International AIDS Vaccine Initiative

2005 Annual Progress Report

Imagine a world without AIDS

IAVI 2005 Annual Progress Report

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Executive Summary

As the AIDS epidemic expands — with the number of new infections and AIDS deaths rising from year to year — the urgent importance of developing a preventive vaccine becomes increasingly apparent. Without major progress in the fight against AIDS, the world has little hope of achieving the sharp reductions in poverty and global health inequities envisioned in the United Nations Millennium Declaration. To reverse the epidemic, immediate efforts to scale up available prevention and treatment tools must be coupled with a robust, sustained, longer-term effort to expedite the development and introduction of an AIDS vaccine for use throughout the world.

IAVI is a global leader in the search for an AIDS vaccine. In 2005, IAVI embarked on a three-year strategic plan to focus unprecedented efforts toward overcoming the key scientific, economic and policy obstacles to progress in AIDS vaccine development. While an AIDS vaccine will not be developed overnight, strategies exist to shorten the time to the vaccine era. In this regard, 2005 was a year of important advances in the field.

Strengthening Research and Development

The centerpiece of IAVI's strategic plan for 2005-2007 is a major expansion of the organization's R&D program. The strategic plan aims to widen the product pipeline with new candidates that improve on previous generations, capitalize on IAVI's catalytic, gap-filling role to obtain answers to critical questions that impede progress in the field, and strengthen clinical trial infrastructure to expedite trials for the most promising vaccine candidates.

Key IAVI achievements in 2005 include the following:

Advancing Candidate Vaccines. In less than a decade, IAVI has expanded the global pipeline by developing six candidate vaccines for testing in human trials. In 2005, IAVI initiated the first human clinical vaccine trial in India and conducted clinical research on multiple candidates in Africa, Asia and North America.

Engaging Private Industry. IAVI entered into an agreement with Crucell, a Dutch biotechnology firm, for exclusive access to the company's intellectual property regarding use of two promising replication-defective adenovirus types as potential HIV vaccine vectors. IAVI also entered into its first formal collaboration with a major vaccine company, announcing an agreement with GlaxoSmithKline Biologicals (GSK Biologicals) to develop and evaluate replication-defective chimpanzee adenovirus vectors as human vaccines for HIV.

Addressing Key Scientific Obstacles. IAVI is spearheading targeted global research efforts to design immunogens that elicit broadly neutralizing antibodies, commissioning some of the world's leading researchers to undertake strategic, carefully framed research projects to advance knowledge in the field. Similarly, the IAVI-convened Live Attenuated Consortium seeks to elucidate the mechanism for the robust protection conferred by live attenuated SIV, and to translate these insights into the design of superior HIV vaccine candidates.

Building IAVI Vaccine Development Capacity. In 2005, IAVI took major steps to establish its first vaccine development laboratory, occupying temporary space in New York City with an eye toward securing permanent space in a new biotech hub being developed by New York City and State. An independent review of IAVI's core laboratory in London found that the facility had surpassed all objectives and had added value to and helped galvanize the entire field. The IAVI lab in Uganda received Good Clinical Laboratory Practices accreditation in 2005. In a move that will benefit the entire clinical research field, IAVI is implementing an independent protocol at each of its trial sites in Africa to establish normal ranges for clinical safety lab tests.

Expanding Clinical Trial Capacity in Developing Countries. IAVI has established clinical and laboratory infrastructure for trial planning at two sites in Kenya, two sites in Uganda, and one site each in Rwanda, South Africa and Zambia. With special funding provided by the U.S. Agency for International Development, IAVI took steps in 2005 and in collaboration with the National Institutes of Health to provide grants to qualified European and developing country scientists to support AIDS vaccine development.

Promoting Global Collaboration. IAVI is a co-founder and active participant in the Global HIV Vaccine Enterprise, a multi-partner alliance designed to accelerate HIV vaccine development through enhanced strategic collaboration among key stakeholders. As part of the implementation of the strategic scientific plan of the Vaccine Enterprise, IAVI was successful in four of five letters of intent for research funding from the Bill & Melinda Gates Foundation, which is expected to make awards in 2006.

Increasing Global Commitment

The strategic plan for 2005-2007 calls for IAVI to implement a global advocacy initiative that will strengthen, expand and maintain strong political commitment to AIDS vaccines. As the most concrete reflection of political commitment, the strategic plan aims for a 50% increase by 2007 in global spending on AIDS vaccine R&D (over 2004 levels, the last year for which data are available). To enable IAVI to uphold its leadership role in support of the field, the strategic plan calls for the organization to establish itself as the leading international organization on AIDS vaccine science, policy and advocacy.

Key IAVI achievements in 2005 include the following:

Global Advocacy. At the high-level UN General Assembly meeting on June 2, 2005, IAVI co-sponsored with the International Partnership for Microbicides a meeting on new prevention technologies, addressed by Secretary General Kofi Annan and attended by senior political leaders from 14 countries. IAVI worked in partnership with other prevention advocates to obtain vaccine-supportive commitments in the report of the UN World Summit on the Millennium Development Goals and in the new UNAIDS prevention strategy.

Developing Country Leadership. IAVI helped facilitate the groundbreaking India-Brazil-South Africa trilateral collaborative, which seeks to increase cooperation between the three countries and has identified AIDS vaccines as a priority issue. With support from IAVI, senior political leadership in India, Kenya and Uganda continued

to prioritize vaccine R&D in their national AIDS responses, with Kenya releasing its first national guidelines for vaccine R&D.

Financing Vaccine R&D. IAVI and other health-oriented public-private partnerships devoted considerable advocacy toward influencing the July 2006 summit of the Group of 8 leading industrialized countries. The Gleneagles communiqué reiterated the strong support of the G8 for vaccine development and embraced exploration of an advance purchase mechanism to spur increased private sector R&D and ensure access to a future vaccine.

Promoting Sound Public Policies

The strategic plan recognizes that policy reform is needed to accelerate AIDS vaccine R&D and to ensure future access. To enable IAVI to lead global efforts to implement sound, vaccine-supportive policies, the strategic plan provides for IAVI's development of a strong evidence base for its advocacy positions, the highest-quality policy analysis, and strong advocacy partnerships.

Key IAVI achievements in 2005 include the following:

Quantifying the Resource Gap. IAVI collaborated with partners in strengthening methodology for monitoring spending for AIDS vaccine R&D. The finding that total 2004 expenditures on AIDS vaccine R&D ($682 million) were roughly half of amounts needed was cited or discussed in leading global forums.

Modeling Impact of an AIDS Vaccine. Modeling by the Futures Group, commissioned by IAVI, found that a vaccine with only modest efficacy and coverage could still avert 45 million infections over 15 years and reduce the rate of new infections by one-third.

Demand for an AIDS Vaccine. An analysis by IAVI found strong evidence of broad public sector willingness to purchase and use an AIDS vaccine, as well as substantial household willingness to purchase a vaccine out of pocket in high-prevalence countries such as Uganda and Thailand.

Encouraging Private Sector Engagement. Sharing its findings with the UK government prior to the G8 summit, IAVI and its research partners concluded following extensive analysis that an advance purchase commitment for vaccines would be technically feasible, credible, and attractive as an incentive to industry, trial sponsors and developing countries. Advocacy by IAVI and a coalition of global health advocates helped ensure inclusion of infectious diseases in new legislation in the U.S. Congress to encourage the development of new vaccines against bioterrorism threats.

Forging Partnerships in Developing Countries

Since its inception, IAVI has pursued its work as a global organization, with active partners in both developed and developing countries. IAVI's vaccine development partnerships have involved researchers and stakeholders from both developed and developing countries, and the organization's country programs educate communities, engage political leaders, and raise public awareness of vaccine-related issues. The strategic plan for 2005-2007 provides that IAVI will build on these achievements to enhance the capacity of developing countries to serve as full partners in the global search for a safe and effective vaccine.

Key IAVI achievements in 2005 include the following:

National Preparedness. IAVI provided assistance to China in preparing for future vaccine trials, including hosting a vaccine preparedness workshop in January 2005 and providing a grant to the Chinese Academy of Medicine to undertake vaccine preparedness activities.

Site Preparedness. IAVI completed physical infrastructure development at its five African field sites to support studies to ascertain infection prevalence and incidence, identify and characterize the genetics of the virus responsible for incident infections, and assess the ability of sites to recruit and retain study cohorts. IAVI also undertook a variety of activities to address such issues as access to voluntary counseling and testing, quality of counseling in trial sites, and the informed consent process for trial participants.

Community Engagement. In 2005, IAVI published the AIDS Vaccine Literacy Core Content, the first component of a tool kit for educating stakeholders on AIDS vaccine issues. IAVI also supported the formation of new Community Advisory Boards (CABs) in India and Kenya, as well as a network of CABs in Uganda, and collaborated with the South Africa AIDS Vaccine Initiative in conducting a workshop on community mobilization at the national AIDS conference.

Improving Organizational Policies and Practices

Having evolved from a tiny organization with a handful of staff into a global organization working in 23 countries, IAVI aims to adhere to state-of-the-art organizational practices to maximize productivity, enhance accountability, and ensure optimal value for IAVI's stakeholders. In particular, IAVI in 2005 implemented policies and practices to promote transparency in governance through the development of clear performance criteria to be used in monitoring and evaluating IAVI departments and units. IAVI's new systems and procedures seek to strike an appropriate balance sound management and responsiveness to donor requirements with the need to remain flexible and take informed risk.

In addition to its advocacy on behalf of the field, IAVI also redoubled its efforts in 2005 to mobilize sufficient resources for its own work. In 2005, IAVI was encouraged by the significantly increased financial support from its multilateral donors and from numerous national governments. Philanthropic foundations continued their strong support for IAVI's work, including a first-ever research grant to IAVI from the New York Community Trust and a special one-time supplement from the Rockefeller Foundation. IAVI prioritized development of new private sector sources of financial support, with emphasis on unrestricted giving, which will be critical to IAVI's ability to move rapidly in response to emerging data and new research opportunities.

IAVI's mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world.

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Introduction

Twenty-five years since the AIDS epidemic was first recognized, it continues its relentless expansion in all regions. More new infections and more AIDS deaths occurred in 2005 than ever before. Over the last five years of this decade, between 50 million and 100 million people will contract HIV and more than half this number will die. Unless AIDS is brought under control, the world has little hope of fulfilling the Millennium Development Goals, which envision a halving of acute poverty by 2015.

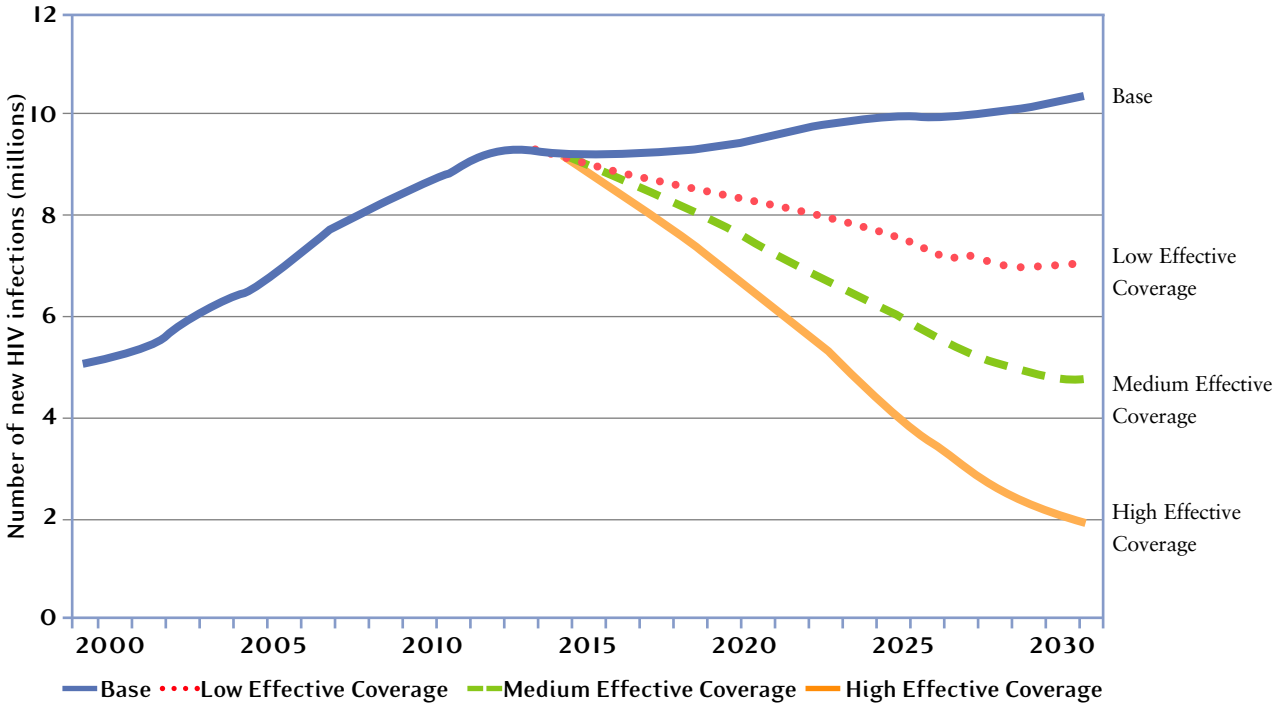
At long last, the world has embarked on a major effort to achieve universal access to HIV treatment and prevention. Yet these initiatives risk foundering unless they are coupled with a longer-term strategy to develop the most potent weapon for fighting AIDS — a preventive vaccine. Without effective prevention, the global push to deliver treatments will quickly become financially and logistically unsustainable. And although available prevention tools can be highly effective, they have inherent weaknesses — none is 100% effective, none offers lifelong protection, and most require correct and voluntary use by the consumer during each episode of risk behavior. Women often have little practical means of protecting themselves from HIV infection, frequently lacking the ability to abstain from sex or to insist that their male partners use a condom.

