office space. Plans to develop increased storage capacity have been finalized and construction will begin in 2005.

Collaborations Within the HIV Vaccine Field. In 2004, the Director of IAVI’s Core Laboratory was invited to participate in two important initiatives: the Global HIV Vaccine Enterprise laboratory standardization working group and the Partnership for AIDS Vaccine Evaluation (PAVE). In addition, the Core Lab team has begun collaborating with the Aeras TB group (a non-profit initiative to develop a vaccine for TB) by sharing methods and materials to support their laboratory development, and with Dr. Elizabeth Hohmann’s team at Massachusetts General Hospital in Boston to help evaluate its HIV vaccine candidate.

IAVI Partnership With Finland’s FIT Biotech. IAVI is partnering with the Finnish biotechnology company FIT Biotech Plc to evaluate its investigational vaccine to prevent AIDS. The vaccine candidate, named GTU(R)-MultiHIV, was developed by FIT Biotech and is being tested in a human trial in Finland. The trial enrolled 28 volunteers in four different treatment groups. The trial was designed to assess safety as well as the immunogenicity of two vaccine doses delivered via two routes. IAVI’s Core Lab in London will conduct analyses of trial volunteers’ responses to GTU-MultiHIV.

In 2004, the Core Lab worked with FIT to design and synthesize peptides specific for this vaccine candidate for use in ELISPOT immunogenicity assays. The clinical trial is underway and samples have been sent to the Core Lab for testing.

Applied Research to Address AIDS Vaccine Challenges

IAVI VACCINE RESEARCH & DESIGN LABORATORY

Project Background Summary. IAVI has taken a crucial step towards the successful completion of its primary mission by establishing its own Vaccine Research and Design Laboratory. This represents a major paradigm shift in which IAVI now will help drive the creation and development of the next-generation HIV vaccine candidates, in addition to advancing promising vaccines developed by its collaborators.

The primary mandate of the IAVI Vaccine R&D Lab is to support the overall scientific effort of the organization. This will be accomplished by:

- Improving the genetic stability and level of immunogen expression of the candidate vaccines brought to IAVI by its collaborators, while developing potency and safety assays required to advance these candidates to clinical evaluation; and

- Determining the genomic sequences of viruses isolated in IAVI’s molecular epidemiology studies, and viruses recovered from human subjects enrolled in vaccine feasibility studies; understanding the molecular structure of such viruses also should assist in improved vaccine design.

Further, IAVI’s Vaccine R&D Lab will add value to existing and future vaccine development programs by:

- Developing novel viral vectors as unique HIV vaccine delivery vehicles;
Incorporating the critical vaccine design elements elucidated by the Neutralizing Antibody Consortium (NAC) and AIDS Vaccine Consortium (AVC) (see below) into these vehicles;

Evaluating these vaccine candidates in non-human primates; and

Rapidly advancing candidates found to be safe and immunogenic into accelerated clinical assessment.

**Progress in 2004**

**Lab Staffing and Site Acquisition.** Dr. Timothy Zamb, a highly experienced vaccine research and development scientist, formerly of Wyeth Vaccines, was hired in September to direct the activities of IAVI’s Vaccine Research & Design Lab. IAVI has conducted a comprehensive survey of twelve potential laboratory sites within the New York Metropolitan area. The search has been narrowed to the top three candidates. A preferred site will be chosen based upon the cost of renovations and the lease agreement, the existence of the requisite infrastructure to ensure efficient and effective laboratory operation, the time to occupancy and the capacity of the site to attract research scientists of the highest caliber. Job descriptions have been completed and IAVI’s Senior Management Team has approved an initial quota of 12 research scientists and support personnel to be hired in 2005 (including non-human primate immunologists, protein and carbohydrate chemists, and experts in the development of viral vectors).

**Neutralizing Antibody Consortium**

**Project Background Summary.** In 2002 IAVI formed an innovative consortium of scientists from leading laboratories working on the design of immunogens to elicit broadly effective neutralizing antibodies against HIV. Given that five naturally occurring human antibodies have been identified that are capable of neutralizing a range of HIV isolates, it is widely believed that this challenge is solvable.

The consortium includes representatives from academia, industry, government and not-for-profit research groups. Established in collaboration with the National Institutes of Health Vaccine Research Center (VRC), the goal of the consortium is to accelerate the development of candidate vaccines that induce effective neutralizing antibodies to circulating and highly variable subtypes of HIV. The principal scientists thus far recruited to the NAC include:

- Dr. Dennis Burton (Program Director) and Dr. Ian Wilson of The Scripps Research Institute;
- Dr. Robert Doms, University of Pennsylvania;
- Dr. John Moore, Weill Medical College, Cornell University;
- Dr. Joseph Sodroski, Dana-Farber Cancer Institute;
- Dr. Gary Nabel, Dr. Peter Kwong and Dr. Richard Wyatt of the VRC;
- Dr. Ronald Desrosiers, Harvard Medical School and New England Primate Research Center.

In addition, work from Maxygen and ViroLogic is included in the Consortium.

Crystal structure determination of the domains on the envelope protein that can elicit broadly neutralizing antibodies, in tandem with the structure of neutralizing monoclonal antibodies, may provide critical clues to these efforts. These data will enable NAC scientists to develop models, similar to a lock and key, where the structure of the lock is known (the antibody) and the structure of the key (the vaccine) is yet to be discovered. All of the applied research studies are managed by an industrial project manager to assure the focus of the effort is the creation of usable products. Any promising products developed will move immediately into accelerated clinical development—a comparative advantage of working in such an integrated approach.

By re-engineering the HIV envelope structures that demonstrate enhanced binding to the broadly neutralizing antibodies, promising vaccine immunogens can be created and then rapidly advanced to preclinical testing. A common, shared reagent panel of envelope proteins and monoclonal antibodies are essential resources for crystallography and as reference reagents for analyzing the antigenic properties of re-engineered proteins. Developing ways to optimize envelope protein production and purification also are critical to this effort and important to the field. Standardized protocols for small animal immunizations will provide the basis for future preclinical immunogenicity studies, and the use of high-throughput neutralization assays, with the flexibility to test a broad array of HIV strains, will be used to determine the unequivocal potency of immune sera.

**Progress in 2004**

This iterative process—from crystal, to re-engineered protein, to production and purification of candidate vaccines, to preclinical testing—has now yielded a second generation of candidates ready to enter preclinical testing. Entering its third
year, the HIV Neutralizing Antibody Consortium has:

- Completed a comparison of sera from small animals immunized with first-generation re-designed envelope protein constructs (produced by the Burton, Moore and Wyatt (VRC) laboratories), using the high-throughput neutralization assay. These studies have demonstrated a modest increase in the immunogenicity of certain constructs, leading to further refinement and improvement in the design of the next-generation immunogens.
- Elucidated the crystal structures of neutralizing determinants present on the HIV envelope protein, leading to the design of a number of novel candidate immunogens that ‘mimic’ these structures.
- Acquired a state-of-the-art, high-throughput, robotic crystallographic system to dramatically improve the efficiency and speed of the structural studies of the HIV envelope protein.
- Established standard protocols for the assessment of the relative immunogenicity of new immunogen constructs in small animals.
- Built a custom panel of clade B virus clones—encompassing a range of neutralization sensitivities—to compare neutralizing potency of immune sera in a standardized way.
- Optimized the vaccinia gene expression vector system for production of envelope proteins and produced over 200 mg of protein constructs for a variety of animal studies.
- Continued to build and maintain the reagent repository to include over 50 monoclonal antibodies and a growing array of envelope proteins representing different strains of HIV, as well as SIV for use in crystallography studies and immunizations. These reagents are being distributed regularly to NAC scientists and to outside collaborators upon request.
- Organized a Glycobiology Think Tank Meeting on 7 March (Palm Springs, CA, US). The meeting was an open forum hosted by IAVI to discuss the potential for designing carbohydrate-based immunogens that would elicit broadly neutralizing antibodies. Experts from around the world in the fields of glycobiology, carbohydrate chemistry and immunology were invited to discuss the work they have done in their own fields of interest, including applications to other infectious disease organisms (viruses, bacteria and fungi) and innovative approaches to the construction of potentially immunogenic complex carbohydrate structures.
- Constructed a first-generation carbohydrate-based immunogen and initiated a small animal immunogenicity study.
- Initiated the first of a series of comparative small animal studies of novel adjuvants designed to boost the humoral immune response.

AIDS VACCINE CONSORTIUM

Project Background Summary. IAVI is using the Neutralizing Antibody Consortium as the foundation for launching a larger-scale initiative, initially termed the AIDS Vaccine Consortium (AVC). This new Consortium will conduct research required to meet the key scientific challenges of creating a safe, effective preventive vaccine. The AVC also will work to rapidly transform novel concepts into product candidates for accelerated clinical testing. The AVC will dedicate a significant portion of its efforts to understanding and developing products that mimic the unmatched level of protection conferred by mutated live-attenuated SIV in non-human primates.

In order to achieve these goals, IAVI will create an industrial project management system linking leading laboratories, companies and other non-governmental institutions around the world required to provide the ‘critical mass’ of senior scientists and multidisciplinary teams who will focus their efforts towards solving these problems (as done on a smaller scale in the current NAC). Centralized resources will contribute to the production of reagents and immunogens and will support access to state-of-the-art biotechnology tools. It is planned that the Consortium will develop multi-year business plans, identify key scientific milestones, facilitate the rapid translation of vaccine concepts into clinical candidates, and provide the basis for accessing
critical candidates through innovative intellectual property arrangements.

IAVI has made provisions to jump-start this work within its core budget. Given the bold and long-term nature of this initiative, IAVI will attempt to acquire funding outside of the normal resource mobilization plan and will only scale up the effort if it is successful in doing so.

**Progress in 2004**

To complement and enrich the expertise provided by the current members of the NAC, IAVI has recruited additional leaders in the AIDS vaccine research field who have focused their energies on the creation and assessment of live-attenuated mutants of SIV, the development of live viral vaccine delivery vehicles, and the use of non-human primate models to assess vaccine immunogenicity and efficacy. These scientists include:

- Dr. Ronald Desrosiers, Harvard Medical School
- Dr. Jeffery Lifson, AIDS Vaccine Program, SAIC, Inc., National Cancer Institute (NCI)
- Dr. Philip Johnson, Children’s Hospital of Philadelphia
- Dr. David Watkins, the University of Wisconsin
- Dr. Kim Hasenkrug, NIAID-Rocky Mountain Laboratories

Existing members of the AVC, including participants from IAVI and its named collaborators, are authoring a comprehensive draft research proposal detailing the scientific objectives of the Consortium, the integrated executive and project management system that will be established to monitor and coordinate its progress, and a set of milestones to be completed once the work is initiated.

Plans are underway for the first comprehensive non-human primate study that will evaluate the sites of live-attenuated SIV replication, the location and magnitude of humoral and cellular immune responses elicited by its administration and the degree of protection conferred.

**NON-HUMAN PRIMATE VACCINE STUDIES**

**Project Background Summary.** IAVI’s Non-human Primate Studies Program was launched in 2002 to generate timely data essential for vaccine design and development. IAVI believes that data from well-designed non-human primate (NHP) studies, along with data from human safety and immunogenicity trials, process development studies for manufacturing feasibility, and intellectual property (IP) assessments regarding freedom of use, will collectively provide the most effective data for prioritizing next-generation candidate vaccines and accelerating the best of these into efficacy trials.

A collaborative network is now in place that includes three participating primate centers, a core laboratory and a data coordinating center. Primates are obtained from USDA-inspected suppliers and all studies are conducted in compliance with regulations pertaining to the experimental use of non-human primates.

**NHP Core Lab.** In 2002, the Non-Human Primate Studies Core Laboratory was established at BD Biosciences, Pharmingen. Immunological data generated at the NHP Core Lab is collected and analyzed by the data coordinating center (EMMES Corporation) using protocols adapted from IAVI’s clinical trials program and customized for the non-human primate studies.

**Progress in 2004**

**DNA.HIVA+MVA.HIVA Vaccine Study.** The combination study of the DNA.HIVA with the MVA.HIVA (clade A vaccines) was completed. The immunogenicity results in the non-human primate study predicted those observed in ongoing clinical trials of these candidates. IAVI is now carefully assessing the future development of this product (see DNA+MVA Vaccine, p. 4).

**SFV Replicon DNA Vaccine Study.** An NHP immunogenicity study was conducted using the SFV replicon DNA. The data from this study were disappointing, and as a result the development of the SFV replicon has ceased (see Semliki Forest Virus Vaccines, p. 11).

**rAAV-HIV Vaccine Studies.** Several studies of the rAAV-HIV vaccine constructs are underway:

- Animals previously immunized with rAAV-HIV were given a booster immunization of the vaccine yielding unexpectedly potent immune responses, again supporting the continued clinical assessment of the AAV vaccine vector platform.
- A second study, investigating another AAV serotype, began in 2003 and is accumulating data, which will be compared to the NHP results of the first AAV product that is now in human trials.
- A third NHP study, combining the AAV candidate currently in human clinical trials with another promising vector has commenced.
- A fourth study, evaluating the capacity of an SIV analog of the vaccine candidate currently under
clinical assessment to protect NHPs from wild-type SIV challenge is nearing completion. Previously, positive results were obtained in the non-human challenge model using an AAV vaccine that included gag, pol and env genes; in the current study, an AAV vaccine expressing only the gag gene was evaluated, as part of a more comprehensive effort by IAVI to determine which antigens of HIV will be required to elicit protective immunity.

**Comparative Antigens Study.** A comprehensive comparative study of antigens required for protection from wild-type SIV challenge has been initiated and the first challenge with SIV was performed. Immunization with one MVA experimental vaccine expressing gag-pol and another expressing gag-pol and env has begun. Manufacture of a third MVA for this study has been completed. Subsequent arms of the study will be phased in and challenges will begin in 2005.

**ADJUVANT SCREENING PROGRAM**

**Project Background Summary.** IAVI has launched a comprehensive program to evaluate adjuvants (immune response stimulators added to vaccine formulations) using a rational, hypothesis-based approach. The central objectives of the program are to:

- Identify novel adjuvants that increase neutralizing antibody responses to HIV envelope immunogens developed by the Neutralizing Antibody Consortium.
- Identify novel adjuvants that potentiate cellular immune responses to immunogens expressed by viral-vectors or DNA vaccines.
- Conduct surveillance of the field to identify promising novel adjuvants and accelerate in vivo assessment through a defined process and prioritization algorithm.

**Progress in 2004**

A research program was initiated in collaboration with the Aaron Diamond AIDS Research Center to evaluate T-cell responses to viral vector vaccines combined with adjuvants in mice.

Meetings with potential collaborators and a first field assessment have been completed to support efforts to identify highly promising adjuvants for evaluation.

A standard Materials Transfer Agreement has been crafted that will allow acquisition of adjuvant materials for testing from different collaborators.

A comprehensive non-human primate study designed to assess the ability of a limited number of promising adjuvants to potentiate immune responses elicited by an AAV-HIV vaccine candidate has been planned.

**IAVI AGREEMENT WITH MAXYGEN**

IAVI is in the fourth year of an agreement with Maxygen, Inc., a California-based biotechnology firm, to explore the use of Maxygen's MolecularBreeding™ technologies to develop novel AIDS vaccines. DBLV, LLC, a venture capital arm of the Rockefeller Foundation, has provided funding for the project.

To date, a large number of novel envelope immunogens have been produced and characterized using Maxygen's proprietary directed molecular evolution technologies. Over 100 of these vaccine candidates have been screened in small animals. These studies have demonstrated modest improvements in immunogenicity for a few of the envelope constructs. Currently, we are in discussions with Maxygen to produce and then evaluate second-generation immunogens created using their technology.

**GLOBAL AIDS VACCINE SURVEILLANCE EFFORTS**

IAVI has continued to maintain a surveillance system to monitor the progress of global efforts in AIDS vaccine R&D and identify new and promising AIDS vaccine development opportunities. These surveillance activities provide IAVI’s R&D staff—and others in the field—with a detailed and current global overview of the state-of-the-art of AIDS vaccine development. These data are particularly useful in identifying promising new technologies, evaluating them, and in some instances further developing them.

In October 2004, IAVI conducted a think-tank with some of the world’s leading scientists focused on early events in HIV transmission. Such research is evaluating virus structure, immune responses to them, and viral-host interactions, with the goal of translating recent observations—that HIV amplifies early after infection in gut-associated lymphoid tissues—into improved vaccine designs.

As discussed on page 50, IAVI also maintains the Database of AIDS Vaccines in Human Trials, a continually updated, searchable archive of past and present AIDS vaccine candidates currently in human testing around the world. The database is available to the scientific community and the public on IAVI’s website (www.iavi.org/trials).
IAVI held the annual meeting of its Scientific Advisory Committee (SAC), and respective subcommittee meetings—including Vaccine Research; Project Management; and Clinical Trials—in August 2004. Major outcomes from these meetings, which were discussed at IAVI’s November 2004 Board meeting included:

**R&D Strategic Plan.** The SAC endorsed the key R&D elements of IAVI’s strategic plan for 2005-2007.

**Product Development.** The SAC endorsed IAVI’s proposed criteria for advancing a vaccine candidate to efficacy trials. The SAC also agreed that based on the latest interim data, the DNA+MVA products in Phase I/II clinical trials in Africa and Europe had not achieved the criteria for advancement. The SAC also concurred that the proposed vaccine development program (adenovirus vectors, see p. 10) were an appropriate addition to IAVI’s portfolio given the current state of the field.

**Clinical Sites.** The SAC reviewed IAVI’s site development program and clinical research activities proposed at the sites, and agreed that the planned scientific studies associated with efficacy trial site preparation are reasonable. There was significant discussion regarding the scale of the site preparation effort relative to the current product pipeline, and there was general consensus that IAVI’s effort in this area was appropriate.

**Research and Design.** The SAC agreed that IAVI’s priorities in research and design regarding the key scientific challenges impeding AIDS vaccine development are appropriate. In this regard, the SAC endorsed further scale-up of the Neutralizing Antibody Consortium, and the key objectives for the AIDS Vaccine Consortium, including efforts to understand and develop products that mimic the unmatched level of protection conferred by the live-attenuated SIV vaccines in non-human primates. In contrast, the SAC did not feel that launching a mucosal vaccine consortium was the most effective strategy for addressing mucosal vaccine-related issues, but that pilot studies in this area would be warranted. The SAC reiterated that IAVI should continue to maintain active surveillance on the global effort, and to consider new opportunities in vaccine design that potentially would be improvements over the current pipeline.

**Staff/Management.** The SAC commended IAVI for the professionalism of its effort, for moving towards greater integration of R&D, and for its ability to be data-driven and to take action on terminating less promising vaccine candidates.

**SAC Membership.** New members who have joined the SAC include Joep Lange, Antonio Lanzavecchia, Douglas Richman, Philip Russell, Bruce Walker, and Carolyn Williamson (see p. 60 for full SAC list and affiliations). Members who completed their terms and retired from the SAC included Dennis Burton, Ron Desrosiers, Phil Johnson, Liming Lee, Andrew McMichael, Norm Letvin, Neal Nathanson, and Hans Wigzell.

**SAC Meetings.** There was discussion regarding the frequency and timing of meetings so as to enable the SAC to provide IAVI with the most effective scientific advice. Recommendations for enhancing the role of the SAC are currently under discussion between the SAC Chair, R&D senior management, and the IAVI Executive Office and will be implemented in 2005.

**International Scientific Meetings**

During 2004, IAVI hosted or participated in a variety of international scientific meetings on AIDS and AIDS vaccines; see p. 56 for a complete listing.

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**Preparations and Support for AIDS Vaccine Research**

**BUILDING LOCAL CAPACITY: SUPPORT FOR CLINICAL TRIAL SITES AND PREPARATORY STUDIES**

IAVI works to ensure that there are adequate services and an informed and supportive environment in the communities surrounding its research sites. These efforts include mobilizing and educating communities, and helping to strengthen health services and other needed programs. IAVI works to build trust by ensuring that its research efforts also provide the community with immediate benefits, such as improved health education and other services.

**Strengthening Voluntary Counseling and Testing and Referral to Health Care Services.** In 2004, IAVI’s country programs launched new efforts to strengthen health care and VCT services in several communities that are hosting HIV vaccine research. IAVI is working to help ensure sufficient access to high-quality VCT in order to minimize stigma and help motivate people to learn their HIV status, all of which are essential to enroll the thousands of volunteers that will be needed for future vaccine efficacy trials.
Access to adequate health care facilities and referral networks must be in place for study participants, as well as potential volunteers who may be screened out because they are HIV-infected or have other health problems that make them ineligible to participate in a trial.

In 2004, IAVI initiated assessments in Kenya and Uganda to help gauge the need for additional health care and VCT services in communities where vaccine trial sites are already established or planned. This process included mapping existing services and VCT resources, together with a review of national-level mechanisms for the distribution of antiretroviral (ARV) treatment. Analysis will be completed in 2005 and recommendations will focus on how IAVI can partner with the public and private sectors, nationally and internationally, to strengthen these community services—including access to ARVs. Following the completion of its HIV prevalence study (see p. 26), IAVI is continuing to fund VCT at some of the sites in East Africa conducting preparatory studies to ensure that these services are provided until they can be strengthened at the community level.

**Clinical Trial Site Partnerships in East Africa**

IAVI’s East Africa Regional Office in Nairobi continues to provide support and oversight to clinical trials, scientific projects and community activities in Kenya, Uganda and Rwanda. In addition, the East Africa Office regularly reaches out to key constituencies and stakeholders in the region, such as government agencies and community-based NGOs, to increase support for AIDS vaccine R&D.

In addition to supporting programmatic activities, the IAVI East Africa office acts a hub for scientific support to the clinical trial and study sites in Kenya, Uganda, Rwanda and Zambia. The office is home to the Regional Medical Director, the Clinical Program Manager and the Laboratory Manager, who provide technical support and oversight to the research sites for quality assurance, clinical monitoring and on-site training.

**Kenya AIDS Vaccine Initiative (KAVI)**

IAVI has a long-standing partnership with the Kenya AIDS Vaccine Initiative, which conducts Phase I and II AIDS vaccine trials, as well as preparatory studies for future efficacy trials in the Kangemi community of Nairobi (see p. 27).

Four IAVI-sponsored Phase I and II studies have been underway at KAVI since October 2001; two of these trials are ongoing. The studies at the KAVI site have demonstrated steady advances in all aspects of vaccine trial management, including regulatory approval of protocols, markedly improved rates of volunteer recruitment, efficient laboratory and clinic operations, staff recruitment and training to Good Clinical Practice (GCP) and Good Clinical Laboratory Practice (GCLP) levels, and the potential for GCLP laboratory accreditation in 2005.

