Joining Forces
Working with Partners to Advance AIDS Vaccine Development
Message from the President

If any single word captures IAVI’s experience of 2011, it is change.

Over the course of the year, the organization completed a comprehensive review of its operations, devised a new strategic plan, said goodbye to its founding CEO, welcomed me in as his successor, and even moved its headquarters further downtown in Manhattan.

What has not changed, however, is IAVI’s mission. We remain an organization dedicated to ensuring the development of a safe, effective, preventive HIV vaccine for use throughout the world. That mission, set in stone these past 16 years, continues to guide and inspire IAVI’s operations and the efforts of its staff.

Yet changes in the field of HIV-prevention research, and a global economic downturn that has severely curtailed the resources available to global health initiatives, prompted IAVI to reconsider how it pursues its objectives. This set in motion a review of the organization’s existing strategy, operations, investments and partnerships that began in 2010 and continued through much of 2011. Led by IAVI’s Chief Operating Officer David Cook, an IAVI team consulted extensively with the organization’s funders, partners, leaders and other stakeholders, and formulated a new five-year strategic plan.

This enormous exercise was well underway when I was recruited from IAVI’s Board of Directors to become its new CEO. Though I was involved in the strategic review as a Director, I learned a good deal about IAVI in overseeing the completion of the process, not least through the many external consultations I held with IAVI’s partners, supporters and donors. I gained a new appreciation for the organization’s intricacies and strengths as well as the sheer dedication of its people. I also have developed an even deeper respect for what Seth Berkley, IAVI’s founder and my predecessor, achieved through his dedication and drive to rid the world of HIV. At the same time, the consultations revealed many areas in which IAVI could improve and ways in which we could become a more effective partner and provide even greater value to the field.

But, as the articles and profiles in our 2011 Annual Progress Report reveal, IAVI is not the sole author of those advances. They are instead the product of its many partnerships for AIDS vaccine development in countries around the world. In fact, every one of IAVI’s initiatives—from vaccine design to advocacy to community engagement—depends on the cultivation of strong, mutually trusting, productive collaborations with other organizations, researchers and institutions. Much of the progress we made in understanding broadly neutralizing antibodies in 2011, for example, stemmed from partnerships with multiple public, commercial and nonprofit research organizations across the globe. Similarly, IAVI’s contributions to HIV-prevention policies were made in partnership with like-minded nongovernmental organizations.

A central element of IAVI’s new strategy is to transform the organization into a partner of choice in every one of its endeavors. I hope that in reading IAVI’s Annual Progress Report you will gain a new appreciation for the many donors, organizations, researchers and advocates around the world who make our work possible. On IAVI’s behalf, I would like to thank them for their support, and invite them to join us in celebrating the advances we have made together toward our shared goal of a world without AIDS.
Field Coordinator Mathias Wambuzi and his colleagues were on a three-hour trip to one of Lake Victoria’s islands in 2008 when the lake, as is its way, rose in a sudden rage from its slumber. Towering waves tossed their small boat about as a driving rain lashed at the crew, a field team from IAVI’s longstanding partner, the Uganda Virus Research Institute (UVRI). The team was heading to a “sensitization meeting” with one of the isolated island communities on the Lake. Theirs was an outreach mission, taken to forge links with people who UVRI researchers hoped would populate a cohort for the assessment of HIV prevalence and incidence in a handful of fishing communities. Cultivating the trust of their leaders would be essential to the feasibility and sustainability of the study. Pitching ahead grimly, the team soon came across fishermen on three tiny boats waving oars in the air to get their attention. The team pulled up to the stranded boats and towed them to the nearest island. As they arrived at the landing site, villagers came pouring out of their houses, chanting and whooping to welcome the rescuers ashore. “I must tell you,” says Wambuzi, “life was very easy for us the next day on that island. People were actually giving us free fish in appreciation.”

The research team would be rewarded in other ways as well. As rumors of their rescue spread through the nearby islands, they developed a certain cachet in the marginalized communities in which they hoped to conduct their research. Recruitment became much easier. The results of the UVRI-led HIV prevalence study that Wambuzi and his colleagues were preparing for on that stormy day three years ago were published in the journal *Sexually Transmitted Infections* in August 2011. They reveal that more than one in four of the people (28%) in five fishing communities are HIV positive, a rate that is more than four times as high as that of Uganda’s general population. Subsequently, the same study found alarmingly high rates of new HIV infections in the study population. Since the completion of the UVRI study, the Medical Research Council-UVRI (MRC-UVRI) Uganda Research Unit on AIDS, with funding from IAVI, has begun working with fishing communities in the Masaka district of Uganda to develop a cohort for HIV-prevention research.

“Our study suggests that fishing communities might be ideal for the conduct of HIV-prevention research.”
The interest is understandable. Fishing communities
the world over are at high risk for communicable
diseases, especially sexually transmitted infections
(STIs) like HIV. This is not surprising. Sex workers
are fixtures at many of the fishing communities on
Lake Victoria’s shore, and a large number of the
men who work the boats are migrants, unrestrained
by the social norms that might prevail at home.
Such communities, often isolated and economically
and socially marginalized, are in great need of
preventive interventions. They could therefore be
important for the conduct of future large-scale
vaccine trials, as the effects of candidate preventive
tools are easier to detect statistically where the
incidence of HIV is high. “Our study suggests that
fishing communities might be ideal for the conduct
of HIV-prevention research,” says Pontiano Kaleebu,
who led the UVRI’s groundbreaking work in fishing
communities.

Located as they are on a peninsula in Lake Victoria,
UVRI researchers had for years pondered reaching
out to fishing communities to include them in health
research. In 2007, the UVRI team finally decided to
give it a shot. Led by Professor Kaleebu, who
directed the UVRI-HAVI program at the time and
today leads the MRC Research Unit in Uganda,
UVRI teamed up with IAVI, The Malawi Liverpool
Wellcome Trust Project, the Liverpool School
of Tropical Medicine and WorldFish to submit
a proposal to the European and Developing
Countries Clinical Trials Partnership (EDCTP)
for funding to conduct an HIV risk, prevalence
and incidence study among fishing communities
of Lakes Victoria and Malawi. “People were very
pessimistic about engaging these populations in
research,” recalls Leslie Nielsen, IAVI Director of
Africa Partnerships, who is based in Uganda
at the UVRI. “They were saying that they’re too
mobile, that their lifestyle was such that they
wouldn’t care about participating in research, that
we wouldn’t be able to retain them in any kind of
study. And, we found, that actually wasn’t true.”

Still, the recruitment of volunteers was an education
in itself. Social scientists have long known that
fishermen, though at pronounced risk for HIV
infection, can be remarkably unconcerned about
that possibility. “A person who has to deal with
winds and waves like that,” explains Wambuzi,
“looks at the risks of drowning as being much
higher than those of HIV.” An odd corollary of this
conviction, the team soon discovered, was that
many in the fishing communities had simply
assumed they were HIV positive. People wondered
aloud why the team bothered to conduct tests, and
didn’t just hand over HIV drugs. They questioned
the validity of negative results. In response, the
team stressed extra counseling to people who
tested negative. “Eventually,” says Wambuzi,
“people started realizing that even in this kind
of environment, it is possible to be HIV negative.”
The team also included medical doctors, who
ensured that research volunteers received basic
health care for other infections—such as
schistosomiasis and malaria—that are endemic to
the region, and supervised the nurses, counselors
and health outreach workers who comprised the
rest of the crew. The perk of rarely obtained medical
care drew large numbers of people for HIV testing.
“Not many organizations reaching fishing
communities provide medical care,” says Simon
Sigirenda, Community Liaison Officer at the
UVRI-HAVI HIV Vaccine Program. “It’s definitely
a risk. Some people freak out, and can’t travel
on the water. The lake can be unpredictable.”

That medical outreach continues today. Near the
Kasenyi landing site where fishermen drop off their
haul, grab meals, shoot pool and down a drink or
two in their off hours, the UVRI-HAVI program has
helped establish a voluntary counseling and HIV
testing (VCT) clinic. It has also engaged teams from
The AIDS Support Organization, Entebbe Hospital
and Marie Stopes International to provide HIV
services, health care and family planning services,
which are not easily accessed by the fishermen,
boat-builders, restaurant workers, merchants and
vendors at the site.

Over the course of the study, which was conducted
across five fishing communities in three districts,
HIV education was supported by local “peer
leaders” who were trained by the UVRI team to
raise HIV awareness and encourage people to
undergo voluntary counseling and testing for HIV.
The peer leaders held VCT programs in conjunction
with functions such as sporting events—soccer for
the men, basketball for the women—in which prizes
included life jackets and goats. The response, says
Nielsen, was overwhelming. Volunteers who tested
positive were provided with counseling and referred
for care. And UVRI easily recruited 1,000 HIV-
negative people for its studies.

Communities touched by this research have
benefited in many tangible ways, and UVRI has
informed policy-makers and service providers of
their findings. HIV education and awareness, which
was virtually nonexistent before the work started, is
now being offered in the settlements involved in
the research. “We have opened a point for these
“We have opened a point for these communities to begin accessing HIV services.”

“communities to begin accessing HIV services,” says Wambuzi. Meanwhile, the development of cohorts for epidemiology has helped to prepare the ground for new studies and future vaccine trials in these communities. The UVRI-IAVI program is conducting formative research in fishing communities in the Wakiso and Mukono districts, while the MRC-IAVI team—in addition to an IAVI-funded prevalence and incidence study—is currently preparing to conduct a mock vaccine trial using the hepatitis B vaccine to assess whether fisher folk can be retained in such studies.

The Lake Victoria experience illustrates how IAVI works, and how its work affects the communities recruited into HIV vaccine-related research. For example, the entire fisher folk study depended, from inspiration to execution, on the establishment of partnerships. IAVI has always worked through such partnerships, whether engaged in applied science for vaccine design, clinical trials or advocacy and policy analysis. IAVI’s Neutralizing Antibody Consortium, for instance, which is breaking new ground in the area of rational vaccine design, is a global collaboration to elicit effective antibodies to HIV through vaccination. IAVI’s vaccine development efforts similarly link research laboratories and pharmaceutical and biotechnology companies around the world to clinical laboratories in Africa.

Partnership, in every form, is in fact a cornerstone of IAVI’s new strategic plan. The accomplishments recorded throughout this year’s Annual Progress Report illustrate the far-reaching impact truly collaborative work can have on vaccine development. They also reveal how much IAVI’s approach to HIV vaccine development depends on the cultivation of strong relationships with communities in which research is conducted, and their recruitment into the larger program of advocacy for HIV prevention. We have sought to bring these themes to life with the stories of volunteers, IAVI staff and collaborating researchers that are scattered through the report. We hope you will enjoy reading here how the efforts of IAVI and its partners have advanced the field of AIDS vaccine development.
Attacking the AIDS Pandemic

IAVI has always maintained that the AIDS pandemic, given its scale and complexity, will not be reversed by any single approach. It must be met with a comprehensive response, one that combines proven, existing HIV-prevention methods, antiretroviral treatment (ART) for people currently living with HIV, and the development and widespread use of all new HIV-prevention tools and strategies.

In 2011, the field saw major strides toward the development of new approaches to HIV prevention. The landmark HPTN 052 trial, the results of which were reported in July, 2011, evaluated the preventive effects of providing ART early to the HIV-positive partner in a sero-discordant relationship, in which the other partner is HIV negative. The results revealed that, when given early, oral ART reduced the sexual transmission of HIV by 96%.