To win the fight against AIDS, immediate efforts to scale up existing preventive and therapeutic tools must be complemented with an urgent, high-level global effort to find and deploy new prevention technologies, such as female-controlled microbicides and a preventive vaccine, as quickly as possible.

Inspired by the vision of a world without AIDS, IAVI was founded nearly 10 years ago to accelerate the development of a preventive vaccine for all, with a particular focus on the developing world, home to 95% of all people living with HIV. This mission has never been more relevant or more urgent. According to modeling commissioned by IAVI, a vaccine with only modest efficacy (60%) that reaches a mere 30% of those at risk of HIV could reduce the annual number of new infections by almost a third during a 15-year period, averting 45 million infections. An even more effective vaccine would produce an even sharper reduction in the rate of new infections and lay the groundwork for the reversal of the AIDS epidemic. (See Figure 1)

Figure 1

New adult and child HIV infections in low and middle income countries by year and vaccine scenario



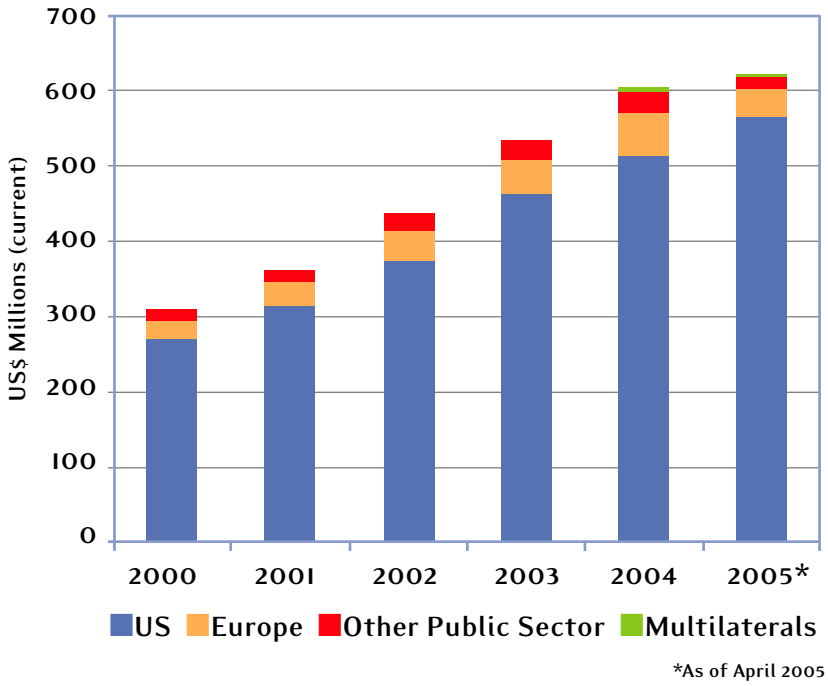
Source: *Estimating the Global Impact of an AIDS Vaccine*. Policy Brief #8. IAVI, 2005.

This report summarizes the work of the International AIDS Vaccine Initiative in 2005. To improve the readability of IAVI's periodic progress reports and to enhance their usefulness to donors and other IAVI partners, IAVI is using a new format for presentation of its 2005 activities. In lieu of department-specific descriptions of activities and achievements, this report places IAVI's work in the context of its current strategic plan, describing how specific activities advance the organization's strategic goals and objectives. The new format also underscores IAVI's commitment to transparency and performance-based management.

IAVI's *Strategic Plan to Accelerate Development of an HIV/AIDS Vaccine* covers the years 2005-2007. The plan grew out of a year-long process that engaged all IAVI departments and offices, as well as numerous external advisors and stakeholders. The strategic plan builds on a comprehensive assessment of key developments in the vaccine field, including growing political commitment and funding for AIDS vaccine research (see Figure 2), expansion of the still-inadequate vaccine pipeline, disappointing results from early clinical trials, growing consensus on the key scientific questions that impede vaccine development, and the emergence of an important new collaborative alliance, the Global HIV Vaccine Enterprise, of which IAVI is a founding member.

FIGURE 2

Annual public sector investment in preventive HIV vaccine R&D (2000 to 2005)



Source: *Tracking Funding for Preventive HIV Vaccine Research & Development: Estimates of Annual Investments and Expenditures 2000 to 2005*. HIV Vaccines and Microbicides Resource Tracking Working Group (AVAC, AMD, IAVI, and UNAIDS), 2005.

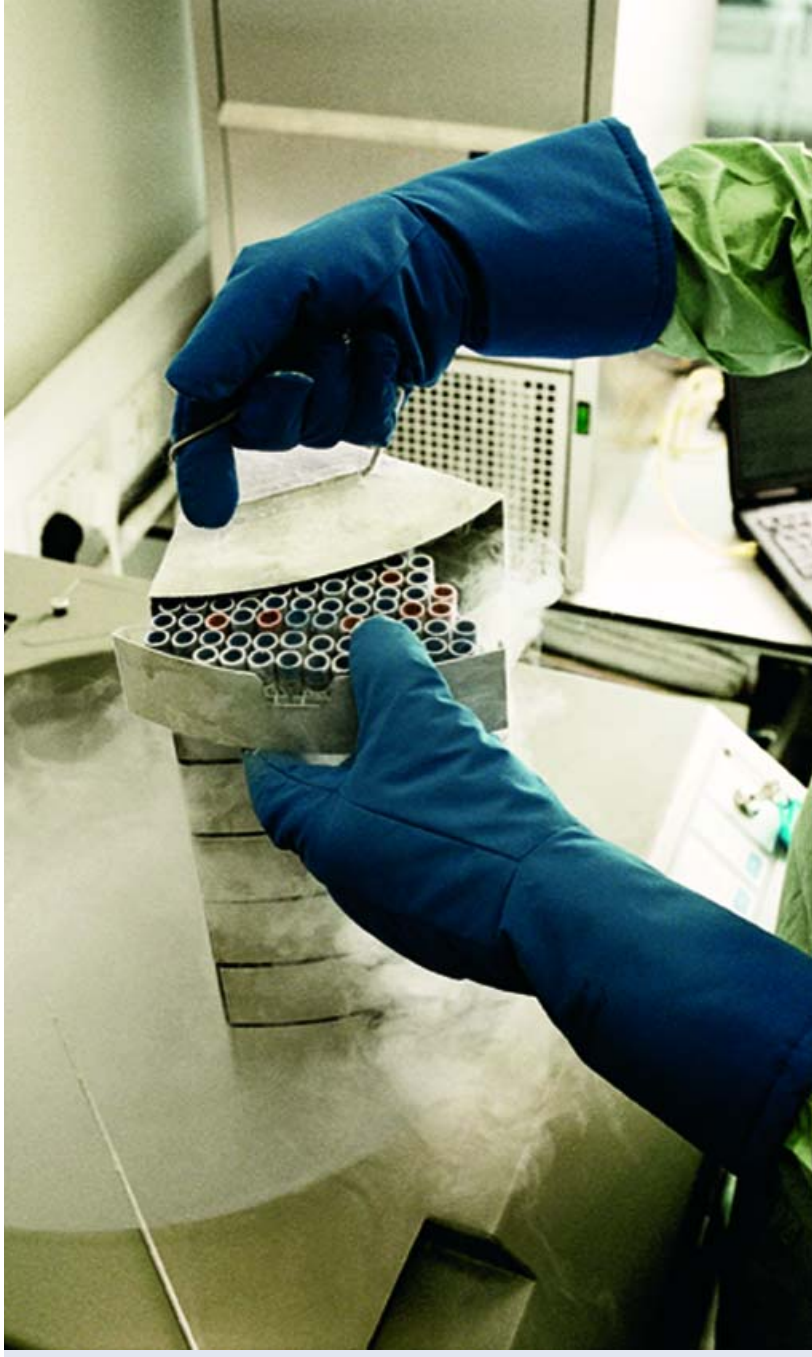
The plan also recognizes that IAVI itself has dramatically changed since its creation in 1996. From its roots as a small but visionary start-up incubated within the Rockefeller Foundation, IAVI has become a recognized leader in the field, bringing forward six different vaccine candidates and working with diverse R&D and public policy partners in 23 countries.

IAVI takes pride in having achieved its earliest organizational aspirations — spurring substantially stronger global awareness and commitment on AIDS vaccines, using the best available science to advance multiple product candidates, and creating an innovative, fully integrated organization that is helping lead the field. In the years since its founding, however, the urgency of IAVI's mission has only grown more acute, as the numbers of new infections and AIDS deaths have continued to increase.

IAVI's three-year strategic plan seeks to address current challenges, capitalize on IAVI's unique role in the vaccine field, and complement the invaluable contributions of IAVI's many partners. To this end, the strategic plan provides that IAVI, in 2005-2007, will:

- *Implement an expanded R&D program,*
- *Secure and sustain strong global commitment to an AIDS vaccine,*
- *Promote public policies that support vaccine R&D and future vaccine access,*
- *Engage as partners the countries where the epidemic is, or is likely to be, most severe, and*
- *Refine IAVI's internal operations to ensure the organization's ability to achieve the goals and objectives in the strategic plan.*

In 2005, IAVI worked to translate the indicators in the strategic plan into department-specific indicators to guide work plan development, budget allocations, and performance evaluation. As this report covers only the first of the three-year period covered by the strategic plan, many of the activities summarized will represent *progress* rather than actual *achievement* of many of the stated goals and objectives. Many of the goals and objectives set forth in the strategic plan cannot be achieved by IAVI alone, underscoring the centrality of strong *partnerships* as a core operating principle for IAVI today and in the years ahead.



Core laboratory technician retrieving cells from liquid nitrogen storage to test in an ELISpot assay

Strategy One:
Implement an Expanded R&D Program

The centerpiece of IAVI's strategic plan for 2005-2007 is a major expansion of the organization's R&D program. The strategic plan seeks to widen the product pipeline with new candidates that improve on previous generations, capitalize on IAVI's catalytic, gap-filling role to obtain answers to critical questions that impede progress in the field, and strengthen clinical trial infrastructure to expedite trials for the most promising vaccine candidates.

Objective: *Significantly improve the product development pipeline with candidates that have greater potential for success compared with those in the current pipeline.*

IAVI's original *Scientific Blueprint* proposed to use the best available scientific evidence to advance multiple product candidates through the research and development pipeline. In its first eight years of work, IAVI placed six candidate vaccines in clinical trials and established a state-of-the-art core laboratory to facilitate IAVI's own scientific efforts and to serve as a resource to the entire field. In 2005, IAVI built on these achievements to undertake additional efforts to expand and accelerate the product pipeline.

IAVI researcher, Aaron Wilson, performing an assay in the biosafety facility of the new IAVI AIDS Vaccine Development Laboratory

AIDS VACCINE TRIALS 2005:
YEAR IN REVIEW

This map depicts the clinical trials of preventive AIDS vaccines that began in 2005. For some of these trials additional sites will be added in 2006. These sites are represented here by dashed lines. For more information about ongoing vaccine trials, please visit www.iavireport.org. Please also e-mail any additions or comments to iavireport@iavireport.org.