Evaluation in February by senior IAVI R&D staff concluded that the current capacity exists at KAVI to handle multiple Phase I and II vaccine trials involving up to 300 additional volunteers at low risk of HIV infection. In addition, work is underway to expand the facilities at the site to include three clinical examination and three counseling rooms, a clinical staff room, additional laboratory space, a freezer and cold storage area and a trial record archives room.

Efforts also are underway to make the KAVI site accessible to both IAVI-sponsored and non-IAVI AIDS vaccine programs so that the site’s Phase I capacity can be optimally used to advance clinical studies in the field as a whole.

Refined community outreach and volunteer recruitment strategies have resulted in an improved gender ratio among potential volunteers. KAVI’s preliminary recruitment system yielded over 300 potential volunteers with a male to female ratio of 2:1.

Dr. Omu Anzala speaks to peer leaders at a town meeting in Kangemi on 18 December. At these biannual meetings, groups of peer leaders and clinicians give presentations and answer questions regarding the work of the clinic, AIDS vaccine research, and safe sex practices.

**Kangemi Preparatory Studies.** In addition, preparatory studies for future efficacy trials (also referred to as HIV vaccine feasibility studies) have commenced in Kangemi, KAVI’s other site located in a very low-income suburb of Nairobi (see p. 27). IAVI has funded a variety of activities with KAVI including expansion of the Kangemi site, support of a peer educator program, and the purchase of two...
vehicles to assist with transportation of specimens from the Kangemi site to the KAVI laboratory. (Please see the section below on Preparatory Studies for Future Efficacy Trials in Africa for more information.)

Community Advisory Boards. IAVI has worked closely with KAVI to develop and train two Community Advisory Boards (CABs), one for the KAVI clinical trial site and one for the research site in Kangemi.

UVRI/IAVI HIV Vaccine Program in Uganda

IAVI’s country program is based at the Uganda Virus Research Institute (UVRI) in Entebbe, as part of the UVRI/IAVI HIV Vaccine Program. This program functions as a Phase I vaccine trials unit and as a training site for other IAVI-sponsored research teams in Africa. The team continues to build broad public support in Uganda and continues to work toward building long-term relationships with communities, policy makers and other stakeholders. With the support of IAVI’s Regional Office in Nairobi, the site team also works closely with the IAVI-sponsored research sites in Kakira and Masaka (see p. 28) to facilitate their community education and vaccine preparedness activities. In 2004, a communications workshop was held for the Phase I site and the HIV vaccine feasibility study sites to support their community involvement efforts.

The IAVI-sponsored vaccine trial at UVRI is following up the 50 volunteers enrolled in the current DNA+MVA trial. All study vaccinations were completed by late March.

UVRI’s preliminary recruitment system yielded over 150 potential volunteers and the team has been collaborating with the US Military Research Program, which is conducting a trial of a vaccine developed by the NIH’s Vaccine Research Center, for the best use of their recruitment capacity.

By working with the institute collaborators to upgrade utilities such as electricity, water, liquid nitrogen and incinerator facilities, the team is building additional capacity at UVRI for continuing HIV vaccine research and community outreach. To accommodate the growth of the UVRI/IAVI team, additional offices have been constructed using locally available materials.

New initiatives in the UVRI/IAVI HIV Vaccine Program include collaborating with the Ugandan AIDS Information Center (AIC) and Entebbe Hospital to increase access to VCT. IAVI is providing support to Entebbe Hospital to improve VCT services within the context of its PMTCT (prevention of mother-to-child transmission) program. IAVI also has provided funding to the AIC, currently the largest provider of VCT in Uganda, to facilitate their youth VCT program. The UVRI/IAVI team established an HIV vaccine information office on the grounds of the AIC, which provides general information on HIV vaccines and vaccine trials and functions as a pre-screening site for potential study volunteers.

The team has also initiated a community mobilization program that will work with volunteer peer leaders who live in communities within the target areas of Kampala and Entebbe. These peer leaders will mobilize greater participation in ongoing HIV vaccine education seminars being conducted in their local communities.

Community Advisory Board. The UVRI/IAVI program has continued to build and support an active and informed Community Advisory Board (CAB). The program is facilitating a CAB network in Uganda so that CAB members may share experiences with other groups. In addition, the team is working closely with other research sites, providing support for development of their CABs.

Building Capacity in Rwanda

In Kigali, Rwanda, IAVI has established a partnership with Projet San Francisco-Emory University to conduct a Phase I AIDS vaccine trial, as well as preparatory studies for future efficacy trials (see p. 29).

In 2004, renovations of the clinical buildings were completed and a clinical laboratory and a laboratory to separate and freeze immune cells were established. The site staff have completed all study-related training—including good clinical practices (GCP), good laboratory practices (GLP),
laboratory EQA, and clinical safety monitoring and data management—and are ready to initiate a Phase I vaccine trial.

IAVI’s Regional office in Nairobi has sponsored site staff to attend a conference in Bangkok, Thailand where the US Military HIV Research Program shared lessons learned in trial recruitment. With funding from IAVI, both site and MOH staff attended a meeting in Botswana on development of national vaccine plans.

In March, IAVI sponsored a workshop for journalists in Kigali that included presentations from IAVI researchers on AIDS vaccine trials (see p. 52).

ACTIVITIES IN SOUTHERN AFRICA

IAVI continues to work with various partners in South Africa, such as the South African AIDS Vaccine Initiative (SAAVI) and the Perinatal HIV Research Unit (PHRU) at Baragwanath Hospital, to ensure collaboration on vaccine research and development, clinical trials, vaccine preparedness programs and community engagement.

In 2004, the follow-up of the 011 trial participants continued in Soweto and Durban. Two additional Phase I and II trial sites were evaluated, and plans are underway for future collaboration. In 2005, cohort development activities will continue in Soweto in collaboration with PHRU. In addition, two sites were evaluated for possible future efficacy trials.

This year IAVI also initiated a new research study site in Zambia in collaboration with Emory University and the Zambia-Emory HIV Research Project (ZEHRP) (see p. 29).

Preparatory Studies for Possible Future Efficacy Trials in Africa

A primary component of IAVI’s R&D agenda is to accelerate the development of preventive AIDS vaccine candidates by advancing the most promising of these from small Phase I and Phase II clinical trials into large-scale efficacy testing in the developing world.
Conducting a large efficacy trial that enrolls thousands of volunteers and lasts several years is a formidable challenge. Rigorous adherence to the research protocol is essential and the safety and efficacy data must be properly collected to be honored by regulatory authorities in future applications for licensure, should the vaccine prove efficacious. Data on the number of new HIV infections (incidence) is required in advance to estimate the necessary size of these trials. These challenges are compounded in developing countries, where:

- clinical, laboratory and information technology/communications infrastructure is limited;
- national vaccine plans and the capacity for regulatory review of products are still being developed; and
- the participation of communities is essential to ensure that volunteers fully understand the nature and requirements of these trials.

Community education requires a rigorous and sustained effort to build a consistent information base on HIV, including the nature of the disease, prevention strategies including voluntary counseling and testing (VCT), preventive vaccines and HIV vaccine research. The community also must be empowered and involved in reviewing recruitment plans and the informed consent process.

**Building Integrated and Sustainable Research.**

Clinical research on preventive HIV vaccines does not occur in a vacuum. Experience has shown that research is accelerated in communities where HIV prevention efforts and access to HIV treatment are already offered or being developed. The recent availability of HIV care—including access to antiretroviral drugs and the treatment and prevention of opportunistic infections through national and international programs—has improved the hope for those infected and will help to decrease stigma associated with the disease. This has increased the willingness of local community members to get tested for HIV, which in turn accelerates HIV vaccine research. Given that the monitoring of HIV treatment involves many of the same laboratory safety and response tests that are used for HIV vaccine trials, the potential for synergy is high. Health care infrastructure—particularly referrals for the diagnosis, counseling and care of people with sexually transmitted diseases and common bacterial and parasitic diseases such as tuberculosis and malaria—is critical to support volunteers participating in clinical studies and the communities surrounding such trial sites. In addition, referral and care for family planning services, prenatal care and the prevention of perinatal HIV transmission are also essential. Finally, improved HIV testing in blood banks and hospitals that includes post-test counseling can identify individuals who are at high risk of infection—including individuals whose partners are HIV-positive—who may benefit from participating in a preventive HIV vaccine study.

Whenever possible, IAVI builds on the work of others at trial sites and utilizes lessons learned from other groups with similar interests in order to avoid duplication and ensure optimal use of resources.

**Site Development for Preparatory Studies in Africa.** As outlined below, work is progressing at six sites in Africa that may be suitable for large-scale efficacy trials of preventive HIV vaccines; these include two sites in Kenya, two in Uganda, one in Rwanda and one in Zambia:

1. **Kangemi-KAVI:** A collaboration between IAVI and the University of Nairobi’s Kenya AIDS Vaccine Initiative (KAVI).
2. **Kilifi-CGMRC:** In Kilifi, IAVI is collaborating with the Centre for Geographic Medicine Research, Coast (CGMRC), which consists of the Kenya Medical Research Institute (KEMRI), The Wellcome Trust and Oxford University.
3. **Masaka-MRC:** A collaboration between IAVI, the Uganda Virus Research Institute (UVRI) and the Entebbe unit of the UK Medical Research Council (MRC).
4. **Kakira-JCRC:** A collaboration in Kakira, Uganda between IAVI, Kakira Sugar Works (a private company) and the Joint Clinical Research Centre (JCRC).
5. **Kigali-PSF**: A collaboration between Project San Francisco (PSF), Emory University and IAVI in Kigali, Rwanda.

6. **Lusaka-ZEHRP**: A collaboration in Lusaka, Zambia between the Zambia-Emory HIV Research Project (ZEHRP) and IAVI.

Community Advisory Boards (CABs) are active at each site to provide critical community input. Detailed site assessments also have been completed at other potential trial sites in South Africa and plans are underway to engage them in preparatory studies.

**Capacity Building.** A plan has been developed and implemented to prepare each selected site for efficacy trials by expanding its capability and capacity. This includes financing the construction of state-of-the-art laboratory and clinical facilities, and training local researchers in international clinical standards (Good Clinical Laboratory Practices, or GCLP, and Good Clinical Practices, or GCP). All sites require:

- Enhanced information technology capacity for communications, to log in samples through a web-based specimen tracking system and to enter data using a centralized data management system using optical recognition software (DataFax®);
- A reliable back up power supply to ensure that sensitive equipment is not affected by power fluctuations and that valuable specimens and future vaccines are kept at a constant and monitored temperature;
- A stable and reliable clean water supply;
- A system for the disposal of medical and biological waste; and
- Availability of liquid nitrogen to hold and ship blood samples.

Where needed, VCT activities are not only being strengthened but expanded, with plans for the introduction and maintenance of quality assurance in both counseling and testing.

**Good Clinical Practice (GCP) Training.** In collaboration with the Johns Hopkins University Bloomberg School of Public Health, the IAVI Medical Affairs team hosted a GCP training workshop in Entebbe on 9-11 November. The program brought together staff from several institutions, including the Medical Research Council (Masaka), the Joint Clinical Research Center (Kakira and Kampala) and the Kenya Medical Research Institute (Kilifi). The course was tailored to address issues specific to AIDS vaccine clinical trials and the sites of the current IAVI-sponsored research studies.

**PROTOCOLS FOR PREPARATORY STUDIES**

Preparatory studies for future efficacy trials of HIV vaccines (also referred to as HIV vaccine “feasibility studies”) are being developed, initiated or are already underway at six sites in Africa. These studies, which consist of six study protocols, are designed to strengthen the capacity for voluntary counseling and testing using rapid HIV tests, and to obtain HIV prevalence and incidence data and other vital information on the local population. All HIV-infected volunteers are referred for staging and treatment as needed, all pregnant women are referred for prenatal care, and those with HIV are referred to programs for prevention of mother to child transmission (PMTCT). The care and referral networks are being evaluated and strengthened through collaborations with local and international agencies and groups.

**Protocol A:** This study was developed to measure the prevalence of HIV in local populations that consented to be tested. The study enrolled approximately 6,300 volunteers and was completed at four sites (Kangemi-KAVI, Kilifi-CGMRC, Kakira-JCRC and Masaka-MRC). The data is being prepared for publication/presentation.

**Protocol B:** This study, which is monitoring the incidence of new infections with follow up for VCT every three months, has begun at Masaka-MRC and enrolled approximately 1,000 volunteers to date. The study will begin at the other five sites in 2005 once the capacity and laboratory support are in place and the research protocol has been approved by the responsible ethics committees. Similar research efforts enrolling HIV discordant couples (where one partner is HIV-positive and the spouse is HIV-negative) at Kigali-PSF and Lusaka-ZEHRP.
have screened over 10,000 couples this year and enrolled over 1,600 of them in a follow-up study to measure incidence. The protocol is being amended to use HIV antigen testing in near real time thus offering the potential for earlier detection of infection, and will collect appropriate samples including lymphocytes or immune cells very early in infection. In addition, the virus will be typed and sequenced, the serum or plasma will be assessed for its ability to neutralize the infecting strain of HIV and other strains of the virus, and the detailed characteristics of the very early immune response will be analyzed in state-of-the-art laboratories. All new or incident infections will be referred to research Protocol C.

Protocol C: This study is in development and will continue to: map in detail the early immune response in recently infected individuals; follow changes in the sequence of the HIV virus; and monitor the ability of the plasma or serum to neutralize HIV isolated from the same individual or other individuals. This information is critical to the design of new vaccine candidates. The progression of disease—viral load, CD4 and clinical manifestations—will be carefully mapped to ensure that systematic data are available in the relevant populations for future HIV vaccine efficacy trials. Such information will be vital to planning the appropriate study design, sample size and selection of relevant end points for CD4 and particularly early clinical manifestations prior to developing clinical immunodeficiency. Understanding how HIV mutates in the human body to escape from the natural immune response will inform the design of future vaccines.

Protocol D: This study, which has enrolled over 100 volunteers at one site, will be conducted at up to eight sites, including two locales where volunteers are recruited for Phase I trials. Protocol D was designed to establish the clinical safety laboratory reference ranges in developing country populations that are: clinically well; not pregnant; not infected with HIV, hepatitis B, hepatitis C or syphilis; and likely to volunteer for future HIV vaccine trials. This will ensure that the entry criteria for participation in future study protocols are realistic and appropriate for local populations. This is crucial given that there are many genetic, nutritional and environmental factors that can influence parameters such as the complete blood count, liver and kidney function tests, nutritional parameters, CD4 counts and urine tests. At some sites (UVRI, Kigali-PSF and Kilifi-CGMRC), these measurements will be taken in both the dry and rainy seasons to assess the variation of these parameters in areas likely to experience seasonal infections such as malaria. In addition, a stool analysis for parasites will be done at selected sites (Kigali-PSF and UVRI) to evaluate the relationship between blood cell parameters, nutritional parameters and the presence of parasites. Socio-demographic and body mass data also will be collected to look for relevant relationships. All laboratories participating in Protocol D are using standardized equipment and taking part in both internal quality control and external quality assurance (EQA) programs to ensure that data can be compared across sites and pooled for efficacy trials without bias.

Protocol E: A preliminary assessment of the specific cellular immune response to the strain(s) of HIV in infected volunteers will be done in preparation for a Phase I study to be conducted at the Kigali-PSF and KAVI sites as a collaboration between IAVI and the National Institutes of Health.

Protocol F: This study is designed to assess the pre-existing immunity to specific viral vectors in representative populations that potentially may participate in future HIV vaccine efficacy trials. This study is critical to the selection of effective viral vectors for candidate vaccines because pre-existing exposure and subsequent immunity to a particular vector might diminish the immune response to an HIV vaccine that uses such a vector for delivery. This study involves serum specimens from several IAVI-sponsored sites, including Kakira-JCRC and Kigali-PSF, and other sites may be added. Non-IAVI sites in South Africa have contributed specimens to increase the geographic scope, thus ensuring that any future candidate vaccine is broadly applicable.

IAVI-Sponsored Preparatory Study Sites in Africa

Kangemi-KAVI (Kenya): The prevalence study (Protocol A) was completed after enrolling 1,000 volunteers. This small, IAVI-funded clinic site is adjacent to the Nairobi City Council Health Center in the Kangemi section of the city. With support from IAVI, additions were made to enhance the clinic’s capacity to conduct Protocols B, C and D. These additions include: providing radiolink access to the Internet; establishing a small laboratory to log, label and process specimens; creating a data management center; and providing space for records management and additional clinic and meeting space for the staff and Community Advisory Board. This center will continue to provide voluntary counseling and testing and basic medical care for study participants, including treatment of sexually transmitted diseases. All laboratory tests and further processing of specimens will take place at the KAVI laboratories funded by IAVI at Kenyatta National Hospital.
Staging and treatment for HIV is being strengthened through grants made directly to the site principal investigator from The Global Fund to Fight AIDS, Tuberculosis and Malaria through the Ministry of Health and other sources. Treatment will be conducted in the adjacent health center in Kangemi.

Completion of a feasibility study site facility in Kangemi. The sites were constructed from prefabricated containers and outfitted with satellite technology to allow high-speed Internet access from remote locations.

Kilifi-CGMRC (Kenya): Well known for pediatric research and publications in malaria and bacterial diseases, the CGMRC initiated an active HIV prevention program in Kilifi in collaboration with IAVI. Protocol A was completed after enrolling 2,000 volunteers from several communities through mobile teams, walk-in clinics and the Kilifi District Hospital (KDH). The site team also has identified 50 discordant couples and a network of STD treatment providers that can refer at-risk individuals for participation in Protocol B (incidence study with follow up VCT).

The small residence that was renovated to house voluntary counseling and testing, data management and site staff is being augmented by a new community VCT center that is being constructed on the grounds of the CGMRC and is slated for completion in April 2005. This center will provide much needed space to conduct Protocol B, which will require visits by approximately 800 volunteers every three months.

The family medicine clinic at Kilifi District Hospital is partially funded by IAVI and provides HIV counseling and testing and care for minor illnesses. A new clinical research center, also funded by IAVI, is under construction on the grounds of the KDH and will absorb the family medicine clinic. The new research center will be supervised by the CGMRC and will house a state of the art laboratory, data management center, pharmacy, staff and volunteer training facilities, and clinical examination and counseling rooms to accommodate Protocols B, C and D. Part of the space will be used to support antenatal care, sexually transmitted diseases and tuberculosis programs, which are vital additions given that pregnant women and people with these conditions are at a significantly higher risk for HIV infection. The close proximity to the research activities will allow for efficient referral and collaboration.

The HIV team has begun an HIV treatment and care program in collaboration with KEMRI, KDH and the US Centers for Disease Control. The clinical research laboratory within the new center will provide laboratory tests for the staging and management of people with HIV who are receiving antiretroviral treatment. Both the clinical space and the pharmacy will be available for use by the treatment and care program when not being used for research.

The Kilifi site has established a peer-driven HIV education program as part of its ongoing women’s football project, “Moving the Goal Post”. The team has evaluated some missed opportunities to counsel and test for HIV at KDH and surrounding communities, including within the blood bank and pediatric department. The team also is recruiting HIV discordant couples—identified through its VCT program and from the hospital—in order to test and counsel them together.

Masaka-MRC (Uganda): The Masaka-MRC site in Entebbe has completed Protocol A, enrolling over 1,300 volunteers in three general population villages in the Masaka district (Kikenene, Kiwangala and Lwengo) using mobile and stationary units. They also have established three research clinics adjacent to the district clinics and these provide new access to electricity and water through rain water collection systems and bore holes. The research clinics will be used primarily to conduct feasibility studies, provide basic medical care and perform voluntary counseling and testing. The Community Advisory Board is operational and active.

The laboratory at the Masaka field office has been completed and upgraded to perform all the laboratory assays associated with Protocols B and D, and to support the clinical aspects of Protocol C. The field laboratory in Kyamulibwa is being upgraded to provide for the separation and cryopreservation of cells for Protocols B and C, and
information technology and back-up power has been upgraded at the Kyamulibwa site and the Masaka field office. Local infrastructure for health care and treatment also is being evaluated by IAVI.

**Kakira-JCRC (Uganda):** At this site, a preliminary census and sensitization activities involving 4,681 people were completed in a working population that has excellent health care support through the Kakira Sugar Works (KSW). KSW also offers a fee for service ARV program not accessible to most of the lower income staff. Renovations of a facility attached to the KSW General Hospital were completed to provide VCT and outpatient care, and to house the staff and data management functions. VCT is also being provided through mobile clinics.

The JCRC completed Protocol A in 2,000 volunteers and is currently analyzing the final data. They also contributed over 1,800 samples from Protocol A to the pre-existing immunity study (Protocol F). Preparations for Protocols B and C include enlarging the clinical space and upgrading the electrical backup system, the information technology and freezer space. Planning is underway to enroll the JCRC laboratory in the External Quality Assurance (EQA) program (see p. 15). Until the lab has completed the EQA program, some of the laboratory assays and cell separations will be performed at the UVRI site in Entebbe. The capacity for HIV treatment and referral also is being evaluated.

**Kigali-PSF (Rwanda):** The project team at the Kigali-PSF site has been conducting VCT in couples and collecting HIV prevalence data. They have identified over 800 HIV discordant couples with known incidence; they are continuing to expand their cohort and provide VCT to couples in the greater Kigali area. The project also has an active family planning and VCT research program involving over 6,000 couples per year. More than 200 of the HIV infected partners in their clinic are receiving HIV treatment through a grant from the Global Fund, and the clinic provides excellent general medical care and diagnosis and treatment of sexually transmitted diseases.

A multi-center training meeting for Protocol D was held in Kigali in October. The project team in Rwanda has enrolled over 100 volunteers in Protocol D with excellent GCP adherence and data quality. They have contributed 200 samples to Protocol F. The NIH conducted a site visit in October 2004 and selected the site to participate in a future Phase I trial. The pharmacy is being upgraded to support the specific needs of the candidate vaccine and the protocol is being finalized.

The project has an active Community Advisory Board that meets regularly to review all activities of the site, including planned protocols and the informed consent process. Videos that explain the research study procedures are used to augment the informed consent process. Participant understanding is assessed by post-consent evaluations of comprehension to ensure that all volunteers are aware of their rights. Functionally illiterate volunteers have both audiovisual means of reviewing protocols and individual explanations, and so are not excluded from studies.