The results of two other trials that examined the efficacy of pre-exposure prophylaxis (PrEP), or the use of oral antiretroviral drugs to prevent HIV acquisition, were also reported in July, 2011. The first, known as Partners PrEP, involved several thousand HIV-discordant couples. The study evaluated whether daily oral regimens of antiretroviral medications given to the HIV-negative partner—tenofovir or Truvada, a combination of emtricitabine and tenofovir—prevent HIV transmission within such relationships. Those who received tenofovir had an average of 62% fewer HIV infections than the volunteers who received placebo. Those who received Truvada, meanwhile, had 73% fewer HIV infections. The findings of this study were echoed in simultaneously released results of a study conducted by the BOTUSA Project in Botswana, a partnership between the US Centers for Disease Control and Prevention and the Government of Botswana. That study found that Truvada reduced the risk of acquiring HIV by roughly 63% in heterosexual men and women in the study population.

But not all trials of alternative HIV prevention strategies provided such positive results. An ongoing study, known as VOICE (Vaginal and Oral Interventions to Control the Epidemic) was designed to determine the safety and efficacy of three different products: oral tenofovir, oral Truvada, and a vaginal microbicide gel infused with tenofovir. VOICE researchers stopped testing the tenofovir tablet and gel after a routine review of study data indicated that, though safe, neither product was effective in preventing HIV acquisition among the women in those study groups. The study is, however, continuing its evaluation of the Truvada regimen, and results are expected in early 2013. A second PrEP study conducted among women in Kenya, South Africa and Tanzania—named FEMPrEP—was also closed early, in April, 2011, when it became clear that the trial wouldn’t be able to prove whether or not the evaluated strategy is effective.

Such stops and starts are not unusual in clinical research and development, and IAVI and other stakeholders continue to believe that multiple strategies will be required to contain and eventually reverse the AIDS pandemic. Efforts to develop novel tools and strategies, such as PrEP and microbicides—and, of course, preventive vaccines against HIV—must be sustained as part of a coherent and comprehensive response to the AIDS pandemic.
Collaborating to Speed AIDS Vaccine Development

Research & Development

IAVI’s R&D strategy has three broad objectives:

1. Blocking HIV infection: Designing vaccines to elicit neutralizing antibodies against HIV

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2. Eliminating HIV-infected cells: Designing vaccines to unleash the cell-mediated response

   PAGE 23

3. Testing new concepts in clinical trials: Evaluating novel HIV vaccine candidates and swiftly advancing the most promising ones into efficacy trials

   PAGE 25
To that end, IAVI has evolved since its launch in 1996 as an advocacy organization to become directly involved in HIV vaccine discovery and development. Its R&D program today supports a range of HIV vaccine-related research, with a special emphasis on emerging strategies for the design of vaccines. IAVI’s scientists work closely with a global network of research institutions, academic laboratories and biotechnology companies to coordinate, support and participate in the design and development of HIV vaccine candidates (see map, page15). The vaccine discovery and applied HIV research conducted through these partnerships is coordinated by IAVI’s AIDS Vaccine Design and Development Laboratory in New York City, and the IAVI Neutralizing Antibody Center in La Jolla, California. A new HIV Vaccine Design Program launched in India in partnership with Indian government institutions will soon contribute to these efforts. Similarly, IAVI’s Human Immunology Laboratory in London coordinates the laboratories located within a global network of clinical research centers—most notably those located in sub-Saharan Africa. In collaboration with IAVI’s Medical Affairs team, the researchers of this network evaluate candidate HIV vaccines in clinical trials and conduct an array of epidemiological studies on HIV. IAVI and its partners have so far devised 22 novel HIV vaccine candidates, 13 of which have been assessed in clinical trials conducted in 11 countries.

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

IAVI’s R&D strategy derives from the conviction that a truly preventive HIV vaccine regimen—one that engenders sterilizing immunity to HIV—will have to work in two major ways. First, it will have to elicit antibodies that block HIV from entering its target cells, which are primarily T cells of the immune system bearing a protein known as CD4. Second, it will have to teach the immune system to quickly detect and destroy those CD4+ T cells that get infected despite the initial antibody barrage. Yet, the only real test of a preventive vaccine is its performance in human trials. Such trials also generate data that support the iterative improvement of vaccine candidates.

The IAVI Scientific Network

IAVI has established a globe-spanning network of partnerships and facilities to accelerate the design, development and testing of AIDS vaccine candidates:

The AIDS Vaccine Design and Development Laboratory
New York, New York, U.S.
This laboratory, established in 2008, connects IAVI’s R&D efforts, linking design and development programs and providing scientific, material, logistical, technical and managerial support to our partners and collaborating scientists.

The IAVI Neutralizing Antibody Center at The Scripps Research Institute
La Jolla, California, U.S.
This facility, a partnership with Scripps launched in 2009, is dedicated to the structural, biochemical and genetic analysis of broadly neutralizing antibodies against HIV and the application of that information to the design of AIDS vaccine candidates. The center also serves as the headquarters of IAVI’s Neutralizing Antibody Consortium.

The Human Immunology Laboratory
London, U.K.
Based at Imperial College London, this lab coordinates the IAVI-supported network of clinical trial centers. It trains and supports researchers and technicians, provides materials and quality assurance to the network, and plays a central role in generating the data that enables prioritization of vaccine candidates. The lab also is pioneering the development of standardized tests to improve the breadth, quality and detail of information researchers can collect on the interaction of HIV with the human immune system.

HIV Vaccine Translational Research Laboratory
Under development
New Delhi, India
Established in partnership with the government of India as part of the newly created HIV Vaccine Design Program, this laboratory will focus on conducting translational research toward the design of effective immunogens based on clues provided by recently discovered broadly neutralizing antibodies to HIV.
The IA VI Scientific Network

● Neutralizing Antibody Consortium

This network of scientific partners from academia and the private sector was formed in 2002, dedicated to designing vaccine candidates that generate broadly neutralizing antibodies against HIV. This is IA VI’s top research priority and is coordinated through the IA VI Neutralizing Antibody Center at The Scripps Research Institute.

List of members

- Academia Sinica, Taipei, Taiwan
- Children’s Hospital of Philadelphia, Philadelphia, PA, U.S.
- Cornell University, New York, NY, U.S.
- Dana-Farber Cancer Institute, Boston, MA, U.S.
- India Institute of Science, Bangalore, India
- International AIDS Vaccine Initiative, New York, NY, U.S.
- International Centre for Genetic Engineering and Biotechnology, New Delhi, India
- Karolinska Institute, Stockholm, Sweden
- The Scripps Research Institute, La Jolla, CA, U.S.
- University of California, San Diego, CA, U.S.
- University of Pennsylvania, Philadelphia, PA, U.S.
- University of Washington, Seattle, WA, U.S.
- Vaccine Research Center, National Institutes of Health, Bethesda, MD, U.S.

● Innovation Fund Grant Recipients

This joint effort of IA VI and the Bill & Melinda Gates Foundation encourages small- and medium-sized entities working outside of HIV vaccine research to experiment with promising ideas that could have a significant impact on the field.

List of recipients

- Academic Medical Center, Amsterdam, The Netherlands
- Algeneon, Ghent, Belgium
- Avatar Biotechnologies, Newark, NJ, U.S.
- Complix NV, Ghent, Belgium
- European Molecular Biology Laboratory, Heidelberg, Germany
- GlycoMimetics, Inc. (GMI), Gaithersburg, MD, U.S.
- Glycosensors and Diagnostics, LLC (G&D), Athens, GA, U.S.
- Lentigen, Gaithersburg, MD, U.S.
- Liposan, London, UK
- Massachusetts Institute of Technology, Cambridge, MA, U.S.
- Membrane Sciences, La Jolla, CA, U.S.
- Pepscan Therapeutics, Leiden, The Netherlands
- ProSci Incorporated, Poway, CA, U.S.
- Rockefeller University, New York, NY, U.S.
- SGHOU Vaccines, Aarhus, Denmark
- Strand Life Sciences, Bangalore, India
- Theracrine Sciences, Seattle, WA, U.S.
- University of Regensburg, Regensburg, Germany
- Xenetic Biosciences, London, UK

IA VI-supported Clinical Research Centers

IA VI supports this web of partner laboratories in five sub-Saharan African countries to test AIDS vaccine candidates and conduct observational studies that inform vaccine discovery and provide baseline information for future efficacy trials.

List of centers

- Kenya AIDS Vaccine Initiative, Kangemi, Kenya
- Kenya AIDS Vaccine Initiative–Kenya National Hospital, Nairobi, Kenya
- Kenya Medical Research Institute–Centre for Geographic Medicine Research-Coast, Kis, Kenya
- Uganda Virus Research Institute, Entebbe, Uganda
- Institute International AIDS Vaccine Initiative, Masaka, Uganda
- Projet San Francisco, Kigali, Rwanda
- Zambia/Emory HIV Research Project, Lusaka, Zambia
- Aurum Institute, Rustenburg, South Africa

Corporate Vaccine Development Partners

List of partners

- Biovex, Woburn, MA, U.S.
- Crucell NV, Leiden, The Netherlands
- DNAVEC Corporation, Tsukuba, Japan
- GlaxoSmithKline Biologicals, Rixensart, Belgium
- MedImmune, Gaithersburg, MD, U.S.
- Menengram Biosciences, San Francisco, CA, U.S.
- Open Monoclonal Technology, Inc., Palo Alto, CA, U.S.
- Pfizer, New York, NY, U.S.
- Proteus Biosciences, Inc., Tarrytown, NY, U.S.
- Selecta Biosciences, Watertown, MA, U.S.
What this means

Vaccines teach the immune system to recognize and destroy a targeted agent of disease—a pathogen—in one of a few general ways. They expose the body to the killed pathogen, to some harmless version of it (live-attenuated vaccines), or to molecules, known as antigens, that are derived from that pathogen and are known to provoke a protective immune response. These active ingredients of vaccines are generally referred to as immunogens.

For safety reasons, intact HIV, dead or alive, is impractical as a preventive vaccine candidate. Instead, IAVI’s vaccine candidates present immunogens, which are not pathogenic, to the immune system. These are either purified protein molecules, or genes encoding the immunogens. Those genes might be delivered, for example, as DNA (a DNA vaccine) or as part of an unrelated virus, known as a vector, engineered to safely deliver HIV immunogens.

Finding the right immunogens, however, has proved far harder than expected a quarter-century ago, when researchers designed the first experimental HIV vaccines. This is primarily due to the fact that HIV is constantly changing. The continuous change (mutation) of HIV acts like a molecular disguise: every time the immune system’s T cells and antibody-producing B cells get a hold on HIV, some sub-population of the virus mutates and so eludes the ensuing assault. Due to its extraordinary mutability, several different major sub-classes of HIV—and countless genetic variants within each of these so-called clades—cause the majority of infections in different regions of the world.

Researchers have long been aware that any broadly preventive HIV vaccine will probably need to elicit antibodies that neutralize multiple clades of the virus. They also know that this is at least possible: some HIV-positive people make precisely such broadly neutralizing antibodies. All of these antibodies target a protein on the surface of HIV known as the spike, or envelope protein. These antibodies do not appear to arrest existing HIV
infection—the virus, once entrenched, simply mutates too rapidly and escapes the immune response. Fortunately, pre-clinical studies suggest that if such antibodies are present before exposure to the virus, they may be able to prevent HIV infection from taking hold. Researchers at several labs, most notably those affiliated with IAVI’s Neutralizing Antibody Consortium (NAC) and the Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID), have independently isolated and characterized scores of such antibodies. Their close study is yielding valuable clues to the design of HIV vaccines.

