WHAT WE KNOW FOR SURE

Lessons to be learned from the STEP study

IN THIS CHAPTER

We may never have all the answers.

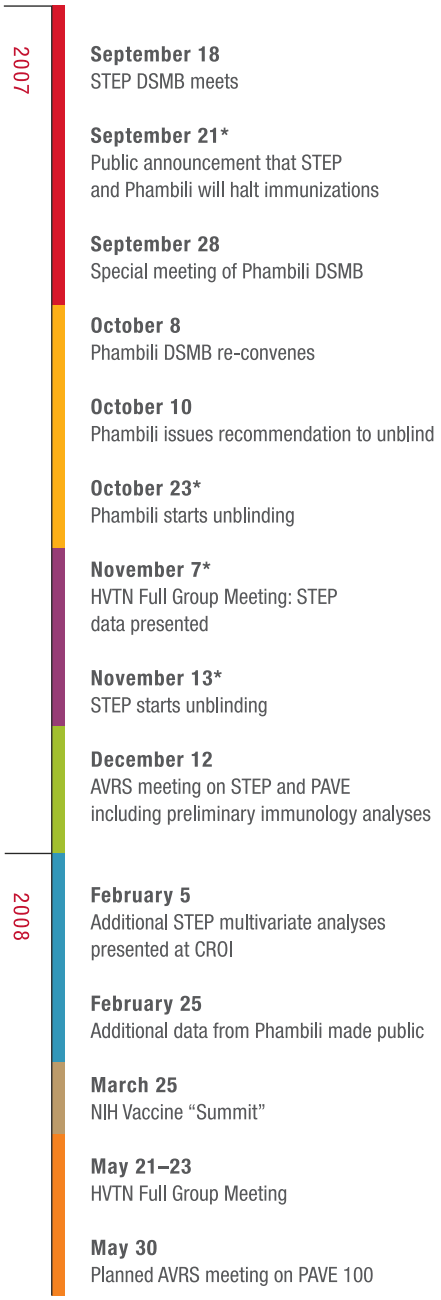
Even after the data are fully analyzed, there are many things we may never know for sure.

These are the refrains from the ringside seats of STEP data analysis when it comes to questions like: What caused the apparent increase in susceptibility to infection? What's the contribution of male circumcision or lack thereof to men's risk of infection during insertive anal sex? Is the STEP finding related to pre-existing Ad5 immunity, or is it associated with some other factor in people's immune systems that we haven't identified? Other studies might shed light on these questions, but STEP samples alone may not.

It's important to keep emphasizing what we know and don't know. The main stakeholders in these studies have done an exemplary job and demonstrated a level of transparency and clarity in their communication that should be a model for future trials.

Turning away from the data on susceptibility—and the possiblity that some STEP vaccine recipients may have had a better level of viral control than comparable placebo recipients—there are other critical and clear messages that emerged from STEP and its aftermath that cannot be overlooked. These deserve attention and demand action.

Figure 6 STARTING THE "POST-STEP" ERA: A TIMELINE



* Event triggering communication with participants

Some of the most important messages have to do with the populations that were engaged in these trials and in other prevention studies this year.

Point 1: THE MRK-AD5 CANDIDATE DIDN'T WORK.

It didn't prevent infection or reduce viral load setpoint. This isn't even news any more. But it, along with the factors that we review below, means that the world of AIDS vaccine and prevention research looks very different than it did at this time last year. And this means that the core messages going out to communities may need to look different too.

ACTION 1

AVAC recommends that every relevant entity that has money committed to advocacy, policy and communications should set aside time and funds to revisit the core messages about AIDS vaccines and HIV prevention in light of the past year's developments. The Enterprise Communications Working Group (for which AVAC serves as the secretariat), IAVI, the NIH HIV Vaccine Research Education Initiative (NHVREI), and other entities should allocate needed resources to this effort, with the goal of generating clear, consistent messages about AIDS vaccine research, including realistic expectations and reasons for staying committed to the search.