**Lusaka-ZEHRP (Zambia):** The site team has been conducting VCT for couples in Lusaka and has collected data on the prevalence, incidence, risk factors and family planning issues relevant to HIV in that population. They have already identified a cohort of over 1,000 HIV discordant couples (20% of all couples who attend couples’ VCT sessions) with a known incidence of HIV infection. In addition, the facilities at this site are being developed to conduct two feasibility studies (Protocols C and D) and a multi-center, Phase I trial. Cohort expansion is supporting the development of the site by renovating an existing building to house both state-of-the-art clinical and laboratory facilities and by providing training to clinical, laboratory and administrative staff. The clinical renovations and power back up system has been completed. All staff have been hired and trained and additional training will be conducted prior to initiation of the studies. An evaluation of health care infrastructure and clinical referral systems also will be conducted.
BUILDING COUNTRY-LEVEL COMMITMENT AND CAPACITY

Background Information. As IAVI’s vaccine research efforts have expanded in areas hard hit by AIDS, so too have the organization’s supportive activities and infrastructure. IAVI works with a diverse range of constituencies to prepare countries and communities for clinical trials—and for eventual distribution of a future vaccine—by building local and national ownership, input and support.

IAVI’s programs seek to improve the overall environment for HIV vaccine research, not just IAVI-sponsored candidates and trials. IAVI’s research and community partnerships focus on building country-level commitment and capacity by:

▪ working with local partners to increase vaccine literacy among communities, policy-makers, medical practitioners and the media.
▪ working with key stakeholders to develop policies that will facilitate research while protecting volunteers’ interests.
▪ sponsoring social science research that contributes to the understanding of trial-related issues such as informed consent and the special needs of women and other vulnerable populations who are potential trial volunteers.
▪ promoting vital information exchanges between countries participating in AIDS vaccine studies to ensure that the perspectives of volunteers, key collaborators and decision-makers are incorporated into the broader dialogue about HIV vaccine research.

IAVI believes that this broad-based approach contributes to an environment that improves the quality of research, while also helping to ensure that countries will be positioned to adopt future vaccines and make them available as quickly as possible.

IAVI opened a field office in India three years ago, and established an East Africa Regional Office in Nairobi in 2003. The field offices and staff have strengthened coordination and communication among sites by exchanging information and lessons learned, and by sharing materials and experience through workshops and other mechanisms. The majority of IAVI’s in-country staff—including its two most senior representatives—are natives of the country or region in which they work. IAVI also supports education and advocacy in Brazil, China and South Africa.

Community Involvement. Conducting AIDS vaccine clinical trials in developing countries requires a thorough and sustained community education effort in which the communities are empowered and active participants in the research process. IAVI’s country programs are supporting the community education and mobilization efforts already underway at its clinical trial and preparatory study sites. An assessment tool is being developed to systematically map the community structures and key players, and to assist in identifying appropriate activities. Support also has been provided for establishing and maintaining community advisory boards (CABs) at many IAVI-sponsored sites. The CABs are comprised of diverse community representatives who play a critical role in providing input and feedback on the trial or study. The CABs also offer invaluable perspectives and insights into volunteer recruitment, informed consent and safeguarding participants’ rights.

Stakeholder Outreach and Advocacy

IAVI is working to build support for AIDS vaccine research by increasing awareness and participation in the vaccine development process by key individuals and organizations at local, national, regional and international levels. Well-informed stakeholders play a key role in building public support:

▪ The media is influential in shaping public opinion at all levels: they can disseminate accurate information, dispel myths, reduce stigma and help mobilize volunteers.
▪ Non-governmental organizations (NGOs) serve as important allies in advocating to support vaccine research by exerting influence on politicians and international stakeholders, and also can incorporate vaccine messages and information into their existing programs.
▪ The medical community plays a key role in advocacy and will be critical in facilitating future access to and use of a licensed vaccine.

Other important stakeholders include policymakers and political leaders, other AIDS researchers, international agencies, donors, and community and religious leaders.

Engaging Civil Society. IAVI is undertaking a series of activities to gather, document and exchange experiences across country programs and among partner organizations. An example of this effort was the inclusion of some of IAVI’s developing country partners in its European Partners’ meeting in Spain in September 2004. IAVI also organized an NGO workshop in India, and sponsored an advocacy event to bring together partners from India, South Africa and Brazil to discuss coordination of efforts around vaccine, microbicide and treatment research. In Kenya, IAVI has developed a network
of NGOs that are supportive of national AIDS vaccine research efforts.

At the global level, IAVI is supporting a project by the International Council of AIDS Service Organizations (ICASO) to document and disseminate lessons learned in community involvement in AIDS vaccine research in developing countries. ICASO and IAVI are working closely to identify and document these experiences for future publication. IAVI also has continued to work in partnership with the Montreal-based Canadian HIV/AIDS Legal Network to develop reference documents to support increased coordination in the field of new preventive technologies. This collaboration has yielded a series of documents highlighting the need for exchange in the fields of microbicides, treatment and vaccines (M-T-V). The documents were distributed by the Legal Network at the Bangkok AIDS conference.

**Vaccine Literacy.** IAVI established its AIDS Vaccine Literacy project to provide clear, accurate information that explains the vaccine research and clinical trials process. The project facilitates the development of educational tools by country offices and partners by providing a *Vaccine Literacy Toolkit* that contains materials which can be readily adapted to various formats, languages and audiences. While all of the Toolkit materials can be adapted for use at the community level, they are generally written for a range of stakeholders who work in AIDS-related areas or who may be familiar with the AIDS vaccine research and development agenda.

The first component of the Toolkit, a reference book on AIDS vaccines entitled the *Core Content*, includes chapters on AIDS vaccine development, the clinical trials process, participation in a trial, gender issues related to AIDS vaccines, building a supportive environment for vaccine trials, and preparing for future access to a licensed vaccine. Completed in 2004, the *Core Content* is now available in electronic form to country offices and partners, and will be available in print for distribution in the first quarter of 2005. The *Core Content* was developed for individuals and organizations that are providing AIDS vaccine-related information and education. It is not intended for distribution to the general public. Groups that may use this material include, but are not limited to: clinical AIDS vaccine trial site staff, NGO staff, medical professionals or institutions (to provide vaccine information to patients or to incorporate into advocacy efforts), VCT centers (to provide clients with vaccine information), and academic or religious leaders.

Additional components of the Toolkit (including a training manual, prototype educational and informational materials, and presentations in Microsoft PowerPoint®) are currently in development and will be completed and available in print and electronic formats in 2005. An *AIDS Vaccine Literacy Resource Center*, which includes AIDS vaccine educational materials in print and electronic formats developed by organizations worldwide, has been established at IAVI’s headquarters in New York and is currently being tested.

**National-Level Policy and Advocacy Efforts.** IAVI is involved in national-level policy and advocacy efforts in developing countries where vaccine trials take place. These efforts focus on building political will, ensuring sustained public support for AIDS vaccine research, and obtaining national-level input in the development and implementation of IAVI’s global policy agenda. Key policy initiatives include promoting effective regulatory review in resource-poor settings and supporting the development of national vaccine plans. A number of activities have been launched to prepare for use of a future vaccine, as well as several cross-cutting initiatives that aim to broadly benefit the AIDS vaccine field.

![Mr. Kapil Sibal (seated), India’s Minister of Science and Technology and Ocean Development (and an IAVI Board member) and Mr. Oscar Fernandes, Minister of State for Statistics and Program Implementation, at a Parliamentarians’ Briefing in New Delhi in August.](image)

**Engaging Policymakers and Parliamentarians.** Parliamentarians play a unique role by raising the level of political attention and by leading legislative action to promote a supportive environment for AIDS vaccine research and future access. Building increased political support, especially in developing countries, is essential to overcome the challenges of finding and delivering a vaccine for countries in the South. IAVI’s outreach activities this year to members of parliament (MPs) included OECD countries and to MPs in India, Kenya and Uganda. The Dublin meeting in June on New Prevention Technologies (see p. 46) and various
regional briefings encouraged exchanges between developing and industrialized countries. Within East Africa, IAVI has continued to collaborate with the Great Lakes Parliamentarians HIV/AIDS Project, which highlights vaccine advocacy as one of its key priority areas.

Global Political Advocacy Initiative. IAVI is helping to create a Global Political Advocacy Initiative (GPAI) that aims to capitalize on South-South and South-North relationships to advocate for increased support and the adoption of effective public policies for developing and deploying preventive AIDS vaccines. Kapil Sibal, India’s new Minister of Science and Technology and Ocean Development (and an IAVI Board member), has assumed a central role in facilitating the GPAI. Headed by leaders of countries from the South, the GPAI’s mandate is to put HIV vaccines on the global agenda as part of a comprehensive strategy to end the AIDS epidemic and promote inter-country collaboration on vaccine development and use.

During the first meeting of the Science & Technology Ministers of the India-Brazil-South Africa (IBSA) Group held in October 2004, Minister Sibal urged greater investment in HIV vaccine R&D. He called upon IBSA to form a core group that would remain at the forefront of an international movement against AIDS. The GPAI plans to use key international gatherings—such as the World Economic Forum, G8 Summits, and United Nations General Assembly Special Session Reviews—as opportunities to urge industrialized and developing countries to make firm commitments to vaccine R&D. To that end, Minister Sibal and IAVI President Seth Berkley delivered the closing address at the World Economic Forum “India Economic Summit” in December, which provided an important opportunity to engage the key stakeholders at all levels within the country.

Collaboration with the WHO/UNAIDS African AIDS Vaccine Program (AAVP). IAVI has an ongoing collaboration with the African AIDS Vaccine Program (AAVP) that involves pan-African advocacy for AIDS vaccines and exchange of information, expertise and lessons learned with various country partners. IAVI provided the AAVP a grant of US $200,000 for the period 2003-2005, to support its work. In 2004, IAVI worked with AAVP on supporting the creation of national guidelines for developing HIV vaccines in Kenya; participated in AAVP meetings in Tanzania and Botswana to share the Kenya experience; participated in meetings organized by AAVP on gender, adolescents and policy; and attended a meeting of the AAVP steering committee. In 2005, collaborative work will continue in the areas of advocacy and policy development, capacity-building for community groups and the media, and strengthening of regulatory capacity.

International AIDS Conference in Bangkok

IAVI’s participation at the Bangkok AIDS Conference sought to ensure that AIDS vaccines were presented from diverse perspectives in the various conference sessions. Through its team members and partners, IAVI was involved in a variety of activities:

- IAVI and its partners presented eight posters and an oral abstract on scientific and vaccine preparedness activities.
- IAVI President and CEO Dr. Seth Berkley chaired a plenary session on prevention, which included presentations on vaccines and microbicides.
- A Meet the Leaders Session, organized by IAVI, promoted an active debate between leaders of different sectors of the global response to AIDS.
- IAVI representatives spoke in several satellite meetings organized by leading global organizations, including Aventis, the Thai MOPH, ICASO and WHO.
- A vaccine booth was organized in collaboration with key global AIDS vaccine institutions, including the HVTN, The US Military HIV Research Program, The VRC and AVAC.
- IAVI participated in several skills-building sessions on AIDS vaccines produced in partnership with other organizations.
- Private parallel meetings were organized with multiple stakeholders during the conference including an IAVI donor’s briefing; a breakfast for parliamentarians and political leaders from East Africa; and a meeting with President Yoweri Museveni from Uganda.
- IAVI chaired the primary AIDS Vaccine session where the results of the Thai HIV Vaccine Efficacy Trial were presented.

In addition, a number of IAVI publications were released and broadly distributed at the Conference, including a synopsis of IAVI’s new Strategic Plan for 2005-2007, an updated version of IAVI’s Scientific Blueprint and a report on Gender Issues in AIDS Vaccine Trials.

UN Briefing Series. In May, IAVI hosted another in its ongoing series of UN luncheon briefings. Attendees included Ambassadors from Thailand, Brazil, India, Canada, Ireland, Kenya, the Netherlands, Rwanda, Switzerland, the UK, and UNAIDS. Dr. Seth Berkley presented an overview of IAVI’s ongoing activities, spoke about the importance of including vaccines as part of a comprehensive strategy to combat HIV/AIDS, and
introduced IAVI’s plans to support a Southern-driven global political advocacy program.

Cross-Cutting Initiatives

Addressing Gender Challenges in AIDS Vaccine Trials. IAVI continues to focus on challenges to participation by women in AIDS vaccine trials. In 2004, IAVI published a paper addressing gender participation by women in AIDS vaccine trials. In 2004, IAVI published a paper addressing gender challenges in AIDS vaccine trials in developing countries, and presented its work on gender at a WHO-UNAIDS consultation in Lausanne, Switzerland, and at a technical seminar in Washington, DC organized by the International Center for Research on Women, The Global Coalition on Women and AIDS, and Horizons. A training curriculum on gender also was developed for AIDS vaccine trials in consultation with IAVI’s Gender Advisory Board in India.

In August 2004, a two-and-a-half day training was held with the NARI research team in Pune, India to sensitize the team to gender issues and develop strategies to conduct the upcoming Phase I trial. A report, describing the consultative process undertaken in India to address these challenges, has been published and is available on the IAVI-India website. A preliminary gender consultation was held in Nairobi with KAVI and other IAVI partners to better understand the barriers to women’s participation in Kenya; a similar meeting is planned in Uganda for 2005.

Standards for Treatment and Care. A challenge facing all HIV prevention trials is the provision of treatment and care for trial participants, including those who, despite counseling, become HIV infected during the trial. IAVI continues to consult and coordinate with key stakeholders, including other researchers, government officials, community representatives, health care providers, and people living with HIV/AIDS, to finalize and implement the appropriate standard of care. Through national consultations and the formation of working groups to define policy and technical guidelines in Uganda, India and Kenya, IAVI has begun to improve its knowledge of and coordination with in-country organizations working in health service delivery and HIV/AIDS care and treatment to ensure that IAVI can implement its commitments, and that trial communities benefit more broadly.

Informed Consent for Trial Participants. Obtaining informed consent for clinical research can be challenging, particularly when complex concepts must be communicated in communities where literacy and educational levels may be low. IAVI has formed a working group to examine and identify the full range of approaches and interventions that can be used to ensure that volunteers clearly understand key concepts and make fully voluntary decisions to participate in studies and trials. Working closely with the research teams at all IAVI-sponsored sites, IAVI has begun examining and documenting the continuum of activities that make up the informed consent process—including community education seminars, individual education and counseling sessions, screening interviews, etc.—as well as protocols in place for and lessons learned from Phase I and II vaccine trials and preparatory studies for future efficacy trials. Possible outcomes of this work may include social science research to determine the most effective approaches to obtaining informed consent; introduction of new quality assurance, training and monitoring tools; or development of guidance documents or job aids, such as resource and reference materials, checklists, etc.

Social Science Research. Several of the cross-cutting issues discussed above can benefit from social science research to better understand the barriers to implementation, and to identify effective interventions to address them. IAVI has recognized the need to identify select social science research studies that will inform the conduct of clinical trials, preparations for future efficacy trials and preparations for future access to and use of a vaccine. To ensure that IAVI makes sound decisions about what types of social science research to undertake and when to do it, an internal committee was formed in 2004 to begin setting a long-term social science research agenda and to advise on short-term activities. The group has begun to identify gaps and priorities in the field and have prioritized two areas for possible short-term research: informed consent and barriers to women’s participation in trials. Social science research studies are currently being designed to address key questions in these areas.

Country and Regional Programs

East Africa Region

Partnerships for Preparedness. With support from the European Union (EU), IAVI has initiated a new project in East Africa called Partnerships for Preparedness. The project is being implemented in Kenya, Uganda and Rwanda, and focuses on building capacity and partnerships with key organizations and stakeholders in trial site communities and in the region as a whole. Project activities include:

- Providing training to NGOs on AIDS vaccines;
- Strengthening health care services and VCT in the communities surrounding HIV vaccine research sites;
Promoting the exchange of best practices and lessons learned among vaccine researchers and researchers working on other prevention technologies (e.g. microbicides);

Engaging key stakeholders, including the medical community, NGOs, the media and policy-makers at the national level; and

Conducting social science research to support clinical trials and future access and use of HIV vaccines.

A number of these activities were implemented in 2004 in collaboration with partners in Kenya and Uganda, as well as limited work in Rwanda.

**Building Awareness and Knowledge Among Key Constituencies.** IAVI is building awareness about AIDS vaccines on a national level in both Kenya and Uganda. The primary vehicle for these activities in Kenya is the Expanded Community Outreach Program, which includes several components:

- **Targeted Outreach and Education:** IAVI is working with various organizations in Kenya to conduct targeted outreach and provide education to the media, policymakers and religious leaders to strengthen their support for the HIV vaccine effort. In 2004 IAVI continued its outreach to the Kenyan media by providing trainings for radio journalists and scholarships to the International AIDS Conference in Bangkok.

- **Vaccine Support Networks:** IAVI is working with civil society organizations in Kenya to ensure that accurate information on AIDS vaccines has the widest possible reach in communities where trials are likely to occur. In early 2004, Vaccine Support Networks (VSNs) of local NGOs and CBOs were established in five regions where clinical trials are planned or underway. IAVI has been working with the VSNs throughout 2004 to train a cadre of master trainers in vaccine literacy, and to support the groups in acting as vaccine advocates and educators. A baseline evaluation of NGO staff knowledge and attitudes related to AIDS vaccines was conducted in 2004 and the report will be available in 2005.

- **Health Care Providers:** The support of health care providers is critical for the successful recruitment and retention of trial volunteers. Working with local partners, IAVI has begun a nationwide program to educate health care providers about AIDS vaccine R&D. The program is initially targeting nurses and clinical officers and is using a specially designed curriculum adapted from IAVI’s Vaccine Literacy tools. In addition, lectures on AIDS vaccine research have been provided to physicians as part of the Kenya Medical Association continuing medical education (CME) program.

Activities in Kenya to support increased HIV vaccine awareness have been intensified. These activities include publicity walks through town centers, “medical camps” done in conjunction with medical NGOs to offer treatment and advice for minor ailments, and assistance in establishing sites for VCT. Two companies with large work forces of several thousand staff have been collaborating to set up additional VCT sites.

The UVRI/IAVI team in Uganda continues to educate the public on HIV and HIV vaccines. The team has continued outreach to other HIV research groups, NGOs, women’s and youth groups, people living with HIV/AIDS, the media, and political and religious leaders. As part of an effort to reach the medical community, Principal Investigator Dr. Pontiano Kaleebu presented on HIV vaccines at the Uganda Medical Association annual scientific conference, for which IAVI also provided financial support. With the recognition that long-term support is needed, much focus is placed on educating and updating these constituencies on the complexities of HIV vaccine research.

The UVRI/IAVI team has forged productive relationships with other HIV Vaccine stakeholders, particularly the Makerere University/Walter Reed Program through sharing experiences and community outreach and community educational seminars. The site continues to build collaborative relationships with the scientific community in Uganda, especially with partners such as the Medical Research Council and the Centers for Disease Control, and they continue to develop plans for collaborating with the Uganda National Council for Science and Technology in order to standardize the HIV vaccine messages in Uganda.

The UVRI/IAVI team continues to produce its quarterly newsletter, *Uganda HIV Vaccine Update*, which is widely distributed in Uganda (5000 issues distributed quarterly), and the East Africa Office has launched *EAVAX*, an East African regional version of IAVI’s popular *VAX* newsletter.

**Building Political Will.** During the second half of 2004, IAVI worked to increase support for HIV vaccines among key figures within the Kenyan and Ugandan Governments. IAVI assisted the Kenyan Ministry of Health’s HIV/AIDS vaccine sub-committee, which met on a regular basis and made strides in the development and implementation of the Kenyan National Guidelines on HIV/AIDS Vaccine Development. The Guidelines will be officially launched in early 2005.
The UVRI/IAVI team is building strong supportive relationships with the Uganda AIDS Commission, Uganda Ministry of Health, the AIDS Control Program, the Uganda National Council for Science and Technology and the Parliamentary Standing Committee on HIV/AIDS. President Yoweri Museveni met with Dr. Seth Berkley at the International AIDS Conference in Bangkok and since that meeting has been speaking publicly about the need for an AIDS vaccine and citing Uganda’s support of HIV vaccine R&D.

Treatment and Care Policy. With the UVRI/IAVI acting as a convening body, the Uganda Treatment and Care Task Force is examining issues related to provision of treatment and care to participants in HIV prevention trials. Participants on the task force include HIV researchers, NGO’s, people living with HIV/AIDS and officials from the Uganda AIDS Commission and the Uganda Ministry of Health. Uganda has taken a leadership role by identifying participants in HIV/AIDS research as a priority group in its scale up strategy. IAVI also facilitated an initial Treatment and Care Consultation in Kenya in December 2004. The meeting brought together high-level stakeholders to help define the appropriate care and treatment for clinical trial participants and host communities, and sustainable approaches to shared responsibility for that care.

Southern Africa

With its high HIV incidence rates, South Africa is likely to be a key country for future efficacy trials of an AIDS vaccine. IAVI works together with the South African AIDS Vaccine Initiative (SAAVI) and maintains strong relationships in South Africa, not only because of the severity of the epidemic there, but also because of the country's scientific, manufacturing and political leadership in the region and globally.

IAVI sponsored a three-day consultation in Durban among South Africa, India and Brazil on lessons learned in microbicides, treatment, and vaccine advocacy and community outreach. The consultation brought together about 27 participants from the three countries as well as international NGOs. IAVI presented on vaccine preparedness as part of the program.

IAVI is exploring a possible collaboration with the University of Natal’s HIV/AIDS Vaccines Ethics Group (HAVEG) that would build upon their innovative study of the best way to assess understanding of informed consent. IAVI also is working with SAAVI’s Socio-behavioral Working Group to plan a consultation for 2005 on social science research related to AIDS vaccines.

In the coming year, IAVI’s South Africa country program will work with its partners and the government to increase political support for AIDS vaccines. The program will reach out to the presidency, parliamentarians and regional bodies, such as SADC, to enlist their support to advocate for vaccine R&D, funding and eventual access. IAVI will strengthen its relationship with SAAVI through collaborative initiatives both within their community preparedness team and their newly formed Socio-behavioral working group.

IAVI-India

Building Awareness And Knowledge Among Key Constituencies. During 2004, IAVI-India consolidated and formalized its work with a number of networks and groups to ensure regular information exchange and interaction with key stakeholder groups whose support will be important during the development, testing and eventual distribution of a licensed AIDS vaccine.

National Advisory Board. Almost from its inception, IAVI has operated in India under the guidance of a National Advisory Board. The Board is comprised of influential members from diverse sectors including women’s health advocates, PLWA groups, international agencies, government departments, scientists and others. This year the Board was divided into sub-groups based on key issues to enable them to provide more detailed input on selected aspects of trials. Members also participated in a skills-building workshop to further enhance their understanding of the vaccine development and distribution process in preparation for upcoming trials.