**Key developments in 2011**

In 2005, IAVI launched a global search for broadly neutralizing antibodies (bNAbs) that has involved the analysis of blood samples collected from more than 2,000 volunteers at 11 research centers on four continents. The effort led to the isolation in 2009 of two remarkably broad and potent antibodies, PG9 and PG16, by a team of researchers at and associated with IAVI, The Scripps Research Institute, and the biotechnology companies Theraclone Sciences and Monogram Biosciences, a LabCorp company. In 2011, they completed a comparative analysis of 17 new antibodies—now known as the PGT series of bNAbs—isolated through this effort and published their findings in *Nature*. Broadly neutralizing antibodies don’t appear ready-made in people. Indeed, those who naturally produce them in response to HIV typically do so only after a few years of infection. This is because antibodies undergo a process of refinement in which they mutate in a manner that enhances their potency and the variety of HIV mutants each can neutralize, known as their breadth of neutralization. The VRC-led team found that the bNAbs that target the CD4 binding site on the spike tend to be derived from a common family of genes. Researchers at Rockefeller University obtained similar results in a parallel analysis of other bNAbs that target the CD4 binding site, including one obtained from a sample provided by IAVI—that bind this site.

In 2011, VRC researchers collaborated with IAVI and NAC scientists, among others, to trace the origins and evolution of these antibodies, and published their findings in *Science*. Broadly neutralizing antibodies don’t appear ready-made in people. Indeed, those who naturally produce them in response to HIV typically do so only after a few years of infection. This is because antibodies undergo a process of refinement in which they mutate in a manner that enhances their potency and the variety of HIV mutants each can neutralize, known as their breadth of neutralization. The VRC-led team found that the bNAbs that target the CD4 binding site on the spike tend to be derived from a common family of genes. Researchers at Rockefeller University obtained similar results in a parallel analysis of other bNAbs that target the CD4 binding site, including one obtained from a sample provided by IAVI—that bind this site.

Some of the newly described antibodies blocked HIV infection of cells as much as 10 to 100 times as potently as previously discovered ones, a feature that makes them particularly attractive models for vaccine design. The antibodies bind novel molecular targets researchers have available to them for immunogen design. Further, following an analysis of the combined HIV-neutralizing power of bNAbs, the team concluded that future vaccines will in all likelihood have to elicit multiple bNAbs to provide truly comprehensive protection from HIV.

**Other progress in 2011**

**Charting the evolution of broadly neutralizing antibodies**

A number of bNAbs target the part of the HIV spike that binds to the CD4 molecule on target cells. This makes sense, because the CD4-binding site is one of the few spots on the HIV spike that the virus can’t afford to change too dramatically; doing so would render the resulting virus incapable of infecting cells. But exploiting this vulnerability has proved to be a challenge in vaccine design. In recent years, however, researchers at the VRC have isolated a number of new bNAbs—including one from a sample provided by IAVI—that bind this site.

Understanding the immunology of the broadly neutralizing antibody response is likely to provide important clues to the development of immunogens and vaccine regimens that aim to elicit bNAbs. This is why a research program funded by the U.S. National Institutes of Health (NIH) and led by scientists at IAVI’s Neutralizing Antibody Center is systematically tracing the emergence of such responses within HIV-infected people. To do so, they are analyzing blood serum samples provided by a handful of volunteers enrolled in IAVI’s Protocol C who produce bNAbs. Protocol C is a long-term study that tracks the evolution of the virus and the body’s response to it from the earliest stages of HIV infection (see page 32).

**Finding new targets for vaccine design**

Extreme mutability is far from the only mechanism HIV has evolved to evade immune attack. Large areas of its spike protein are, for example, covered with a dense coat of complex sugar chains (glycans) that are largely identical to those found on the surface of human cells. Mistaking them for parts of the human body, the immune system ignores those parts of the spike. This glycan shield also restricts antibody access to the protein underneath, which would otherwise provoke neutralizing antibody responses.

But the sugar coat is not impenetrable. Two studies published in *Nature* and *Science* in 2011—led, respectively, by NAC researchers at the VRC and at IAVI’s Neutralizing Antibody Center—described how some bNAbs use elements of the glycan shield to bind sites of vulnerability on the HIV spike. The VRC team described in atomic detail how the bNAb touches a pair of sugar molecules and reaches down to make firmer contact with a relatively immutable, sheet-like element of the spike protein’s structure. The teams also figured out the precise structure of the region of the HIV spike that is targeted by PG9. This itself could prove very useful to vaccine designers, since this portion of the spike—known as the variable regions 1 and 2 (V1/V2)—is at once a major vulnerability of the virus and the place where it frequently mutates to fool the immune response. Researchers have long sought to determine its precise structure.
The team at the Neutralizing Antibody Center, meanwhile, led a study that solved the structure of the epitope for two extremely potent anti-HIV antibodies, PGT122 and PGT128. These antibodies too, it turns out, touch a couple of conserved sugar molecules in another variable region of the HIV spike, and reach down to firmly grasp a sheet-like element of the protein backbone there. In other words, these antibodies—like the bNAbs against the V1/V2 region—appear to exploit a common mode of HIV neutralization that could prove useful to vaccine designers.

Designing immunogens

In 2011, IAVI significantly stepped up its efforts to translate antibody discoveries into immunogen design. Researchers at IAVI, the NAC and other collaborating institutions are taking two general approaches to the problem.

First, IAVI and its partners are applying the structural information obtained from studies of bNAbs interactions with their epitopes to engineer immunogens. This structure-based approach to immunogen design is at the cutting edge of vaccinology, and scientists affiliated with IAVI are contributing significantly to its advancement (see A Matter of Form, page 22). In 2011, IAVI and NAC researchers described in Science how they used structural information, computational modeling and sophisticated genetic engineering strategies to recreate and refine an epitope that contains the CD4 binding site. Efforts to reconstruct epitopes for the more recently isolated bNAbs continue in the laboratories of the NAC. Meanwhile, the NAC’s pioneering contributions to structure-based vaccine design have had a broad impact on the general field of vaccinology. Vaccinologists are applying strategies pioneered by the consortium to devise novel vaccine candidates against unrelated viruses that also tend to mutate frequently, including hepatitis C and influenza.

IAVI’s second approach to vaccine design involves using the PG and PGT series of bNAbs to identify proteins that could prove to be promising immunogens. The antibodies, in this approach, are used to isolate a variety of HIV envelope proteins in the laboratory. The idea is that molecules that fit the antibodies well, if used as immunogens, might elicit antibodies similar to the ones that originally bound them in the lab assays. IAVI and NAC researchers are developing and refining a variety of strategies to capture such immunogens. They are, for example, generating a range of proteins in yeast and using bNAbs to screen them and so isolate proteins coincidentally shaped in places exactly like the bNAbs’ epitopes. Several immunogens devised using these methods are currently being assessed in animal models—the first step of the vaccine discovery process.

Such efforts are now about to get some support from a dedicated program for immunogen design and discovery in India. In March, 2011, IAVI and the Translational Health Sciences and Technology Institute (THSTI), an autonomous institute of the Indian government’s Department of Biotechnology, signed an agreement to launch an HIV Vaccine Design Program in India. The program will develop, test and implement strategies to rapidly screen large numbers of bNAbs-based immunogens against HIV-1 and prioritize them for further evaluation in preclinical studies. A center at the THSTI dedicated to this task will open in 2012.

Finally, with support primarily from NIAID, the NAC is collaborating with a University of Pennsylvania researcher to develop a vector derived from the adeno-associated virus (AAV) that encodes the full PG9 bNA. The long-term aim is to find out whether a passive immunization strategy—in which the antibody is not elicited from the immune response but introduced externally using a vector—is a feasible means of HIV prevention. Once injected into people, the AAV vector is designed to be taken up by muscle cells, which should then produce the PG9 antibody. This unconventional approach to HIV prevention has been put on an accelerated timeline, with the aim of submitting a regulatory dossier for clinical studies before the end of 2012.

A Matter of Form: Structure-based vaccine design

Many HIV researchers have long believed that a truly effective vaccine against HIV will have to elicit antibodies that can neutralize its countless circulating variants. But eliciting such antibodies through vaccination has proved a challenge for the same reason that there are so many variants of the virus—HIV’s extraordinary mutability.

To understand why this matters, it helps to know how antibodies work. Antibodies recognize and target large biological molecules, chiefly proteins, but complex sugars as well. The immune system and antibodies in particular can recognize foreign targets and bind to what is called an epitope on the surface of the pathogen. Antibody binding to epitopes can block function, thereby inactivating some pathogens.

HIV, unfortunately, offers up a target that is both unstable and highly mutable, complicating the binding by antibodies. Many of the mutations in HIV have the effect of altering the shapes, or epitopes, targeted by antibodies. The result is a kind of molecular confusion in which antibodies uselessly target epitopes that have already been altered in other variants of the virus. Yet some HIV-positive people do in fact produce antibodies that neutralize a broad spectrum of their HIV variants. Although these broadly neutralizing antibodies (bNAbs) cannot arrest the progression of HIV infection to AIDS, scientific evidence suggests that, if elicited by a vaccine, they might be able to block HIV from establishing an infection in the first place. Researchers are attempting to reproduce the epitopes targeted by these rare broadly binding antibodies with the goal of generating a vaccine that might elicit similar antibodies to provide broad protection from HIV.

This approach is known as structure-based vaccine design. It requires that the protein structure of both the bNAbs and its epitope on the HIV spike be worked out in atomic detail. This first step has now been taken for several bNAbs and more such information is on the way. The next big challenge is figuring out how to recreate the epitope. This may be particularly difficult if it has a complex structure, or is created by the juxtaposition in space of distant parts of a protein molecule—much as the opposite ends of a sheet of paper may be juxtaposed in origami. To elicit antibodies similar to the bNAbs, the shape and spatial orientation of a potential immunogen will likely have to closely resemble that of the original epitope.

Scientists at IAVI’s Neutralizing Antibody Consortium (NAC) and the Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases are on the forefront of this young field. Having obtained the structure of a number of bNAbs in complex with their epitopes, they are now applying cutting-edge computational, biochemical and genetic engineering tools to recreate their chosen epitopes. For example, researchers at the VRC and NAC recently recreated an epitope for an antibody known as b12 using such methods, and described their strategy in an article in the journal Science.

The explosion of information on bNAbs and their epitope targets is likely to generate many candidate vaccine concepts for testing in the next few years. The first such designs are entering testing in animals as prototype vaccine concepts. Researchers eagerly anticipate results that demonstrate that this “reverse engineering” approach will lead us toward an effective vaccine.
Goal 2
Eliminating HIV-infected cells: Designing vaccines to unleash the cell-mediated response

What this means
After HIV enters the body, it begins infecting CD4+ T cells in the mucosal tissues that line the inner cavities of the body, most significantly those of the gut. Any effective vaccine must train the cell-mediated immune response—primarily through CD8+ or cytotoxic T cells—to detect infected cells and destroy them before HIV can establish a reservoir of persistent infection. The cell-mediated immune (CMI) response is essential to vaccine responses, and serves to mop up viruses that slip past the antibody assault. The CMI response helps to control infection for several years in HIV-positive people, and has been shown to play a major role in those who suppress HIV infection for extraordinary lengths of time.