Point 2: THE STEP AND PHAMBILI TRIALS AREN'T OVER.

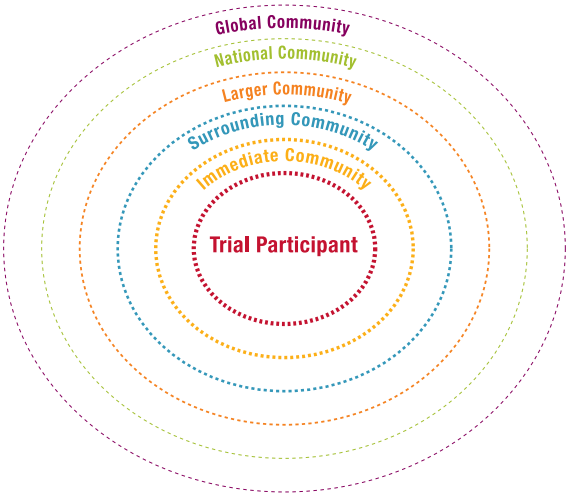
They've just halted immunizations. We say this to underscore that there's still a lot to be learned about community engagement by listening to sites about what worked and what didn't in the context of updating participants on the events related to the trials, unblinding them, informing local and national political leaders, and maintaining good will towards AIDS vaccine trials over the long haul. There are also additional data coming in from volunteers, which will help shed light on the effect of host genetics and immune responses on viral setpoint.

ACTION 2

AVAC recommends that NIAID, HVTN and Merck invest in a social science-focused agenda that documents what happened, and what's still happening in terms of community involvement at STEP and Phambili sites.

Over the past several months, AVAC has visited or interviewed staff at nine different STEP and Phambili sites. We've asked site staff to describe what happened in the initial waves

Figure 7 ALL IN THIS TOGETHER: LAYERS OF THE AIDS VACCINE COMMUNITY



GLOBAL COMMUNITY— International NGOs, vaccine trial sponsors and networks, WHO/UNAIDS, other international organizations, international foundations, donors, funders

NATIONAL COMMUNITY— National NGOs, parliamentarians, Ministries of Health, media, regulatory bodies, ethical review committees

LARGER COMMUNITY— NGOs, local policymakers, local media, medical professionals

SURROUNDING COMMUNITY— CBOs, religious institutions, traditional healers, schools/universities, vaccine trial site staff, Community Advisory Board

IMMEDIATE COMMUNITY— Participant's family, friends, collegues and peers

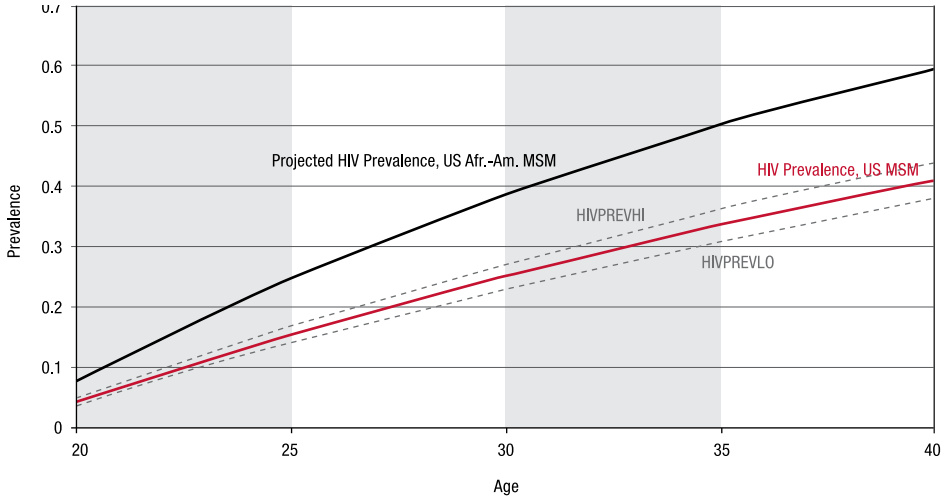
of communication to volunteers and how reactions have changed over time. We learned that sites used a range of strategies to communicate with volunteers and that there were no cookie-cutter approaches. These kinds of conversations need to happen in a broad and systematic way; trial sponsors should take the lead on this.