NGO Working Group skills building workshop in Delhi, 31 May and 1 June. The workshop, organized by IAVI’s India and New York offices, focused on building capacity on AIDS vaccines among IAVI’s key NGO partners in India.

NGO Working Group. The NGO Working Group is comprised of representatives from the six high HIV prevalence states, including YRG Care and NAZ Foundation. The group members are developing
strategies to integrate vaccines into their existing prevention programs. A plan for disseminating vaccine literacy information amongst the NGOs in two Phase I trial sites in Maharashtra and Tamil Nadu is planned for 2005. In order to build their capacity in the area of community involvement for research and development of HIV vaccines, The Working Group is also looking at developing linkages with global NGO forums engaged in the similar areas.

Corporate Sector. IAVI-India has undertaken several activities in 2004 aimed at engaging the private sector. A meeting was held with the Corporate Subgroup, representatives of corporations expressing interest in the AIDS vaccine program, as a follow-up to an initial meeting in 2003. Possible collaborations between IAVI and the corporations were outlined, and IAVI will seek specific support as needed going forward. An interactive session was also held with representatives of some Indian pharmaceutical and biotech industries to highlight market opportunities for the industry in preventive health technologies with a specific focus on an AIDS vaccine. This meeting was attended by prominent senior pharmaceutical industry representatives, R&D executives, as well as IAVI’s president, Dr. Seth Berkley and Mr. Kapil Sibal, Minister for Science and Technology and Ocean Development.

Gender Advisory Board. IAVI-India’s Gender Advisory Board worked with New York staff to develop a gender training curriculum for India trial staff, based on the initial findings of a gender consultation held in November 2002. NAZ Foundation, an AIDS NGO partner of the India program worked with IAVI to pilot the modules and trained all 18 members of the NARI team in Pune to recognize and address potential barriers to women’s participation in trials and ensure that trials are conducted in a gender-sensitive manner.

Religious Leaders Program. The involvement and support of religious and spiritual leaders from major religious and faith groups in India is particularly significant as religious belief is a strong and motivating force in peoples’ lives. Under the Religious Leaders Program, advocacy activities were initiated to help mobilise communities and build their preparedness for the AIDS vaccine program. State-specific one-on-one consultations, documentation and research in the states of Maharashtra and Tamil Nadu have been initiated. A database of prominent religious groups and faith-based organizations in these states has been established and will be updated regularly.

Sankalp and Website. The IAVI-India bimonthly newsletter Sankalp published five issues in 2004 in both English and Marathi. An editorial committee comprised of NGOs, networks of PLWHIV, international organizations, NACO and ICMR representatives has been set up so that the newsletter truly reflects and addresses the needs of an Indian audience.

The IAVI-India website (www.iavi.org.in) contains general and India-specific information about HIV/AIDS, vaccine research and advocacy and is updated regularly in English, Hindi and Marathi. A proposed Tamil site is currently being tested and should be live by the end of January 2005.

Building Political Will. HIV is a problem that transcends political divisions and IAVI-India has successfully maintained positive relationships across the political spectrum. IAVI continues to have strong supporters at the highest levels of government.

- Dr. Seth Berkley and IAVI staff met with the new Minister of Health and Family Welfare, Dr. Anbumani Ramadoss, and the Minister for Science and Technology and Ocean Development (who is also an IAVI Board member);
- Dr. Berkley and IAVI staff met with both the Indian President and Prime Minister who have agreed to include support of AIDS vaccines in key addresses;
- IAVI briefed Members of Parliament on the progress in preparation for the clinical trials for an AIDS vaccine in India; and
- IAVI participated in a ‘Student and Youth Parliament’ and made a presentation on the AIDS vaccine program in India.

Treatment and Care - In partnership with NACO and ICMR, IAVI convened a National Consultation on HIV Care and Treatment for AIDS Vaccine Clinical Trial Participants. Recommendations were formulated for policy and guidelines for the care and treatment of trial participants, including those who become HIV-infected during the course of AIDS vaccine clinical trials, within the framework of NACO’s HIV/AIDS care and treatment policy guidelines.

Planning For Access. A consultation on access was held in December to discuss a research project that IAVI is supporting with Dr. Indrani Gupta from the Institute of Economic Growth. The project plans to initiate a study entitled ‘The adoption and use of health technologies in India: Preparing for access to an AIDS vaccine’. The discussions also helped identify important issues for the development of a blueprint for an access program in India for 2005 and beyond, in the context of IAVI’s global program on public policy and access.
China

In China, IAVI is supporting activities that will promote HIV vaccine development by ensuring that Chinese researchers and vaccine stakeholders are aware of trials underway in other countries and have access to state-of-the-art materials and information. IAVI has been working closely with partners in China to organize the first Vaccine Preparedness Workshop to be held in early 2005. The workshop will take place in Kunming, Yunnan province and is intended to support upcoming trials that will take place in China. Several partners working in-country will be involved, including the Yunnan CDC, The Chinese Academy of Medical Sciences and The Aaron Diamond AIDS Research Center. Although IAVI is not currently planning to conduct clinical research in China, this workshop will help create momentum and provide support for upcoming research being carried out by other sponsors. The workshop will introduce an agenda of activities to build capacity in selected areas and sustain support for AIDS vaccines in China.

Mobilizing International Support and Assuring Future Vaccine Access

Overview. IAVI’s Public Policy Program supports the development and implementation of public policies at the national and international levels to speed the development of safe and effective AIDS vaccines, and to ensure their accessibility throughout the world. The Program’s strategic areas of focus include: mobilizing funding to accelerate vaccine development and future use; building political support for AIDS vaccine R&D; estimating need and demand for a vaccine; and developing strategies to ensure eventual access, particularly in developing countries.

New Senior Leadership. In May, Dr. Robert Hecht joined IAVI as the Senior Vice President for Public Policy. Dr. Hecht comes to IAVI following a 20-year tenure at the World Bank where he served as Acting Director and Sector Manager of the Bank’s central unit for Health, Nutrition, and Population, managing the unit responsible for global strategies, technical services, knowledge and partnerships. He formerly also served as an Associate Director of UNAIDS.

Under Dr. Hecht’s leadership, a new work plan was formulated for IAVI’s Public Policy program and recruitment is underway to expand staff capacity.

Policy Advisory Committee. IAVI’s Policy Advisory Committee was established in 2002 and is composed of experts from a range of fields, including public health, vaccine development, and international governance. At the second annual meeting of the committee, held in October 2004, the Policy team presented its work plan for 2005-07, highlighting IAVI’s strategic priorities, and sought advice on policy analysis currently underway or planned for the coming year. The Committee endorsed plans to focus on vaccine R&D spending, benefit-cost assessment, and demand forecasting, and encouraged further work on manufacturing and process engineering.

Publications. In 2004, IAVI’s Public Policy team launched a series of publications designed to disseminate a growing body of research and analysis, support advocacy efforts, and drive debate on key HIV vaccine policy issues. These publications also have informed external presentations by IAVI senior staff at legislative briefings, government meetings and conferences in the US and other countries.

Policy Advocacy

During 2004, IAVI began work on a number of activities to increase political and financial support for AIDS vaccine R&D, encourage greater involvement by industry, and ensure access to future AIDS vaccines.


Incentives to Accelerate R&D. IAVI developed a policy brief on push and pull mechanisms that outlines various incentive options and lessons learned from past efforts to engage industry in the development of global goods for public health. In the US, IAVI has led an informal coalition of product developers and organizations focused on neglected diseases to evaluate proposed legislation known as “Bioshield II”. IAVI’s Public Policy team is developing a strategy on the possible inclusion of an HIV vaccine in this legislation (among a number of preventive technologies), which would include patent, tax and liability measures to encourage increases in industry investment in HIV vaccine R&D.

Engaging Industry. In April, Seth Berkley, Robert Hecht and other IAVI staff met with the head of Merck vaccines and other company representatives to discuss areas of possible collaboration related to public policy and vaccine access. Merck and IAVI identified a number of topics of shared interest.
and agreed to further discussions in order to define a common agenda and develop a plan of action.
IAVI had several follow-up meetings with the Merck AIDS policy group in the spring, at the Bangkok conference in July, and in Washington in November. Merck expressed interest in attending IAVI-hosted consultations on other topics such as standards of care for vaccine trial participants and manufacturing.

**Microbicides 2004.** At the Microbicides 2004 conference held in London in April, IAVI staff presented on opportunities for the AIDS vaccine, treatment and microbicides fields to jointly advocate for the development and distribution of critical health technologies to combat HIV/AIDS. The meeting provided an opportunity for IAVI to strengthen ties with others developing new prevention technologies, and to identify areas in which developments in the microbicides field could inform and advance AIDS vaccine R&D and future vaccine use.

**Product Development Public-Private Partnerships.** In April, IAVI also attended a meeting in London co-organized by the Initiative on Public-Private Partnerships for Health (IPPPH), the Wellcome Trust, DFID and the Rockefeller Foundation. The purpose of the meeting was to examine financing strategies for product development and the potential role of public-private partnerships (PPPs) in combating diseases associated with poverty. The meeting, attended by the key PPPs engaged in product development and a number of donor organizations, provided a forum for PPPs to share their experiences with funding agencies. Speaking on behalf of PPPs working on vaccines, IAVI President Dr. Seth Berkley discussed common challenges and opportunities in the field.

In late June, Dr. Berkley and Dr. Hecht attended a meeting of vaccine product development PPPs hosted by the Aeras Global TB Vaccine Foundation in Washington, DC. The three organizations—Aeras, the Malaria Vaccine Initiative (MVI) and IAVI—discussed areas of common action related to intellectual property management and incentives such as “pull” mechanisms to increase private sector investment in vaccine R&D targeted at neglected diseases in the developing world.

Dr. Hecht also met in June with the senior staff of organizations working to speed the development of new health technologies—including the Alliance for Microbicides, the International Partnership for Microbicides (IPM), and the program for the Accelerated Development and Introduction of a Pneumococcal Vaccine—to explore areas of common interest and possible collaboration on public policy issues. IAVI and the Alliance for Microbicides subsequently presented data on global expenditures for AIDS vaccines and microbicides at the International AIDS Conference in Bangkok.

**G8 support for HIV Vaccine Development.** At their June 2004 Summit in Sea Island (Georgia, US), the Group of Eight industrialized nations (the G8) endorsed the establishment of a Global HIV Vaccine Enterprise consortium to accelerate HIV vaccine development. In the lead-up to the meeting, IAVI coordinated with its NGO partners to encourage member countries to call for greater resources for AIDS vaccine research. The resulting communiqué highlights AIDS vaccines as a top priority and includes IAVI as a key stakeholder. In the ensuing discussions and vaccine meeting to be convened by the G8 on this issue, IAVI will encourage the process to be as broadly inclusive as possible, involving non-G8 countries and particularly partners in the developing world.

**EU Support for New Prevention Technologies.** On 24 June, a high-level meeting was held in Dublin to establish an agenda for the forthcoming Dutch, Luxembourg and UK presidencies of the European Union (EU) and mark the transition of the EU Presidency from Ireland to the Netherlands. The meeting included a discussion on the need for increased efforts to develop new HIV prevention technologies (see p. 46 for more information).

**European Commission.** In August, IAVI staff attended a small consultation on proposals for a new Commission communication on HIV/AIDS, TB and Malaria to build on earlier progress made through the Programme for Action on HIV/AIDS, TB and Malaria. In September, IAVI staff attended a larger civil society consultation in Brussels. On both occasions, the Commission emphasized continued support for HIV vaccine R&D.

**Global Forum for Health Research.** The annual conference of the Global Forum for Health Research (GFHR), held in Mexico City in November, brought together key international public health researchers, health and development ministries, representatives of the media and academia, and activists to consider the role of health research in achieving the Millennium Development Goals (MDGs). During the session on HIV/AIDS, IAVI staff presented a paper entitled “Improving Access to HIV/AIDS Vaccines: Assessing Public and Private Demand in Developing Countries”.

The IPPPH sponsored an all-day satellite session on public-private partnerships and their role in health development efforts. IAVI staff presented on the range of partnerships the organization has established, including collaborations with research entities, clinical sites, community advisory boards, ethics committees and regulatory authorities. IAVI also presented on the need to provide well-
documented research on demand estimates, assessments of epidemiological impact, and studies on the adoption and use of health technologies to make the case for developing and introducing vaccines.

**WHO Ministerial Summit on Health Research.** The World Health Organization (WHO) sponsored a Ministerial Summit in November in tandem with activities sponsored by the GFHR. At a session for international policymakers and public health experts, Dr. Hecht participated in a panel discussion on “New Technologies from Public-Private Partnerships to Achieve the MDGs: Developing country leadership, clinical trials and new product approvals.” Dr. Hecht’s remarks emphasized the potential for these partnerships to join public and private sector resources to develop innovative technologies to end global epidemics.

**GAVI Financing Task Force.** The Global Alliance for Vaccines and Immunization (GAVI) established its Financing Task Force (FTF) to prevent disease by making new vaccines accessible. To date, the FTF has focused on: (1) financial sustainability planning and implementation for countries receiving GAVI funds; (2) the development of international and national investment cases for vaccine funding; (3) exploring creative financing mechanisms such as capital market mechanisms and debt relief; and (4) examining the potential impact of supply, procurement and pricing issues on future financing. As the NGO representative, IAVI attended several 2004 meetings of the FTF. However, as this task force will be phased out in 2005, discussions at the April meeting focused on how best to wind-down the work of the FTF and transition key activities to other groups.

**Centre for Global Health Research.** In November, Dr. Robert Hecht served as a panelist at the Toronto conference “Controlling the Risk: Science to Combat Global Infectious Diseases”, sponsored by the Centre for Global Health Research. Dr. Hecht’s remarks highlighted IAVI’s work in developing countries, the organization’s policy research priorities and the crucial role of PPPs in the global battle against infectious diseases. The conference was an opportunity for IAVI to engage in and inform debate with leading international public health experts and key Canadian policymakers and researchers.

**UK Treasury.** In April, Dr. Seth Berkley and other IAVI staff met with officials of the UK Treasury’s Global Poverty Reduction Team to discuss UK plans for the establishment of an International Finance Facility for Immunization (IFFIm). IAVI Policy staff met with Treasury officials in August to discuss progress in the development of the IFFIm and to outline IAVI’s project to develop an economic case for investing in AIDS vaccine development. Discussions with the Treasury continued in the fall of 2004 and covered a range of topics including various push and pull mechanisms to accelerate AIDS vaccine development and ensure future access. On 9 December, Dr. Berkley met with the Chancellor of the Exchequer, Gordon Brown. The Chancellor has become a strong advocate for expanded investment in AIDS vaccine R&D, through both additional public sector spending now and through commitments to “Advance Purchases” as a way of stimulating industry. The Chancellor indicated that Britain was prepared to spend several hundred million pounds to establish such an advance purchase facility for AIDS and for malaria vaccines.

**Consultations With DFID.** IAVI participated in several consultations with the UK Department for International Development (DFID) (see p. 47).

**POLICY RESEARCH & DEVELOPMENT**

**Monitoring Global Investment in R&D.** In February, IAVI participated in a meeting of the UNAIDS Resource Tracking Project in Geneva and presented on the challenges of developing estimates of global investment in AIDS vaccine R&D. As an active member of UNAIDS Resource Tracking Consortium (UNRTC), IAVI is working closely with the UNAIDS Resource Tracking Unit, the Alliance for Microbicide Development (AMD), and the AIDS Vaccine Advocacy Coalition (AVAC) to improve and streamline methods for estimating investments in emerging prevention technologies such as microbicides and AIDS vaccines. These data will be used in monitoring progress on the second of the UNGASS global action and commitment indicators, which focuses on the level of public funds available for research and development of vaccines and microbicides.

In July, IAVI’s Policy team released the results of its research to estimate global investment in HIV vaccine R&D. These findings were published as the first in a series of IAVI ‘Policy Research Working Papers’. The data also were presented in a poster at the International AIDS Conference in Bangkok and at a pre-conference satellite meeting organized by the UNRTC. The report contains 2002 estimates—a baseline from which future global spending can be monitored to assess the level, adequacy, and distribution of expenditures for AIDS vaccine R&D. An analysis of 2003 AIDS vaccine expenditure figures will be released in early 2005.

**Estimating Required Spending on HIV Vaccine R&D.** In collaboration with the Bill and Melinda Gates Foundation’s Global Health Program, IAVI’s Policy team is developing an estimate of the level
of R&D spending required to develop an effective HIV vaccine. This analysis seeks to determine how much the world needs to spend to find a vaccine and to evaluate by how much the development timeline could be reduced by increasing current levels of spending.

Manufacturing Challenges to Vaccine Development and Use. In December, IAVI completed work on a policy discussion paper on manufacturing challenges to AIDS vaccine development and future use. The paper will be released with an accompanying Policy Brief in January 2005. The paper examines challenges to the rapid development of HIV vaccines related to the areas of manufacturing and bioprocess development, and identifies options for public policy action to address critical issues such as the manufacture of clinical trials materials, process development, and the eventual large-scale production of future vaccines for use by developing countries. A draft of the paper was distributed to selected participants in the discussions of the Global HIV Vaccine Enterprise in Washington on 21 October.

India Vaccine Industry. In preparation for the December visit to India by Dr. Berkley and Dr. Hecht, the Public Policy team worked with IAVI’s Delhi office to prepare a background paper on the drug and vaccine industry in India. The paper’s main objective was to explore the potential for Indian researchers and companies to play an active role in the innovative aspects of vaccine R&D. The paper was used in a workshop for policymakers and industry representatives on engaging Indian pharmaceutical and biotech companies, held in Delhi on 3 December, and in subsequent dialogues with Indian government officials and the media. The document will be revised and issued as a Research Working Paper in the first quarter of 2005.

Ensuring Vaccines are Available and Accessible. The Institute of Public Health at Makerere University in Kampala concluded its IAVI-sponsored project examining the factors affecting the approval and uptake of health technologies in Uganda. Researchers produced a working paper on the study findings, which focused on Ugandan experiences with six health technologies, including two vaccines, two reproductive health technologies and two anti-retrovirals.

In December, the Health Policy Unit of the Institute of Economic Growth (Delhi) began work on an IAVI-funded study to assess the adoption of new health technologies in India. The study will examine the processes of approval and licensure, procurement, uptake and utilization for four technologies: the Hepatitis B vaccine; antiretroviral therapies; sterilization methods; and VCT services. The study also will assess the role of the public and private sectors in the provision and distribution of these technologies, in order to identify areas in which lessons learned from prior experiences can improve future access to HIV vaccines.

Understanding Demand. In August, IAVI hosted an expert consultation to refine its policy research agenda on the demand for an HIV vaccine. The group reviewed existing work on vaccine demand estimates and their determinants to identify key issues and gaps in knowledge. The group’s work also will be used to advise on the role that IAVI should play in implementing this research agenda, potential contributions of other institutions and individuals, and how best to organize this effort.

Final results from a study, co-sponsored by IAVI, surveying Ugandans to assess determinants of individual demand for an HIV vaccine were published in the September Bulletin of the World Health Organization. The study, carried out by a team of researchers from the Johns Hopkins University Bloomberg School of Public Health and the Institute of Public Health at Makerere University, found that household wealth, vaccine price, and perceived risk of infection were significant factors in respondents’ demand.

A Policy Research Working Paper is forthcoming on the findings of a study to estimate household demand for an HIV/AIDS vaccine in Thailand and to identify key determinants. The study, completed in October by Prof. Dale Whittington of the University of North Carolina under an IAVI grant, builds on data collected by the International Health Policy Program of the Thai Ministry of Public Health. The final paper was submitted for journal publication.

In November the Policy Team published a first draft of a Research Working Paper on existing demand work, excerpts of which were presented at a session of the Global Forum for Health Research. The final Research Working Paper will be published in the first quarter of 2005.

IAVI’s Demand Project Manager, Chutima Suraratdecha, Martha Ainsworth of the World Bank, and Robert Hecht authored a paper assessing public and private sector demand for a preventive HIV vaccine in developing countries. The paper was presented in November during an oral session on HIV/AIDS health policy and systems research at the Global Forum for Health Research in Mexico City.

OTHER INTERNATIONAL COLLABORATIONS

IAVI continues to build political and financial commitment to AIDS vaccine research, development and delivery through numerous other international collaborations.
SUPPORT FROM CANADA

Relationships with Canadian Government. IAVI continued to work closely with its partners in the Canadian Government throughout the past year. IAVI welcomed Canada’s new Prime Minister, Paul Martin, and the new Minister of International Cooperation, Aileen Carroll.

Last year the Government of Canada demonstrated impressive leadership in responding to the global HIV/AIDS pandemic. In 2004, Canada:

▪ contributed CAD$100 million to the World Health Organization’s “3x5 Strategy”;
▪ doubled its contribution to the Global Fund to Fight AIDS, TB and Malaria;
▪ doubled funding to the Canadian Strategy on HIV/AIDS;
▪ passed Bill C-9: An Act to Amend the patent Act and the Food and Drugs Act, now known as the Jean Chretien Pledge to Africa;
▪ pledged over CAD$100 million to HIV/AIDS programs focusing on women and girls, including ongoing support for new prevention technologies for HIV/AIDS through its CAD$15 million grant to the International Partnership for Microbicides.

Canadian International Development Agency (CIDA). IAVI’s three-year grant from the Canada Fund for Africa is administered through CIDA and was announced at the 2002 G8 Summit in Kananaskis as part of Canada’s commitment to the Africa Action Plan. Both the Canada Fund for Africa and the Africa Action Plan are built on the principles of NEPAD – the New Partnership for Africa’s Development - that recognize the right of Africans to take control and ownership of their own path to development. CIDA’s generous contribution to IAVI directly supported AIDS vaccine development, clinical trials and community development activities in Uganda, Kenya, Rwanda South Africa and Zambia.

Following a visit from CIDA representatives at its New York office in April to review progress on the grant, IAVI welcomed senior CIDA policy makers to its donor meeting in Bangkok, Thailand held in conjunction to the International AIDS Conference. This meeting also was attended by community partners from the Canadian AIDS Society and the Canadian HIV/AIDS Legal Network.

In November, IAVI President and CEO Seth Berkley met with Minister for International Cooperation Aileen Carroll and senior members of the Prime Minister’s Office to discuss the role of HIV vaccines in the global response to HIV/AIDS and IAVI’s public-private partnership model. Dr. Berkley also met with CIDA President Paul Thibault and his senior staff to update them on Canada’s contribution and discuss future challenges.