Many current HIV vaccine strategies are thought to be limited in two key ways. First, most current viral vectors that deliver HIV immunogens are engineered, for safety reasons, not to multiply as any normal virus would. Yet vaccinologists have long known that live-attenuated vaccines—such as those against measles, mumps and polio—are among the most effective of vaccines. Their ability to multiply in the body without causing disease is thought to optimize immune responses to the antigens they share with their disease-causing counterparts.

Another potential limitation of most HIV vaccine vectors is that they are not devised to induce immunity in mucosal tissues. Many researchers suspect that candidates that do so might prove more effective—by priming immune responses to HIV in the very places where the virus establishes a beachhead.

IAV’s vector development program is testing non-replicating vectors—the most recent of which, based on the adenovirus serotype 35, is now in clinical trials (see page 27). But it has also pushed ahead, in partnership with academic laboratories and biotechnology companies, to develop vectors engineered to safely replicate, or multiply, inside the body, in some cases specifically in mucosal tissues. Other organizations are also testing replicating vectors. Indeed, three such vectors recently advanced to Phase I trials. These include a pox vector in China, a measles vector developed by GlaxoSmithKline and a vector derived from the vesicular stomatitis virus, which has been developed by Profectus BioSciences, a partner of IAVI.

Key development in 2011
IAVI has been working closely with the Japanese biotechnology company, DNAVEC, to develop a replicating vector based on the Sendai virus. This virus replicates in human mucosal tissues without causing illness. Further, Sendai vectors have already been safely tested in humans. The one developed by IAVI and DNAVEC expresses an HIV protein known as Gag, which is being used as a prototype. If it is shown to be safe and to provoke strong immune responses, other immunogens will be incorporated into the vector.

All of the materials required for clinical trials of the Sendai vector were manufactured in 2011. IAVI also had a successful preliminary investigational new drug (pre-IND) meeting with the U.S. Food and Drug Administration, a step toward obtaining approval to begin clinical trials.

Other progress in 2011
Cytomegalovirus vector
IAVI has in recent years worked with Dr. Louis Picker, an IAVI partner at Oregon Health & Science University, to begin developing the cytomegalovirus (CMV) as a vector. This virus is a strong candidate for vaccine design because it is known to persist in people, in most cases without causing illness. In 2010, Picker’s laboratory demonstrated that about half of the nonhuman primates that received a CMV-based vaccine against the simian immunodeficiency virus (SIV)—the monkey version of HIV—suppressed their SIV virus infections to undetectable levels. In 2011, Picker and his colleagues published a paper in Nature that revealed that, a year later, the vast majority of those primates had so effectively suppressed SIV that they seemed never to have been infected at all. The pattern of immune responses in the immunized monkeys could inform AIDS vaccine design. IAVI continues to support Picker’s efforts to adapt the CMV vector as an HIV vaccine candidate.

Canine distemper virus and vesicular stomatitis virus vectors
IAVI has sought to develop the canine distemper virus (CDV)—a vaccine against a measles-like virus of dogs, but not humans—to specifically target immune cells in the mucosal tissues of the gut, which are also targeted by HIV. In 2011, IAVI researchers completed preliminary studies of the vector in small animals and advanced the vector into studies in non-human primates. The weakened version of vesicular stomatitis virus (VSV), meanwhile, is being developed as a replicating vector that also targets immune cells similar to those that are infected by HIV.
Goal 3

Testing new concepts in clinical trials: Evaluating novel HIV vaccine candidates and swiftly advancing the most promising ones toward efficacy trials

What this means

No matter how compelling a vaccine concept might be, it must be evaluated in randomized and controlled studies conducted in human volunteers to establish its safety and ability to prevent HIV. Such trials provide essential measures of a candidate vaccine’s breadth and scope of protection, which are required for regulatory approval and can shape future immunization policies. Even when such candidates fail, their clinical assessment often reveals valuable information that can help improve vaccine design.

This is why IAVI has long advocated the continuous, parallel evaluation of novel vaccine candidates in clinical trials. To that end, it has built a global network of partnerships to conduct vaccine trials and epidemiological research into local HIV epidemics. The clinics and laboratories of IAVI’s clinical trials network in sub-Saharan Africa, which are locally staffed and almost all led by local researchers, have played a central role in these efforts. With the support of partners, most notably the U.S. Agency for International Development (USAID), U.K.’s Department for International Development (DFID) and other European donors, IAVI has equipped the research centers and helped to train their personnel to conduct clinical research at the highest of international standards.

The network has had a busy year, chiefly due to its central role in the evaluation of IAVI’s adenovirus serotype 35 (Ad35) vector platform in combination with DNA, vector and protein HIV vaccine candidates in prime-boost regimens. Prime-boost regimens, the sequential delivery of different vaccines to the same pathogen several weeks apart, can elicit stronger and more comprehensive immune responses than when just one vaccine is used. The IAVI-supported trials are also testing a novel mode of vaccine delivery, known as electroporation, and the addition of adjuvants, substances devised to boost immune responses to vaccines.
the components of the HIV spike).

env genes—
gag, RT, int, nef (the last encodes
the boosting component in the regimen is IAVI's DNA by cells, and previous studies have shown electrical pulses. This increases the uptake of delivers the DNA vaccine candidate with small
The prime was given to volunteers using Ichor DNA adjuvant that encodes a gene for the
vaccine made by Profectus that encodes multiple
The priming component in this trial is a DNA
research center in Kigali, Rwanda.
Projet San Francisco (PSF)—Emory University’s
Vaccine Initiative (KAVI) in Kangemi, Kenya; and
Uganda Virus Research Institute
with Profectus BioSciences; Ichor Medical
trials themselves are being conducted in partnership with Profectus BioSciences; Ichor Medical Systems; the Uganda Virus Research Institute
(UVRI) in Entebbe, Uganda; the Kenya AIDS Vaccine Initiative (KAVI) in Kangemi, Kenya; and
Project San Francisco (PSF)—Emory University’s
research center in Kigali, Rwanda.

The priming component in this trial is a DNA vaccine made by Profectus that encodes multiple HIV immunogens. It has been formulated with a DNA adjuvant that encodes a gene for the stimulatory immune factor interleukin 12 (IL12). The prime was given to volunteers using Ichor Medical Systems’ electrocorporation device, which delivers the DNA vaccine candidate with small electrical pulses. This increases the uptake of DNA by cells, and previous studies have shown that it amplifies responses to vaccine immunogens. The boosting component in the regimen is IAVI’s Ad35-GRIN/ENV candidate, which carries four HIV genes—gag, RT, int, nef and env (the last encodes the components of the HIV spike).

The prime-boost strategy for the B004 trial was inspired by a similar study in non-human primates, the results of which were published in the Journal of Virology in 2011. That study, led by researchers at IAVI, revealed that an analogous prime-boost regimen using DNA and vectors devised to protect from SIV (with IL12 as adjuvant in the DNA prime) provided dramatic control of infection in thensus macaques. Armed with these results, IAVI and its partners moved with remarkable speed to design the B004 trial, complete initial discussions with regulatory agencies, submit final dossiers for regulatory approval, get the green light from local institutional ethics boards and start vaccination. Results from this trial are expected in late 2012.

Other progress in 2011

The Ad 35 platform

In partnership with the University of Rochester Medical Center, IAVI completed a Phase I trial of two candidate vaccines built on its Ad35 platform. One candidate was Ad35-GRIN/ENV, the other Ad35-GRIN, which lacked the env gene. Separating out the candidate’s immunogens in this way allows researchers to determine which of them ought to be inserted into a vaccine on the basis of the immune responses each provokes. Initial analyses of data from the trial, named B001, indicate that both the candidates are immunogenic and safe to use in people.

Key development in 2011

The IAVI-sponsored trial named B004 employs every one of those strategies. Launched in December, 2011, this study is evaluating a prime-boost regimen of a DNA vaccine candidate and IAVI’s Ad35 candidate, which is manufactured by the biopharmaceutical company Transgene. The trials themselves are being conducted in partnership with Profectus BioSciences; Ichor Medical Systems; the Uganda Virus Research Institute (UVRI) in Entebbe, Uganda; the Kenya AIDS Vaccine Initiative (KAVI) in Kangemi, Kenya; and Projet San Francisco (PSF)—Emory University’s research center in Kigali, Rwanda.

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Ad35 and Protein
IAVI completed vaccinations for an ongoing Phase I multicenter trial in three African countries. The trial, named B002, is evaluating a prime-boost regimen of IAVI’s Ad35-GRIN candidate and an adjuvanted recombinant protein candidate developed and manufactured by the pharmaceutical firm GlaxoSmithKline, headquartered in Brentford, England. In a Phase I study conducted in Ghent, Belgium, the adjuvanted protein component was found to be safe, generally well-tolerated and to elicit strong CD4+ T-cell immune responses in humans (the related Ad35-GRIN/ENV candidate has been found in Phase I studies to elicit strong CD8+ T-cell responses). The trial is being conducted by KAVI, in Nairobi; the Uganda Virus Research Institute (UVRI)-IAVI team in Kampala; the Medical Research Council-UVRI team in Masaka, Uganda; and the Zambia Emory HIV Research Project in Lusaka, Zambia.

Ad35 and Ad26
IAVI and its partners completed vaccinations in an IAVI-sponsored Phase I clinical trial assessing the safety and immunogenicity of a prime-boost regimen of two vectors, one an Ad35-ENV candidate and the other derived from adenovirus serotype 26 that also bears an env gene (Ad26-ENV). That candidate was developed at the Beth Israel Deaconess Medical Center (BIDMC) and is manufactured by Crucell N.V., a company now owned by Johnson & Johnson. The trial was conducted at the Brigham and Women’s Hospital in Boston, the KAVI and PSF research centers and three research centers in South Africa that collaborate with the HIV Vaccine Trials Network (HVTN). Other partners involved in the trial are the U.S. National Institute of Allergy and Infectious Diseases’ Division of AIDS (DAIDS) and the Ragon Institute of Massachusetts General Hospital, the Massachusetts Institute of Technology and Harvard University. Study visits will continue through late 2012.

New vaccine design strategies in development for clinical trials
IAVI began preparing in 2011 for a Phase I vaccine trial of the replicating vector based on the Sendai virus (see page 24). The Sendai HIV vaccine candidate will be evaluated alone and in combination with an Ad35 candidate to see if these vaccines can induce both systemic and mucosal protective immune responses. The Sendai vaccine will be given by the nasal route (intranasal) because this may more effectively engage the immune responses at genital mucosal surfaces. This trial is scheduled to begin by early 2013. IAVI is also planning to evaluate another new strategy for an HIV preventive vaccine, often called immunophylaxis. In this strategy, a non-replicating adenovirus-associated (rAAV) viral vector containing an antibody gene will be given like a vaccine. The goal is for the antibody gene to produce high levels of a neutralizing antibody, PG9, which will prevent HIV infection by blocking HIV binding on target cells. This trial is scheduled to begin in 2013.

MVA and DNA
A Phase I trial of a prime-boost regimen of two vaccine candidates, which was supported by IAVI and conducted by the Indian Council of Medical Research; the National AIDS Research Institute in Pune, India; and the Tuberculosis Research Centre in Chennai, India, was completed, analyzed and reported in 2011. The two HIV vaccine candidates assessed in the regimen were ADVAX, a DNA vaccine candidate developed by the Aaron Diamond AIDS Research Center in partnership with IAVI, and TBC–M4 (based on MVA), a modified version of smallpox vaccine. A separate trial of the same candidates administered differently, using a needle-free method of administration for the DNA vaccine candidate, was conducted in the U.K. in collaboration with Imperial College London and the St. Stephen’s AIDS Trust at the Chelsea and Westminster Hospital. Antibody responses were modestly improved in the DNA + MVA groups compared to groups that received MVA alone.