January 2006 — U S A, Peru
HVTN 064
Phase I, 124 volunteers
EP-1043, EP HIV-1090 alone or in combination
HVTN, NIAID, Pharmexa-Epimmune

February — USA
N/A
Phase I, 6 volunteers
EnvDNA
St. Jude, NIH

September — USA, Brazil, South Africa (Later: Haiti, Jamaica)
HVTN 204
Phase II, 480 volunteers
VRC-HIVDNA-016-00-VP; VRC-ADV-014-00-VP
NIAID, VRC, HVTN, Vical, GenVec

January — USA
IAVI C002
Phase I, 48 volunteers
ADMVA
IAVI, ADARC

January — USA
VRC 009 (05-I-0081)
Phase I, 32 volunteers
VRC-HIVADV014-00-VP
NIAID, VRC

April — USA
HVTN 054
Phase I, 48 volunteers
VRC-HIVVADV014-00-VP
HVTN, NIAID, VRC

August — USA, Thailand
HVTN 060
Phase I, 144 volunteers
GENEVAX Gag-2692 +/- IL-12 DNA; DNA plasmids or RC529-SE/GM-CSF
HVTN, NIAID, Wyeth

September — USA, Brazil
HVTN 063
Phase I, 156 volunteers
GENEVAX Gag-2962 +/- IL-15 DNA; RC529-SE or GENEVAX Gag-2962 + IL-15 DNA or GENEVAX Gag-2962 + IL-12 DNA
HVTN, NIAID, Wyeth

November — USA (Later: Thailand)
RV 158
Phase I, 48 volunteers
MVA-CMDR
WRAIR, NIH

November — South Africa (Later: Uganda, Zambia)
IAVI A002
Phase II, 78 Volunteers
tgAAC09
IAVI, Targeted Genetics

November — Rwanda, Kenya
IAVI V001
Phase I, 64 volunteers
VRC-HIVDNA-016-00-VP; VRC-ADV-014-00-VP
IAVI, NIAID, VRC

March — China
N/A
Phase I, 49 volunteers
DNA plasmid vaccine
Guangxi CDC

December — India
IAVI D001
Phase I, 32 volunteers
TBC-M4 MVA
IAVI, Therion

Map Key

TRIAL INFORMATION
- Month — Countries
  Trial Number
  Phase, Number of volunteers
  Vaccine
  Trial Sponsor, Manufacturer

VACCINE TYPE
- DNA
- Viral Vector
- Protein Subunit

COLOR KEY
- Dark green denotes countries where trials started in 2005.
- Medium green denotes countries where trials are currently ongoing (began 2002-2004).
- Light green indicates countries where trials will soon begin.

Abbreviations: **ADARC:** Aaron Diamond AIDS Research Center; **Guangxi CDC:** Guangxi Centre for Disease Control and Prevention; **HVTN:** HIV Vaccine Trials Network; **IAVI:** International AIDS Vaccine Initiative; **NIAID:** US National Institute Allergy and Infectious Diseases; **NIH:** US National Institutes of Health; **St. Jude:** St. Jude Children's Research Hospital; **VRC:** Vaccine Research Center at the US National Institutes of Health; **WRAIR:** Walter Reed Army Institute of Research

To achieve the vision articulated in IAVI's strategic plan and to acquire the data needed to advance the field, IAVI has developed a five-year R&D plan (2006-2010) with input from IAVI's own scientific leadership, as well as its Scientific Advisory Committee and Board of Directors. Focusing on strategic priorities, probability of success, and IAVI's particular added value to the vaccine search, this plan identifies specific strategic aims to guide the organization's scientific work over the next five years.

AAV. In partnership with the Government of India — through the Indian Council of Medical Research and the National AIDS Control Organization — IAVI in February 2005 initiated the first-ever human clinical trial in India of an investigational vaccine candidate designed to prevent HIV/AIDS. The trial, conducted by the National AIDS Research Institute in Pune, is testing a vaccine that uses a replication-defective, recombinant adeno-associated viral vector type 2. Targeted Genetics Corp., a Seattle-based biotechnology company, and Columbus Children's Research Institute in Ohio designed the vaccine candidate in partnership with IAVI. The vaccine candidate tgAAC09 is modeled after subtype C of HIV, the subtype that accounts for the most infections worldwide and is prevalent in many developing countries, including China, Ethiopia, India and South Africa.

The trial is part of an IAVI-sponsored multi-country Phase I trial. Interim results from Germany and Belgium indicated that the vector's immunogenic potential is less than anticipated. Final results, including data from India, are awaited. Phase II testing of a higher dose of the AAV2 candidate began at the first of three sites in South Africa, with startup anticipated in 2006, pending approvals, at sites in Uganda and Zambia. The trial is the first Phase II preventive HIV vaccine trial in South Africa.

Additionally, a new vaccine candidate, tgABF66 (an AAV1 analogue of tgAAC09), is currently under preclinical development, as non-human primate studies using an AAV1-based vaccine indicated that AAV1 is superior to AAV2 in its ability to transduce muscle and may therefore be the preferred vaccine platform.

Oxford DNA/MVA Vaccine. In partnership with Oxford University and the Kenya AIDS Vaccine Initiative (University of Nairobi), IAVI developed a vaccine consisting of both a DNA vector and a modified vaccinia Ankara (MVA) attenuated poxvirus vector, expressing Clade A HIV-1 proteins accompanying gag plus a series of CTL determinants. Phase I/II trials in Europe and Africa — which assessed safety and immunogenicity, alone and in prime-boost combinations, using different routes of transmission, different dose levels, and varying prime-boost dosing intervals — demonstrated that the vaccines are safe and generally well-tolerated but had relatively poor immunogenicity. Careful evaluation of the immune responses of a small number of volunteers in a separate study found that DNA priming and MVA boosting, at high doses of each, was capable of eliciting specific antiviral CD4 T-cell immune responses. However, in the absence of a significant CD8 response, it was determined that the vaccine-elicited immunity observed in the study is unlikely to have an adequate antiviral effect. After a careful review of all available data, the ongoing studies were completed and the program terminated in September 2005.

Therion Multigenic MVA Vaccine. In 2005, IAVI moved forward with development of a candidate using an MVA vector designed to express various HIV-1 proteins whose sequences were derived from a Clade C Indian isolate. This vector is sufficiently different from the Oxford MVA to warrant human study; in particular, additional research will help determine whether the immune responses elicited by the Oxford MVA are specific only to the Oxford product or are characteristic of MVA vectors in general. A clinical trial application was approved in India for this candidate vaccine, testing of which began in January 2006 at the Tuberculosis Research Centre in Chennai.

Aaron Diamond DNA/MVA Vaccines. In January 2005, an IAVI-sponsored trial at the Aaron Diamond AIDS Research Center began recruiting volunteers for a clinical trial of a vaccine candidate called ADMVA. The MVA-based vaccine candidate expresses HIV genes of Chinese Clade C HIV isolate. A prior Phase I trial of the corresponding DNA vector found that it was well-tolerated but had poor immunogenicity at all dose levels tested. IAVI and ADARC are currently reviewing preliminary data from the MVA vector Phase I trial to reach a decision on further studies, including the potential use of the DNA and MVA vectors in a prime-boost combination.

Low-Seroprevalence Human Adenovirus Vectors. IAVI entered into an agreement with Crucell, a Dutch biotechnology firm, for exclusive access to the company's intellectual property regarding use of replication-defective adenovirus types 35 and 11 as HIV vaccine vectors. To date, the most encouraging human immunogenicity data have been those reported using the Merck replication-defective adenovirus type 5 vector vaccine. However, surveys indicate that strong anti-adenovirus type 5 immunity is widespread in developing countries, potentially compromising the immunogenicity of adenovirus type 5 vector vaccine. There is notably lower seroprevalence in developing countries for the two adenovirus types to which Crucell's intellectual property relates.

IAVI has contracted Crucell to produce both adenovirus (AdVac®) vectors, adenovirus serotypes 11 and 35, which have shown promising results as vectors for AIDS vaccines in a series of studies by Crucell in collaboration with Harvard Medical School. AdVac® technology is also being applied by Crucell in the production of a malaria vaccine in collaboration with GlaxoSmithKline, Walter Reed Army Institute of Research and the National Institute of Allergy and Infectious Diseases of the U.S. National Institutes of Health (NIH), as well as a TB vaccine in collaboration with the Aeras Global TB Vaccine Foundation. Generation of Ad35 and Ad11 viral vector material was completed before year's end and was expected to be available for research purposes in early 2006. Through the collaboration with Crucell, a cell line was also initiated for production of Ad35/11 material, which may have broader utility for those working in the field.

Non-Human Primate Adenovirus Vectors. In June 2005, IAVI entered into its first formal product development collaboration with a major vaccine company, announcing a partnership with GlaxoSmithKline Biologicals (GSK Biologicals) to develop and evaluate replication-defective chimpanzee adenovirus vectors as human vaccines for HIV. Adenoviruses derived from chimpanzees hold potential promise as an HIV vaccine vector, given their proven ability to mediate strong immune responses in animals and the general absence of anti-vector immunity in people.

Under an agreement with IAVI and GSK, the University of Pennsylvania is developing two vectors using the identical HIV genes prepared by Crucell, potentially facilitating use of vectors from both programs in combined studies. Under the IAVI-GSK partnership, IAVI and GSK will each contribute technical expertise and funding, and GSK and IAVI researchers will form a joint R&D team.

The IAVI-GSK collaborative research will initially focus on vaccines designed to elicit immune responses against variants of HIV that circulate predominantly in Africa, although the goal of the collaboration is to develop vaccines that would be applicable worldwide. After pre-clinical evaluation, GSK Biologicals and IAVI plan to conduct Phase I clinical trials of the vaccine candidates.

Objective: *Address the major scientific obstacles that are impeding global efforts to develop superior product candidates.*

As reflected in the strategic plan and confirmed by an IAVI-sponsored strategic meeting of scientific experts in May 2005, IAVI's fully integrated, industrial-style R&D program plays a unique role in advancing global efforts to overcome existing scientific impediments to vaccine development. In particular, early clinical trials have underscored the need for insight into strategies to generate neutralizing antibody responses to HIV — an area of inquiry in which IAVI continued to lead the field in 2005.

Neutralizing Antibody Consortium. In March 2005, IAVI undertook a comprehensive review of progress to date by the IAVI-convened consortium and the broader field in designing immunogens to elicit broadly neutralizing antibodies. Key findings included the following:

- *No significant differences have been observed among existing monomeric gp120 antigens.*
- *First-generation attempts to develop trimers (the native state of the HIV envelope spike proteins) provide modest improvement with respect to neutralization over monomeric gp120.*
- *In the quest for approaches capable of eliciting broadly neutralizing antibodies, a comprehensive, large-scale effort is needed to identify more and better HIV monoclonal antibodies to probe the surface of the HIV envelope antigen.*

Members of the Consortium in 2005 generated 18 scientific articles on issues relating to neutralizing antibodies in leading peer-reviewed journals, including *Science, Virology, Journal of Virology, and Journal of Immunological Methods.*

The following investigators were added to the Consortium in 2005:

- *Dr. Pascal Poignard of the University of Marseille (France) aims to focus his work with the consortium on elucidation of the important differences between HIV-sensitive and HIV-resistant viruses with respect to neutralization.*
- *Dr. Raymond Dwek will study a well-characterized carbohydrate-dependent neutralizing antibody epitope on gp120.*
- *Dr. Quentin Sattentau will address basic questions related to antibody neutralization of HIV-1 by taking advantage of recent advances in cryo-electron tomography and fluorescene activated flow cytometry.*

- *Dr. Ben Davis intends to focus on the use of protein immunogenic scaffold and glycodendriprotein methodology as well as carbohydrate biology to fill a gap in the HIV vaccine field.*

Live Attenuated Consortium. The IAVI-convened Live Attenuated Consortium seeks to elucidate the mechanism for the robust protection conferred by live attenuated SIV, and to translate these insights into the design of superior HIV vaccine candidates. Significant progress occurred in 2005 in accelerating the work of the Consortium, which intends to conduct a series of large-scale, non-human primate studies that have sufficient power to answer key scientific questions. In particular, agreement was reached on standard reagents for multi-center studies. Scientific questions to be addressed by the Consortium include:

- *Is the protection conferred by live attenuated SIV due to the targeting of the vaccine to the gut-associated lymphoid tissue (GALT) and to subsequent induction of antiviral immune responses in the GALT?*
- *Does live attenuated SIV confer enhanced protection by contributing to the persistence of the vaccine virus?*
- *Is protection due to neutralizing antibodies, to cell-mediated immunity, or to both?*
- *Does the full complement of genes included in the vaccine play an active role in the protection conferred?*
- *Can the protection seen as a result of live attenuated SIV be mimicked by one or more viral vectors currently in development?*

In 2005, the following scientists were added to the live attenuated virus consortium:

- *Dr. Philip R. Johnson, Children's Hospital of Philadelphia, will study the contribution of ENV from live-attenuated SIV in conferring protection from pathogenic SIV challenge.*
- *Dr. Ashley Haase, Institute for Molecular Virology of the University of Minnesota, will characterize the primary site of live-attenuated SIV replication and tissue-specific immunological responses elicited.*
- *Dr. Louis Picker, Oregon Health and Science University, will lead the effort to develop CMV vectors, including studies on the characterization, safety and construct of attenuated HuCMV.*
- *Dr. Robert Johnston, Global Vaccines Inc., is working to produce a stably transfected Vero cell line that expresses lentivirus receptor (CD4) and co-receptor (CCR5), meant for the production of chimeric viral particles.*

IAVI Vaccine Development. As a key step toward IAVI's goal of fully integrating its R&D efforts, the organization took major steps in 2005 toward the establishment of an AIDS Vaccine Development Laboratory to support and complement its research activities. The lab will support an industrial-style staff of 25 technical experts to facilitate immunogen design, vector design, process development, and research on primate immunobiology.