Looking ahead, the PAVE 100 partners need to do far more to facilitate community input into discussions and decisions about the redesigned protocol. Community involvement in the discussions around protocol revisions has been inadequate—with limited participation from even the community representatives assigned to the protocol team. This is no fault of either the representatives or the sponsors—a lot has happened in a compressed time frame. But now is the time to hold the meetings, calls, and community consultations that bring the issues related to PAVE 100 to the communities where the trial might take place. AVAC is offering support for community-based meetings in any locales of potential PAVE 100 trial sites, and is actively working to create other opportunities for input. This activity is also the responsibility of the PAVE 100 collaborators. We'd like to see their community outreach plan detailing the ways that input will be collected and incorporated prior to any final decision about a redesigned PAVE study.

Point 3: REGARDING MEN WHO HAVE SEX WITH MEN

American men who have sex with men (MSM) have long been at the forefront of AIDS vaccine and prevention advocacy, and these diverse communities have played an active role in early and large-scale vaccine trials, including STEP and VAXGEN, as well as early preparedness studies. In the US, rates of new HIV infections

Figure 8 PROJECTED HIV PREVALENCE BY AGE: US AND AFRICAN-AMERICAN MSM



This projects prevalence in US men and African-American men of different ages, assuming an incidence rate of 2.38% among all MSM and 4% for African-American MSM. Based on this projection, 60% of African-American MSM who are 20 years old today could have HIV by the time they're 40—unless HIV prevention and treatment for these communities are improved. This closely matches reality: see Figure 9 page 36. The hatched curves are based on alternative estimates.

Courtesy of Ron Stall, Ph.D., M.P.H. Professor and Chair, Dept. of Behavioral and Community Health Sciences, Graduate School of Public Health, University of Pittsburgh

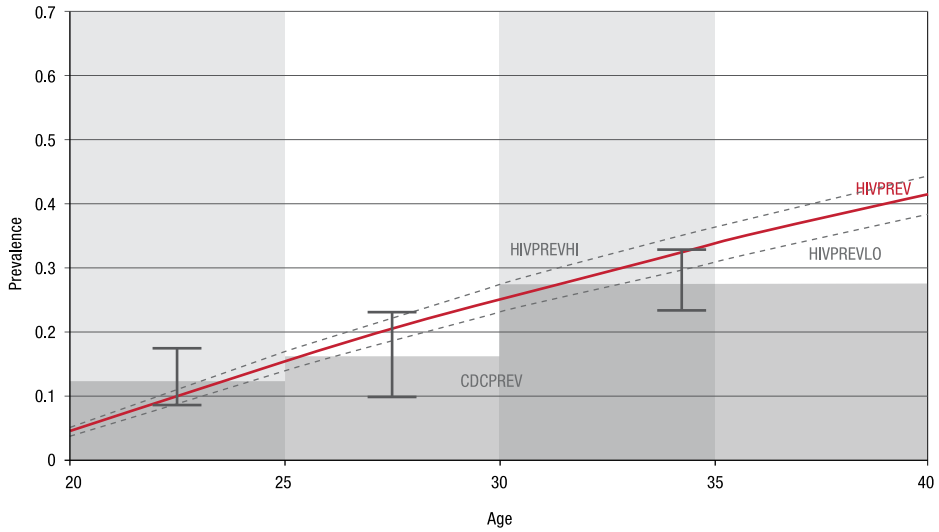
in young MSM of color are comparable to those seen in the hardest-hit developing countries. This isn't because young MSM of color have more high-risk behavior than their white counterparts. Important emerging work has identified higher viral loads in HIV-infected black MSM as one potential contributing factor. When men with HIV don't get timely, comprehensive treatment and care due to stigma, provider bias or inability to access affordable services, then their viral loads are higher—among many other outcomes. This means a higher "population level" viral load, which means more likelihood of transmission in some sexual networks.