IAVI is also planning to evaluate another new immune responses at genital mucosal surfaces. The Sendai virus (see page 24). The Sendai HIV vaccine candidate will be evaluated alone and in combination with an Ad35 candidate to see if these vaccines can induce both systemic and mucosal protective immune responses. The Sendai vaccine will be given by the nasal route (intranasal) because this may more effectively engage the immune responses at genital mucosal surfaces. This trial is scheduled to begin by early 2013. IAVI is also planning to evaluate another new strategy for an HIV preventive vaccine, often called immunophylaxis. In this strategy, a non-replicating adenovirus-associated (rAAV) viral vector containing an antibody gene will be given like a vaccine. The goal is for the antibody gene to produce high levels of a neutralizing antibody, PG9, which will prevent HIV infection by blocking HIV binding on target cells. This trial is scheduled to begin in 2013.

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IAVI made the decision to shift its focus to other vaccine candidates in its pipeline.

Trial Monitor Kundai Chinyenze
Kundai Chinyenze was born and grew up in Harare, Zimbabwe. As a child, she aspired to become a chemical engineer. But when she was still in her early teens, her mother got very sick and, to Kundai’s sorrow and bewilderment, just would not get better. Then, one day, when she went to visit her mother at the hospital, she heard the nurses whispering about HIV. “That’s how I actually discovered that she was HIV positive,” recalls Kundai. “But no one would actually say it openly to me. One time, I remember, I asked the doctor to explain to me what was going on, and he refused to say anything. I was very upset. I remember standing there and looking at my mom, and wishing I could do something. It was there that I decided that I was going to become a doctor. That I was going to learn everything I could about HIV.”

Kundai’s mother died when she was 16, and her father, when she was 18. Still, she completed medical school and started her own practice. Her first stint in HIV-prevention research was in a microbicide trial in her home country.

After moving to Kenya in 2008 with her three children and husband, a communications officer and filmmaker, Kundai left the country again to get a masters degree in public health from Leeds University. Soon after returning in March, 2011, she started working as a clinical research associate—a clinical trial monitor—at IAVI’s Nairobi office. The job requires quite an eye for detail: she visits collaborating research centers and pores over their records and clinical laboratory data. She must ensure that regulatory documents are properly filed, data accurately recorded, that all contacts with volunteers have been appropriately conducted and noted and—if necessary—unusual results followed up. “When I was on the other side as a researcher, I was being monitored. But I’ve always wanted to learn what’s required to set up and run a research project.”

And there is, of course, the rather large fringe benefit of taking part in the battle against AIDS. “I lost both parents to HIV,” says Kundai, “so prevention research has always been a passion of mine. I would love to help find some tool to prevent this disease.”
Assessing mucosal responses

As IAVI and its partners have turned their attention to designing vaccines that generate immune responses in mucosal tissues, they have had to develop the scientific methodology and capacity to detect such responses. IAVI’s Human Immunology Laboratory (HIL) has led the field in such efforts, and its researchers have actively transferred the skills required to perform mucosal immunology assays to partners in Africa. In 2011, researchers at KAVI applied those skills in two studies supported by IAVI. In one study conducted by KAVI researchers at the Kenyatta National Hospital, cellular immune function in gastrointestinal mucosal tissues and blood was evaluated in 31 HIV-negative volunteers who were having endoscopies for non-research-related clinical purposes. The other mucosal study recruited 65 volunteers participating in the B002 and B003 trials to assess immune responses to HIV induced in the mucosal tissues in response to the candidate vaccines. Volunteers from the B004 trial are participating in the same mucosal study. Another epidemiological study characterizes systemic and mucosal immunological markers of exposure to HIV in individuals who are persistently exposed to HIV, comparing them with unexposed and HIV-seropositive volunteers. This study, which provides a platform for development of clinical and laboratory methods, is being conducted by researchers at KAVI and the Kenya Medical Research Institute–Centre of Geographical Medical Research-Coast (KEMRI-CGMRC).

Charting HIV infection

To design an AIDS vaccine trial, researchers must at a minimum know the HIV prevalence and rate of new infections in the communities in which they expect to conduct their studies. Those data determine how many people must be enrolled in future efficacy trials and permit an approximation of how long it will take to complete such studies. IAVI has therefore long supported cohorts of volunteers who are followed by collaborating research centers to ascertain the incidence of new HIV infections in a variety of communities, including populations most at risk of HIV infection, such as sex workers, men who have sex with men and fishing communities.

As a corollary benefit, epidemiological studies conducted with the aid of such cohorts strengthen HIV-prevention efforts in vulnerable communities. They also enable the transfer of technical knowhow and skills to collaborating research centers. Further, ongoing work helps research staff at these institutions maintain skills in clinical, laboratory and data management that will be essential to the future conduct of large-scale efficacy trials.

In 2011, IAVI supported the enrollment of new volunteers into Protocol B at research centers in Kilifi, Kenya; Masaka, Uganda; and in Rustenburg, South Africa. A total of 884 volunteers were enrolled in these Protocol B cohorts at the close of the year. So far, more than 10,000 volunteers at risk of HIV infection have been enrolled and followed for at least a year in Protocol B since 2004 at research centers in Kenya, Uganda, South Africa, Zambia and Rwanda.

Volunteers in Protocol B who, despite counseling and condom provision, became infected with HIV, were offered enrollment in IAVI’s Protocol C, which is a long-term study of HIV infection from the earliest stages onward that has been conducted at eight research centers in Kenya, Rwanda, Zambia, Uganda and South Africa. Volunteers are infected by HIV subtypes A, C, D and several recombinant varieties of the virus, and some were enrolled in Protocol C as early as two weeks after infection. Vaccine designers have great interest in the early events of HIV infection, when a preventive vaccine must exert its effects. Information gleaned from Protocol C can also be used to improve the design of vaccines and vaccination regimens.

IAVI’s Protocol G collects blood serum specimens for the study and isolation of broadly neutralizing antibodies (see Page 11). IAVI and its partners had completed sample collection for Protocol G in Africa and elsewhere, but began doing so in India in 2011.

With 479 people actively enrolled in Protocol C, IAVI also stopped taking new volunteers into this cohort at the end of 2011. But volunteers are still being followed for clinical and scientific reasons. Blood samples sequentially collected from them are being used in several ongoing studies, including one multicenter study led by IAVI researchers unraveling the emergence of bNAb responses. Already, some 16 participants who produce potent antibodies to HIV have been identified in the cohort. Studies on Protocol C samples by NAC researchers revealed in 2011 that bNAb responses tend to emerge on average about three to four years after infection, underscoring the need to incorporate strategies to accelerate such responses into HIV vaccine development.

IAVI collaborates with many organizations and researchers on Protocol C-related studies. These include investigators funded by the Gates Foundation, the Center for HIV-AIDS Vaccine Immunology and the Ragon Institute. Such studies contribute significantly to advancing HIV vaccine research. Further, IAVI worked with the CEPHIA collaboration (an outgrowth of the World Health Organization’s Working Group on HIV Incidence Assays, which is funded by the Gates Foundation), which is trying to develop new scientific methods to detect the proportion of new HIV infections in a population. Improved assays to estimate HIV incidence could minimize the need for the large, expensive population studies that inform efficacy trials and public health policy. IAVI’s African partners, through the HIL, provided nearly 7,000 samples from individuals with known time of infection, which will be crucial to the success of this initiative.

Cohorts supported by IAVI continue to contribute significantly to HIV research and vaccine development. In 2011 alone, researchers at IAVI and collaborating institutions presented data collected from IAVI-supported cohorts at several conferences and in 98 publications in peer-reviewed journals.
Soon after he got his first professional degree in biomedical laboratory technology a decade ago, Aloysious Ssemaganda was snapped up as an intern by the Uganda Virus Research Institute (UVRI) in Entebbe, Uganda. A couple of months later, he was recruited by the fledgling UVRI-IAVI HIV Vaccine Program as a lab technologist for their safety and immunogenicity laboratories. His life since then has been filled with travel, study and hands-on research that has made him a proficient laboratory scientist, experienced in supporting clinical trials research, and skilled in a broad variety of immunological assays.

Ssemaganda’s bailiwick, however, is the BD LSRII flow cytometer, a state-of-the-art instrument that brings a special light to the budding researcher’s eyes. Supplied to the program to support its previous role as a central laboratory for the Collaboration for AIDS Vaccine Discovery (CAVD), the cytometer allows researchers to analyze cells for immune responses by labeling specific molecules they express with unique dyes. After his basic training on the use of the machine at UVRI, Ssemaganda traveled with IAVI support to hone those skills at the Vaccine Research Center in Bethesda, Maryland, and IAVI’s Human Immunology Laboratory in London. Finally, IAVI Pfizer fellow Larry Kahn worked with him at UVRI to optimize the machine and ensure that the data collected from it are valid.

The cytometer, explains Ssemaganda, allows researchers to probe how the immune system responds to different vaccine candidates being evaluated in clinical trials. But the machine has also opened the doors to other research for Ssemaganda. He has collaborated with teams from the UK’s Medical Research Council and Hematological Malignancies Diagnostic Service in Leeds, using the cytometer to study the prevalence of a molecular marker, Monoclonal B-cell Lymphocytosis, associated with B-cell cancers. He is now working with researchers from the University of Toronto to examine whether schistosomiasis—a parasitic infection endemic to the region—increases the risk of HIV acquisition among men in fishing communities around Lake Victoria. It is also Ssemaganda’s first foray into the immunology of mucosal tissues, which is where sexually transmitted HIV infection typically begins. “Our role in the partnership comes in because we have this amazing machine that can simultaneously look at a range of markers of immune activation,” says Ssemaganda.

Ssemaganda says his decade-long experience in HIV vaccine research at UVRI has inspired him to pursue a master’s degree—and he has won a grant from the European and Developing Countries Clinical Trials Partnership to support his studies. “When I started,” says Ssemaganda, “I was just a young boy. I didn’t know what to go for. Before I knew it, I was very interested in the work I was doing. Right now my main interest is immunology and I intend to pursue a PhD in that field.”

IAVI’s support, says Ssemaganda, has guided his career and shaped his aspirations. “Basically,” he says, “all the hands-on training I’ve had, all the experience, is due to IAVI.”
Preparing the Ground

Engaging Communities, Building Capacity and Working with Volunteers
HIV vaccines must be tested in the places where they will be eventually used and in the populations for whom they are intended. This helps ensure that they will be effective against the predominant subtypes of HIV that vary from place to place and will suit the environmental conditions in which they will be used and the biological traits of their users. It is therefore essential to evaluate vaccines globally, particularly in countries hardest hit by the AIDS pandemic, such as those of sub-Saharan Africa.