Health Canada. IAVI has enjoyed participation on the Health Canada-led Canadian HIV Vaccines Plan. IAVI is supporting this important effort through participation on the steering committee along with representatives from the Canadian AIDS Society, the Canadian Network for Vaccines and Immunotherapeutics (CANVAC), and the Canadian Treatment Action Council.

Foreign Affairs Canada. In December, Foreign Affairs Canada released the first draft of its HIV/AIDS Strategy. Within this strategy, IAVI was pleased to acknowledge Canada’s commitment to the Global HIV Vaccine Enterprise as a priority at the 2005 G8 Summit.

…so much of what we’re doing in response to the pandemic, while monumentally vital, will not, ultimately, subdue it... only a vaccine will write an end to the pandemic.

Stephen Lewis
UN Secretary-General’s Special Envoy for HIV/AIDS in Africa
Address to the Rotary Club of Toronto
Toronto, Canada—January 2004

Relationships with Canadian Civil Society. In 2004, IAVI renewed agreements with its three Canadian civil society partners.

The Canadian AIDS Society (CAS) has been IAVI’s national NGO partner since 2001. This year the two organizations renewed their joint memorandum of understanding. As part of this agreement, IAVI is supporting a range of vaccine-related CAS activities, including advocacy and policy analysis, community capacity building in Canada, and the cultivation of strategic alliances to enhance Canada’s domestic and international response to the global AIDS vaccine effort. In September, CAS participated in IAVI’s European community partners meeting, which is a vital forum for sharing ideas and insights about community-based advocacy in the quest for HIV vaccines.

IAVI also initiated a new collaboration with its long-time partner ICASO (the International Council of AIDS Service Organizations) by funding an advocacy research project that is documenting case studies from developing countries that highlight examples of community involvement in HIV vaccine trials.
IAVI also provided renewed support for HIV vaccine work being done by the Canadian HIV/AIDS Legal Network, which includes joint HIV microbicide/treatment/vaccine (“MTV”) advocacy within a rights-based, comprehensive response to HIV/AIDS. In addition, IAVI is supporting the development of HIV vaccine fact sheets to complement its existing range of education and advocacy materials.

Relationships with Canadian Researchers. In 2004, IAVI also expanded its relationships with Canadian researchers:

- In February, IAVI participated in an HIV Vaccine Community Mobilization meeting convened by CAS and CANVAC. The meeting was one of several offshoots of a study conducted jointly by CAS and CANAVAC on attitudes towards HIV, Hepatitis C and cancer vaccines.
- In April, IAVI and CAS delivered a presentation on HIV vaccines at the annual research conference of the Canadian Association of Nurses in AIDS Care in Toronto.
- In May, IAVI participated with research and community partners at the 13th Annual Canadian Conference on HIV/AIDS research in Montreal.
- In October, CAS and IAVI presented on the public policy implications of combination HIV prevention at the Canadian Conference on International Health in Ottawa.
- In November, IAVI presented at the “Controlling the Risk Conference” in Toronto (see p. 39). The occasion also provided the opportunity for a meeting with the president and two of the institute chairs from the Canadian Institutes of Health Research (CIHR) to explore international research collaborations.
- IAVI’s Senior Vice-President & Chief Vaccine Development Officer and Senior Vice President & Chief of Vaccine Research were named to the organizing committee of AIDS Vaccines 2005, an international conference being held in Montreal.

CANVAC. In November, IAVI’s Senior Vice-President and Chief of Vaccine Research, Director of Research and Design, and Canada Coordinator participated in the annual conference of the Canadian Network for Vaccines and Immunotherapeutics. Two pilot studies are being developed by IAVI and CANVAC: one related to immune monitoring and the other using an anthropological approach to community development at IAVI’s African trial sites. This collaboration builds on other joint activities throughout the year, including CANVAC’s contribution to a study conducted by IAVI’s Public Policy Department on global HIV vaccine funding as well as a collaboration with CANVAC anthropologist Dennis Willms who has been exploring aspects of vaccine preparedness in Africa. In addition, IAVI’s President continues to serve on CANVAC’s Board.

### Activities in Europe

Throughout 2004, IAVI’s efforts in Europe were focused on four key areas:

1. Building broad-based political, financial and community support for HIV vaccines as a vital part of a comprehensive response to AIDS and the global health effort;
2. Defining and promoting a new preventive technologies agenda, together with the International Partnership for Microbicides (IPM) and the Global Campaign for Microbicides (GCM);
3. Collaborating with major stakeholders in developing a long-term policy agenda; and
4. Supporting the organization’s R&D efforts in Europe and working with members of the European scientific community.

AIDS Vaccine Advocacy. In 2004, IAVI’s advocacy efforts in Europe included working with NGOs, the media and elected officials, among others. These efforts resulted in the publication of a series of OpEd articles in leading European newspapers on and around World AIDS Vaccine Day (18 May) and World AIDS Day (1 December), as well as a series of strong supportive public statements on the need for an increased AIDS vaccine effort by numerous high-ranking public officials—including cabinet ministers, state secretaries and HIV ambassadors—from the governments of Ireland, the Netherlands, Norway, Spain, Sweden and the UK. At the EU level, the ACP-EU (Africa Caribbean Pacific—European Union) Joint Parliamentary Assembly, the Global Progressive Forum, the EU Council of Health Ministers and the European Parliament have firmly included vaccines in the AIDS agenda.

New Preventive Technologies. IAVI and IPM worked closely together on preparing the background materials for the meeting on New Preventive Technologies (NPTs) that took place in Dublin in June (see p. 46). IAVI, IPM and GCM subsequently worked in close cooperation on the Vilnius Declaration, and on the symposium in the European Parliament on Women, Girls and HIV/AIDS on World AIDS Day.

Developing a Long-term Policy Agenda. As discussed in greater detail below, IAVI staff participated in and contributed to: the evaluation of the Programme for Action (PfA), the definition of a new multi-year policy program on HIV/AIDS, the evaluation of the Sixth Framework for
Research, and the preparation of the Seventh Framework. IAVI also worked with DFID, the UK Treasury and Prime Minister’s Office on innovative international finance mechanisms for AIDS vaccine R&D and advance purchase mechanisms, among other issues.

IAVI’s R&D Program in Europe. A substantial part of IAVI’s R&D program has been implemented in collaboration with European institutions and organizations (see AIDS Vaccine Research and Development section above). In 2004, a new collaboration with Crucell, a Dutch biotechnology company, was started to develop AIDS vaccine candidates using Crucell’s AdVac® technology. This collaboration reflects one of the key tenets of IAVI’s strategy to advance the global vaccine effort: the need to engage industry as meaningful partners in this process. Letters of Understanding were signed with EDCTP and EuroVacc to pursue meaningful venues for collaboration.

In 2004, a number of IAVI-sponsored AIDS vaccine clinical trials were implemented in Germany, the UK, Belgium and Switzerland. IAVI staff worked with community groups to increase their understanding of and involvement with AIDS vaccine trials. Discussions took place in Germany before the start of the rAAV trials, and in the UK where trials with MVA and DNA were ongoing.

Collaboration with NGO Partners in Europe. IAVI continues to build strong relationships with its NGO partners in Europe. These organizations play a vital role in building national and EU support for AIDS vaccine R&D and future delivery. In 2004, task groups were established to focus on and address issues around the European Developing Countries Clinical Trial Partnership (EDCTP), vaccine clinical trials, World AIDS Vaccine Day, the G8 and the EU Presidency. IAVI’s biannual meeting with its European partner NGOs took place in September in Sitges, Barcelona (Spain) and provided an excellent opportunity to work together on a number of important issues.

European Union

In 2004, IAVI’s work with the European Union (EU) coincided with the EU’s enlargement from 15 to 25 Member States in May, the election of a new European Parliament in June and a new European Commission taking office in November. The first European Constitution was signed by Europe’s heads of state, which envisions an even larger role for the EU in foreign policy, including development, trade and other areas.

G8 Meeting. IAVI and its partners consulted with European government representatives of G8 countries, including France, Germany and the UK, to advocate for inclusion of vaccines in the overall agenda of the G8 summit in June. IAVI also provided input to DFID and other partners on proposals agreed upon at the G8 Summit to establish a Global HIV Vaccine Enterprise.

European Parliament (EP). A newly created European Parliamentary initiative known as the ‘Global Progressive Forum’ (GPF), chaired by Paul Nyrup Rasmussen, former Prime Minister of Denmark, launched an AIDS Campaign in February chaired by Glenys Kinnock, IAVI Board Member and Member of the European Parliament (MEP). A parliamentary declaration for EU Development Ministers on the Millennium Development Goals specifically mentioned the development of vaccines as a crucial element of the global fight against HIV/AIDS. IAVI’s contribution, based on the Dublin declaration, was fully integrated in a sub-chapter entitled “Vaccines as Prevention”.

EP Working Group on Reproductive Health. IAVI met with various MEPs after the elections and participated in a new parliamentarian initiative to expand the existing EP Working Group on Reproductive Health (EPWG) to include a stronger HIV/AIDS commitment as well as MEPs from the New Member States.

IAVI co-hosted a World AIDS Day event in the EP on ‘Women, Girls and HIV/AIDS’ in collaboration with the EPWG, the Stop AIDS Alliance (SAA), the IPM and the GCM. IAVI senior consultant Dr. Florence Manguyu from Kenya was a panel participant and focused her presentation on research into vaccines against HIV/AIDS. Representatives from the European Commission, the European Council, the European Parliament, UNAIDS, embassies of ACP countries and civil society attended the meeting. The Parliament adopted a resolution that same day endorsing the urgent development of vaccines.

ACP-EU Joint Assembly. IAVI participated in a first-ever dialogue with Brussels-based ambassadors from ACP (Africa Caribbean Pacific) countries on integrating HIV/AIDS interventions into their development plans for EDF funds. As a result of the meeting, the Declaration of the 80th Session of the ACP Council of Ministers on World AIDS Day 2004 urged the EU to focus specific research on therapeutic and preventive technologies, such as microbicides and vaccines, that meet the health needs and delivery conditions of developing countries.

European Commission (EC). IAVI staff attended a meeting at the EC with Richard Feacham, Executive Director of the Global Fund, that was organized by DG Development. IAVI also participated in the consultation on the Programme for Action on HIV/AIDS, TB and Malaria, submitted
written comments on the Programme document, and attended a consultation in Brussels on 14 September. IAVI’s contribution to a new HIV/AIDS strategy was highlighted in a presentation by new EU Development Commissioner Louis Michel on World AIDS Day. Commissioner Michel’s presentation underscored the need to invest in the development of an effective and affordable HIV/AIDS vaccine for developing countries as a means to control the disease.

IAVI worked with the EC’s Directorate on Research by contributing to the first online consultation for the upcoming Seventh Framework Programme for R&D. Further contributions to the consultations process included presentations by IAVI staff at the WTO meeting on Priority Medicines and at a meeting of the new Technology Platform on innovative Medicine, both in Brussels. IAVI also participated in a roundtable on the DG research’s new information video on ‘AIDS vaccines and microbicides’.

EU Presidency. The hand over of the EU Presidency from the Irish to the Dutch took place during a June meeting in Dublin (see p. 46).

The Dublin meeting was followed by the first EU Ministerial Conference on HIV/AIDS in the new East European Member States: “Europe and HIV/AIDS: New Challenges New Opportunities” in Vilnius, Lithuania on 16-17 September. The ‘Vilnius declaration’ emphasized investment in the research and development of vaccines, and included the issue in the EU research program. Another outcome of the Vilnius conference was a Working Paper adopted by the Commission: “Coordinated and Integrated Approach to Combat HIV/AIDS in the European Union and in its Neighbourhood”, which also endorsed support for new and effective vaccines.

The Netherlands held the EU Presidency from July to December 2004. One of the key priorities was the preparation of the Seventh Framework for Research. Two objectives were defined: to create a European Research Council and to pursue a project on priority medicines under the auspices of the Ministry of Health and with the involvement of the World Health Organization. The final report, “Priority Medicines for Europe and the World” highlighted the relevance of increased EU investments into areas of shared concern, such as TB and HIV/AIDS, in both Europe and developing countries, and spoke positively about public-private partnerships.

On 18 November, the Dutch Presidency presented the findings of the Priority Report at a high level meeting in The Hague attended by stakeholders from more than 30 countries. The Dutch Minister of Health, Hans Hoogervorst, reiterated the need to invest in AIDS vaccine R&D in order to end the HIV epidemic and included AIDS vaccines in the list of priority areas for the EU.

EU Think Tanks. In September, IAVI became a member of one of the most influential Brussels-based think tanks, the European Policy Centre (EPC). The EPC organized its first public discussion on the HIV/AIDS pandemic, mentioning IAVI and the HIV/AIDS vaccine efforts in the keynote speech of Development Commissioner Poul Nielson. IAVI has been invited by the EPC to join the “Global Governance” steering committee.

Seth Berkley gave a speech at “The Centre”, a Brussels-based think tank, in December. The event also included presentations by Dr. Peter Piot of UNAIDS, Dr. Lieve Fransen, Head of Unit for Human and Social Development at DG Development, and Deo K. Rwabita, the Ugandan Ambassador to the EU. The discussion in Brussels gave rise to a debate about an appropriate EU response to the problem of HIV/AIDS in the developing world.

IAVI also participated in a roundtable organized by UNAIDS and the Heinrich Böll Foundation of Germany to strengthen the ‘Global Coalition on Women and AIDS’ on the eve of World Aids Day.

EDCTP. Following a series of intensive discussions with the secretariat and Board of the European Developing Countries Clinical Trial Partnership, a Memorandum of Understanding was signed between EDCTP and IAVI in March. The MOU provides a general framework for effective collaboration in the field of AIDS vaccine development.

In April, IAVI staff participated in a meeting in The Hague organized by EDCTP together with representatives from WHO, the Adults AIDS Clinical Trials Group, the International AIDS Society, SAAVI, AAVP and the IPM. The discussion focused on defining the role of the EDCTP and reviewing the state of the art in the AIDS vaccine and microbicides fields. A unanimous recommendation was reached that the work of the EDCTP should focus on site development in preparation for future efficacy trials.

World Health Organization. In April, IAVI staff presented the organization’s intellectual property (IP) policy at a workshop in Geneva on Intellectual Property Rights and Vaccines in Developing Countries organized by the WHO. The purpose of the workshop was to review how intellectual property protection affects access to vaccines in developing countries and to discuss possible directions and options for ensuring an appropriate balance between stimulating R&D and enhancing
access to the vaccines most needed in the developing world.

Denmark

In February, Dr. Seth Berkley and IAVI staff visited Denmark to meet the new Under Secretary of State, Ambassador Ole Moesby, as well as the new Head of the UN/World Bank Office, Kirsten Geelan, and other senior staff from DANIDA.

During the early part of the year, IAVI’s Danish NGO partner, AIDS-Fondet, held meetings with representatives from all of the political parties in Denmark to raise the issue of AIDS vaccines. As part of an advocacy initiative, AIDS-Fondet also organized a series of meetings with the development NGO Ibis, DanChurchAid and spokespersons from all parties in the Danish Parliament. The meetings focused on Denmark’s strategy for combating HIV/AIDS, including DANIDA’s HIV/AIDS workplace policy and those of its grant recipients, as well as new prevention technologies.

A concerted advocacy effort by AIDS-Fondet volunteers effectively highlighted HIV/AIDS in the public debate leading up to the European Parliamentary elections in June. Pre-election media reports called for the EU to increase its role in combating the spread of HIV/AIDS. IAVI looks forward to a productive collaboration with among others, the new Danish MEP Poul Nyrup Rasmussen, who shares a commitment to AIDS vaccines.

In 2004, the Royal Danish Ministry of Foreign Affairs concentrated on reviewing its HIV/AIDS strategy and AIDS-Fondet participated in the consultations. The draft of the Ministry’s new strategy will be presented soon. The Government of Denmark also extended its financial support for IAVI through mid-2005.

World AIDS Day provided a major platform for NGO outreach in Denmark and AIDS-Fondet organized activities across the country also involving other groups (especially women) and individuals who heretofore had not had a voice in the HIV/AIDS debate. Vaccines and other NPTs were featured in the press coverage generated by these events.

France

In January, IAVI formalized its partnership with AIDS, the largest HIV NGO in France, by signing a Memorandum of Understanding. Joint activities focus on disseminating the AIDS vaccine message and on building political support within France as well as internationally, including Francophone communities across Western Africa.

In addition to the regular translation and dissemination of the French version of IAVI’s VAX bulletin, an article by Dr. Seth Berkley on the need for AIDS vaccines, was included in the Parliamentary Dossier Primer (“Dossier de l’abécédaire Parlementaire”), published in June. Approximately 10,000 copies of the Dossier were distributed to members of France’s entire political spectrum and among French representatives in the EU. The Dossier also was disseminated among the network of West-African NGOs partnering with AIDES in their “Reseau Afrique 2000” project.

In October, IAVI participated in the National Convention for AIDES and gave a plenary presentation on the need for global mobilization for AIDS vaccines to AIDES directors and managerial cadres representing the group’s 67 branches in France.

During the end-of-year partnership meeting with AIDES in Paris, best approaches were discussed to ensure French support for global AIDS vaccine R&D efforts, with emphasis on future G8 meetings. IAVI had a related meeting with scientific attaché, Mr. Robert Dry, at the US embassy in Paris on 20 December to present IAVI’s work and discuss potential areas for collaboration in France.

IAVI also has strengthened its partnership with Fondation Mérieux, including involving the foundation’s new Director General, Darshna Tanna, in a session planned for the European Foundation Annual Conference in Budapest in mid 2005.

Germany

In January, IAVI and its German advocacy partner, Deutsche AIDS Stiftung (DAS), held a meeting to inform German NGOs about the planned Phase I clinical trials in Hamburg and Bonn of the rAAV vaccine candidate developed by Columbus Children’s Research Institute, Targeted Genetics Corp. and IAVI. In February, IAVI held a press conference in Berlin with DAS at the Robert Koch Institute to announce the start of the Phase I trials at the University of Hamburg. The briefing was well attended by the German media—more than 50 journalists participated—and included presentations by the Principal Investigator Dr. Jan van Lunzen and Professor Reinhard Kurth of the Robert Koch Institute. In April, IAVI presented at a round table with scientific media organized to coincide with the start of the trial at the University of Bonn, with Professor Jurgen Rockstroh as the Principal Investigator. The start of the trials in Hamburg and Bonn generated extensive press coverage throughout Germany and in many other countries. IAVI’s policy and advocacy partner, DAS, contributed €100,000 in sponsorship for the trials. IAVI also attended the Munich AIDS Conference in
November, which included a presentation of the Hamburg trial by Dr. Jan van Luntzen.

With the assistance of Andrea Fischer, former Minister of Health in Germany, IAVI continued its efforts to extend political support for AIDS vaccines. Vaccines were included in a parliamentary resolution submitted by the Green Party, and a meeting with German parliamentarians was organized. Ms. Fischer also built relationships with the German Ministry of Science and Technology and with the senior officials working on the G8.

In 2004, IAVI’s collaboration with DAS was intensified by signing a Letter of Understanding and establishing a common communication plan. DAS included information about IAVI in its recent publications, including “Anthologie 2004” and the “Opera Book” distributed in June at the First DAS Opera Gala in Cologne.

On World AIDS Vaccine Day in May and World AIDS Day in December, DAS and IAVI generated substantial media coverage through joint OpEd articles and interviews on vaccines.

Ireland (see also European Presidency)

In February, Dr. Berkley and IAVI European Director, Dr. Frans van den Boom, met with then-Minister of Development Cooperation Tom Kitt and senior staff of Development Cooperation Ireland (DCI) to provide an update on IAVI’s program and to discuss the Irish EU Presidency. The Irish reaffirmed their commitment to a comprehensive AIDS agenda. While in Ireland, Dr. Berkley also gave interviews for Morning Ireland and The Irish Times, and delivered a lecture for the medical faculty at the University College of Dublin.

Dublin Meeting on New Prevention Technologies. The Governments of Ireland and the Netherlands, both strong advocates for HIV/AIDS and vaccines, sponsored a high-level political meeting in Dublin on 24 June to develop an agenda for the forthcoming Dutch, Luxembourg and UK presidencies of the EU. Hosted by Minister Kitt and Development Cooperation Ireland (DCI) and entitled “New Preventive Technologies: Providing New Options to Help Stop the Spread of HIV/AIDS”, the meeting marked the transition of the EU Presidency from Ireland to the Netherlands, and focused on the need for increased efforts to develop new HIV prevention technologies. Dr. Seth Berkley gave a keynote address on challenges and actions needed to support effective global AIDS vaccine development efforts.

The meeting signaled a new chapter in the EU’s response to HIV/AIDS. Eight action points were identified that define the key commitments of the EU to the accelerated development of vaccines and microbicides. The UK, Luxembourg (holders of the Presidency in 2005) and the European Commission were engaged in planning the meeting with the Dutch and Irish, and key technical and planning support was provided by IAVI and the International Partnership for Microbicides. IAVI also authored background papers focusing on the essential role of R&D and new prevention technologies in comprehensive HIV and AIDS strategies. The conclusions of the meeting were endorsed in several EU Council resolutions in 2004 and IAVI and its partners will be working together closely to follow the outcomes of this historic gathering.

The Netherlands (see also European Presidency)

The Netherlands remains a leading supporter of vaccines as part of its comprehensive HIV/AIDS agenda. The Dutch Government has renewed its 2003 commitment to double its investment in HIV/AIDS by the end of 2006 by increasing its overall HIV/AIDS budget.

In January, IAVI presented an update on the global state of AIDS vaccine research to its Dutch NGO partner, AIDS Fonds—whose support remains instrumental in firmly positioning AIDS vaccines at both the domestic and EU levels—in order to reach the wider AIDS Fonds and STOP AIDS NOW network of staff.

IAVI worked very closely with AIDS Fonds to place AIDS vaccines prominently on the agenda at the National HIV/AIDS and Sexually Transmitted Diseases meeting on World AIDS Day. IAVI’s Dr. Emilio Emini gave a plenary presentation on the challenges and hopes of AIDS vaccine R&D, and IAVI organized a workshop on the ethical aspects of research on new HIV preventive technologies (vaccines, microbicides and pre-exposure chemoprophylaxis).

Dutch-Irish Meeting on New Prevention Technologies. The Governments of Ireland and the Netherlands hosted a June conference in Dublin on New Preventive Technologies against HIV/AIDS (see section above on Ireland for complete details).