Looking at MSM from the Americas, Australia and the Carribbean in the STEP study, the incidence data confirm the severity of the global epidemic. All of the questions about possible vaccine effects on HIV susceptibility cannot be allowed to obscure this fact: overall incidence in the placebo group for men who have sex with men was 3 percent; in the vaccine arm, it was 4.6 percent. This incidence happened in the context of a prevention package including condoms, STI treatment and counseling. In general, men's reported risk behaviors dropped over time in the trial (see Figure 10, page 37).

ACTION 3

AVAC recommends that sponsors of vaccine trials and other HIV prevention work expand and innovate in their work with MSM. One step is recognizing that HIV in MSM isn't a single epidemic—it's many epidemics defined by geography, culture, ethnicity, economics, legal protections and lack thereof, access to health care and a range of other factors. STEP sites in

Figure 9 HIV PREVALENCE BY AGE AMONG US AND AFRICAN-AMERICAN MSM: CURRENT ESTIMATES

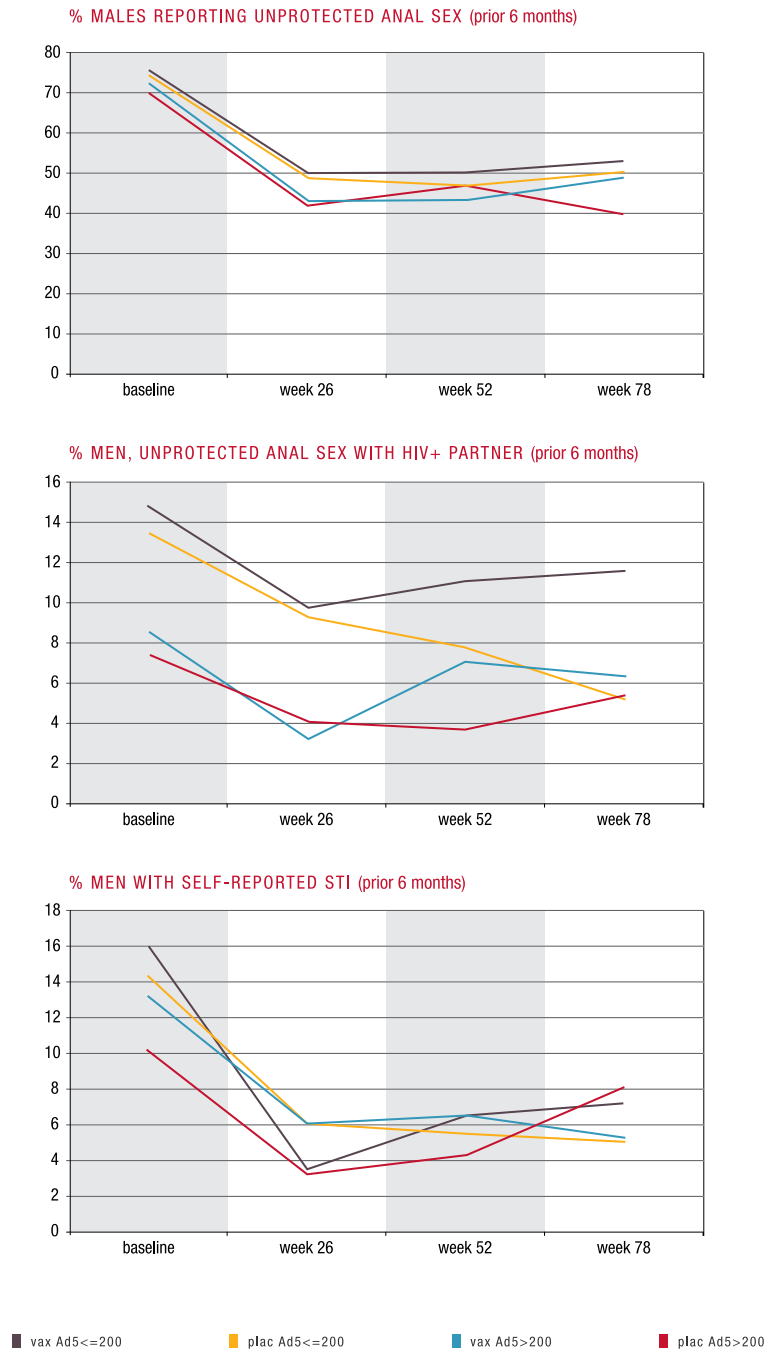


Current estimates of HIV incidence and prevalence in the US are imprecise, but the best available data show the toll HIV is taking on MSM in general and African-American MSM in particular. How will this look in 20 years? See Figure 8. The confidence intervals are derived from CDC data, see citation below. The hatched curves are based on alternative estimates.

Source for CDC estimate: CDC (2005). HIV prevalence, unrecognized infection, and HIV testing among men who have sex with men in U.S. cities, June 2004-April 2005. MMWR, 54, 597-601.

Courtesy of Ron Stall, Ph.D., M.P.H. Professor and Chair, Dept. of Behavioral and Community Health Sciences, Graduate School of Public Health, University of Pittsburgh

Figure 10 DATA ON RATES OF REPORTED RISK BEHAVIOR AMONG MALE VOLUNTEERS IN THE STEP TRIAL



For the most part, STEP volunteers' reported rates of risk behavior dropped from baseline over the course of the trial. This is consistent with what's seen in other HIV prevention trials.

Source: "STEP Trial: Exploring hypotheses for differential HIV acquisition rates," presentation by Susan Buchbinder, HVTN Full Group Meeting, November 7, 2007, www.hvtn.org.