IAVI convened an internal project team, supplemented by external consultants, to drive the process to create the laboratory. In 2005, IAVI began occupying temporary laboratory space at the State University of New York Downstate. IAVI's collaboration with SUNY-Downstate holds numerous potential advantages, including access to critical infrastructure, such as animal facilities, biohazard agent oversight, full library access and support, access to vendor supply agreements, use of core research facilities, and the potential for joint academic appointments to facilitate recruiting. With an eye toward housing the laboratory at the Brooklyn Army Terminal and aligning it with SUNY-Downstate, IAVI initiated discussions for acquisition of approximately 12,000 square feet, with an option for acquisition of additional space for future expansion. Current plans call for the organization's occupancy of the laboratory space by the end of 2006. Both New York City and State aim to convert the Brooklyn Army Terminal into a major biotech hub.

IAVI Core Immunology Laboratory. Under the strategic plan, IAVI's core immunology laboratory in London will be strengthened to facilitate the human testing of candidate HIV vaccines. In keeping with standard practice for all IAVI R&D programs, an independent review of the core laboratory was initiated in June 2005, with the goals of assessing progress to date and helping chart future directions. The review indicated that the core laboratory had surpassed all objectives and added value to, and galvanized, the entire vaccine field.

The core laboratory is continuing its Good Clinical Laboratory Practices (GCLP) accreditation program in east Africa, southern Africa and India. An IAVI site in Uganda received GCLP accreditation in 2005, joining the previously accredited IAVI labs in Johannesburg and London. It is anticipated that additional IAVI sites will become accredited in 2006.

Global HIV Vaccine Enterprise. IAVI is a co-founder and active participant in the Global HIV Vaccine Enterprise, a

multi-partner alliance designed to accelerate HIV vaccine development through enhanced strategic collaboration among key stakeholders. Since the Vaccine Enterprise was first conceived in a June 2003 *Science* article co-authored by leading vaccine scientists, including IAVI President/CEO Seth Berkley, the Bill & Melinda Gates Foundation has served as the alliance Secretariat during its formative phase. Stakeholders in the Enterprise collaborated in the development of a strategic scientific plan, which identifies key scientific and logistical roadblocks to swifter vaccine development.

Berkley represents the organization on the Enterprise Coordinating Committee, which in 2005 focused on such issues as the search for an executive director of the Enterprise Secretariat, the future role of the Coordinating Committee, and the potential creation of a board of directors. Berkley attended a meeting of the Vaccine Enterprise stakeholders, co-hosted by the UK Department for International Development, and made a presentation on IAVI to a meeting of potential Enterprise funders in October 2005.

In 2005, steps were taken by NIH and the Bill & Melinda Gates Foundation to implement various aspects of the Enterprise's strategic scientific plan. IAVI participated with Harvard Medical School (USA; Dr. Bruce Walker, principal investigator) in one of four applications received by NIH in response to its Request for Proposals for a Center for HIV and AIDS Vaccine Immunology (CHAVI), intended to function as a consortium of universities and academic medical centers working to solve key problems in vaccine development; following site visits and peer review, NIH made the award to Duke University (USA; Dr. Bart Haynes, principal investigator). IAVI is in the process of forging a collaborative relationship with the new CHAVI leadership.

In addition, the Bill & Melinda Gates Foundation solicited proposals for research consortia or centers targeting three key priority areas — design of immunogens producing broadly reactive neutralizing antibodies, design of immunogens that induce persistent high levels of cell-mediated immunity, and standardization and development of laboratory assays. IAVI was successful in four of five Letters of Intent to the Gates Foundation for establishment of vaccine discovery consortia for neutralizing antibody and T cell immunity/viral vectors. For all applicants submitting Letters of Intent, the Gates Foundation approved one-third for submission of full applications. IAVI submitted three proposals and expects the results to be announced in the first half of 2006.

Objective: Strengthen the infrastructure to expedite clinical testing of the most promising candidates in the developing world.

One IAVI's primary aim is a significant expansion of worldwide clinical trial capacity to facilitate rapid future testing of the most promising vaccine candidates. Under the strategic plan for 2005-2007, IAVI will establish core clinical sites and cohorts sufficient to enroll and follow volunteers for efficacy trials in Clade A and C regions. Although IAVI is actively working to develop new and better candidates of its own for future testing, these expanded clinical trials sites would be available for evaluation of the most promising candidates, regardless of their sponsor.

In 2005, IAVI made major strides in expanding clinical trial capacity — using its infrastructure and expertise in eastern Africa to partner with NIH in the testing of a new vaccine candidate, taking steps to strengthen IAVI's core immunology lab, creating the above-mentioned vaccine development laboratory to complement IAVI's vaccine design and development efforts, and expanding clinical trial capacity in Africa and Asia. (Cohort development efforts, community engagement, and other preparatory activities for future trials are discussed in Section IV, which addresses IAVI's partnerships with developing countries.)

Expanding Clinical Trial Capacity. IAVI is actively engaged in preparation of a number of clinical sites in eastern and southern Africa for future vaccine efficacy studies of the most promising candidates. This years-long process involves protocol development and implementation, identification and analysis of potential cohorts (see Section IV), and creation of a network of experienced investigators. IAVI has established clinical and laboratory infrastructure for trial planning at two sites in Kenya, two sites in Uganda, and one site each in Rwanda, South Africa and Zambia.

In South Asia, IAVI initiated the first vaccine trial in India. In 2005, progress was also made in establishing clinical and laboratory facilities at the Tuberculosis Research Center in Chennai, India, to support planned trials of a multigenic MVA vaccine. Staff has been recruited for the Chennai site and are undergoing training.

Seth Berkley and Indian Prime Minister, Dr. Manmohan Singh, meet in December of 2005 to discuss India's leadership role in advocacy, research and development of an AIDS vaccine

Developing Country and European Research Partnerships. Responding to U.S. Congressional interest and consistent with the strategic plans of IAVI and the Global HIV Vaccine Enterprise, IAVI issued a Program Announcement requesting Letters of Intent from European and developing country researchers to support vaccine development programs. Awards will be made in early 2006, based on proposals reviewed in collaboration with NIH.

Field Laboratory Capacity. IAVI is implementing an independent protocol at each of its trial sites in Africa to establish normal variance ranges for normal clinical safety lab tests in these populations. Understanding the normal ranges of clinical blood tests is important in safety studies of candidate vaccines, and such ranges can significantly differ between developing and developed country populations. This protocol will have broad utility for the entire clinical research field, not merely for IAVI and its affiliated researchers. By the end of 2005, a study to assess safety lab tests had completed enrollment at sites in Kenya, Uganda and Rwanda, was ongoing at separate sites in Uganda and Zambia, and was expected to begin enrollment at a final site in Kenya in the first quarter of 2006.

Expanding the Scope of AIDS Vaccine Program in India. IAVI entered into two memoranda of understanding with the Indian national government to capitalize on opportunities for applied research on AIDS vaccines. Areas of possible collaboration were identified at a meeting involving IAVI President/CEO Seth Berkley and officials from the Department of Biotechnology in the Indian Ministry of Science and Technology. A meeting in early 2006 will explore how India's extensive scientific expertise — in research institutions and in the biotechnology and pharmaceutical industries — can be harnessed to solve some of the major scientific questions facing the field.

Strategy Two:
Secure and Sustain Global Commitment

IAVI is widely recognized as having injected renewed enthusiasm in the AIDS vaccine field and contributed to a significant increase in global political and financial support for AIDS vaccine R&D. The strategic plan recognizes, however, that the history of global health is checkered with causes that briefly captured global attention only to fade from view.

To speed the era of AIDS vaccination, unprecedented global resolve will need to be sustained over many years. The strategic plan for 2005-2007 calls for IAVI to implement a global advocacy initiative that will strengthen, expand and maintain strong political commitment to AIDS vaccines. As the most concrete reflection of political commitment, the strategic plan aims for a 50% increase by 2007 in global spending on AIDS vaccine R&D (over 2004 levels, the last year for which data are available). To enable IAVI to uphold its leadership role in support of the field, the strategic plan calls for the organization to establish itself as the leading international organization on AIDS vaccine science, policy and advocacy.

Objective: *Enhance global public and political commitment to accelerate the development of a safe and effective HIV/AIDS vaccine and to ensure that such a vaccine, once developed, is available, acceptable, affordable, and effectively used (particularly in developing countries).*

In recognition of the important challenge of building and sustaining strong political commitment for vaccine development, the 2005-2007 strategic plan provides for energetic and visionary advocacy supported by sound evidence and analysis. Building on prior achievements, the strategic plan aims to develop committed leadership among decision-makers and influential stakeholders in a broad array of constituencies, including government, civil society, media, science and the private sector. The strategic plan recognizes that IAVI's advocacy and leadership development activities must be global in scope, generating needed commitment in both developed and developing countries. For 2005-2007, IAVI is focusing heightened attention on positioning HIV vaccine efforts within broader public health and development efforts and on persuading key decision-makers that vaccines represent a key component of a comprehensive, long-term response to the HIV/AIDS epidemic.

Building Global Political Commitment. The 2005-2007 strategy calls for strong and sustained advocacy to ensure that AIDS vaccines are high on the global political agenda. In 2005, IAVI continued and strengthened its ongoing partnerships with advocates and governments around the world, capitalizing on major political gatherings and forging new relationships with key decision-makers to highlight the global importance of a preventive vaccine.

IAVI used the occasion of the June 2 high-level meeting of the United Nations General Assembly to highlight the importance of vaccines and other new prevention technologies and to strengthen working alliances with other prevention technology advocates. Approximately 150 people attended a luncheon briefing co-sponsored by IAVI and the International Partnership for Microbicides (IPM). Senior representatives joined from the governments of Botswana, El Salvador, France, Iceland, Serbia, South Africa, Sweden, Ukraine, and Zimbabwe; major donor agencies; non-governmental organizations; and other key stakeholders. UN Secretary General Kofi Annan provided the keynote address; Dr. Stephen Lewis, Special UN Envoy for HIV/AIDS in Africa, moderated a panel discussion of government ministers from Brazil, Rwanda and India, as well as a Member of Parliament from the UK; and Dr. Peter Piot, executive director of UNAIDS, made closing remarks. The event was webcast by the Henry J. Kaiser Family Foundation. In addition to co-sponsoring the luncheon, IAVI served as one of five civil society groups that participated in the summit's prevention roundtable, where high-level officials from Canada, Denmark, Gambia and India declared support for greater commitment to the development of vaccines and microbicides as part of a comprehensive prevention response.

In collaboration with IPM, the Medicines for Malaria Venture, the Global Alliance for TB Drug Development, and many national governments, IAVI drafted and advocated for the insertion of language on new health technolo-

gies into the report of the UN World Summit on the Millennium Development Goals. As a result of this effort by IAVI and its partners, the final summit document contained language on long-term funding for AIDS vaccine R&D, public-private partnerships, and market incentives for biomedical research on neglected diseases, such as advance purchase commitments.

IAVI participated in the inaugural Clinton Global Initiative in September 2005. At this high-profile meeting of world leaders, IAVI committed to working with the Clinton Foundation HIV/AIDS Initiative to carry forward President Clinton's AIDS vaccine legacy, which includes his visionary call to action on vaccine R&D in 1997. IAVI followed up on this commitment with a meeting with Clinton Foundation leadership in November 2005 to explore potential areas of collaboration, such as the provision of treatment and care for communities where vaccine trials occur, initiatives to spur greater private sector investment in vaccine R&D, and intellectual property issues.

Political Leadership in Developing Countries. IAVI helped facilitate the India-Brazil-South Africa (IBSA) trilateral collaborative, which seeks to increase cooperation between the three countries and has identified AIDS vaccines as a priority issue. Following an earlier meeting of science and technology ministers, the foreign ministers of the three countries convened in early 2005 and agreed to hold workshops to exchange information, experience and strategies on the three leading infectious killer diseases — HIV/AIDS, tuberculosis, and malaria. In June, the ministers of science from each of the countries signed the Rio Declaration, confirming commitment and support on AIDS vaccines and urging the G8 to reiterate and strengthen its support for vaccine R&D. At an October 2005 meeting in Cape Town, the countries shared needs and priority areas for joint work. IAVI President/CEO Seth Berkley made a presentation on IAVI at the Cape Town meeting, focusing on strategies to build on the India-Brazil-South Africa collaboration to intensify international political commitment on AIDS vaccines. During a meeting with Berkley, the Indian Minister of Finance agreed to host a meeting of his IBSA counterparts to discuss supportive financial policies, incentives and mechanisms to spur AIDS vaccine R&D. IAVI will continue to offer technical advice and support to this collaborative effort.