Norway

In 2004, the government of Norway extended and increased it financial contribution to IAVI, and is increasingly committed to the global AIDS vaccine effort. Last year, Dr. Seth Berkley and Dr. Frans van den Boom met on several occasions with the Norwegian Minister of International Development, Ms. Hilde Frafjord Johnson, and senior staff to update them on the state of the global effort and IAVI’s program.
In April, Dr. Berkley addressed the AIDS-Forum in Oslo that advises the Norwegian Minister of International Development, and is comprised of representatives from the national army as well as members of civil society institutions such as the HIV/AIDS NGOs and the church. Mr. Lennarth Hjelmåker, Sweden’s HIV/AIDS Ambassador, also addressed the AIDS-Forum.

In April, Dr. Berkley also met with the Secretary General of the Norwegian Red Cross, Mr. Jonas Gahr Større, and the Secretary General of the HIV/AIDS NGO Pluss-LMA, Ms. Laila Stang. In addition, Dr. Berkley attended the annual meeting for Nordic AIDS NGOs together with UNAIDS Executive Director and IAVI Board member Peter Piot. IAVI staff had follow up meetings with The Red Cross and the Ministry of Foreign Affairs in October.

Spain

IAVI and its Spanish NGO partner, Grupo de Trabajo sobre Tratamientos del VIH (gTt), continue to work closely and 2004 marked a year of extremely effective collaboration.

Following the invitation of the Autonomous Basque Government, a full proposal seeking support for site-development at Chennai, India, was submitted to the International Cooperation (IC) office in July. The Minister in charge of International Cooperation for the Basque Government, Mr. Javier Madrazo, as well as IAVI’s primary contact at the IC office, Mr. Igor Irigoyen, expressed satisfaction with the proposal and announced their intention to enter into an agreement of cooperation, or “convenio”, which will be formalized in early 2005. IAVI is working closely with gTt and with Itxarobide, its NGO supporter in the Basque Country, to prepare for a hearing before the Basque Parliament to obtain their formal support for international AIDS vaccine R&D efforts and for IAVI’s work.

Political advocacy efforts at a Central Government level in Spain were renewed following the March 2004 general elections, and individual meetings with MP’s on the International Development Committee were successfully completed in December. An all-parties briefing to the International Development Committee of the Parliament is currently being planned for the first quarter of 2005, as well as a number of high-level meetings with relevant decision makers at the Central Government level.

In cooperation with gTt’s partner organizations, IAVI hosted a workshop in March on New Prevention Technologies for representatives of HIV NGOs in Spain. Initial contacts with representatives from development NGOs took place in early 2004. A follow-up meeting with development NGOs active in Spain has been scheduled for 2005 to discuss AIDS vaccines within the wider context of development work.

Both IAVI and gTt have developed digital and printed vaccine information and education tools in Spanish that are regularly produced and distributed through gTt’s networks in Spain and Latin America. A printed anthology of the VAX bulletin in Spanish was distributed with 15,000 copies of gTt’s magazine as part of a pilot project that may be replicated for other European languages.

Sweden

In February, Dr. Berkley and members of IAVI’s European team visited Sweden to meet with the new Swedish Minister for Development Cooperation, Ms. Carin Jämtin. The IAVI group also met with the HIV/AIDS Ambassador, Lennarth Hjelmåker, senior government staff, SIDA/SAREC staff and IAVI’s Swedish partner organization, Noah’s Arc.

Political support for AIDS vaccines has grown significantly, with Minister Jämtin, the Secretary of State for Development Annika Söder, and the HIV/AIDS Ambassador Lennarth Hjelmåker all expressing their commitment to vaccines. This increased support resulted in a new contribution to IAVI from the Swedish Ministry of Foreign Affairs in addition to the support that has come through SIDA/SAREC.

Noah’s Ark continues to contribute to advocacy efforts by involving IAVI in key meetings within the Swedish Ministry of Foreign Affairs, and through participation in other meetings and conferences that provide a forum for raising awareness of the need for a preventive AIDS vaccine.

Switzerland

In March and April, IAVI’s European team held a number of successful meetings with The Swiss Tropical Institute (STI) in Basel. The initial meeting with Professor Marcel Tanner, Director of the STI, and Christian Burri, Deputy Head of the Swiss Centre for International Health, confirmed the shared vision of the two organizations regarding the HIV/AIDS crisis in the developing world. STI offered its support in expanding awareness of the importance of advancing preventive AIDS vaccine R&D in Switzerland. A representative of the Swiss Development Cooperation agency also attended the IAVI donor briefing in Bangkok in July.

United Kingdom

UK Department for International Development (DFID). In 2004, IAVI contributed to several
consultations and one-on-one meetings with DFID staff on UK strategies on HIV/AIDS, research and access to medicines.

The UK Strategy on HIV and AIDS in Developing Countries calls for investment in ‘Long-Term’ solutions, including HIV vaccine R&D. Dr. Seth Berkley attended the launch of the strategy at Number 10 Downing Street, hosted by the Prime Minister. The Central Research Strategy confirms DFID’s support for investment in new health technologies that meet the needs of the poor, identifies HIV vaccines among DFID research priorities and recognizes PPPs as an effective approach to accelerating product development. In “Increasing Access to Essential Medicines in the Developing World: UK Government Policy and Plans”, DFID identifies the need to support R&D for diseases that affect the poor through a range of policy interventions, including more coordinated support for PPPs and incentives for industry. DFID's support for IAVI is noted positively in each of these three strategy and policy papers.

In March, IAVI staff attended a workshop hosted by DFID on strategies to enhance knowledge sharing and information access in an effort to accelerate R&D for diseases of poverty.

Dr. Berkley met in June with officials from DFID’s Central Research Department, and IAVI staff provided briefings to DFID on proposals to establish a Global HIV Vaccine Enterprise that were agreed upon at the Sea Island G8 Summit. The UK is supportive of moves to increase global AIDS vaccine efforts and to develop more effective international collaboration.

UK Treasury. Dr. Berkley and other IAVI staff met with UK Treasury officials from the Global Poverty Reduction Team in April to discuss UK plans for the establishment of an International Finance Facility for Immunization (IFFIm) (see p. 39).

UK NGO Outreach. In February, IAVI’s Public Policy staff and Regional Representative in East Africa, Dr. Sam Kalibala, participated in the quarterly meeting of the UK NGO Consortium on HIV/AIDS and Development. At the meeting, IAVI presented on the need for HIV vaccines and the central role of developing countries in the R&D process. The Consortium brings together over 60 UK-based NGOs working on HIV and development issues.

IAVI staff presented on opportunities for joint advocacy on treatment, microbicides and vaccine issues at a day-long training on microbicides organized by the National AIDS Trust and the Global Campaign for Microbicides in London in September. IAVI also made presentations on HIV vaccine development and the related social science agenda at the Seventh Annual CHAPS Conference on HIV prevention for gay men in Liverpool, UK, and on the need for HIV vaccines at a national conference on HIV prevention for African communities living in the UK organized by the African HIV Policy Network and supported by the UK Department of Health.

IAVI and its UK NGO partner the National AIDS Trust (NAT) finalized a Memorandum of Understanding in June. NAT continues to champion the issue of AIDS vaccines in the UK and is leading discussions to increase community participation in the design and conduct of AIDS vaccine trials in the UK. NAT also supports the training of Helpline volunteers from the Terrence Higgins Trust to enable them to provide information about participating in AIDS vaccine trials.

All-Party Parliamentary Group on AIDS. In June, Dr. Berkley attended a Parliamentary lunch organized by the NAT, and also presented at a special meeting on vaccines of the All-Party Parliamentary Group on AIDS. Kapil Sibal, Indian Minister of State for Science and Technology, joined Dr. Berkley for these meetings acting in his capacity as an IAVI board member. In a follow up to this meeting, IAVI staff presented on AIDS vaccine development and the role of the UK in global AIDS vaccine efforts at a meeting of Parliamentary researchers.

IAVI Report Publications

Overview. Together, the redesigned IAVI Report newsletter and the monthly VAX bulletin represent the only media uniquely focused on global efforts to develop an AIDS vaccine. The IAVI Report continues to provide comprehensive coverage of the field from research, policy, advocacy and community perspectives, while VAX, available in a range of languages and formats, is geared to a wider, non-technical audience.

Both publications provide news and analysis, while adding context and highlighting trends and gaps in the search for a vaccine. Available in print and online in digital format, the IAVI Report and the VAX bulletin reach over 8,500 subscribers in 140 countries, with thousands of additional readers accessing the online editions. With a global readership, the VAX bulletin is now regularly translated into French, German, Spanish and Portuguese and can be downloaded as a PDF file from the iavireport.org website.

With the launch of the iavireport.org website in May, the Report team has expanded access to its information products and has begun to fill the need
for a one-stop information hub on AIDS vaccine research. The website serves as the publishing hub for all IAVI Report products, with Early Edition articles attracting over 21,000 “hits” per month—roughly 96% of which are repeat visits. The site provides scientists and non-scientists alike with current and relevant information on the challenges facing the field.

The IAVI Report Newsletter. The IAVI Report continues to deliver in-depth analysis of advances and ongoing challenges in virology, immunology and vaccinology while expanding its scope of coverage to closely related fields and issues.

With the May-August issue, the IAVI Report team debuted a new graphic design. The layout is modeled on leading scientific journals and original illustrations are used to easily convey complex scientific concepts.

Interviews, cross-disciplinary reporting, reviews of recent literature in the field and commissioned articles from leading scientists provide the research community a forum for debate and dialogue with a wide range of perspectives. The new “Research Briefs” feature offers readers a synthesis of recently published journal articles of particular importance to the field.

The Report continues to give voice to leaders in the field, including an interview with Dr. Susan Allen, a prominent investigator of the HIV epidemic in Africa and a pioneer in the study of HIV transmission between couples, and articles by eminent researchers, such as Dr. Mauro Schechter (“Treatment in Vaccine Trials and AIDS in Brazil”) and Dr. David Ho (“Addressing AIDS in China”).

VAX Conference Anthology. The growing interest in VAX confirms the demand for information about AIDS vaccines. With print and distribution centers now established in Brazil and eastern and southern Africa, VAX has emerged as an important vaccine-literacy tool. The Special Issue: 2003 Year in Review featured a global map of all AIDS vaccine trials begun in 2003, including trial information and types of vaccines. Demand for the map has been tremendous; it is in its third printing since publication in January 2004. A second Special Issue, completed for the XV International AIDS Conference in Bangkok, included an article on AIDS vaccine research in Asia and the Pacific region plus all of the AIDS vaccine-related presentations, workshops and posters from the Conference.

Multilingual VAX Anthologies. VAX includes non-technical, “primer” articles that are particularly popular. These articles focus on topics relevant to AIDS vaccines and allow lay individuals to broaden their understanding and become familiar with scientific concepts. Consequently, special VAX publications were designed and distributed for the XV International AIDS Conference in Bangkok. A special issue in English and Thai was distributed to Conference attendees as a guide to HIV vaccine-related presentations. The issue also included an article entitled “AIDS in Asia” that provided regional context. An anthology of the popular Primers from VAX also were produced in English, French and Thai for the Conference.

In addition to its value as a communication tool, VAX has become a vehicle for strengthening global partnerships. IAVI’s Brazilian partner, GIV (Grupo de Incentivo à Vida), now prints the Portuguese edition of VAX and distributes over 2,500 copies to its network of NGOs as well as to the Brazilian Ministry of Health, whose website directs visitors to VAX. Similarly, IAVI’s European team has used the French, German and Spanish editions of VAX to enhance its work with NGO partners (AIDES in France, Deutsche AIDS Stiftung in Germany, and gTt in Spain). The NGO gTt recently created a Spanish anthology of VAX articles and Primers as a supplement to their quarterly treatment magazine Lo+Positivo. With a circulation of over 15,000, VAX—and the message of AIDS vaccines linked to treatment issues—is reaching new audiences throughout Spain and Latin and South America.

IAVI Report Online. The IAVI Report Online (www.iavireport.org) is a central source of information on all aspects of AIDS vaccine research and associated scientific disciplines—from basic science such as molecular virology to more applied fields like HIV prevention research.

Updated daily with highlights of HIV/AIDS news from around the world, plus the latest published research related to AIDS vaccine development, IAVI Report Online is a one-stop resource for HIV researchers, advocates, policy makers, and others with an interest in the progress towards a preventive AIDS vaccine.

All of the current and archived articles from the print editions of the IAVI Report and VAX are available online. The site also incorporates a new Early Edition feature that publishes IAVI Report articles directly to the web as soon as they are available, in advance of print publication.

Visitors to the website can subscribe to any of the IAVI Report products in a variety of electronic and print formats, all free of charge. The cost savings of providing these publications in digital formats is considerable, with the added benefit of improved speed and accuracy of delivery. This also has allowed the publication and distribution of more printed copies in regions of the world where computer/internet access is limited or absent.
Database of AIDS Vaccines in Human Trials.

Created and updated by the IAVI Report staff, the Human Trials database is the most comprehensive and inclusive source of trials information available (www.iavi.org/trials). A searchable research tool on AIDS vaccine clinical trials, the database also functions as a unique and important living archive of AIDS vaccine candidates tested in people.

Since its initial publication in September 2003, the Clinical Trials Watch poster—a time-stamped snapshot of all ongoing trials derived from the database—has significantly raised awareness of the database in the scientific community; it is now often cited in conference presentations on AIDS vaccines as the best source of this information. This poster, which is regularly updated and available as a PDF, is the most frequently visited item on the IAVI website, with more than 6,000 copies downloaded in 2004.

Communications Activities

In 2004, IAVI’s Communications efforts continued to promote global awareness of AIDS vaccine R&D.

New Leadership. Ellena Friedman joined IAVI as Vice President for Communications in September. Ellena brings to IAVI more than 16 years of experience in the fields of strategic communications, public policy and advocacy. She has broad knowledge of the pharmaceutical and biotechnology industries, and was most recently at Centocor, a subsidiary of Johnson & Johnson, where she served as Director of Strategic Alliances. She also served as Director of Communications at Bayer Pharmaceuticals. Ellena also has held senior positions at leading international public relations agencies, including Edelman Public Relations Worldwide, where she served as Senior Vice President and Group Head, and Hill and Knowlton. As Vice President at Hill & Knowlton representing a range of global health clients, she helped establish one of the first client groups dedicated to HIV/AIDS and helped create some of the first programs on HIV/AIDS pain management and nutrition. She also spent several years working on pricing and efficacy of drugs to treat HIV and built alliances between industry and community groups.

Events and Conferences. On World AIDS Vaccine Day, 18 May, IAVI released a press statement and background paper on the state of AIDS vaccine R&D. IAVI’s website also featured a special section with resources including materials from IAVI’s partner organizations. Media outreach resulted in coverage in several European countries and the US. In Finland, Professor Kai Krohn, Senior Vice President of Finnish Biotech (FIT), and IAVI’s European Director, Dr. Frans van den Boom, co-authored an article on AIDS vaccines in a leading Finnish daily newspaper Helsingin Sanomat. In Spain, IAVI’s partner NGO gTt collaborated on the publication of an OpEd on AIDS vaccines in the leading Spanish paper El Pais. Coverage also appeared in Germany’s leading newspaper the Frankfurter Rundschau, on the AIDS website and newsletter (France), on the websites of AIDS Fonds (Netherlands) SENSOA (Belgium) and gTt (Spain), and in the French language newspaper La Libre Belgique (Belgium), among others.

At the International AIDS Conference XV in Bangkok, IAVI’s communications effort focused on advancing the case that although the vaccine field is making progress, it needs smarter ways of working to overcome the significant challenges that remain. IAVI released Scientific Blueprint 2004: Accelerating Global Efforts in AIDS Vaccine Development, a scientific paper assessing progress and challenges in vaccine R&D (see p. 3). IAVI also published an eight-page version of the Blueprint’s executive summary. More than 300 copies of the Blueprint and more than 1,000 copies of the executive summary were distributed at Bangkok. They continue to be distributed and are a popular download on IAVI’s web site.

IAVI held a press conference with Seth Berkley, Wayne Koff and Helene Gayle of the Bill & Melinda Gates Foundation. More than 70 journalists attended and a dozen global news outlets covered the event, among them Agence France-Press, BusinessWeek, CNN, The Miami Herald, The Nation (Kenya), The New Scientist, The New Vision (Uganda), Reuters and USA Today. Dr. Seth Berkley also met in Bangkok with 20 editorial board members from major US newspapers to brief them on the need for a vaccine and answer questions. The Minneapolis Star-Tribune, published a positive editorial, echoing the themes of the Blueprint.

In September, IAVI and its research collaborators presented interim data from small-scale clinical trials of the DNA.HIVA and MVA.HIVA vaccine candidates (see p. 6) at the AIDS Vaccine 2004 conference in Lausanne, Switzerland. IAVI’s Communications team worked closely with global partners to put the data in context with other developments in the field. Given that many of the trials were conducted in Africa and the University of Nairobi was a co-developer of the candidates, IAVI worked to develop messages that were specific to Kenya, Uganda and South Africa, highlighting IAVI’s commitment to continue work in these countries. Articles appeared in The New Scientist, Science and The Wall Street Journal, reporting that although the results were disappointing, the field learned from testing these candidates, and other approaches are in development. Seth Berkley
and Wayne Koff also were quoted in a Financial Times update on the vaccine field, in which they again stressed that progress is being made but significant challenges remain.

Following the Lausanne conference, IAVI held a press briefing at the Palais des Nations in Geneva for reporters who regularly cover world health and development, but rarely cover vaccines. The briefing was well attended by journalists from western and eastern Europe, India and Russia. Seth Berkley and Wayne Koff spoke on vaccines and answered questions for 90 minutes.

The theme for World AIDS Day for 2004 was Women and AIDS. IAVI took part in two major World AIDS Day activities in Europe: the National Conference on HIV/AIDS and STDs hosted by Aids Fonds in Amsterdam, and a panel discussion at the European Parliament in Brussels. To commemorate this year’s focus on women, IAVI published a paper entitled, “Gender in AIDS vaccine trials: Addressing challenges in developing countries”. The paper was disseminated to partners and other organizations around the world. The Voice of America interviewed IAVI staff on women and AIDS vaccines, and Seth Berkley was interviewed on the Canadian Broadcast Corporation’s radio program, Dispatches, on the global vaccine effort. Frans Van Den Boom was quoted in an article in the Frankfurter Rundschau (Germany). In addition, an OpEd entitled, “The search for a vaccine and the female face of AIDS,” was placed in three European publications: El Correo Vasco (Spain), Het Financiele Dagblad (Netherlands), and Svenska Dagbladet (Sweden). The OpEd was also posted on the EU web site, www.euractiv.com, and on the web site of IAVI’s partner organization, AIDS, in French and English.

A special section of the redesigned IAVI web site was created for World AIDS Day. The section featured a series of profiles of women at the forefront of prevention efforts and materials related to the new UN statistics on the epidemic. IAVI created links to websites of other organizations, including: AIDS-Fondet, AVAC, Deutsche AIDS-Stiftung, Finnish AIDS Council, Gender-AIDS discussion List & Forum, Global Health Council, KAVI, National AIDS Trust, UNAIDS, UNFPA, UNIFEM, and the World AIDS Campaign.

Media Coverage

In February, IAVI held a press conference in Berlin to announce the start of a Phase I clinical trial of the rAAV vaccine candidate at the University of Hamburg. In April, IAVI presented at a round table with scientific media to coincide with the launch of the second trial at the University of Bonn (see p. 45 for details).

Scientific publications also featured articles about IAVI’s R&D programs. In early March, the journal Nature Immunology published an article authored by members of the IAVI Neutralizing Antibody Consortium (NAC), describing the NAC’s applied research consortium model as a means of solving the multiple scientific challenges posed by the neutralizing antibody problem. IAVI Senior VPs Emilio Emini and Wayne Koff co-authored a paper that appeared in the 25 June 2004 issue of Science magazine. The paper, “Developing an AIDS vaccine: Science, Uncertainty, Hope” outlines the scientific challenges in AIDS vaccine R&D.

In June, the EU hosted a meeting in Dublin on new prevention technologies (see p. 46). Seth Berkley and Zeda Rosenberg of the International Partnership for Microbicides published a joint OpEd in The Irish Examiner, calling for the European Union to increase funding for the development of a vaccine and microbicides and to enact incentives for private industry to increase investment.

In September, The New York Review of Books published an article written by Dr. Richard Horton, editor of The Lancet medical journal, raising questions about the feasibility of developing an effective AIDS vaccine. IAVI’s Wayne Koff and three other leading vaccine researchers—Dennis Burton of The Scripps Research Institute, Ronald Desrosiers of Harvard Medical School and Philip Johnson of Columbus Children’s Research Institute—wrote a detailed response that appeared in The Lancet’s Nov. 27 issue. The authors wrote, “Given the magnitude of the health crisis faced, a major push in the areas suggested by encouraging observations is surely worthwhile.”

In late October, Seth Berkley was quoted in the Financial Times on talks being held in France among European scientists seeking to play a greater role in vaccine R&D. Dr. Berkley encouraged increased involvement from Europe, emphasizing “we must prioritize the best science in the world, regardless of where it originates.”

In its year-end “Breakthrough of the Year” issue, Science Magazine named IAVI as the forerunner in the formation of public-private partnerships (PPPs) related to health. According to Science, such “healthy partnerships” are “shifting the way medicines are developed and delivered to the world’s poorest people.” The epidemiologist, Roy Widdus, who founded the Initiative for Public-Private Partnerships for Health, credits the start of the PPP movement to the creation of IAVI in 1996. According to Widdus, there are about 20 PPPs that “follow IAVI’s lead to develop new preventives and treatments” for diseases such as HIV/AIDS, malaria and tuberculosis. He also cited partnerships that
aim to improve access to existing medicines such as the Global Fund.

IAVI Website. In November, IAVI launched a redesigned version of its web site, www.iavi.org. The new site features an updated look and feel and a database-driven platform for its underlying structure. This new structure improves the site’s capability to serve multiple audiences and contributors. The new site also adds automated news feeds from the IAVI Report and the Kaiser Network, and sends periodic email updates for subscribers. In 2004, traffic on the web site remained steady, averaging around 3,500 unique visitors per day. The most popular areas of the site include the Call for Action and Vaccine Science sections. The site had nearly a 60 percent increase in traffic on 1 December, World AIDS Day.

Workshops for Journalists. IAVI’s Communications team continued its efforts to inform journalists in developing countries about the science of AIDS vaccine R&D, in order to promote accurate coverage in the communities hosting vaccine trials. In March, IAVI sponsored a workshop for 13 journalists in Kigali, Rwanda, where IAVI expects to conduct trials in the future. The workshop included presentations from IAVI researchers on AIDS vaccine trials and offered reporters an opportunity to write and critique sample stories. Building on the success of the workshop, the agenda, presentations and reporter surveys are being used to create standard protocols for additional events.