This is, in essence, what IAVI’s mission is about. When IAVI was launched in 1996, many believed that developing countries lacked the technical knowhow to conduct HIV vaccine trials. IAVI challenged that assumption and, in 2001, in partnership with the U.K. Medical Research Council (MRC) and leading HIV researchers at the University of Nairobi in Kenya, helped create the Kenya AIDS Vaccine Initiative (KAVI). Over the next several years, IAVI established similar partnerships in five sub-Saharan Africa and training personnel across this network in skills essential to vaccine development. IAVI’s Human Immunology Laboratory (HIL) in the U.K., and Contract Laboratory Services (CLS) in South Africa coordinated the training of network laboratory personnel in Good Clinical Laboratory Practices (GCLP), and the IAVI Medical Affairs staff worked with the experienced staff at CRCs to train others in Good Clinical Practices (GCP). These together ensure that CRCs conduct all aspects of vaccine development and epidemiological studies at the highest of international standards. Thanks to the efforts of IAVI and CRC staff, all laboratories in the network have received GCLP accreditation, and more than 200 technicians have been trained with IAVI support to appropriately handle and process samples collected in studies. IAVI is now beginning to launch an e-learning platform to enable distance learning of some laboratory techniques.

Beyond that, the CRCs themselves have over the years helped to train scores of researchers in sub-Saharan Africa in GCLP methodologies and requirements, helping to build capacity for biomedical research in developing countries. On the strength of this experience, KAVI won a grant from the Canadian government in 2011 to expand the capacity building done so far with IAVI’s support to appropriately handle and process samples collected in studies. IAVI is now beginning to launch an e-learning platform to enable distance learning of some laboratory techniques.

Significant effort went into equipping facilities in Africa and training personnel across this network. The CRCs themselves have over the years helped to train scores of researchers in sub-Saharan Africa in GCLP methodologies and requirements, helping to build capacity for biomedical research in developing countries. On the strength of this experience, KAVI won a grant from the Canadian government in 2011 to expand the capacity building done so far with IAVI’s support to appropriately handle and process samples collected in studies. IAVI is now beginning to launch an e-learning platform to enable distance learning of some laboratory techniques.

Nombeko Mpongo is many things: a health worker for the City of Cape Town, a 39-year-old mother, an AIDS activist and a Community Advisory Board (CAB) member with the Desmond Tutu HIV Foundation (DTHF).

She is also a force of nature.

Consider the facts. Mpongo was born in the Eastern Cape Province of South Africa to an abusive father and a sickly mother who left her husband when Nombeko was just a toddler. Raised by an assortment of relatives, often separated from her siblings, she escaped her father’s cruel grasp when she was 15, hunted down her mother in Cape Town, and moved into her two-room shack—only to be compelled to drop out of school and labor at odd jobs for four years because her mother was too sick to work. She became pregnant and had a child at 17, yet made her way back to school, and after winning an essay competition and a monetary prize, completed just one year of a course in computers and administration because she used some of the money to extend her family’s shack. Still, she knew she somehow found steady work at the pawn shop chain store Cash Converters. One Saturday morning, as she walked to the train station, she was gang-raped on the street. Two years later, she learned that the scarring experience had also left her HIV positive.

“That,” she says in her inimitable way, “was when my life started to begin.”

Mpongo came across the legendary Treatment Action Campaign, which had begun agitating for access to antiretroviral drugs (ARVs) in South Africa with the support of Medicins Sans Frontieres. Soon she was in the thick of it, educating people about HIV and the prevention of mother-to-child transmission. “I knew what it is like to be diagnosed HIV positive and have nothing,” she says. “People were dying like flies. That’s how I became an activist.” But she had other dreams as well, namely reflexology—which she had studied in her spare time. So she left Cash Converters and was about to start her own practice when, in 2001, she was hired by the City of Cape Town’s Employee Wellness Program. After the government began post-exposure prophylaxis for rape victims in 2002, and expanded its treatment program for AIDS patients two years later, Mpongo turned increasingly to HIV prevention.

One day, a woman doing community work for DTHF—which collaborates with IAVI on vaccine development—invited her to a seminar on the subject. Mpongo had participated in an ARV trial before and could explain clinical research and HIV to people, so she decided to get involved. She is today a veteran member of DTHF’s Community Advisory Board, which monitors and supports researchers’ interactions with volunteers.

“As a mother,” says Mpongo, “one day I would love to see an HIV-free generation.” A vaccine would mean many things to her—not least, protection for women who, she notes, cannot always negotiate safe sex practices with their partners. But more than anything else, says Mpongo, “an HIV vaccine would mean life.”

CAB Member
Nombeko Mpongo

Nombeko Mpongo is many things: a health worker for the City of Cape Town, a 39-year-old mother, an AIDS activist and a Community Advisory Board (CAB) member with the Desmond Tutu HIV Foundation (DTHF).

She is also a force of nature.

Consider the facts. Mpongo was born in the Eastern Cape Province of South Africa to an abusive father and a sickly mother who left her husband when Nombeko was just a toddler. Raised by an assortment of relatives, often separated from her siblings, she escaped her father’s cruel grasp when she was 15, hunted down her mother in Cape Town, and moved into her two-room shack—only to be compelled to drop out of school and labor at odd jobs for four years because her mother was too sick to work. She became pregnant and had a child at 17, yet made her way back to school, and after winning an essay competition and a monetary prize, completed just one year of a course in computers and administration because she used some of the money to extend her family’s shack. Still, she somehow found steady work at the pawn shop chain store Cash Converters. One Saturday morning, as she walked to the train station, she was gang-raped on the street. Two years later, she learned that the scarring experience had also left her HIV positive.

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support, assist in the development of labs across the region and aid in their GCLP accreditation. The grant also funds an expansion of IAVI’s mucosal immunology research, which it will undertake in collaboration with the University of Manitoba. It has further begun to apply the technical capacity it has developed with IAVI’s support to become a center of excellence in clinical trials and research.

But the maintenance of scientific capacity is only one part of the preparation required for a sustained program of vaccine development. The other is working with the people who are most intimately affected by research—not only volunteers, but the communities they’re drawn from. IAVI and its partners have long sought to identify and systematically address the needs of both.

Volunteers must understand what will occur when they participate in clinical research. They must have a clear understanding of what happens during a clinical trial and understand their rights as well as their responsibilities as participants in research. In 2011, IAVI and its partners advanced efforts to improve the process by which volunteers are informed of such matters by CRC staff. IAVI staff worked with their peers at CRCs to develop innovative pictorial tools and other materials to aid these efforts—and completed a social science research project to evaluate three different methods to assess how well volunteers have understood what they were taught. When initial results showed that a method incorporating stories about hypothetical volunteers as well as true/false questions was a better measure of understanding, it was adapted for use in the Phase I B004 trial in Kenya, Uganda and Rwanda.

To prevent the enrollment of volunteers in more than one clinical trial, which can both disqualify the data collected from such individuals and possibly harm the volunteer’s health, IAVI worked with a US software developer to devise a fingerprint-based technology platform for the identification of participants in clinical trials. A pilot test of the platform was completed in 2011.

It is also important to ensure that the identity of all volunteers is protected because if the identity of a participant in HIV-related research is known, there’s a risk that person might be stigmatized. Men who have sex with men (MSM) are a case in point. Indeed, many MSM can be targeted for violence, ostracized and legally marginalized in many societies. In such populations, HIV has historically taken a disproportionate toll, fueled by widespread misperceptions about HIV and the risk of infection. Education and outreach are essential to curtailing HIV in such communities.

This is why CRCs in Kenya have worked with IAVI to develop materials and community outreach skills tailored to these most vulnerable of people. In 2011, IAVI and its partner at the Kenya Medical Research Institute Centre for Geographic Medicine Research-Coast (KEMRI-CGMRC) shared information on the risk of HIV infection in the MSM community with Kenyan government public health officials. KEMRI-CGMRC staff used the MSM manual they have developed with IAVI’s support to train government health workers in working with such populations. Initial data suggests that this effort has significantly increased acceptance of homosexuality among participants. They also contributed to the government’s development of educational material on HIV transmission and its prevention tailored to the needs of MSM. In doing so, KEMRI-CGMRC has established strong ties to MSM and sex worker communities that will aid HIV-prevention efforts as well as vaccine research in the long run.

Similarly, IAVI partners in Uganda (UVRI-IAVI and MRC-Uganda) have recently completed a study, funded in part by the European and Developing Countries Trials Platform, that has revealed that HIV infections are more than four times more common in some of the fishing villages on Lake Victoria than in the general Ugandan population. This information has stimulated increased interest in providing prevention and treatment services for this population, as well as in conducting research there.

The support of all affected communities is essential to the stable conduct of long-term biomedical research. Those communities must at least be open to such work. IAVI thus established in 2011, in partnership with the Government of India and local nongovernmental organizations, an extension of the National AIDS Research Institute (NARI) in rural Maharashtra. The purpose of this project is to enhance HIV research capacities in rural areas by establishing an HIV research center and concurrently assessing research preparedness among rural communities for HIV prevention by building partnerships with local communities and stakeholders. This project is primarily led by government researchers, with IAVI providing technical and financial support to the effort.
Not everyone has what it takes to work with the remote fishing communities scattered along Lake Victoria’s islands and shores. Fortunately, Tonny Mwanjuzi is well equipped for the job. As chairman of the beach management unit near the Uganda Virus Research Institute (UVRI) campus in Kampala, the tall, soft-spoken Mwanjuzi manages everything from security to fishing practices for the communities he oversees. He has also proved to be an invaluable asset—and champion—of the epidemiological research the UVRI-IAVI team has conducted in the area in recent years. Mwanjuzi has guided the UVRI-IAVI researchers in how to best forge links with the fishing communities, conduct HIV outreach and education and generally begin building the trust essential to their work.

When the team sought him out in 2007 to help them build a cohort for the HIV prevalence and incidence studies they were planning in those communities (see article, page 3), Mwanjuzi saw an opportunity. He had lost his mother to HIV six years ago. Though she knew she had AIDS—and had told Mwanjuzi’s sisters—she had stubbornly shielded him from that knowledge. “She didn’t want to hurt me,” he says, choking on the words. “She was getting TB treatment, but I think it was too late.” He only learned she had AIDS when she was close to death, Mwanjuzi recalls, saying that he knew very little about HIV at the time.

The virus is, however, an especially serious threat to Uganda’s lakeside communities, and dealing with that threat began to matter to Mwanjuzi a great deal after he began working with its people. ”I was yearning to do something, but I didn’t know the way forward,” he says. “So the day UVRI-IAVI came here to begin their research, I became involved. That’s when I really started learning about AIDS, and how one can help and counsel others. And I began working with the youth and others over here.” He also learned, he says, that a preventive vaccine is possible. It won’t be easy, he acknowledges, but the mere thought of it inspires him. Being a part of that effort is a reward in itself.

What would such a vaccine mean to Mwanjuzi? “A vaccine,” he says, “would be a miracle. The HIV virus has killed so many people. I think it would be a great achievement in this wild world.”

But such bridge-building doesn’t cease once a vaccine study has started. Indeed, it intensifies. Staff at CRCs must keep a finger on the pulse of their communities and create channels through which people can express their views and learn about the ongoing work. Community Advisory Boards (CABs), whose volunteers act as liaisons between the community and CRCs, play a central role in such efforts. IAVI works hard to support them in this work.

IAVI has, for example, developed guidance documents to help CRC staff convene CABs and train them for their vital role. In 2011, IAVI, AVAC: Global Advocacy for HIV Prevention and the South African AIDS Vaccine Initiative hosted a meeting in South Africa to ensure that the tools developed by IAVI and partners—especially the Vaccine Literacy Toolkit—are widely disseminated and used by HIV-prevention researchers in Southern Africa. IAVI also collaborated with AVAC to roll out a program for CRCs to assess and improve implementation of Good Participatory Practice (GPP), the UNAIDS guidelines that are the gold standard for stakeholder engagement in HIV-prevention trials. IAVI last year also supported a training of trainers on GPP guidelines to help enhance adherence to these guidelines and improve community engagement in HIV-prevention research in the region. Finally, IAVI staff completed the IAVI CAB guidance tool and published it online for free dissemination last year.