With coordinating support from IAVI, the Kenyan Ministry of Health's National Subcommittee on HIV Vaccines issued the *Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines* on March 31, 2005. The Kenya vaccine guidelines provide a roadmap for future vaccine development in Kenya based on a template developed by WHO's African AIDS Vaccine Program. In Uganda, IAVI also played a critical role in the formation in March 2005 of the National HIV/AIDS Vaccine Advocacy and Coordination Committee, which will oversee finalization of a new national HIV vaccine plan.

Following up on a successful meeting in 2004 between Ugandan President Yoweri Museveni and IAVI President/CEO Seth Berkley, President Museveni displayed continued leadership in 2005 in prioritizing AIDS vaccines on the national agenda. Working with the Uganda AIDS Commission and the Office of the President, IAVI worked with President Museveni's office on a letter from the President encouraging G8 members to make good on their expressions of commitment by increasing financial resources, scientific expertise, and political support for the global vaccine effort.

The government of India continued to demonstrate its strong commitment to AIDS vaccine development in 2005. With strong support from the Indian Minister of Health and Family Welfare, accelerated regulatory clearance facilitated timely initiation of the country's first vaccine clinical trial in February 2005. The Pune trial attracted strong and favorable coverage in the national media, in part due to a successful press briefing that included the Indian Health Minister and Kapil Sibal, the Minister of Science and Technology and IAVI board member. In December 2005, IAVI President/CEO Seth Berkley met with President Dr. Avul Pakir Jainulabdeen Abdul Kalam of India, during which the President reiterated his strong support for new prevention technologies, specifically AIDS vaccines.

During a visit to Brazil, Berkley met with Deputy Health Minister Jarbas Barbosa, the National AIDS Program, the National AIDS Commission, leading vaccine researchers, and five parliamentarians who are in the forefront on AIDS issues. IAVI helped organize a site assessment in Brazil attended by several African researchers. Brazil's health minister also participated in the above-noted IAVI-cosponsored roundtable on new prevention technologies at the United Nations.

Political Leadership in Developed Countries. As explained below in Section III, IAVI devoted extensive efforts toward advocacy to influence G8 leaders at their annual summit meeting, hosted this year by the United Kingdom. In May 2005, a Spanish parliamentary commission passed a resolution asking the national government to provide tangible support for "ongoing international efforts on AIDS vaccine R&D." IAVI is collaborating with Professor Mariano Esteban, a leading AIDS vaccine scientist and member of the EuroVacc network, to develop strategies to engage the government of Spain on AIDS vaccine issues.

Following strong advocacy by Danish NGOs, including AIDS Fondet, IAVI's partner in Denmark, the country's new HIV/AIDS strategy for 2005-2008 strongly supports

Laboratory at the Vaccine Trial Centre, National AIDS Research Institute (NARI) in Pune, India

vaccine development. The Swedish HIV/AIDS policy also prioritizes vaccine R&D, and the Norwegian government has similarly indicated a desire to work with IAVI on policy matters.

In 2005, IAVI engaged in extensive advocacy targeting the broader European Union. Advocacy by IAVI influenced the "European Programme for Action to Confront HIV/AIDS, Malaria and Tuberculosis through External Action (2007-2011)," which prioritizes stronger support for public-private partnerships and global initiatives to accelerate development of AIDS vaccines and other key health tools. The new "Framework Programme for R&D 2007-2013" includes, for the first time, support for translational research to address the global threats of AIDS, tuberculosis, and malaria.

Building Strong Public Support. IAVI played a visible role in awareness-raising activities to commemorate World AIDS Vaccine Day (May 18). In Kenya, coordinated activities occurred in five provinces, including an advocacy walk, entertainment and speeches in each setting. IAVI distributed T-shirts, banners, placards, stickers and a one-page flier for the events, which attracted an estimated 3,200 people.

In Uganda, 3,000 people attended a rally on World AIDS Vaccine Day in Kampala, which also attracted significant television, radio and print coverage. IAVI participated in the committee that organized the event, which included participation by the Uganda Minister of Health, the director of the national AIDS commission, the municipal health minister for Kampala, the UNAIDS Country Coordinator, and non-governmental organizations.

In Brazil, IAVI sponsored a series of regional journalist training workshops in the five states in which vaccine research is either underway or planned. In 2005, IAVI supported training for 50 journalists on AIDS vaccines. In the U.S., IAVI helped organize a well-attended panel discussion at the Global Health Council in Washington D.C., featuring speakers from IAVI, the South African AIDS Vaccine Initiative, and the AIDS Vaccine Advocacy Coalition.

Civil Society Partnerships. A cornerstone of IAVI's historic advocacy efforts — and of the strategic plan — is strong partnerships with civil society organizations. As discussed elsewhere in this report, IAVI in 2005 strengthened its joint advocacy work with other public-private partnerships, such as the International Partnership for Microbicides and the Malaria Vaccine Initiative. In the U.S., Canada and Europe, working partnerships with non-governmental organizations enhance IAVI's capacity to increase political commitment, raise public awareness, promote vaccine-supportive public policies, and position AIDS vaccines as a critical element of the broader AIDS response and international development.

The 2005-2007 strategic plan prioritizes development of working partnerships with women's groups on vaccine advocacy. In 2005, IAVI initiated a collaboration with UWONET, a network of women's NGOs in Uganda, to provide feedback on gender issues relating to the conduct of clinical trials, including effective strategies to overcome barriers to women's participation. IAVI sponsored two consultations in collaboreation with UWONET — one for community-level stakeholders and a second for national-level stakeholders.

In 2005, IAVI intensified its partnership with Deutsche AIDS-Stiftung, the German AIDS foundation; DAS endorsed IAVI's advocacy regarding the G8 summit, worked with IAVI to generate media coverage of vaccine issues, and facilitated IAVI contacts with influential German politicians. In the Netherlands, IAVI worked with Share-Net, a Dutch network of more than 30 development NGOs, to organize an experts meeting in Amsterdam on "Ethical issues in biomedical research in developing countries."

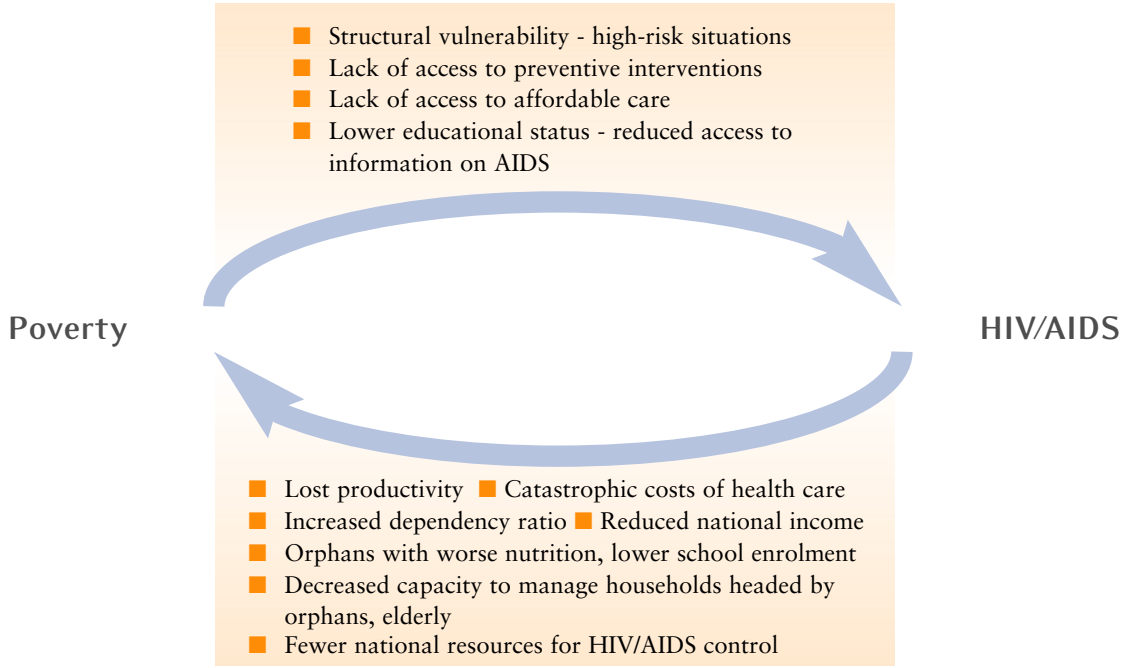
IAVI is one of six founding members of the Informal EU

HIV/AIDS Group and continues to meet regularly with its Brussels-based NGO partners. In March, IAVI was one of 27 development and AIDS NGOs that submitted a joint call for enhanced integration of HIV/AIDS in the EU's new development policy, including increased resources for research on AIDS vaccines. IAVI also continued its active membership in the European Policy Centre, one of the most influential Brussels-based think tanks. IAVI participated in a June seminar sponsored by The Centre, another Brussels-based think tank, on the private sector's role in advancing the Millennium Development Goals in Africa.

Positioning Vaccines as Part of a Comprehensive Response. Development of a vaccine capable of reversing the global AIDS epidemic is essential to international poverty reduction efforts. (See Figure 3) As envisaged by the strategic plan, IAVI in 2005 took steps to emphasize vaccines as a comprehensive response to AIDS, global health, and international development. This broad-based approach to vaccine advocacy was reflected in the successful advocacy by IAVI and its partners, noted above, to influence the deliberations and formal declarations of key UN meetings in 2005.

FIGURE 3

The contribution of AIDS to poverty



Source: *AIDS, Poverty Reduction, and Debt Relief*. UNAIDS, 2001

After providing input into the initial draft of the UNAIDS prevention strategy, IAVI joined with the IPM in successful advocacy resulting in the inclusion of strong language in the strategy approved by the UNAIDS Programme Coordinating Board that emphasizes key actions to accelerate development and use of vaccines, microbicides and other new prevention technologies. The new UNAIDS prevention strategy — *Intensifying HIV Prevention*, released in 2005 — identifies action to accelerate development of vaccines, microbicides and other new HIV prevention technologies as one of 12 essential policy actions required in a comprehensive response to AIDS. Similarly, the new UNAIDS prevention strategy identifies preparation to ensure future access to vaccines and other new prevention technologies as one of 11 essential programmatic actions for HIV prevention.

IAVI President/CEO Seth Berkley addressed a plenary session of the July 2005 International Congress on AIDS in Asia and the Pacific in Kobe (Japan) on "The Critical Role of AIDS Vaccines in a Comprehensive Response to HIV: An Update," and also participated in the World Economic Forum in Davos (Switzerland) in January 2005. IAVI was invited by Development Cooperation Ireland, the country's official development assistance agency, to submit recommendations on AIDS vaccines for consideration in development of a new roadmap for Ireland's ODA efforts (to be released in 2006). In its submission to the government of Ireland, IAVI recommended that the country encourage the European Commission to support adoption of an international convention requiring all countries to contribute to health-related R&D. IAVI also urged that Ireland use its standing in the donor community to promote increased investment in global public goods, including vaccine R&D.

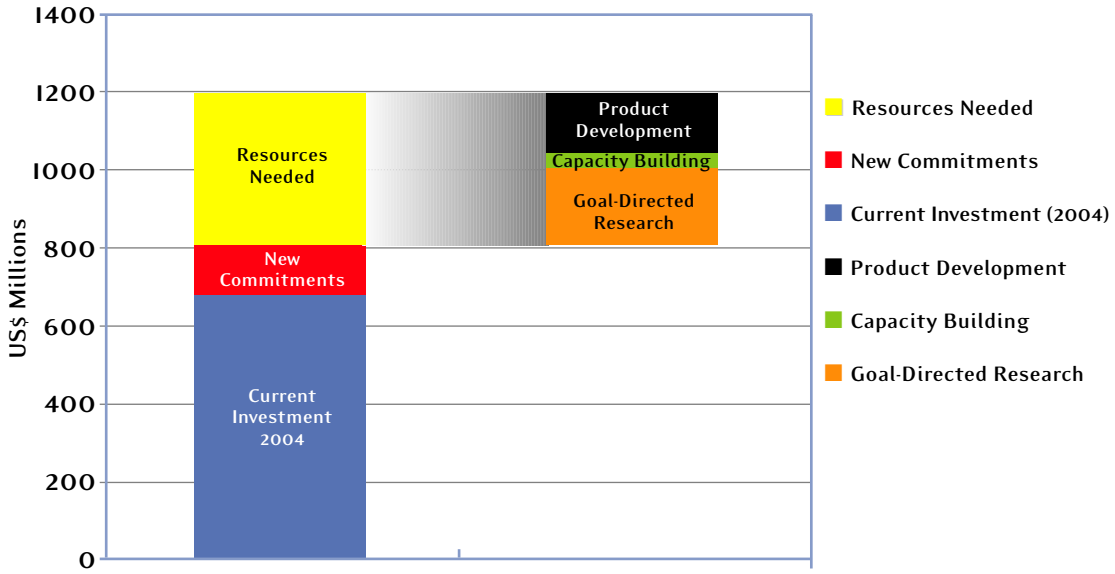
Objective: Enhance global financial commitment to HIV/AIDS vaccine R&D and to ensure that any future vaccine, once developed, is available, acceptable, affordable and effectively used (particularly in developing countries).