IAVI sponsored seven developing country journalists to attend the International AIDS Conference in Bangkok as media fellows. The fellows were selected through a competitive application process and included four reporters from Kenya, one from Uganda, one from South Africa and one from India. The seven IAVI media fellows produced more than 35 AIDS-related articles, radio broadcasts and short films covering a range of topics based on their experiences at the conference. IAVI presented on the state of the vaccine effort at two media workshops, one for 30 journalists mostly from Africa and sponsored by the Kaiser Family Foundation, and the second for 20 journalists mostly from Asia and sponsored by SciDev.net.

Resource Development

This year marks a turning point in the scope and level of IAVI’s scientific and policy work, creating new requirements for IAVI’s revenue strategy. Since its inception in 1996, IAVI has expanded rapidly to build its organizational infrastructure, fund and manage a portfolio of promising vaccine candidates, and extend the global reach of its policy and advocacy efforts. IAVI’s operating expenses grew at a compound annual rate of 108% for the period 1996 to 2002. In 2004, IAVI’s annual operating expenses exceeded US $65 million, compared to less than a quarter of a million dollars in its founding year.

IAVI’s new Strategic Plan calls for a significantly expanded applied R&D agenda to answer key scientific questions and to accelerate new and more promising vaccine candidates toward large-scale efficacy trials with IAVI itself taking on a larger R&D role. Total operating expenses from 1996 through 2009 are expected to reach nearly US $654 million. With more than US $380 million in total committed revenue, which includes the US $100 million grant from the Bill & Melinda Gates Foundation, the organization must raise more than US $270 million in new and renewed commitments to ensure IAVI’s ability to achieve its goals.

In this next phase of vaccine development, a significant level of unrestricted resources is needed for IAVI to move rapidly on new fronts as new data become available. In 2004 IAVI launched plans for a new, diversified revenue strategy necessary to support a flexible approach to vaccine R&D. This strategy is designed to generate revenue from a range of private sources in order to expand the private sector donor base. IAVI’s Board of Directors will assist in private sector fundraising efforts through its newly formed Resource Mobilization Committee, which will help to sustain IAVI’s ambitious fundraising goals.

IAVI will continue to rely heavily on expanded multi-year public sector support through overseas development assistance funds from donor governments and multilateral agencies. IAVI’s financial and in-kind supporters include the Bill & Melinda Gates, Rockefeller, Alfred P. Sloan and Starr foundations; the governments of Canada, Denmark, the European Union, Ireland, the Netherlands, Norway, Sweden, the United Kingdom and the United States; multilateral organizations including The World Bank; corporations such as BD (Becton, Dickinson & Co.), Continental Airlines and DHL; leading AIDS charities such as Crusaid, Deutsche AIDS Stiftung, and the Until There’s A Cure Foundation; and other private donors such as the Phoebe W. Haas Charitable Trust B.

Public Sector Support

European Union. In January, IAVI received the first installment of a three-year matching grant of €3 million (US $3.9 million) from the European Commission’s Directorate General for Development. This funding, which represents the European Union’s first commitment to IAVI, is made through IAVI’s European foundation, Stichting
IAVI, in Amsterdam. The EU grant is supporting *Partnerships for Preparedness: Building local capacity and ownership in the development of AIDS vaccines*, a program to assist IAVI and its East African partner organizations in building local clinical and social research capacity in preparation for AIDS vaccine trials in Kenya, Uganda and Rwanda.

**World Bank.** In June, IAVI received US $700,000 in renewed funding from the World Bank through the Global Forum for Health Research for general support of IAVI’s vaccine R&D and related activities. In December, the Bank announced that it would increase its support to $1 million in 2005.

**Basque Autonomous Government of Spain.** In 2004, IAVI submitted its first proposal to the Basque government. Funds administered through the Basque International Cooperation office will support IAVI’s clinical trial site in Chennai, India. IAVI also submitted a complementary request for funding for a public awareness campaign on AIDS vaccines in the Basque Country. A decision on the proposals is expected in early 2005.

**Canada.** In 2004, IAVI concluded year two of its 3-year grant of CAD $45 million (US $32.9 million) from the Canada Fund for Africa of the Canadian International Development Agency (CIDA).

**Denmark.** In July, Denmark reconfirmed its commitment to IAVI by awarding DKK 10 million (US $1.5 million) in support through mid-2005. Funds are administered through the Danish International Development Agency (DANIDA).

**Norway.** The Norwegian government made an increased commitment to IAVI of NOK 15 million (US $2.4 million) for 2005. This continues a trend of incremental annual increases from the Norwegian Ministry of Foreign Affairs, from an initial grant of NOK 10 million in 2001.

**Sweden.** IAVI submitted a proposal to the Swedish International Development Cooperation Agency (SIDA)/Department of Research Cooperation (SAREC) for renewal of multi-year funding for 2005-2007. In December, IAVI received a contribution of SEK 4 million (US $594,000) from the Swedish Ministry of Foreign Affairs for 2005, which represents IAVI’s first funding from the Ministry.

**United Kingdom.** The UK Department for International Development (DFID) extended its funding for IAVI with a contribution of GBP 4 million (US $7.7 million) for 2004-2005.

**United States.** The United States Congress voted to provide IAVI with US $27 million for the 2005 fiscal year, which began on 1 October 2004. An across-the-board “rescission” of .8% for discretionary spending reduced the award to US $26.8 million.

**Donor Visits.** IAVI hosted visits from the Canadian International Development Agency in April and USAID in October. These visits allowed representatives of two of IAVI’s largest government donors to engage in dialogues with program staff directly involved in project implementation and to gain a better understanding of IAVI’s work.

**Private Support**

**Becton, Dickinson and Company (BD).** IAVI continued its expansive partnership with BD, a leading medical technology company that has been in business since 1897. BD’s corporate contributions include direct financial support (2004 represented year three of a five-year US $1 million grant for AIDS vaccine clinical trials), in-kind donations, preferential pricing on equipment, and opportunities for IAVI to beta test novel technologies used in vaccine clinical trials.

**Deutshe AIDS Stiftung (DAS).** In March, IAVI’s German NGO partner organization announced it would contribute €100,000 (US $129,500) toward sponsorship of IAVI’s AIDS vaccine trial of the rAAV candidate in Bonn.

**DHL.** IAVI’s partnership with DHL, the world’s leading express delivery and logistics company, expanded significantly in 2004. DHL’s in-kind support includes free international shipping of printed materials and non-perishable supplies from IAVI’s Core Lab in London to more than a dozen field laboratories. DHL also provided free shipping of IAVI materials from New York to the XV International AIDS Conference in Bangkok.

**Rockefeller Foundation.** In October, The Rockefeller Foundation announced a two-year grant of US $500,000. The announcement came nearly 10 years to the day that the Rockefeller Foundation co-convened the historic Paris meeting of an international scientific committee that helped lay the groundwork for IAVI’s creation. Renewed support from one of IAVI’s founding donors sends a strong signal to the philanthropic community regarding the importance and urgency of IAVI’s mission.
Until There’s A Cure (UTAC). IAVI was pleased to receive a renewed commitment from another of its founding donors, the Until There’s A Cure Foundation (UTAC), of US $40,000 for 2005.

European Foundation Centre (EFC). In May, IAVI staff attended the annual EFC conference in Athens, which brought increased attention to AIDS vaccines and HIV/AIDS. In addition, IAVI organized a pre-conference briefing chaired by Peter Laugharn of the Bernard Van Leer Foundation that was well attended by European foundations interested in biomedical research, Sub-Saharan Africa and HIV/AIDS.

Reports to Donors. Staff completed work on IAVI’s 2003 Annual Progress Report in March and the 2004 Mid-Year Progress Report in October. Copies of these reports were mailed to more than 120 representatives at IAVI’s donor agencies and hundreds of additional copies were distributed to members of the IAVI team worldwide. In late April and early May, staff completed work preparing and submitting 2003 Annual Grant Financial Reports to IAVI’s donor agencies. Copies of IAVI’s 2003 Audited Financial Statements were sent to donors shortly thereafter.

Bangkok Donor Meeting. IAVI held a donor meeting in Bangkok prior to the official opening of the XV International AIDS Conference. There were more than 55 attendees including donor representatives, NGO partners and staff. The purpose of the briefing was to update donors and others in the international community on IAVI’s R&D, clinical trials, policy and access agendas, and to provide an opportunity for dialogue about key issues and challenges that affect IAVI’s work. The meeting also featured brief presentations and updates from India, Uganda, and Kenya.

Governance, Operations and Finance


IAVI typically operates on a three-year timetable for strategic planning supplemented by annual operational and budget planning. However, given the organization’s dramatic growth and the significant changes in the external environment, IAVI began the process for 2005-2007 a year early.

Working with an experienced strategy consultant specializing in the health care sector, IAVI began the strategic planning process in the fall of 2003 with a careful analysis of its portfolio. This involved a rigorous examination and prioritization of IAVI’s operations and strategic opportunities. This stage of the work concluded with scenario planning and outputs that were discussed with the IAVI Board at its November 2003 meeting.

The next phase involved IAVI staff throughout the organization as well as gaining advice and counsel from key external stakeholders. This process began with a two-day retreat of IAVI senior managers and advisors drafting an outline of the organization’s goals and strategies, and culminated with a group of the senior management team being appointed to serve as the Core Group for carrying the entire process forward. To ensure an interdisciplinary approach, IAVI established teams with representatives from all of its units, including the New York office and its international field offices.

Three teams were established—Research & Development, Access and Business & Operations—and led by staff rather than senior management. This staff-driven model was augmented by periodic input from content leaders and stakeholders, with a final high-level meeting with external advisors prior to review by IAVI’s Board of Directors.

The plan was presented to the Board at their June meeting and was approved with some important changes incorporated later. This document became the basis for a preliminary synopsis that was developed and released at the International AIDS Conference in Bangkok, as well as a longer document used for operational planning and other purposes. The final version of the plan was published in late 2004 and includes a brief history of IAVI, an analysis of the current state of the vaccine research field, and a discussion of how IAVI plans to expand its already ambitious efforts to find a vaccine. The plan also includes specific indicators to better measure the actions needed to help IAVI reach its goal.

Board of Directors

IAVI’s Board of Directors is comprised of leading authorities in public health, biotechnology, business, international development and public policy. Its members are drawn from both the public and private sectors worldwide including Asia, Africa, Europe and North and South America.

Charged with providing fiduciary and operational oversight as well as overall strategic guidance for the organization, the Board meets three times a year. Board members are elected for an initial term of three years, and may be re-elected for a total of three times at the expiration of each term. In 2004, Angela Gómez de Mogollón, President of Profamilia in Columbia, joined IAVI’s Board and four members—Geeta Rao Gupta, Malegapuru William Makgoba, Philip Russell and Sir Richard Sykes—completed their terms.
Last year, IAVI’s Board of Directors met in January, June and November. At the January meeting, the Board approved the FY 2004 operating plan and budget and new committee structures and charters. This meeting also served as the annual meeting of the IAVI Stichting, the organization’s Foundation in Europe.

The Board’s annual meeting took place in East Africa in June and included a tour of the Kenya AIDS Vaccine Initiative (KAVI) facility, a visit to the IAVI-sponsored KAVI site in Kangemi, and briefings with a number of political leaders in Kenya and Uganda. At this meeting, the board approved IAVI’s new 2005-2007 strategic plan.

At its November meeting, the Board approved the organization’s budget for FY2005, previewed initial strategic priorities for the Public Policy program, and held an in-depth discussion of governance issues within the context of the organization’s history, rapid growth and evolving R&D agenda.

Committees of the Board

The Board Committees were very active in 2004.

The Nominating Committee continued to review and interview prospective candidates for Board membership. With the completion of four Board member’s terms in 2004, the Nominating Committee is busy working to identify potential candidates to nominate for Board membership.

The Resource Mobilization Committee (RMC), which was formed in 2004, is charged with approving, assisting and monitoring the performance of the organization’s resource mobilization strategy. The first meeting of the RMC was held in June. Planning is now underway to ramp up Board efforts to help sustain IAVI’s ambitious fundraising goals.

The Compensation Committee commissioned a Compensation Study in 2004, the findings of which were fully implemented across the organization. The Compensation Committee also approved the FY2005 Organizational Objectives.

The activities of the Audit & Finance Committee are noted in the Operations and Finance section below.

Operations and Finance

Annual Financial Audit. Ernst & Young, LLP completed the FY2003 annual audit of IAVI in March 2004 and the process yielded no material findings. IAVI received a clean audit opinion that the organization’s financial statements fairly present the organization’s financial position. Ernst & Young also completed the 2003 A-133 audit of IAVI (required for recipients of US government funds) to ensure that proper financial control is exercised over such funds. The A-133 audit yielded no material findings and resulted in a clean audit opinion.

Risk Management. In 2004, IAVI continued moving forward on an organization-wide discussion of risk management, with focus on the manufacturing and clinical areas within R&D. Thus far this process has resulted in operational improvements, increased clinical trial liability coverage, and a process for creating an organization-wide communications crisis management plan.

Investment Strategy. At the request of the CFO and the Treasurer, the Board and the Audit & Finance Committee approved the hiring of CRA Rogers Casey, an investment advisory firm, to provide additional due diligence over management of the organization’s assets. The firm has been engaged for one year and the continuation of the relationship will be evaluated on the basis of earnings enhancement, and the value to management in the ongoing monitoring of the portfolio and the managers of our portfolio. By the end of 2004, CRA Rogers Casey had performed an initial due diligence review of IAVI’s portfolio managers and investment strategy, and affirmed management’s decision-making on investment strategy and selection of portfolio managers.

New York Headquarters. In February 2004, IAVI hired an Internal Auditor/Controller of Field Operations to increase the organization’s level of internal oversight and to assist in expanding financial expertise and capacity across field offices and projects around the globe. In addition, work is underway to automate IAVI’s grants and contracts management process using a secure software program that, when fully implemented, will allow staff to draft, authorize, budget, pay and analyze grants and contracts electronically.

Global Field Office Operations

European Office. In 2004, the organization leased additional space in Amsterdam to house the growing operations of IAVI’s European office. Since January, the European Program has increased its staff capacity considerably, including a European Liaison Officer and Assistant working in Brussels to raise awareness and build support for IAVI’s program within the EU, and to monitor and prepare for ongoing changes related to the European elections and EU expansion. Capacity also was increased with the addition of two new staff in Finance and Administration.
East Africa Regional Office. A full-time Finance Manager was hired in January to facilitate financial and administrative operations for the East Africa Regional Office. In March, an in-country Clinical Program Manager was hired to assist in the development and monitoring of clinical sites and trials. Additionally, IAVI’s Host Country Agreement with Kenya has moved a step further and is currently awaiting presentation to the Cabinet by the Minister of Health.

IAVI-India Office. In April, a new Finance Manager was hired for IAVI’s India Office. Both internal and external audits of IAVI’s India operations were successfully completed. In addition, the IAVI-India Office completed registration under the Companies Act of India in May 2004 and is working towards changing its status to a branch office from the current liaison office designation.

Institutional Support. In 2004, staff continued efforts to strengthen overall capacity to oversee and manage compliance with IAVI’s major government donors, including the US Agency for International Development (USAID). A consultant was engaged to conduct an on-site training in New York in March to review cost principles related to US government grants. IAVI continues to enhance capacity in this area and in September hired an International Grants Manager with specialized experience in managing US government grants.

Information Technology. Throughout 2004, IAVI’s Information Technology (IT) department performed a number of maintenance and update functions in the NY headquarters, including installing an internal conference call manager to give the organization increased flexibility and cost efficiencies in conducting teleconferences, and adding an additional T1 line to provide backup Internet connectivity.

The IT department’s submission to the 15th International AIDS Conference in Bangkok, Thailand, in July was accepted for poster presentation. Entitled “Implementing an Information Technology (IT) Infrastructure for HIV Vaccine Clinical Trials in Resource-Constrained Settings”, the abstract outlined IAVI’s IT solutions and infrastructure development work in supporting clinical trials in developing countries.

IAVI’s IT department also was awarded an Honorable Mention in the prestigious Cisco Systems Growing with Technology 2004 competition for computer network development work in the developing world.

Human Resources (HR)
In 2004, IAVI enhanced efforts to recruit positions across the organization. Human Resources added one new full-time staff position to support global recruiting and employee relations.

In 2004, IAVI’s hires totaled 41 new staff, which included replacements, additions and reconfigurations of existing positions. In addition to direct sourcing of candidates through the use of a research firm, recruiting via the Internet was increased. Work is underway to increase use of IAVI’s Website as a resource to attract external candidates and promote internal career development.

As part of international HR activities, work on employment manuals for the field was completed in the third quarter and these were provided to staff in India and Kenya. The Global HR Generalist traveled to IAVI’s field offices during the fourth quarter to provide on-site follow up regarding several employment matters as well as to communicate IAVI’s Performance Management Program to field staff.

HR has been working to improve the policies and practices associated with relocating staff. IAVI’s Expatriate Policy is under review using a benchmark organization renowned in the field, and the selection of a new Relocation Services provider is in its final stages.

The work on IAVI’s Compensation Program was completed and information sessions were held with all IAVI departments to ensure understanding of the program. The Board reviewed and approved recommendations for merit and bonus awards based upon IAVI’s organizational performance and financial position.

Finally, in the fourth quarter HR launched the first module of its Learning and Development series to promote professional and personal growth. The first module was introduced through “lunch and learn” sessions and focused on interviewing techniques and the selection of candidates.

International Scientific Meetings
During 2004, IAVI hosted or participated in a variety of international scientific meetings on AIDS and AIDS vaccines; these included:

- NIAID Workshop on Selection of Standard Panel of Isolates for Neutralization Assays (6 January, Durham, NC, US); workshop held at Duke University to design an appropriate panel of HIV-1 isolates that will be used to assess the potency
and breadth of neutralizing antibodies generated by candidate HIV vaccines in preclinical and clinical trials.

- Global HIV Vaccine Enterprise "Laboratory Standardization: Cellular Subgroup" (10 January, Washington, DC, US).
- Global HIV Vaccine Enterprise "Vaccine Discovery" (19 January, Washington, DC).
- "Clinical Trials Capacity" (22 January, Seattle, WA, US); organized by the Global HIV Vaccine Enterprise.
- WHO-UNAIDS Consultation on "Progress in the development and evaluation of HIV-1 preventive vaccines and related regulatory issues" (2-3 February, Geneva, Switzerland); review of the current state of development of HIV vaccines, clinical trials, regulatory processes, and assay standardization.
- WHO-UNAIDS Vaccine Advisory Committee (3-4 February, Geneva, Switzerland).
- Global HIV Vaccine Enterprise "Regulatory Subcommittee" (5 February, Geneva, Switzerland); identification of and potential ways of addressing the challenges facing regulatory agencies in the development of HIV vaccines.
- European Medicines Evaluation Agency "Gene Therapy Experts" (26-27 February, London, UK); meeting to review data on gene therapy vectors and their safety considerations, whether used for therapy or vaccines.
- European & Developing Countries Clinical Trials Partnership (EDCTP) Partners Meeting (2 April, The Hague, the Netherlands); meeting to discuss the EDCTP's first call for proposals regarding efficacy trial site preparation for vaccines (for AIDS, tuberculosis and malaria) and microbicides.
- Keystone Symposia on "HIV Vaccine Development: Progress and Prospects (X8)" (12-18 April, Whistler, BC, Canada).
- NIH/FDA meeting on "HIV Vaccine clinical trial endpoints" (26-27 April, Rockville, MD, US), discussion of efficacy endpoints for Phase III clinical trials of HIV vaccines.
- Harvard AIDS Think Tank (29 April - 1 May, Gaborone, Botswana).
- NIH meeting on "Vaccine Cell Substrates" (29 June - 1 July, Rockville MD, US); review of the latest developments for testing, characterization and regulatory requirements for cell substrates used for the manufacture of vaccines.
- HIV-1 Vaccine Consensus Meeting (22 July, Lusaka, Zambia).
- Launch of the EDCTP Secretariat (26-27 July, Cape Town, South Africa); held at the Medical Research Council of South Africa. The meeting brought together key African and European leaders delivering keynote addresses on HIV/AIDS, tuberculosis and malaria vaccines and disease management.
- WHO-UNAIDS Consultation on "Gender, Age and Race Factors in HIV Vaccine-related Research and Clinical Trials" (26-28 August, Lausanne, Switzerland); review and discussion of the challenges in conducting vaccine trials in women, adolescents and different ethnic groups.
- AIDS Vaccine 2004 Conference (30 August - 1 September, Lausanne, Switzerland).
- Modern Vaccine Adjuvant Formulation 2004 (15-17 September, Prague, Czech Republic).
- 1st Annual EDCTP Forum (27-29 September, Rome, Italy); hosted by Istituto Superiore di Sanità, this was the first annual gathering of scientists, international organizations and policymakers from Africa and Europe to share information and views on how best to address the challenges of controlling HIV/AIDS, tuberculosis and malaria in Africa.
- “State of HIV-1 Vaccine Development” Workshop (30 September, Johannesburg, South Africa); organized by AfricaBio, a South African biotechnology group.
- HIV Vaccine Trials Network (HVTN) Full Group Meeting (13-15 October, Seattle, WA, US); biannual meeting of all HVTN investigators and site staff in which groups update each other on activities, invited speakers update on the latest developments and training sessions are held.
- Vaccine Research Center Scientific Training Retreat (18-19 October, Richmond, VA, US); sponsored through NIAID and NIH.
- Institute of Tropical Medicine Colloquium "European Science & Training for the Promotion of Health in Developing Countries: Networking
the Networks” (24-26 November, Antwerp, Belgium); meeting to exchange views with a number of European and international networks.

▪ “Promoting R&D in Preventive Health Technologies: Opportunities for the Indian Pharmaceutical and Biotechnology Sector” (3 December, New Delhi, India); workshop highlighted the market opportunities for the India biopharmaceutical industry in AIDS vaccine research and development and addressed some of the challenges that have traditionally constrained companies from participating more aggressively in R&D activities.
BOARD OF DIRECTORS

The Board of Directors is the governing body of IAVI and is responsible for overseeing the organization and its management. This year, four members completed their two terms and extensions: Geeta Rao Gupta, Malegapuru William Makgoba, Philip Russell and Sir Richard Sykes. The Board also welcomed one new member: Angela Gómez de Mogollón, President of Profamilia in Columbia.