Latin America had high incidence—reinforcing that this is a global epidemic. AmfAR's new MSM initiative is an important step towards addressing the gap in resources flowing toward grassroots groups that are breaking the silence around the needs, desires and health issues of MSM worldwide.

More action is needed. University of Pittsburgh researcher Ron Stall has laid out the unthinkable consequences of inaction in the US (see pages 35 and 36). Similar scenarios are possible worldwide, particularly if resources are not allocated for respectful, safe, comprehensive services for MSM. Today these resources don't exist in most settings, with scant prevention funding going to MSM-specific programs (see Table 3, page 38). Even while keeping a focus on research priorities, vaccine and other prevention trial sponsors can help fill this gap.

More specifically, when it comes to STEP, co-sponsors HVTN and Merck should investigate and share data on where the infections occurred and where they didn't occur. This should include mining data from site-specific approaches to delivering the prevention package.This can help guide future interventions.

We also need to hear from MSM communities about their priorities and concerns related to understanding whether male circumcision played a role in reducing risk. The STEP data show that highest risk of acquiring HIV was among vaccine recipients who were uncircumcised and had pre-existing immunity to Ad5. The relative contributions of Ad5 and lack of circumcision are almost impossible to tease out in this post-hoc analysis—the study simply wasn't designed to answer this question. For all this confusion, the STEP data on circumcision seem to be getting more attention than other research,

Table 3 PROPORTION OF STI PREVENTION EXPENDITURES TARGETED AT MSM IN ASIA

Country, City, or Province	MSM Prevention Expenditure (Thousands)	Total Prevention Expenditure (Thousands)	Share of Prevention Expenditure
Thailand	482.5	12,517	3.9 %
Vietnam	220	20,670	2.6 %
Ho Chi Mihn City	4.2	430	0.05 %
Cambodia	190	8, 506	2.2 %
China	140	N/A	N/A
China Province 1	28	21,000	0.13 %
China Province 2	0	3,000	0 %
Lao People's Democratic Republic	40	2,694	1.5 %

Severely restricted or nonexistent funding for MSM-specific HIV prevention is part of a broader pattern of missing or substandard health services for MSM communities.