With the goal of increasing total funding for HIV/AIDS vaccine R&D by 50% by 2007 (compared to 2004 baseline), the strategic plan provides that IAVI will intensify its advocacy and resource mobilization efforts targeting diverse sources of financial support for the entire vaccine field, including G8 countries and the private sector. (Financing mechanisms needed to ensure rapid introduction of future vaccines is addressed, below, in Section III.)

The G8 summit in July 2005 was the focus of advocacy by IAVI and its partners. IAVI met in early 2005 with senior officials in HM Treasury and with the Department for International Development to advocate for a substantial increase in financial support for vaccine R&D, development of an advance purchase commitment for AIDS vaccines, and strengthened political leadership with a focus on a strong partnership between developed and developing countries.

FIGURE 4

Estimated Annual Resources Required to Accelerate R&D



Source: *Investing in AIDS Vaccines: Estimated Resources Required to Accelerate R&D*. IAVI. June 2005.

As the summit approached, IAVI worked with Medicines for Malaria Venture and a coalition of product-oriented public-private health partnerships to advocate for strong language in the final communiqué regarding public-private strategies to address diseases of the developing world. IAVI also released a statement calling on G8 leaders to increase the magnitude and strategic targeting of funding for vaccine R&D, create a multi-billion advance market commitment for AIDS vaccines, and enhance assistance to developing countries on vaccine research. The final communiqué of the Gleneagles summit called for further work on market incentives (such as advance market commitments), endorsed public-private partnerships as a critical strategy for accelerating the production of new health tools, called for increased public sector funding for vaccine research, and reiterated support for the Global HIV/AIDS Vaccine Enterprise.

In India, IAVI has actively worked in 2005 to engage a broad array of donors in discussions regarding IAVI's work and the broader field of vaccine R&D. As a member of the expanded UN Theme Group on HIV/AIDS in India, IAVI has advocated for the integration of AIDS vaccines in the research agenda of the National AIDS Control Program. The Netherlands AIDS Ambassador Laetitia van den Assum met with IAVI's India staff and visited IAVI's trial sites in Pune and Chennai.

(For a discussion of IAVI efforts to quantify the resource gap for AIDS vaccines, please see the discussion under Strategy Three.)

(For a discussion of IAVI's efforts to mobilize resources for its own activities, see the discussion under Cross-cutting Organizational Strategy.)

Objective: Establish IAVI as the leading international organization on HIV/AIDS vaccine science, policy and advocacy.

As the world's leading AIDS vaccine advocate — and with a fully integrated R&D program — IAVI seeks to spur the global search for an AIDS vaccine by serving as an intellectual and information clearinghouse on vaccine-related issues. In addition to generating a broad range of timely, relevant materials on AIDS vaccine R&D and policy, the strategic plan provides that IAVI will maintain a state-of-the-art communications infrastructure to make IAVI materials as accessible, attractive and user-friendly as possible.

Publications. In 2005, IAVI disseminated findings from its policy research, analysis and advocacy projects through a series of policy briefs, discussion papers and reports. In addition to being easily accessible on the IAVI web site, these publications are personally distributed to more than 500 policy-makers, researchers, private sector representatives, academics and others in the AIDS and global health fields. In addition to the longer policy reports that are discussed elsewhere in this report, IAVI produced six new policy briefs in 2005. Examples include:

- *"Why Women Especially Need an AIDS Vaccine," designed to increase understanding of AIDS vaccines as a vital women's health issue, was widely distributed at the June 2 high-level meeting of the UN General Assembly.*
- *"The Contribution of AIDS Vaccines to Poverty Reduction" emphasizes vaccines as a critical component of global development and poverty reduction initiatives.*

In 2005, IAVI worked to improve the quality of the content featured in *IAVI Report* and *VAX*. *IAVI Report*, which was published five times in 2005, covered a variety of engaging and challenging topics, including an in-depth examination of cutting-edge scientific concepts and perspective articles from leading scientists. IAVI produced 12 issues of *VAX* in 2005. Distribution of these publications also significantly increased in 2005. In addition to 4,200 individual e-mail subscribers to *VAX*, the number of print copies shipped increased five-fold in 2005. Similarly, bulk subscriptions to IAVI Report increased from 300 copies per issue to more than 1,800, not including the 7,500 individual subscribers. In 2005, IAVI secured registration of *IAVI Report* on PubMed, the National Library of Medicine's database of citations and search and retrieval system for biomedical publications.

Organizational Positioning Project. To increase IAVI's visibility as a global knowledge center and integrated vaccine development operation, IAVI must effectively market itself to a broad array of audiences. In 2005, IAVI launched an organization-wide initiative to develop communications and management strategies that accurately convey the organization's vision and breadth of activities and that emphasize IAVI's added value to global vaccine R&D. As part of the organization's long-term communications effort for diverse audiences, an internal IAVI team is planning a series of events to mark the organization's 10th anniversary in 2006, which will provide a platform for showcasing IAVI's achievements in its first decade and for building momentum for the challenges ahead.

Social Science Research. IAVI collaborated with the socio-behavioral working group of the South Africa AIDS Vaccine Initiative to organize a June 2005 meeting on social science research and AIDS. In collaboration with the International Center for Research on Women, IAVI is conducting a preliminary assessment of gender issues in vaccine research, with the goal of identifying and addressing barriers to women's participation in vaccine trials.

Clinical Trial Ethics. In addition to ensuring that IAVI-sponsored trials adhere to the highest ethical standards, IAVI is also working with others to identify and disseminate best practices in the field. In May 2005, IAVI participated in an Informed Consent Workshop organized for the microbicide community by the Population Council and Family Health International. IAVI is currently exploring a possible vaccine-specific meeting on trial ethics for site staff and experts.

BIO Panel. IAVI organized and participated in a panel discussion for the annual conference of BIO — the biotechnology trade organization — on collaborations between not-for-profit developers and private industry to address critical health issues facing developing countries. The panel highlighted the unique role of public-private partnerships in developing products for neglected diseases.

Global Forum for Health Research. An IAVI presentation on policy reforms to promote biomedical R&D received coverage in the international media. The global forum, a leading source of information on financing trends for health research, has played a major role in bringing global attention to the severe neglect of health conditions in developing countries in the allocation of resources for health R&D.

HIV Vaccines and Human Rights. IAVI co-sponsored a project by the Canadian HIV/AIDS Legal Network to develop advocacy materials on the legal, ethical and human rights issues arising in the context of HIV vaccine development and access. It is anticipated that these materials, such as several fact sheets developed in 2005, will complement IAVI's work to educate and mobilize communities on HIV vaccines.

Women and children in waiting area of KEMRI/IAVI Family Health Clinic at Kilifi District Hospital in Kenya

Objective: *Promote a positive media environment in international, regional and local outlets on IAVI, AIDS vaccines including the cost of product development and the economics of a vaccine.*

Working with communications professionals at GlaxoSmithKline, IAVI generated favorable, high-profile media coverage of the announcement of the organization's groundbreaking agreement with GSK Biologicals. Similar widespread coverage greeted IAVI's launch of the first-ever human vaccine trial in India. To promote positive media coverage on vaccines, IAVI and the Brazilian national AIDS program co-sponsored a successful journalists training seminar in Rio de Janeiro that attracted leading science and health reporters.

IAVI President/CEO Seth Berkley participated in the *Time* summit, which received substantial media coverage worldwide. Berkley also delivered a keynote address to 23 health care journalists from developing countries who were attending a Reuters Foundation journalism workshop on coverage of the AIDS epidemic.

Strategy Three:
Promote Public Policies that Support Vaccine R&D and Future Access

The strategic plan recognizes that policy reform is needed to accelerate AIDS vaccine R&D and to ensure future access. To enable IAVI to lead global efforts to implement sound, vaccine-supportive policies, the strategic plan provides for IAVI's development of a strong evidence base for its advocacy positions, the highest-quality policy analysis, and strong advocacy partnerships.

In 2005, IAVI undertook high-level policy studies to build the evidence base on AIDS vaccine policy, including leading global efforts to significantly strengthen the methodology for estimating R&D spending on AIDS vaccines. Economic modeling and other analyses commissioned by IAVI seek to enable IAVI to make the strongest and most comprehensive economic case possible for increased investment in AIDS vaccines.

Objective: *Make the case for increased/improved public sector investment in an HIV/AIDS vaccine.*

In 2005, IAVI produced numerous new analytical research products to build a compelling investment case for increased public sector spending on AIDS vaccine R&D.

Quantifying the Resource Gap. While IAVI and other vaccine advocates have long argued for increased funding for vaccine R&D, citing the tiny percentage of biomedical R&D devoted to this paramount global scientific challenge, there has historically been only limited data regarding total amounts spent annually on vaccine R&D and on the sums required to support a robust, comprehensive global vaccine effort. Consistent with the strategic plan, IAVI in 2005 took major steps to close this important knowledge gap, with an eye toward enhancing the magnitude and strategic effectiveness of global financing for vaccine R&D.

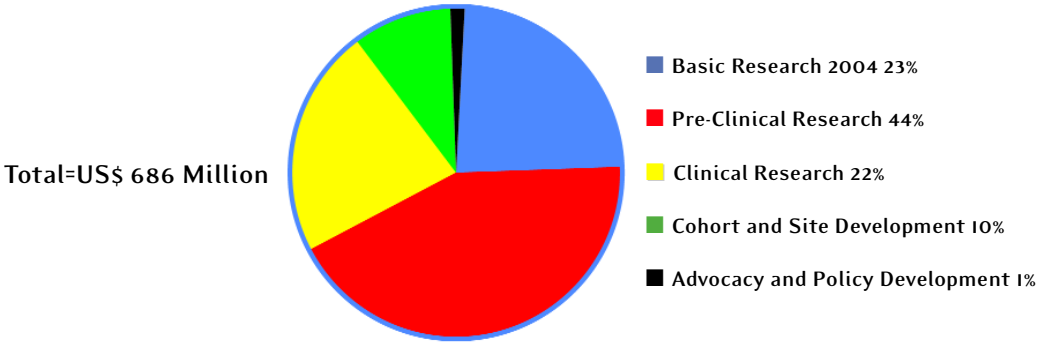
In December 2004, IAVI joined with the AIDS Vaccine Advocacy Coalition, the Alliance for Microbicide Development, and the UNAIDS Resource Tracking Unit to form the HIV Vaccines & Microbicides Resource Tracking Working Group, which monitors public, philanthropic and commercial sector resources for vaccine and microbicide R&D. In June 2005, the working group published its findings, which estimated total spending on AIDS vaccine R&D at $682 million in 2004. Key results from the study have been cited or discussed in such forums as the annual meeting of the UNAIDS Programme Coordinating Board, the Global HIV Vaccine Enterprise coordinating committee meeting, the International Conference on AIDS in the Asia/Pacific region, and AIDS Vaccines 2005 conference in Montreal.

Based on the resource tracking studies, IAVI developed an estimate of the overall shortfall in current R&D "push" financing for AIDS vaccines, and examined how this shortfall is distributed across key stages of vaccine R&D. A June brief, which supported discussions on resource mobilization for AIDS vaccines at the Gleneagles G8 summit, concluded that $1.2 billion annually is needed to support R&D for AIDS vaccines. This figure has been cited by the Global HIV Vaccine Enterprise and other thought leaders in the field. Estimated resource gaps for HIV vaccines in 2004 are $182 million - $207 million for basic and applied science, $130 million - $155 million for product development, and $28 million for capacity, infrastructure and policy development. (See Figure 4)

Modeling the Impact of an AIDS Vaccine. Working with the Futures Group, IAVI began analyzing the potential epidemiological impact — both globally and for countries — of introducing HIV vaccines with various characteristics. Two complementary reviews of the existing literature on vaccine impact were completed in 2005, and a first round of global modeling suggests that even a partially effective vaccine would have a considerable impact on the epidemic. A vaccine with only modest efficacy and coverage could still avert 45 million new infections over 15 years and reduce the rate of new infections by one-third, according to IAVI's initial analyses.

FIGURE 5

Breakdown of HIV vaccine expenditures (2004)



Source: *Tracking Funding for Preventive HIV Vaccine Research & Development: Estimates of Annual Investments and Expenditures 2000 to 2005*. HIV Vaccines and Microbicides Resource Tracking Working Group (AVAC, AMD, IAVI, and UNAIDS), 2005.

Objective: *Pursue initiatives to increase and/or accelerate R&D by the private sector or by public-private partnerships.*

An important aim of IAVI since its creation has been to encourage substantially greater engagement by private industry in the search for a preventive HIV vaccine. In addition to forging numerous collaborative relationships with private industry, as previously described, IAVI in 2005 intensified its advocacy for policy reforms to create greater financial incentives for private sector investment in vaccine R&D.