▪ Seth Berkley, MD, President and Chief Executive Officer, IAVI
▪ Awa Marie Coll-Seck, Executive Secretary, Roll Back Malaria Partnership, WHO, Geneva; Former Director, Policy, Strategy and Research, UNAIDS
▪ Ciro de Quadros, MD, MPH, Director, International Programs, Sabin Vaccine Institute; Former Director, Vaccines and Immunization, Pan American Health Organization
▪ John D. Evans, Treasurer, Chairman & CEO, Evans Telecommunications Co. and The John D. Evans Foundation
▪ Angela Gómez de Mogollón, President, Profamilia, Columbia
▪ Michel Greco, Former President, COO and Deputy CEO, Aventis Pasteur
▪ Ian Gust, MD, Secretary, Ex-officio, Chair, IAVI Scientific Advisory Committee, Professor and Professional Fellow, Department of Microbiology & Immunology, The University of Melbourne; Former Director of R&D, CSL Ltd.
▪ Glenys Kinnock, Member of European Parliament, Wales
▪ Chrispus Kiyonga, MD, Minister without Portfolio, Uganda; Former Chair of the Global Fund to Fight AIDS, Tuberculosis, and Malaria; Former Minister of Health, Uganda
▪ Paul Klingenstein, General Partner, Aberdare Ventures
▪ Geoffrey Lamb, Board Chair, Vice President for Concessional Finance and Global Partnerships, The World Bank
▪ Peter Piot, MD, PhD, Ex-officio, Executive Director, Joint United Nations Programme on HIV/AIDS
▪ Kapil Sibal, JD, Member of Parliament, India; Minister of Science & Technology and Ocean Development, Council for Science and Industrial Research
▪ Lee Smith, Founding Board Chair, Former President, Levi Strauss International; Former Chair, US National Leadership Coalition on AIDS

MEMBERS EMERITUS

▪ Michèle Barzach, MD, Former Minister of Health, France
▪ R. Gordon Douglas, Jr., MD, Director, Strategic Planning, Dale and Betty Bumpers Vaccine Research Center, US National Institutes of Health; Former President, Merck Vaccines, Merck and Co., Inc.
▪ Richard G. A. Feachem, PhD, DSc (Med), Executive Director, Global Fund to Fight AIDS, Tuberculosis, and Malaria; Founding Director, Institute for Global Health, University of California
▪ Jaap Goudsmit, MD, PhD, Executive Vice President, Research & Development, Chief Scientific Officer, Crucell NV; Co-Founder, European Vaccine Effort Against HIV/AIDS
▪ Geeta Rao Gupta, PhD, President, International Center for Research on Women
▪ Malegapuru William Makgoba, MBShB, DPhil, FRCP, FRSSAf, MASSAf, Interim Vice-Chancellor, University of KwaZulu-Natal; Former President, Medical Research Council, South Africa
▪ Jacques-François Martin, President, Vaccine Fund; Former Chief Executive Officer, Pasteur-Mérieux
▪ Philip K. Russell, MD, Special Advisor, Vaccine Development and Production, US Department of Health and Human Services; Professor, International Health, Johns Hopkins University
▪ Sir Richard Sykes, Dsc, FRS, Rector, Imperial College of Science, Technology, and Medicine; Former Chairperson and Chief Executive Officer, GlaxoSmithKline plc
▪ Shudo Yamazaki, MD, PhD, Director-General Emeritus, National Institute of Infectious Diseases, Japan
An internationally recognized Scientific Advisory Committee (SAC) meets annually to review the state-of-the-art in AIDS vaccine development and to advise IAVI on new initiatives under consideration. Subcommittees of the SAC meet quarterly, or as needed, to provide additional advice regarding the state-of-the-art in AIDS vaccine research, project management, and the conduct of clinical trials of AIDS vaccines in the developing world.

- John G. Curd, MD, President & Chief Medical Officer, Novacea, Inc.
- Michel De Wilde, PhD, Executive Vice President, Research and Development, Sanofi Pasteur
- Ian Gust, MD, Chair, Professor, Microbiology and Immunology, University of Melbourne; Former Director of R&D, CSL Ltd.
- Joep Lange, PhD, Professor, Universiteit van Amsterdam
- Antonio Lanzavecchia, MD, Director, Institute for Research in Biomedicine, Switzerland
- Rosemary Mubanga Musonda, Acting Director General, Zambia National AIDS Council
- Helen Rees, MBBCh, Executive Director, Reproductive Health Research Unit, Chris Hani Baragwanath Hospital
- Douglas Richman, MD, University of California San Diego Department of Pathology & Medicine
- Philip Russell, MD, Acting Director of the Office of Research & Development Coordination, Department of Health and Human Services
- Jerald C. Sadoff, MD, President & CEO, AERAS Global Tuberculosis Foundation; Former Clinical Director for Vaccine Development, Merck and Co. Inc.
- Mauro Schechter, MD, PhD, Professor, Infectious Diseases, Federal University of Rio de Janeiro
- Bruce Walker, MD, Director, AIDS Research Center, Massachusetts General Hospital
- Carolyn Williamson, PhD, Professor, University of Cape Town

**Vaccine Research & Design Subcommittee**
- Rafi Ahmed, Emory University
- Dennis Burton, *Ex-officio*, Scripps Research Institute
- Ronald Desrosiers, *Ex-officio*, Harvard Medical School
- Kim J. Hasenkrug, NIAID, NIH
- Shiu Lok Hu, University of Washington
- Philip Johnson, *Ex-officio*, Chair, Columbus Children’s Hospital
- Marie-Paul Kieny, *Ex-officio*, WHO/IVR
- Antonio Lanzavecchia, Institute for Research in Biomedicine, Switzerland
- Kelly MacDonald, University of Toronto
- Doug Nixon, Gladstone Institute of Virology and Immunology
- Douglas Richman, University of California, San Diego
- Quentin Sattentau, University of Oxford
- Bruce Walker, Massachusetts General Hospital
- David Watkins, University of Wisconsin Medical School
- Lindsey Whitton, Scripps Research Institute
- Carolyn Williamson, University of Cape Town

**Project Management Subcommittee**
- John Curd, Novacea
- Marie-Paule Kieny, Chair, WHO/IVR
- Jack Melling, Consultant
- John Petricciani, CancerVax Corp.
- Stanley Plotkin, Aventis Pasteur
- Vijay Samant, Vical Inc.
- Michel De Wilde, Sanofi Pasteur
- Jerry Sadoff, AERAS Global Tuberculosis Foundation

**Clinical Trials Subcommittee**
- Donald S. Burke, Johns Hopkins University
- Beryl Koblin, New York Blood Center
- Ira Longini, Emory University School of Public Health
- Helen Rees, Chair, University of the Witwatersrand
- Wasima Rida, Statistics Collaborative, Inc.
- Mauro Schechter, Federal University of Rio de Janeiro
- Haynes W. Sheppard, California Department of Health Services
- Hilton Whittle, MRC Laboratories
- James Whitworth, The London School of Hygiene & Tropical Medicine
- Lalit Kant, Indian Council of Medical Research
- Mohan D. Gupte, National Institute of Epidemiology (Indian Council of Medical Research), Chennai
IAVI established a Policy Advisory Committee in 2002 to serve as a sounding board on key issues and to assist the policy team in setting priorities, reviewing policy research proposals, and expanding IAVI’s network in the field. The committee is comprised of experts from a range of related fields, including public health, vaccine research and development, and international governance. The current members of the committee and observers are listed below.

- **David Kihumuro Apuuli, MD**
  Director-General, Uganda AIDS Commission

- **Amie Batson, MPPM**
  Senior Health Specialist, World Bank and Co-chair of Global Alliance for Vaccines & Immunization Financing Task Force

- **Donald S. Burke, MD**
  Director, Center for Immunization Research, Department of International Health, Johns Hopkins University School of Hygiene & Public Health

- **Ciro de Quadros, MD, MPH**
  Member, IAVI Board of Directors; Director of International Programs, Albert B. Sabin Vaccine Institute

- **R. Gordon Douglas Jr., MD**
  Member Emeritus, IAVI Board of Directors; Director, Strategic Planning, Dale & Betty Bumpers Vaccine Research Center, US National Institutes of Health; Former President, Merck Vaccines, Merck and Co. Inc.

- **Christopher J. Elias, MD, MPH**
  President, PATH

- **Jose Esparza, MD, PhD**
  Senior Advisor, HIV Vaccines, The Bill & Melinda Gates Foundation

- **David L. Heymann, MD (Observer)**
  Executive Director, Communicable Diseases, World Health Organization

- **Purnima Mane, MA, MPhil, PhD**
  Director, Social Mobilization & Information Department, UNAIDS

- **Jean-Marie Okwo-Bele, MD, MPH**
  Director, Immunizations, Vaccines and Biologicals, World Health Organization

- **Bernard Pécoul, MD, MPH**
  Executive Director, Drugs for Neglected Diseases Initiative

- **Seung-il Shin, PhD**
  Senior Advisor, International Development, VaxGen Inc.

- **Jean Stéphenne**
  President & General Manager, GlaxoSmithKline Biologicals

- **Joseph Stiglitz, PhD**
  Professor of Economics & Finance, Columbia University; former Chief Economist, The World Bank

- **Mark Wainberg, PhD**
  Director, McGill University AIDS Centre

- **Mitchell Warren (Observer)**
  Executive Director, AIDS Vaccine Advocacy Coalition
AAV adeno-associated virus.

Adjuvant A substance sometimes included in a vaccine formulation to enhance or modify its ability to stimulate immune responses.

Animal model In research, the use of animals to mimic a human disease or condition in order to evaluate safety and potential efficacy of an experimental vaccine or treatment.

Antibody An infection-fighting protein in the blood or secretory fluids that recognizes, neutralizes, and helps destroy disease-causing microorganisms, or toxins as part of an immune response to antigens or foreign bodies. Antibodies are made and secreted by B lymphocytes in response to stimulation by antigens. Generally, each antibody binds only to the specific antigen that stimulated its production. Antibodies are coordinated by helper T cells. See neutralizing antibody.

Antigen Any substance that is recognized by a component of the immune system. Antigens are often agents such as invading bacteria or viruses.

Assay Determination of the amount of a particular constituent of a mixture, or determination of the biological or pharmacological potency of a drug.

Attenuated Weakened.

Biodistribution The extent to which a substance is distributed throughout tissues and organs.

Boost / Booster A second or subsequent vaccine dose given after the prime dose, to increase immune responses. A booster vaccine may or may not be the same as the primary one.

Canarypox A virus that infects birds and is being used as a vector to carry HIV genes into human cells in several HIV vaccines now in clinical trials. Canarypox virus cannot grow in human cells, an important safety feature.

Capsid Protein coating.

CBO Community-based organization.

CD4+ See Helper T cell.

CD8+ See CTL.

Cell line Human cells that have been adapted to grow continuously in culture without dying out.

Cell-mediated immunity (cellular immunity) An immune response that targets host cells infected with microorganisms such as viruses, fungi, and certain bacteria. It is coordinated by CTLs and helper T cells.

CFC (cytokine flow cytometry) Assay An assay that identifies responding cells through their ability to produce certain proteins known as cytokines, which form part of the immune response.

Challenge In vaccine experiments, the deliberate exposure of an immunized animal to the infectious agent. Challenge experiments are never done in human HIV vaccine research.

Clade A group of related HIV isolates classified by their degree of genetic similarity. There are two major groups of HIV-1 isolates, called M and O. Group M consists of at least eight clades, A through H.

Clinical trial A human trial.

Combination vaccine A vaccine consisting of multiple constructs. A prime-boost vaccine is a combination vaccine.

Construct Design of a vaccine.

Controlled trial In a controlled vaccine trial, a control group receiving a placebo is compared with one or more groups of volunteers given experimental vaccines.

Correlates of immunity (correlates of protection) The specific immune responses that correlate with protection from a certain infection. The precise correlates of immunity for HIV are unknown.

Crystallography Crystallography is an experimental technique that exploits the fact that X-rays are diffracted by crystals. Based on the diffraction pattern obtained from X-ray scattering off the repeated array of molecules or atoms in a crystal, a fairly accurate molecular structure of the crystal can be obtained. The study of crystallized structures and their formation aids rational vaccine design by allowing researchers to elucidate and mimic the interaction between neutralizing antibodies and HIV envelope.

CTL (cytotoxic T lymphocyte, killer CD8+ cell) A component of cell-mediated immunity that destroys host cells infected with viruses, fungi, or certain bacteria. CTLs carry the CD8+ surface marker and are thought to play an important role in immunity to HIV, but this is still unproven.

Cytokine A group of soluble, hormone-like proteins produced by white blood cells and that act as messengers between cells. Cytokines can stimulate or inhibit the activity of immune cells and may prove useful as immunologic adjuvants.

Cytotoxicity The destruction of specific target cells by activated effector cells such as CD8+ “killer” T-cells.

Degranulation The process by which granules contained within a cell are expelled. This is one method by which CD8+ T-cells kill virally infected cells—once expelled the granules are toxic to nearby cells.

Delivery system See vector.
DNA (deoxyribonucleic acid) The genetic material of all living things, except for RNA-carrying viruses, such as HIV. DNA is a double-stranded, helical molecular chain found within each cell. It contains the information needed for cells to produce proteins, molecules that enable cells to reproduce and carry out their functions.

DNA vaccine (naked DNA vaccine) An experimental vaccine technology in which one or more genes coding for specific antigen(s) are directly injected into the body, where they hopefully produce antigen(s) in the recipient and trigger immune responses.

Dose-escalation study A dose escalation study is conducted in stages separated by temporary intervals; volunteers are enrolled first for the lowest dosage group (or arm), then for the mid-dosage group(s), and finally for the highest dose group when it has been established that each of the lower dose(s) is safe and well tolerated.

Efficacy In clinical vaccine research, the ability of a vaccine to protect vaccinated subjects against a specific infection or disease. A vaccine may be tested for efficacy in Phase III trials if Phase I and Phase II trials show it to be safe and promising. Efficacy is distinct from immunogenicity.

ELISPOT (Enzyme-Linked Immuno-Sorbent spot) A blood test that detects antibodies and is often used to test whether a person is infected with HIV.

gp120 The glycoprotein on the outer surface of the HIV envelope; gp120 binds to the CD4+ molecule on helper T cells during infection. It has been studied as an experimental HIV vaccine because the outer envelope is the first part of the virus “seen” by antibodies. See gp41.

gp41 A protein embedded in the outer envelope of HIV that anchors gp120. gp41 plays a key role in HIV’s entry into helper T cells by facilitating the fusion of the viral and cell membranes.

Helper T cell (helper CD4+ cell) T lymphocyte bearing the CD4+ cell surface marker. Helper T cells are the chief regulatory cells of the immune system, controlling activities such as coordinating cell-mediated immunity and turning antibody production on and off. They are the main targets of HIV infection.

Heterologous Different. Used with reference to either a different strain of HIV, for example in an animal experiment where following vaccination with one strain of virus there is challenge with a different, or heterologous, strain. Alternatively, may be used in the context of a different viral vector boost, for example the priming vaccination might be AAV and a heterologous boosting vaccination of MVA.

HIV (Human Immunodeficiency Virus) The etiologic agent that causes AIDS.

HIVA An AIDS vaccine under investigation by IAVI that consists of the gag gene of HIV subtype A, p24, p17 and a series of mini-genes representing the CTL epitopes from env-gag-pol-nef. HIVA is intended to be combined with RENTA.

Homologous Identical. For HIV, the same strain of the virus, or the same vector to boost the priming vaccination, e.g. a homologous boost would be a prime with MVA followed by a boost with MVA.
Immune response The body’s reaction to foreign antigens. This response may neutralize or eliminate the antigens. See cell-mediated immunity, mucosal immunity, neutralizing antibody.

Immunogen A substance capable of provoking an immune response.

Immunogenicity The extent to which an immunogen stimulates immune responses. Immunogenicity is distinct from efficacy.

Inactivated Altered to prevent harmful biologic activity.

IND Investigative New Drug regulatory application required by the US FDA.

Informed consent An agreement signed by all volunteers participating in a clinical trial, indicating their understanding of: (1) why the research is being done; (2) what researchers hope to learn; (3) what will be done during the trial, and for how long; (4) what risks are involved; (5) what, if any, benefits can be expected from the trial; (6) what other interventions are available; and (7) the participant’s right to leave the trial at any time.

Isolate A particular strain of HIV from a person (primary isolate) or cultured cell line (laboratory isolate).

Lymphocyte A type of white blood cell.

Monoclonal antibodies A collection of identical antibodies that recognizes the same single epitope.

Mucosal immunity Immune response conferring resistance to infection across the body’s mucous membranes. Mucosal immunity depends on antibodies and other immune components present in the linings of the reproductive and gastrointestinal tracts and other moist body surfaces exposed to the outside world, the most frequent routes of HIV infection.

Multigenic Containing more than one gene.

MVA Modified Vaccinia virus Ankara, under consideration as a vector.

 nef A gene present in HIV that is not required for but regulates viral reproduction, now being studied as a component of an HIV vaccine.

Neutralizing antibody An antibody that prevents virus from infecting a cell, usually by blocking viral entry points on the virus.

NGO Non-governmental organization.

OECD Organization for Economic Cooperation and Development.

p17, p24, p7, and p6 Proteins that form HIV’s core. See Gag.

Phase I vaccine trial A clinical trial with a small number of healthy volunteers, typically at low risk for HIV infection. Phase I trials test a vaccine’s safety in humans, including its metabolic and pharmacologic actions and any side effects seen with increasing doses. Phase I trials may gather data on the vaccine’s immunogenicity.

Phase I double blind, randomized, placebo controlled, dose escalation trial A safety trial that includes an investigational product and a placebo arm. In a double blind trial, neither the researchers/trial staff nor the participants will know who has been given the placebo or the vaccine until the end of the trial. The schedule includes an escalation in the product dose over a predefined time period and the higher doses will be administered only after the safety and tolerability of the lower doses has been established.

Phase I/II vaccine trial A preliminary safety and immunogenicity clinical trial that is larger than a Phase I trial.

Phase II vaccine trial Controlled clinical trial to identify common short-term side effects and risks associated with the test vaccine and to collect information on its immunogenicity. Phase II trials can include up to several hundred participants.

Phase III vaccine trial Large controlled clinical trial to determine the ability of a vaccine, at an optimally selected dose and schedule, to provide efficacy. These trials also gather additional information about safety needed to evaluate the overall benefit-risk relationship of the vaccine. Phase III trials usually include several hundred to several thousand volunteers.

Placebo An inactive substance given to some participants in a controlled clinical trial, while others receive the test substance. Placebos provide a basis for comparison.

Plasmid Circular DNA molecules that multiply independent of the host chromosome and transmit desired genetic information through cell divisions. See DNA vaccine.

 pol An HIV gene that codes for reverse transcriptase and other molecules that the virus uses to replicate. pol is under consideration as a component of an HIV vaccine.

Potentiate Increase the effect of or act synergistically with.

Preclinical In vaccine research and development, the stages before clinical trials.

Prime-boost (priming) Giving one vaccine dose to induce certain immune responses, to be followed by or together with a second type of vaccine, a booster. A prime-boost combination may induce different types of immune responses and/or enhance overall responses beyond those seen with only one type of vaccine.
Process development The optimization of the processes for manufacturing a vaccine.

Protocol The detailed plan for a clinical trial, outlining its rationale, purpose, methodologies, and other aspects of trial design.

QA Quality assurance.

QC Quality control.

R&D Research and development.

rAAV Recombinant Adeno-Associated Virus, under consideration as a vector.

Randomized Describes a clinical trial in which human subjects are assigned by chance (as in a lottery) to separate groups that compare different treatments.

Reagent A substance used to produce a chemical reaction so as to detect, measure, or produce other substances.

Recombinant A cell or an individual with a new combination of genes not found together in either parents; usually applied to linked genes. See genetic engineering.

RENTA An AIDS vaccine under investigation by IAVI that consists of genes expressing inactivated HIV clade A tat and nef, the reverse transcriptase gene, and the two most immunogenic regions of env. RENTA is intended to be combined with HIVA.

Replicon A unit of DNA that contains an initiation point and a termination point and is capable of self-replication. See DNA vaccine.

rev An HIV gene that helps regulate the virus’ life cycle, now being studied as a component of an HIV vaccine.

Reverse transcriptase A retroviral enzyme that is capable of copying RNA into DNA, an essential step in the life cycle of HIV. See pol.

RNA (ribonucleic acid) A single-stranded molecule composed of chemical building blocks similar to those of DNA. RNA is the sole genetic material of retroviruses, including HIV, and an intermediary in making proteins in all living things.

Salmonella typhii A genetically engineered, harmless derivative bacteria that can live in the human gut, under consideration as a vector.

Second-generation AIDS vaccine candidate AIDS vaccine candidate now in preclinical development; distinct from first-generation candidate.

SFV Semliki Forest Virus, under consideration as a vector.

Serotype A group of closely related microorganisms distinguished by a characteristic set of antigens. Each serotype is characterized by the induction of a different specific antibody response.

Shigella A genus of gram-negative, facultatively anaerobic, rod-shaped bacteria of the family Enterobacteriaceae, under consideration as a vector.

Simian Immunodeficiency Virus (SIV) An HIV-like virus that infects monkeys and causes an AIDS-like disease in some species.

Strain See clade, isolate.

Subtype See clade.

tat An HIV gene that helps regulate the virus’ life cycle, now being studied as a component of an HIV vaccine.

T-cell One of two main types of white blood cells critical to the immune system. They include CD4+ and CD8+ T-cells. The “T” stands for the thymus, where T-lymphocytes mature. (See lymphocyte.)

Vaccinia A cowpox virus, formerly used in human smallpox vaccines and now as a vector in some experimental HIV vaccines. See MVA.

Vaccinia gene expression vector system Vaccinia gene expression vectors are constructed by inserting foreign genes such as HIV into the vaccinia virus. Vaccinia is a “pox”-type virus related to the one used in the smallpox vaccine. When given to humans as a vaccine, it is safe and cannot cause illness, but it helps the body to develop immunity to smallpox. Recombinant vaccinia vectors enter cells and allow the foreign proteins to be generated inside the cells; these proteins are then presented to the immune system in the same way that proteins from a virus-infected cell would be.

VDP IAVI AIDS Vaccine Development Partnership.

Vector A bacterium or virus that does not cause disease in humans and is used in genetically engineered vaccines to transport antigen-encoding genes into the body to induce an immune response.

VEE Venezuelan Equine Encephalitis, under consideration as a vector.

Viral load The level of HIV circulating in the bloodstream. Viral load is inversely correlated with HIV disease progression.
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