Source: Chris Beyrer, MD, MPH, Professor and Director of the Johns Hopkins Center for Public Health & Human Rights at the Johns Hopkins Bloomberg School of Public Health

like that presented by CDC researcher Greg Millett and colleagues at the 2007 National HIV Prevention Conference. Millet's team surveyed just over 2000 black and Latino MSM who received an HIV test—and found no association between circumcision and HIV status. Again, this kind of cross-sectional study cannot provide a definitive answer either. Any HIV prevention research trial working with MSM should, in its preparatory phases, engage MSM communities to identify questions and priorities including research on male circumcision. These same trials should build in appropriate services or, where possible, nested substudies to help shed light on the issue. There may also be a need for a study specifically looking at male circumcision for HIV prevention in MSM.

There are also some age-old questions that need answering: How can the trials help to improve conditions for communities? What are the human-rights implications of enrolling MSM in countries where they're closeted and often criminalized—and how can trial sites be change agents and allies for the good? What are the barriers to treatment access? How can trial-related funds be used to leave MSM communities better off—especially when it may be hard to publicly define and convene these communities for consultations? These issues should be addressed across networks and sites, and the Global HIV Vaccine Enterprise should take a lead role in convening these discussions, compiling results and tracking progress towards milestones.

Some of the biggest unanswered questions in the US MSM epidemic have to do with men of color. AVAC recommends that the sponsors of vaccine trials in the US explicitly identify ways to invest in and support studies that answer the key questions that have been laid out by a cadre of African-American researchers who published a suite of essential articles in the January 2008 issue of *Journal of the National Medical Association*. We've included an edited and condensed list of their recommendations on page 40 and urge the HVTN, HPTN, CDC and other US stakeholders to overlay their planned research

with these specific priorities to ensure that there's a well-funded and coordinated approach to filling in the gaps.

Point 4: KNOWLEDGE GAPS ABOUT HIGH-RISK WOMEN OF COLOR IN THE US

When immunizations were stopped in STEP, there was only one infection out of the 1150 women enrolled in the study. Some of the female STEP volunteers in the US contracted sexually transmitted infections and others became pregnant—evidence that the low incidence rate in women was not due to consistent condom use. Low incidence had to do with other factors, including, perhaps, women's response to prevention counseling or low levels of HIV in women's sexual networks. In the absence of a clear explanation, or accurate criteria to identify US women at high risk for HIV, the groups involved with the proposed PAVE 100 trial have said that women in the US would not be enrolled in that proposed trial.

We can't turn back the clock to the days when women were an afterthought for vaccine efficacy.

ACTION 4

We can't turn back the clock to the days when women were an afterthought to the AIDSVAX trial—recruited in such small numbers that it was impossible to do a disaggregated gender analysis. We also can't justify spending large amounts of money on enrolling women in the US as vaccine trial participants if—as appears to be the case—the risk criteria being used are insufficient.

What we can do is to invest in finding out what can be done better. 62 percent of women in STEP were black. Both the high incidence in black MSM in the US and the low incidence in STEP's female volunteers point to severe gaps in the understanding of the drivers of the epidemic among blacks in the US.

AVAC recommends that the HVTN undertake research to help identify factors behind the low incidence in African-American women vaccine trial volunteers with a broader agenda in mind. This agenda needs to be ambitious, and needs to address the specific vulnerabilities of adolescent boys and girls. The NIH National Institute on Drug Abuse, the US Substance Abuse and Mental Health Services Administration and other groups need to be pulled together for a review of the research gaps and priorities, such as those outlined on page 40, so that the work that's done by any single network or entity fits into the broader framework of a comprehensive response to one of the worst HIV/AIDS epidemics in the developed world.