Advance Market Commitments. To entice greater industry investment in HIV vaccines, it is vital to increase industry confidence that a robust market for a vaccine will exist in developing countries. An advance purchase commitment (APC) is a legally binding commitment by one or more donors and/or governments to pay a fair market price for a qualifying vaccine procured by developing countries. IAVI's analysis suggests that an advance market commitment for vaccines would be technically feasible, credible and attractive to industry, sponsors and developing countries.

In early April, IAVI and the Malaria Vaccine Initiative (MVI) shared their work on APCs with officials from the UK Treasury and Department for International Development, as well as the Center for Global Development, BioVentures for Global Health, the Global Alliance for Vaccines and Immunization, and the Bill & Melinda Gates Foundation. In preparation for the G8 summit in Gleneagles, the World Bank convened a meeting on APCs for new vaccines, at which IAVI provided background materials on APCs to finance ministries, major vaccine producers, and to a number of biotech companies and developing country vaccine suppliers. Following continued advocacy by IAVI and its partners, the G8 communiqué at Gleneagles announced the group's intention to develop an APC pilot program in 2006. Subsequently, IAVI worked to ensure the inclusion of AIDS vaccines as an option paper exploring a multi-product APC presented by the Italian government to G7 finance ministers in December 2005.

In December 2005, IAVI President/CEO Seth Berkley met with P. Chidambaram, Indian Finance Minister, as well as Kapil Sibal, Indian Minister of State for Science and Technology. The Indian Finance Minister endorsed the need for dialogue between the finance ministers of India, Brazil and South Africa and with UK Chancellor Gordon Brown to explore policy options to support the development and delivery of AIDS vaccines, including an advance purchase commitment. While in India, Berkley presented to the partners meeting of the Global Alliance on Vaccines and Immunization regarding potential new financing mechanisms to improve access to vaccines.

Legislative Initiatives in the U.S. Congress. Advocacy by IAVI and a coalition of global health advocates helped ensure inclusion of infectious diseases in follow-up BioShield legislation. The first version of BioShield, adopted following the terrorist attacks of September 11, 2001, sought to stimulate greater pharmaceutical and biotech investment in research on new tools to fight bioterrorism. The BioShield II legislation, introduced in April 2005,

includes a broad array of incentives to increase industry involvement in R&D. IAVI has also actively supported the Vaccines for the New Millennium Act — introduced by Senators Kerry and Lugar — which calls for the establishment of AMCs for vaccines and microbicides.

Collaborations with Private Industry. In addition to IAVI's extensive research collaborations with private industry, described above under Strategy I, IAVI has also forged meaningful partnerships with private industry on key policy initiatives. Following a December 2004 discussion forum between IAVI and Indian industry, IAVI's India office collaborated in the first half of 2005 with its New York-based counterparts in the R&D and Policy departments to identify research possibilities to engage the biopharma sector in India. In September 2005, IAVI met with the Indian Department of Biotechnology to discuss potential areas of joint collaboration with Indian scientists. In addition, IAVI has engaged representatives from both big pharma and biotech companies on policy analysis work on advance market commitments, resource tracking, R&D costs, and demand forecasting. Berkley addressed CEOs of biotech companies at the sector's annual biotech conference at Laguna Niguel (California, USA).

Objective: Ensure that manufacturing and regulatory processes facilitate R&D and rapid access to an AIDS vaccine.

IAVI's strategic plan for 2005-2007 recognizes that numerous legal and logistical factors can delay access to new vaccines for many years. To be available for use in the field, vaccines must be licensed by national regulatory authorities, yet regulatory capacity is weak in many countries. In addition, to ensure that a sufficient supply of a new vaccine is available to meet global demand, manufacturing scale-up must be initiated years prior to completion of Phase III trials. IAVI aims to address such access barriers through effective advocacy which emphasizes that needed policy reform must begin immediately to ensure rapid future access to new vaccines.

Regulatory Reform. In advance of the assumption by the UK of the EU presidency, IAVI and IPM met with British development officials to emphasize the importance of continuing momentum toward implementation of initiatives begun during the previous Dutch and Irish presidencies. These initiatives include the EU's role in supporting improved regulatory processes in developing countries.

Bioprocess Development and Manufacturing of AIDS Vaccines. With the aim of informing discussions with the Vaccine Enterprise regarding the shortage of bioprocess development skills available in AIDS vaccine R&D, IAVI released a discussion paper on problems and policy options in bioengineering and manufacturing of AIDS vaccines, disseminating the report to donors and other key stakeholders.

Expediting Approval of Clinical Trials. IAVI also studied the clinical trial approval process in developing countries, publishing a case study of Brazil and beginning work on a best practices paper on five countries. The project seeks to build on national experience to identify strategies for minimizing delays in clinical trial approval.

Good Clinical Practice workshop in Entebbe, Uganda

Objective: *Build the knowledge base to better understand need and demand for HIV/AIDS vaccines, and advocate for policy initiatives to ensure adequate global supply and the rapid adoption of HIV/AIDS vaccines by countries and individuals.*

A sound, accurate understanding of future demand for a vaccine is vital not only to efforts to encourage greater industry engagement and public sector support on vaccine R&D, but also to promote reliable decision-making regarding manufacturing capacity. The 2005-2007 strategic plan provides for analytic work by IAVI to inform efforts to gauge future demand for a preventive vaccine.

Demand. IAVI joined with the Uganda Virus Research Institute and Makerere University to co-convene a March 2005 meeting to review the results of a Makarere University study on demand for future vaccines. In April, the organization published a research working paper that surveyed the existing literature on previous demand studies and highlighted the need to estimate both public sector and individual demand for an AIDS vaccine in developing countries. The paper presents strong evidence of broad public sector willingness to purchase and use an AIDS vaccine and of substantial household willingness to purchase a vaccine out of pocket in high-prevalence countries such as Uganda and Thailand. In November, IAVI initiated a project to develop and apply a robust and credible model of global demand for a future preventive vaccine, which in turn will be used to support a comprehensive investment case for vaccines.

AIDS and the Millennium Development Goals. In 2005, IAVI undertook a comprehensive analysis of the potential impact of AIDS on achievement of the Millennium Development Goals, summarizing findings in a report — *Putting It Together: AIDS and the Millennium Development Goals* — that was released prior to the UN World Summit on the MDGs. The paper concludes that failure to halt the AIDS epidemic will jeopardize progress on a broad range of MDGs and that new prevention technologies, including vaccines and microbicides, represent the best hope for controlling the epidemic. The findings from the report have been cited by influential speakers, including Stephen Lewis, the UN Special Envoy for AIDS in Africa.

Ensuring Future Availability and Accessibility of Vaccines. The Health Policy Unit of the Institute of Economic Growth (Delhi) continued work on an IAVI-funded study to assess the adoption and use of new health technologies in India. The study details the processes for approval and licensure, procurement, uptake and utilization in India for four technologies — the hepatitis B vaccine, antiretroviral therapies, sterilization methods, and HIV voluntary counseling and testing services.

Strategy Four:

Engage as Partners the Countries Where the Epidemic Is, Or Is Likely to Be, Most Severe

Since its inception, IAVI has pursued its work as a global organization, with active partners in both developed and developing countries. IAVI's vaccine development partnerships have involved researchers and stakeholders from both North and South, and the organization's country programs educate communities, engage political leaders, and raise public awareness of vaccine-related issues.

The strategic plan for 2005-2007 provides that IAVI will build on these achievements to enhance the capacity of developing countries to serve as full partners in the global search for a safe and effective vaccine. In particular, IAVI seeks to contribute to a substantial expansion of global clinical trial capacity and to assist countries in preparing for eventual introduction of future vaccines.

Key to IAVI's ongoing partnerships with stakeholders in developing countries are the organization's field staff in India, Kenya and Uganda, as well as core staff based in New York. IAVI strives for consistency and coherence across country programs, harmonization of country-based efforts with IAVI goals, representation of field interests and perspectives in organizational operations and decision-making, and management of relationships with developing country stakeholders and with networks of organizations that focus on developing countries. In addition to providing country-level operational and technical support, IAVI seeks to improve the political and logistical environment for AIDS vaccine research in developing countries.

Objective: Ensure national and site preparedness is in place to accelerate all stages of HIV/AIDS vaccine trials, especially in countries where the epidemic is most severe and incidence is high.

To expedite future testing of the most promising vaccine candidates, extensive preparation is required to ensure that clinical trial capacity is available in all regions that are heavily affected by the epidemic. In addition to developing core clinical trial infrastructure in clade A and clade C regions, IAVI uses the best available epidemiological methods to identify populations for rapid recruitment in future trials. Under the 2005-2007 strategic plan, IAVI seeks to ensure that national policies are in place to accelerate clinical trials and that the communities where trials will occur are fully educated and supportive.

National Preparedness. IAVI sponsored an extremely successful vaccine preparedness workshop in January 2005 in Kungming, China. Subsequently, IAVI participated in a series of discussions with leadership of the Aaron Diamond AIDS Research Center and the Chinese Academy of Medical Sciences, among others, to assess current vaccine-related activities and to plan for expanded vaccine preparedness nationally. IAVI approved a grant to the Chinese Academy of Medical Sciences to undertake vaccine preparedness activities, and a national meeting on vaccine preparedness in China is anticipated in the first quarter of 2006. IAVI intends to sponsor an ethics training workshop for Chinese counterparts and to support a satellite meeting at the International Conference on Bioethics, which will be held in China in 2006.

In Africa, IAVI assisted the government of Kenya in developing its national vaccine strategy and is playing a supporting role in the efforts of Uganda to finalize its own revised national plan. With respect to South Africa, IAVI submitted a proposal to the European Commission for capacity-building support in South Africa and Zambia. IAVI co-hosted (with Masikhulisane, the community involvement program of the South Africa AIDS Vaccine Initiative) a satellite session at the 2nd South Africa AIDS Conference, and collaborated with SAAVI in convening a working meeting on social and behavioral issues relating to vaccine research.

Cohort Development. IAVI significantly enhanced its capacity to identify and characterize patient cohorts for future vaccine trials. As noted in Section I, IAVI completed physical infrastructure development at its five African field sites to support long-term cohort studies required for the study of early infection. Protocols have been or will be developed at each of the sites to permit ascertainment of infection prevalence and incidence, identification and characterization of the genetics of the virus responsible for incident infections, and assessment of the ability of the sites to recruit and maintain study cohorts. With respect to incident infections, IAVI will also ascertain the nature and genetics of the initial immune response, which

will inform efforts to develop vaccines eliciting immune responses comparable to those that follow infection with currently circulating virus.

At its Uganda and Kenya sites, IAVI began recruiting participants in a study to assess HIV incidence and undertake in-depth immunologic and genetic study on new infections.

Site Preparedness. In January 2005, IAVI's East African field offices undertook comprehensive assessments of national and district-level access to voluntary counseling and testing (VCT) and HIV health care services, with particular focus on access at each of IAVI's feasibility study sites. This assessment, designed to strengthen future IAVI efforts to recruit and retain trial volunteers, resulted in a series of recommendations, which are now being implemented. In Kenya, VCT training curricula were adapted to provide refresher training for nurse counselors at IAVI sites. Initial guidelines were developed to ensure ongoing supportive supervision and to implement quality assurance mechanisms for counseling during studies. IAVI also worked with site staff to develop informed consent videos at the Kangemi and Kilifi sites. IAVI made small grants to Kisubi Hospital and the AIDS Information Centre in Uganda to build VCT capacity in communities surrounding the Entebbe trial site. IAVI also trained VCT counselors at both Phase I sites in India.

The Uganda Virus Research Institute, IAVI's partner in Uganda, named Dr. Edward Mbidde as its new director. Dr. Mbidde is a former member of the IAVI Scientific Advisory Board and is a strong supporter of both vaccine development and IAVI. In India, IAVI began implementing care and treatment guidelines for its trial sites, which were developed following a 2004 national consultation and endorsed by the national government.

Community Engagement. To build public support and lay the groundwork for volunteer recruitment for future trials, IAVI routinely engages diverse stakeholders in the countries and communities where IAVI-sponsored trials occur. In 2005, IAVI published the AIDS Vaccine Literacy Core Content, the first component of a tool kit for educating stakeholders on AIDS vaccine issues; the Core Content is now being used by site staff and stakeholders in at least eight countries. IAVI is at work on developing additional components of the tool kit, including a training curriculum and three prototype educational materials. IAVI supported the formation of new Community Advisory Boards in India and Kenya, as well as a network of CABs in Uganda, and collaborated with the South Africa AIDS Vaccine Initiative in conducting a workshop on community mobilization at the national AIDS conference.