IAVI hopes that the materials and mechanisms it has developed with its partners to support community outreach and engagement will have a lasting influence on the conduct of HIV-prevention research around the world.
Building Support and Informing Public Policy

Spreading the Word
When it was launched in 1996, IAVI was essentially an advocacy organization. It remained true to its roots, even as it expanded into a research and development organization. IAVI, after all, exists primarily to ensure the development of an AIDS vaccine. This requires that it work in close partnership with many other champions of HIV prevention to build global support for that objective and to help shape public health policies that are conducive to its achievement. Without political support, and the funding that engenders, research into new vaccine concepts would shudder to a halt.

IAVI’s advocacy, however, is of a unique flavor. Because it is a product development partnership (PDP) actively engaged in the discovery and evaluation of new vaccine concepts, IAVI is well positioned to champion the merits of HIV vaccine development as a scientific opportunity as well as a public health imperative. In 2011, IAVI worked with its longstanding partners—primarily nongovernmental organizations (NGOs)—to advocate along these and other lines for HIV vaccine research as part of the comprehensive response to the pandemic.

**Shaping Policy**

In early 2011, IAVI, AVAC: Global Advocacy for HIV Prevention and the International Partnership for Microbicides (IPM) mobilized more than 40 AIDS and global health organizations from around the world to call for the United Nations High-Level Meeting on the Comprehensive Review on HIV/AIDS to commit firmly to the research, development and delivery of new HIV-prevention options. During the High-Level Meeting, IAVI met with senior delegates from Belgium, Sweden, Kenya, U.K., India and Australia to secure support for AIDS vaccine R&D specifically and to promote the document. IAVI representatives also participated in an official panel discussion on ‘Innovation and New Technologies,’ a bilateral meeting with Rwandan President Paul Kagame, and a side event on HIV hosted by the Council on Foreign Relations. Through such efforts, the coalition secured the inclusion of language in the UN Political Declaration on HIV and AIDS that commits to speeding the development of AIDS vaccines. The Declaration will serve as a guiding document for the global AIDS response over the next decade.

IAVI also has been working with a number of NGOs in the Decade of Vaccines Collaboration (DoVC), established in 2010 after the Bill & Melinda Gates Foundation announced a US $10 billion commitment to the discovery, development and distribution of vaccines. As part of that group, IAVI participated in the creation of a Global Vaccine Action Plan and articulated the needs of the HIV vaccine field to the DoVC Working Groups on Research and Development and on Global Access.

Governments and civil society were also a focus of the advocacy of IAVI and its partners throughout 2011. In an effort to increase awareness of recent progress in AIDS vaccine R&D and reiterate the importance of developing a preventive HIV vaccine, IAVI and its partners made presentations to the Select Committee in the U.K. House of Lords, the East African Legislative Health Assembly and the Kenyan and Ugandan Parliamentarian Health Committee, the Australian parliamentary group on HIV/AIDS, as well as to civil society coalitions in the U.K., Denmark, Australia and Norway. IAVI also collaborated with partners to profile AIDS vaccine R&D at international conferences, including the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; the World Health Summit 2011; and the 7th European Congress on Tropical Medicine & International Health.

IAVI collaborated with other product development partners, including Aeras, the Drugs for Neglected Diseases initiative (DNDi), IPM and the PATH Malaria Vaccine Initiative to raise awareness of R&D for poverty-related and neglected diseases and support for such efforts in the European Commission and EU Parliament, and in the U.K. and Germany. The European PDP Coalition, to which IAVI belongs, together with a broad network of global health advocates, called for the European Union to continue to prioritize R&D for poverty-related and neglected diseases in the EU Framework Programme for Research and Innovation, Horizon 2020.

Securing the U.S. government’s support for vaccine research and development is crucial to the global AIDS vaccine effort. To that end, IAVI partnered with Research!America, Aeras, IPM and OneWorld Health to host a Congressional briefing on the role of PDPs in global health research. At the event, co-sponsored by Representatives Brian Bilbray and Chris Van Hollen, an IAVI representative illustrated how PDPs can promote innovation of general relevance to biomedical product development as they address diseases of the developing world.
IAVI also collaborated with the Global Health Technologies Coalition to convene a congressional briefing hosted by Senator Sherrod Brown on the promise of vaccines for global health, Spinning health and wealth through medical breakthroughs. Panelists included Michael Gerson, Washington Post columnist and former top aide to President George W. Bush; Dr. John Lusingu, Principal Research Scientist at the Tanzania National Institute for Medical Research and Co-principal investigator of the RTS,S malaria vaccine trial in Tanzania; and Margie McGlynn, then a Director of IAVI. The panel discussed the potential impact new vaccines could have on diseases such as AIDS and malaria. Finally, IAVI joined other organizations to encourage the U.S. Congress to continue to fund the Military HIV Research Program, which led the RV144 clinical trial that provided the first proof of concept for an HIV vaccine.

To broaden the resource base and geographic scope of support for AIDS vaccine development, IAVI has similarly worked with local advocacy groups to engage the governments of emerging economies in the effort. It has, for example, worked with NGO and governmental research institutions in India for a decade to evaluate vaccine candidates and conduct applied research on HIV. In 2011, however, the organization refocused its scientific program in the country on applied research for vaccine design to better harness the nation’s strengths in science and engineering.

As part of that initiative, IAVI and the Translational Health Sciences and Technology Institute (THSTI), an autonomous arm of the Indian government’s Department of Biotechnology (DBT), formally signed an agreement in early 2011 to fund and operate an HIV Vaccine Design Program in India in the country on applied research for vaccine design to better harness the nation’s strengths in science and engineering.

IAVI and its partners engaged with the Indian government’s Department of AIDS Control to facilitate the inclusion of AIDS vaccines as a priority research area in the National AIDS Control Programme (NACP) IV. NACP embeds policy and resource allocation for AIDS prevention at the national level through five-year plans.

IAVI has also begun working with Chinese researchers and agencies to promote AIDS vaccine development. IAVI participated in the 5th AIDS vaccine network meeting held in Beijing in partnership with the Chinese AIDS Vaccine Initiative and the Chinese Academy of Medical Sciences. IAVI provided an update on advances in viral vector design and the investigation of broadly neutralizing antibodies, and explained its approach to intellectual property. In partnership with the Department of Medical Sciences, Technology and Education of China’s Ministry of Health and McKinsey and Co., IAVI also published a policy brief titled Opportunities for Accelerating AIDS Vaccine R&D in China. The brief explores a number of policy options by which China might increase its existing engagement in AIDS vaccine R&D.

IAVI’s policy research informs its advocacy in other ways as well. The organization, for example, contributed substantively in 2011 to the formulation of a South African Strategic Plan for HIV/AIDS and the development of a National AIDS Vaccine Plan for South Africa. In India, IAVI was invited by the government’s Department of Health Research to join an expert group devising policies to guide the development of new prevention technologies for HIV.

Beyond that, IAVI continued to participate in the HIV Vaccines and Microbicides Resource Tracking Working Group, which publishes an annual study on global R&D investments in new prevention technology (NPT) research. The report, released at the IAS Pathogenesis Conference in Rome, revealed that the NPT field overall had seen a 9% increase in funding between 2009 and 2010, returning funding to the peak level set in 2007. Funding for AIDS vaccine R&D, however, declined by 1% in that time, while that for microbicide research grew by 7%.
Researcher and Advocate Edward Katongole Mbidde

Edward Katongole Mbidde first met HIV in 1986. An oncologist trained in Uganda and the U.K., Mbidde had just returned to the Uganda Cancer Institute (UCI) after completing advanced studies abroad. In April that year, just a month after his return, an air stewardess with Hodgkin’s disease and severe diarrhea visited his office. He quickly realized he was dealing with his first case of AIDS. Soon, his colleagues at the teaching hospital began telling him that they too were seeing an alarming number of such cases. That, Mbidde recalls, was when they all realized Uganda was on the brink of a devastating HIV epidemic.

And so began Mbidde’s war on HIV. That same year, he joined Uganda’s AIDS control program and soon became chair of what would evolve into the nation’s National HIV Research Committee, which he has led ever since. By 1987, Mbidde had begun collaborating with researchers at Case Western Reserve University, the University of California at San Francisco and Makerere University to conduct clinical trials of the antiretroviral drug AZT. That collaboration played a part in the establishment in 1991 of the Joint Clinical Research Center (JCRC), a partnership dedicated to AIDS research in Uganda.

But Mbidde and his colleagues prevailed, setting a precedent that would encourage and inform IAVI’s own efforts to establish its clinical trial network in sub-Saharan Africa. After retiring from the UCI at the age of 60, Mbidde was appointed director of UVRI. He has been a steadfast advocate for IAVI and the work of IAVI’s other partners based at UVRI—the MRC/UVRI Uganda Research Unit led by the prominent virologist Pontiano Kaleebu and the UVRI-IAVI HIV Vaccine Program, which is today led by Noah Kiwanuka, another accomplished HIV researcher.

A survivor of polio, which left one of his legs severely disabled, Mbidde has no doubts about the power of vaccines. “When I speak about vaccines, I speak with a lot of passion because, looking back, I think, well, if the vaccine had arrived here earlier, maybe I would never have had polio. But the good thing is that my disability has never pushed me back. Maybe it was just something that drove me to work harder. And maybe I would not have reached where I am in my career without it.”

An AIDS vaccine, to his mind, remains the most convincing answer to the pandemic. “The task is daunting,” says Mbidde. “We are more than 30 years down the road since the epidemic started, and we don’t have a vaccine. That should not be cause for desperation, or to give up and believe it will never happen. I believe it will one day. But I do hope it happens while I’m still around, so that I can say, ‘I was part of that effort!’"
Sustaining funding for research and development depends on the continued support of both opinion leaders and the public. To sustain such support, IAVI representatives co-authored commentaries in a variety of publications throughout 2011. On the 30th anniversary of the discovery of AIDS, for example, IAVI tapped mass media to underscore the need for new biomedical HIV-prevention tools. This outreach resulted in the publication of eight supportive articles along those lines, four of which were widely distributed through newswire services.

IAVI also placed several opinion pieces in mass media outlets as part of the organizational effort to emphasize the role of an AIDS vaccine as a potentially game-changing component of a future HIV-prevention toolkit. Articles discussed funding for HIV vaccine development, the use of innovative IP strategies to accelerate the process and the need for a strong continuum from R&D to vaccine delivery. Other commentaries and IAVI web statements over the year promoted AIDS vaccine R&D as critical elements of science, technology and innovation in both new and traditional media outlets around the world.

**IAVI in the News**

As it always has, IAVI worked with partners to publicize scientific breakthroughs authored by its own and affiliated researchers. It coordinated, for example, with the Oregon Health & Science University’s (OHSU) Vaccine and Gene Therapy Institute to develop a media strategy to promote the remarkable findings of Louis Picker’s non-human primate study (see page 24) of a replicating vector. Media outreach by IAVI and OHSU resulted in widespread coverage of the paper—including a Reuters article that appeared in more than 12 publications worldwide. Similarly, IAVI worked with partners to promote the Nature paper describing 17 novel broadly neutralizing antibodies (see page 19). This resulted in the publication of 23 unique articles, several of which were featured in multiple publications, primarily in the U.S. and U.K.