This work also needs to be multidisciplinary. The recently-approved "ISIS" (Women's HIV SeroIncidence Study) protocol from the HPTN is one project that will gather more information on how to reach high-risk women. The HVTN is also looking at a research project to understand how to identify high-risk US women. These efforts are important, but they are not sufficient. They should be integrated into a more comprehensive research agenda that addresses broader questions related to risk in women in the US, particularly in communities of color.

TOWARDS AN AFRICAN-AMERICAN AIDS RESEARCH AGENDA: REQUIRED READING

The January 2008 edition of the Journal of the National Medical Association *included a line-up of critically important articles about the African-American AIDS epidemic, which is among the worst in the developed world. These pieces systematically identify what is known, and what is not known, and lay out research priorities for a range of populations. We've condensed and edited these lists for space here—but think this agenda should be fully fleshed out and implemented, with HIV prevention research entities as active partners in funding, conducting research, and analyzing results.*

WHAT IS NOT KNOWN

1. What are characteristics of high-risk and HIV-infected African Americans.
2. What are the relative contributions of poverty, unemployment, homelessness, incarceration, having a history of sexual and/or physical abuse or mental illness to HIV risk? Which contributes most? What are the cumulative effects of these factors?
3. What factors influence African-American male sexuality and sexual identity development?
4. The specific reasons for "partner unavailability" [sometimes attributed to incarceration of a high proportion of African-American men] and its impact on family formation, sexual decision-making and psychological health.
5. The impact on HIV risk of childhood sexual abuse among African-American women.
6. Developmental vulnerabilities in African-American adolescents.

RESEARCH RECOMMENDATIONS

1. Conduct research to describe African-American sexuality, prioritized to pursue variables most pertinent to African-American sexual health.
2. Understand the sociocultural context of [African-American] interpersonal relationships and its impact on sexual health. Multidisciplinary groups of African-American experts need to be at the forefront of developing a research agenda that can help to identify what we do not know about African-American sexuality.
3. Understand the impact of diversity within African-American communities.
4. Address cultural elements for African-American interventions.
5. Develop clear educational programs around sexuality within a cultural and religious context towards different age groups.
6. Build on existing work and develop a nationally representative cohort of young African-American men who have sex with men that can be prospectively evaluated for risk of HIV and STI acquisition.
7. Design and fund additional research to enhance understanding of potentially important factors such as STD coinfections, sexual and social networks, knowledge of HIV status and discrimination towards MSM that may place African-American MSM at risk.
8. Support and conduct research to elucidate effective ways to decrease discrimination toward African-American MSM.
9. Develop and support research that enhances understanding of how resiliency, cultural and social factors specific to African American MSM can be used in a positive way to strengthen HIV prevention and care for MSM.

The above text was selected, condensed and adapted from articles appearing in the January 2008 Journal of the National Medical Association. *The issue can be accessed at http://www.nmanet.org/index.php/pub_past_issues/january_2008.*

MOVING FORWARD, LOOKING BACK

Studying the IAVI model

IN THIS CHAPTER

What's worked, what hasn't—and what it all means

How IAVI, an original maverick, can contribute in the post-STEP era

A "to-do" list for the Global HIV Vaccine Enterprise

This period of disappointing trial results and difficult self-reflection in AIDS vaccine research has been punctuated by calls for a careful look at the major research and development models in the field. As we discuss in chapter two, some of these calls have been prompted by the broader context of flat-funding for the National Institutes of Health. As the Treatment Action Group wrote in its must-read basic science blog (tagbasicscienceproject.typepad.com/) after the NIAID vaccine summit:

"Essentially, frustration with the dismal, unacceptably low NIAID payline for investigator-initiated grants appears to have caused a number of basic researchers to see the failure of Merck's HIV vaccine candidate as an appropriate latch on which to hang their argument that money should be directed away from human trials of other experimental HIV vaccine candidates and into basic research and discovery."