- Kenya. *IAVI continued to develop and support its network of civil society organizations, the Vaccine Support Network. In early 2005, IAVI sponsored a "train the trainers" workshop for the network's master trainers, with plans for 10 additional regional training programs to take place by the end of the year. As part of a planned nationwide vaccine education program for health care service providers, IAVI in 2005 undertook an inventory of health institutions in five priority provinces, conducted a baseline study of knowledge and attitudes, and initiated sensitization workshops. IAVI produced an educational comic book for East African audiences entitled "Finding New Hope Together," which was adapted with permission from similar material from South Africa.*

- India. *An NGO Working Group has been established to advise IAVI's India program on grassroots community engagement. The working group intends to organize regional NGO workshops in four high-prevalence states in southern India and two high-prevalence states in western India to engage local communities and to raise awareness about AIDS vaccine issues, with the first occurring before the end of 2005. In addition, the Tuberculosis Research Center, a second site for IAVI trials in India, entered into a Memorandum of Understanding with YRG Care, a Chennai-based non-governmental organization, to assist in preparedness activities for recruitment and retention of future trial volunteers. A preliminary consultation identified key areas of social research to be undertaken at potential sites; follow-up areas identified included community mobilization, human rights, ethics and gender.*

Gender. Early vaccine trials demonstrated that despite a willingness by women to participate, a variety of barriers led to low enrollment of women. In response, IAVI has prioritized identifying and addressing gender issues that affect the successful conduct of trials. As part of this emphasis, IAVI developed gender training manuals and conducted gender training for IAVI's trial teams in India, with a similar exercise planned for trial teams in east and southern Africa. The South Africa AIDS Vaccine Initiative has expressed interest in partnering with IAVI in this effort. IAVI is in process of developing a global gender strategy to strengthen advocacy at local, national and international levels to promote AIDS vaccines as a crucial response to the vulnerability of women and men who have sex with men.

IAVI is also working to better understand the multi-layered and complex needs of men who have sex with men, a high-risk and often-stigmatized population that could be involved in future vaccine trials. In India, many men who have sex with men have personal identities based in large measure on their expression of gender and sexual roles.

Cross-Cutting Organizational Strategy:
Refine the IAVI Business Model and Operational Structure to Maximize IAVI's Ability to Implement the Strategic Plan

Implementation of the strategic plan is guided by the principles of speed, flexibility, and the willingness to take *informed risks* in the pursuit of IAVI's mission. Putting these principles into practice, IAVI has taken steps to strengthen and streamline its internal operations — sharpening accountability, mobilizing resources, and looking to the state-of-the-art as the standard for internal policies and practices.

Best Operational Practices

Having evolved from a tiny organization with a handful of staff into a global organization working in 23 countries, IAVI aims to adhere to state-of-the-art organizational practices to maximize productivity, enhance accountability, and ensure optimal value for IAVI's stakeholders. In particular, IAVI in 2005 implemented policies and practices to promote transparency in governance through the development of clear performance criteria to be used in monitoring and evaluating IAVI departments and units. Updating its infrastructure and business approaches, IAVI also continued its transition from a grant-making institution to one that drives, manages, and is fully responsible for the projects it funds and the products it sponsors.

General Counsel. As part of IAVI's effort to strengthen its policies and procedures and to provide an organization-wide mechanism for managing legal and other risks, it established the Office of General Counsel within the Executive Office. In 2005, the General Counsel initiated a risk management review and analysis, provided advice on intellectual property matters, and provided support for the negotiation of IAVI's scientific partnership with GSK Biologics. The General Counsel worked with the Executive Office to develop new approaches to IAVI business development, revised by-laws of the IAVI Board of Directors, and developed terms of reference for all Board committees. In 2005, IAVI also issued a code of conduct and updated its conflict-of-interest policy, each of which is available on the IAVI web site (www.iavi.org).

Budgeting. In 2005, extensive staff effort focused on implementation of performance based budgeting, which will permit the IAVI Board and management to link particular financial allocations (or "investments") with specific objectives and goals of the strategic plan. Performance based budgeting, which is being introduced in 2006, will enable the organization to quantify spending on a particular goal, compare spending levels for multiple goals, and better assess how budget allocations are contributing to the organization's identified strategic goals.

Financial Audits. Ernst & Young LLP completed their fourth annual audit of IAVI, which yielded no material adjustments and a clean audit opinion that IAVI's financial statements represent a fair depiction of the organization's financial condition. Ernst & Young also completed their third A-133 audit on proper financial controls, also generating a favorable opinion for the organization. IAVI obtained a clean audit opinion for the organization's European Union grant from Mazars Audit in the Netherlands.

Investments. IAVI continues to work with CRA Rogers Casey, the organization's investment advisor, to sharpen IAVI's investment strategy. In particular, attention is being paid to currency planning and forecasting, with the goal of minimizing currency exposure and enhancing management of cash flow in all operational currencies.

Grants, Contracts and Compliance Management. In recognition of the fact that much of IAVI's funding is restricted to particular uses, IAVI in 2005 hired a senior director to oversee the organization's grant and contract compliance and management. In May 2005, IAVI implemented its first electronic time and effort reporting system, permitting the organization to track personnel time by project and product. IAVI also enhanced its capacity for procurement oversight and field compliance. IAVI conducted its first finance workshop for field site partners in 2005, reviewing IAVI financial policies and donor compliance requirements.

Human Resources

To implement the organization's strategic plan for 2005-2007, IAVI requires a highly qualified, well-managed staff, as well as human resource practices that help manage growth, ensure continuous quality improvement, and comport with all aspects of the organization's mission, including its global dimensions.

As part of IAVI's efforts to increase human resource support to field offices, the Senior Human Resource Director and a Global Human Resource Associate visited the India office in December 2005. During the visit, the Senior Human Resource Director met with each member of the team to discuss career plans and professional development. The visit also provided opportunities for a review of personnel practices in the office, as well as improved collective understanding of Indian labor laws and regulations.

In 2005, IAVI launched a new Applicant Tracking System

(SonicRecruit) to systematically track the most promising candidates for staff positions at the organization. (The system can be accessed on the IAVI web site by clicking "Careers at IAVI.") All IAVI managers have been trained in the use of new system.

Over the last 12 months, IAVI sharpened its performance management tool, with human resource staff providing training in this area to managers and staff in late 2005. IAVI collected benchmark data and analysis from comparable organizations to inform its continuing exploration of optimal compensation models appropriate for IAVI at this stage of its organizational development.

Objective: Expand and diversify IAVI's funding base to ensure adequate resources are available to supports its strategic and operational objectives.

Resource Mobilization

To finance its strategic vision, IAVI in 2005 redoubled its efforts to mobilize sufficient resources. (IAVI's efforts to mobilize greater financial resources for the entire field are discussed above, under Strategy II.)

IAVI is greatly encouraged by, and deeply appreciates, the significantly increased financial support from its government and multilateral donors, including the European Union, the World Bank, and various national governments. Denmark, Ireland, Norway, and the United Kingdom increased their funding to IAVI in 2005 through multi-year commitments. The Netherlands provided a supplemental grant of 4.5 million in 2005, and two different national ministries in Sweden made awards to IAVI totaling SEK 12 million (U.S. $1.45 million). The European Union awarded IAVI's European foundation, Stichting IAVI, a new three-year 3 million grant for vaccine preparedness in South Africa; as part of this grant, IAVI plans to establish an office in Johannesburg. In 2005, Canada made its third grant to IAVI, a one-year commitment of CAD $12 million (U.S. $10.2 million), bringing total Canadian contributions to IAVI to U.S. $57.8 million in today's dollars. The Basque government became the newest public sector donor in 2005, supporting the creation of a new clinical trial site in Chennai, India.

IAVI also applied to the U.S. Agency for International Development for funding for 2006-2010, with actual future contributions contingent on Congressional appropriations. U.S. government support for IAVI has significantly grown since the initial grant in 2001, amounting to U.S. $27 million in 2005.

Philanthropic foundations continued to provide strong support for IAVI's work in 2005. Previous IAVI supporters, including the Otto Haas Charitable Trust and the Until There's a Cure Foundation, renewed their financial support in 2005. The New York Community Trust awarded its first research grant to IAVI, a two-year U.S. $575,000 grant to support IAVI's new vaccine development laboratory, which is the organization's first scientific venture in its headquarters city and its first in-house clinical vaccine development facility.

In recognition of the success of the public-private partnership model of product development, which the Rockefeller Foundation helped pioneer, the Rockefeller Foundation announced a special one-time grant of U.S. $250,000 to provide general support to IAVI in 2006. The award supplements the foundation's current two-year grant of U.S. $500,000 for 2005-2006.

In 2005, IAVI benefited from substantial in-kind support from corporate donors. Google awarded IAVI participation in its *AdWords Program*, which more prominently features IAVI's web site address when keywords such as "AIDS" or "HIV" are entered into the Google search engine. Pfizer and IAVI also initiated a new partnership through the company's Global Health Fellows Program, which deploys Pfizer medical and managerial volunteers to help NGOs in developing countries build capacity to address health threats. In 2005, Pfizer contributed two fellows to assist in IAVI's work — a medical monitor to support IAVI's medical affairs group in Nairobi, and a senior clinical research associate in Johannesburg working under the supervision of IAVI's clinical immunology laboratory manager.

Previous corporate donors renewed their financial support for IAVI in 2005. Continental Airlines renewed its in-kind sponsorship agreement with IAVI, extending the 2004-2005 agreement into 2006-2007. As in prior years, DHL, the world's leading express delivery and logistics company, provided free shipping, valued in 2005 at U.S. $135,000; since 2003, DHL has provided free shipping for documents and sample containers between IAVI's core laboratory in London and field sites in East and West Africa. A five-year, U.S. $1 million grant from Becton, Dickinson and Company is now in its fourth year; in addition to financial support, Becton, Dickinson provided ongoing product and service discounts valued at approximately U.S. $85,000 annually. Several law firms collectively provided IAVI with pro bono legal services totaling more than U.S. $100,000.

IAVI strengthened its efforts in 2005 to solicit financial

Community partners participate in an advocacy walk on World AIDS Vaccine Day in Kenya

support from the corporate sector. In June 2005, IAVI worked closely with the Business Coalition for International Understanding, a U.S. business association of which IAVI is the only NGO member, to host a breakfast meeting sponsored by Forbes, Inc. for IAVI board member Kapil Sibal, Indian Minister of State for Science and Technology. Minister Sibal was also the featured speaker at a breakfast meeting of the Council on Foreign Relations, whose membership includes more than 250 companies. *Business & AIDS* — the magazine of the Global Business Coalition on HIV/AIDS — featured IAVI President/CEO Seth Berkley in a 2005 article.

In August 2005, IAVI launched its first donor newsletter, which was distributed via e-mail to approximately 70 current and prospective donors, mostly in the private sector. In 2006, the newsletter will become a regular quarterly publication.

Consistent with IAVI's organizational growth and the long-term vision articulated in the strategic plan, IAVI focused substantial staff resources in 2005 on the cultivation of new funding sources for the organization. In particular, IAVI prioritized development of new private sector sources of financial support, with emphasis on unrestricted giving, which will be critical to IAVI's ability in the future to move rapidly in response to emerging data and new research opportunities. Targeted initiatives to foundations, corporations and high net-worth individuals also offer IAVI critical entrée to philanthropic, policy and business circles where the increased visibility of vaccines may contribute to achievement of IAVI's R&D and policy goals. Planning is well underway to leverage the organization's 10th anniversary events and the recent opening of IAVI's New York City vaccine development laboratory to expand and diversify donor support.

Small gifts nearly tripled between 2004 and 2005 — both in terms of the number of donors and total contributions (more than $90,000). Two-thirds of donors made their contributions online, compared to 40% in 2004, and the total amount contributed online tripled. These trends stem from several changes implemented in 2005, including a complete revamping of the "Donate" page on IAVI's web site, new technology to streamline donations over the Internet, and Google *AdWords* that drives traffic to IAVI's web site.

Conclusion

While much has changed in the AIDS response and the vaccine field since IAVI was created, at least one thing has not. Long-term success in the fight against AIDS depends on the development and effective use of a preventive vaccine.

IAVI continues to believe in the possibility of a world without AIDS. It is this vision that inspires the work of IAVI staff and partners in 23 countries around the world.

In 2005, IAVI substantially strengthened its R&D program, its policy analysis and advocacy, its partnerships and capacity-building initiatives in developing countries, and its own internal operations. These advances will enable IAVI to identify and capitalize on new opportunities as they arise, help answer key scientific questions that currently slow vaccine development, rapidly translate basic research breakthroughs into products suitable for clinical testing, and support the broader vaccine field. In all of these endeavors, IAVI will continue to forge and maintain working partnerships with a broad range of stakeholders in both developed and developing countries.

Developing a vaccine capable of defeating AIDS will not occur overnight. The time to an AIDS vaccine, however, can be dramatically shortened. With its fully integrated organizational model, combining the positive attributes of public and private sectors, IAVI is poised to lead global efforts to accelerate the development of a safe and effective vaccine for use throughout the world.

150,000 children, many of them infected with HIV, have been placed in Romanian state run orphanages

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