These efforts were greatly aided by IAVI’s new emphasis on digital media as a cost-effective tool for advocacy. As IAVI has expanded its digital presence, hundreds of new followers have signed up every month to stay abreast of developments in HIV prevention. In 2011, IAVI relied heavily on new media to promote the call for new prevention technologies in the lead-up to the UN High Level Meeting. Over the year, IAVI spokespeople also highlighted the economic benefits of global health research and progress in AIDS vaccine development in several high-profile blogs, including Scidev.net, the USAID Impact Blog, Nature’s Spoonful of Medicine Blog and the Modernizing Foreign Assistance Network Blog.

They had plenty to write about: HIV-prevention research has lately generated a bounty of scientific breakthroughs. Yet few of them would have been possible without the dedicated advocacy of countless activists and organizations that have championed the cause of HIV prevention and research for more than two decades. Their advocacy has helped to place AIDS vaccine development on the global health radar and the budget lines of governments around the world, keeping the cause alive through the bad years as well as the good. Any future AIDS vaccine will owe its existence in some measure to their hard work and steadfast support.
Planning a New Strategy

IAVI will be a respected and effective product development partnership that works with other stakeholders to play a key role in accelerating the development of an AIDS vaccine accessible to all.

This is an exciting time to be involved in AIDS vaccine development. The field has recently witnessed the first demonstration that a vaccine may prevent HIV infection and a series of scientific breakthroughs that could revolutionize HIV vaccine discovery.

These advances have contributed greatly to a growing optimism about the prospects of a future vaccine against HIV. Yet they have occurred in the context of an extended economic downturn that has taken a toll on donor nations, threatening funding for many global health initiatives, including efforts to develop AIDS vaccines.

In response to this troubling reality, IAVI began in 2011 a process of internal assessment and stakeholder engagement to lay the foundation for a new organizational strategy, one better suited to the changed external environment. This required an analysis of the AIDS vaccine field, extensive consultation with partners, donors and its own leaders, and an assessment of the organization’s current strengths and weaknesses to determine how and where it can add the most value to the field.

What IAVI discovered is that its mission and vision unifies employees and resonates deeply with partners, donors, policymakers and communities in developing countries. On the other hand, IAVI detected a need to reconsider how it might best ensure the development of an AIDS vaccine—through what it does in its own programs, how it partners with others, and how it applies the resources at its disposal and the talent of its employees and partners to the broader benefit of the field.

IAVI developed its strategic vision for the organization for the period 2011-2015 on the basis of these analyses. The plan seeks to clarify how IAVI can best serve the field of AIDS vaccine development. It also presents a roadmap for improving the effectiveness of the organization and ensuring the most efficient application of its resources and assets in partnership with other organizations.

The strategic vision is built around three overarching objectives that should help IAVI advance the development of an AIDS vaccine. These are:

**Objective 1**
Accelerate the development of AIDS vaccines by identifying opportunities and gaps in the field and ensuring that IAVI invests its resources in areas that add most value

**Objective 2**
Harness partnerships to expand the diversity and number of novel AIDS vaccine candidates

**Objective 3**
Build global support for AIDS vaccine development

IAVI has also formulated an organizational vision statement that enunciates how it aspires to be regarded by stakeholders and partners. That statement is as follows: IAVI will be a respected and effective product development partnership that works with other stakeholders to play a key role in accelerating the development of an AIDS vaccine accessible to all.

IAVI thus seeks to become an organization that stakeholders seek out as a partner. It equates its success with the success of the AIDS vaccine field, emphasizing urgency and speed in advancing the most promising vaccine candidates, whether they have been developed internally or externally. IAVI's advocacy and policy programs will similarly be conducted in collaboration with others. IAVI is, further, committed to enhancing internal efficiencies and business practices to improve the quality of its partnerships. By establishing priorities and making decisions in a consultative and transparent fashion, IAVI will clarify its role in the field, enhancing the organization’s effectiveness in pursuit of its mission.
The overall fundraising environment for nonprofits remained extremely challenging in 2011 due to persistent financial difficulties for most donors, and ongoing economic uncertainties in the United States and in Europe. Against this backdrop, IAVI was delighted to secure a new five-year agreement with its biggest donor, USAID, and grateful for the confidence the U.S. government has shown in the organization and the new leadership.

Given the tough economic outlook, IAVI’s focus has been on donor stewardship to ensure the retention of core donors and recapturing of former donors. This approach showed results, with almost all of IAVI’s public-sector donors remaining committed to supporting the organization, albeit many at lower levels of funding. As part of our focus on increasing our engagement with major funders, IAVI hosted two donor meetings in 2011 to communicate and share information with donors and to solicit donor feedback on the strategic direction of the organization. Donors have been supportive of the organization but have suggested that it be cautious about the medium-term economic outlook.

Furthermore, donor priorities have been shifting away from HIV/AIDS as a vertical program and, even in the context of HIV/AIDS funding, the focus is on existing interventions rather than new, unproven technologies. IAVI worked extensively with other partners in 2011 to address this and to adapt the future fundraising strategy accordingly.

IAVI’s unaudited revenues for 2011 amounted to US $59.7 million against a budget of $83.2 million. The difference of approximately $23 million was covered in part by a required spend-down of reserves from a previous grant. The remainder of the difference was due to a late shift in the timing of the contribution from a grant renewal. IAVI adjusted its budget mid-year in anticipation of the reduced revenue, and to ensure that spending in 2012 matched our projected revenue and required spend-down for that year.

IAVI’s new strategic direction takes into account the reduced funding level anticipated for the organization and a focused prioritization of programmatic activities, begun in 2011, will continue. The organization remains committed to delivering value for its donors and to making rapid progress toward an AIDS vaccine. Sustained funding for this undertaking is essential and IAVI will continue to advocate for financing for the entire vaccine field, as well as for its own activities, with energy and commitment.
### Board of Directors, Emeritus (continued)

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<td>Vice-Chair for Principal, University of KwaZulu-Natal</td>
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<td>Past President, Medical Research Council, South Africa</td>
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<td>Ciro de Quadros, MD, MPH</td>
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<td>Philip K. Russell, MD</td>
<td>(Former Secretary) Professor Emeritus, Johns Hopkins School of Public Health; Former Principal Science Advisor, Vaccine Development, U.S. Department of Health and Human Services</td>
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<td>Thomas P. Monath, MD</td>
<td>Partner, Klein Perkins Caudfield &amp; Byars, Pandemic &amp; Biodefense Fund</td>
</tr>
<tr>
<td>Lynn Morrie, PhD</td>
<td>Head, AIDS Research Unit, National Institute for Communicable Diseases</td>
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<tr>
<td>Marian R. Neutra, PhD</td>
<td>Professor of Pediatrics, Harvard Medical School &amp; Children's Hospital of Boston</td>
</tr>
<tr>
<td>Stanley Plotkin, PhD</td>
<td>Professor, Pediatrics, University of Pennsylvania, Sanford Pasteur</td>
</tr>
<tr>
<td>Thomas L. Richie, MD, PhD</td>
<td>Captain, Medical Corps, USN, Director, Malaria Program, Navy Component, U.S. Military Malaria Vaccine Program, Naval Medical Research Center/Walter Reed Army Institute of Research</td>
</tr>
<tr>
<td>Robin Shattock, PhD</td>
<td>Professor of Molecular Infection, Imperial College</td>
</tr>
<tr>
<td>Alan Shaw, PhD</td>
<td>Chairman &amp; Chief Scientific Officer, Vaxdome Corporation</td>
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### Policy Advisory Committee

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>David Kihumuro Apululi, MD</td>
<td>Director-General, Uganda AIDS Commission</td>
</tr>
<tr>
<td>José Espanza, MD, PhD</td>
<td>Senior Advisor, HIV Vaccines, Bill &amp; Melinda Gates Foundation Global Health Program</td>
</tr>
<tr>
<td>Michel Guéno, MS, MBA</td>
<td>Former President, Chief Operating Officer and Deputy Chief Executive Officer, Aventis Pasteur; Former President and Chief Operating Officer, Pasteur Mérieux MSD</td>
</tr>
<tr>
<td>Purnima Mann, PhD, MA, MPhil</td>
<td>CEO, Pathfinder International</td>
</tr>
<tr>
<td>Cristina de Albuquerque Possas</td>
<td>Director of Graduate Programs in Clinical Research, Institute for Clinical Research (IPEC), FIOCRUZ and Scientific Advisor for Bio-Manguinhos-Fiocruz</td>
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### Scientific Advisory Committee

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<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Alan A. Aderem, PhD</td>
<td>Director, Seattle Biomed</td>
</tr>
<tr>
<td>Michel De Wilde, PhD</td>
<td>Executive Vice President, Research and Development, Sanofi Pasteur</td>
</tr>
<tr>
<td>Peter C. Dobertz, PhD</td>
<td>Michael F. Tamer Chai, Department of Immunology, St. Jude Children’s Research Hospital; Laureate Professor, The University of Melbourne, Microbiology &amp; Immunology</td>
</tr>
<tr>
<td>José Espanza, MD, PhD</td>
<td>Senior Advisor, HIV Vaccines, Bill &amp; Melinda Gates Foundation Global Health Program</td>
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<tr>
<td>Phillip L. Gomez III, PhD</td>
<td>Principal, PRISM Management Consultants</td>
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### Venture Advisory Committee

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<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Paul Klingenstein</td>
<td>Managing Partner, Aberdare Ventures</td>
</tr>
<tr>
<td>Amir Nashat</td>
<td>General Partner, Polaris Ventures</td>
</tr>
<tr>
<td>Mike Powell</td>
<td>General Partner, Sofinnova Ventures, Inc.</td>
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### Senior Management Team

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<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Margaret G. McGlynn</td>
<td>President and Chief Executive Officer</td>
</tr>
<tr>
<td>David H. Cook</td>
<td>Executive Vice President and Chief Operating Officer</td>
</tr>
<tr>
<td>Wayne C. Roff</td>
<td>Senior Vice President and Chief Scientific Officer</td>
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### General Management Team

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<thead>
<tr>
<th>Name</th>
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<tr>
<td>Louis Schwartz (As of May 2012)</td>
<td>Chief Financial Officer</td>
</tr>
<tr>
<td>Labeeb M. Abboud</td>
<td>Senior Vice President and General Counsel</td>
</tr>
<tr>
<td>Dianne Stewart</td>
<td>Vice President, Resource Mobilization</td>
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### Board of Advisors

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Jeffrey Sturchio, PhD</td>
<td>Senior Partner, Robin Martin</td>
</tr>
<tr>
<td>Mark A. Wainberg, PhD</td>
<td>Professor and Director, McGill University AIDS Centre</td>
</tr>
<tr>
<td>Mitchell Warren</td>
<td>Observer, Executive Director, AVAC; Global Advocacy for HIV Prevention</td>
</tr>
<tr>
<td>Alan Whiteside, MD, D Econ</td>
<td>Director, Health Economics and HIV/AIDS Research Division, University of KwaZulu-Natal</td>
</tr>
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<table>
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<tr>
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<tbody>
<tr>
<td>Jane Waterman</td>
<td>Executive Director, AVH Europe</td>
</tr>
<tr>
<td>Anthony Musyoka</td>
<td>Vice President, Human Resources</td>
</tr>
<tr>
<td>Bonnie Bender</td>
<td>Regional Director, East Africa</td>
</tr>
<tr>
<td>Rajat Goyal</td>
<td>Country Director, India</td>
</tr>
</tbody>
</table>
IAVI's mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world.