As critical as it is to consider the NIH and its priorities, this is not the only model for vaccine development. Europrise, the European collective founded in 2007, has brought major researchers and industry partners together to look at vaccines, microbicides and other new prevention strategies in cross-disciplinary collaborations. The Canadian HIV Vaccine Initiative was also launched in 2007.

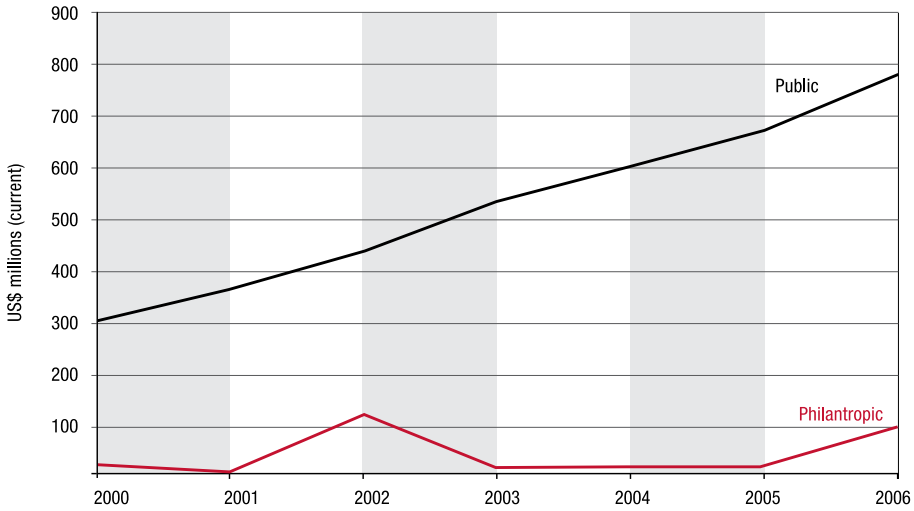
But when it comes to models that are worth considering for what they've accomplished, and what they might contribute to the future of the field, the International AIDS Vaccine Initiative (IAVI) tops the list. One of the world's first "public-private partnerships"—a term that has since morphed into "product development partnerships (PDPs)"—IAVI brought a new model to the field of AIDS vaccine research when it was founded in 1996.

As the field faces what to do next, what can we learn from IAVI? The core questions are: How well has IAVI performed in its first 12 years? What can this teach us? And, how well is its current approach and structure suited to the considerable challenges left in the wake of the STEP trial results?

These are important questions not just for IAVI but for all the organizations and entities in the field. As AVAC stated in last year's Report, one of our priorities in each of our annual surveys of the field is to examine a core organization with the potential of being a game-changing player, and make recommendations for improving its effectiveness. Last year we looked at the Global HIV Vaccine Enterprise. This year, IAVI is our focus because we believe its entrepreneurial history, maverick identity and diverse financial support position it as a leading AIDS vaccine research organization.

By way of full disclosure: IAVI is also a collaborator with and a financial contributor to some AVAC activities. Several AVAC staff members have worked at IAVI in the past, and we have past and present IAVI staff among our board and advisors.

Figure 11 ANNUAL PUBLIC AND PHILANTHROPIC INVESTMENTS IN PREVENTIVE HIV VACCINE R&D FROM 2000 TO 2006



Source: Building a Comprehensive Response: Funding for HIV Vaccines, Microbicides, and Other New Prevention Options 2006. www.hivresourcetracking.org.

For this article, AVAC interviewed 14 individuals —4 senior IAVI staff members and 10 leaders in the field outside the organization—to get their perspectives. All the interviews were confidential, though some individuals have been quoted with their approval. We asked both insiders and outsiders about IAVI's contributions (real and potential) in four distinct areas that are essential to the overall field, in which IAVI has set its own explicit goals for leadership and accomplishment. These are (1) advocacy, (2) expanded research and product development, (3) increased attention to the global South, and, (4) new research directions for the future.

ADVOCATING GLOBALLY

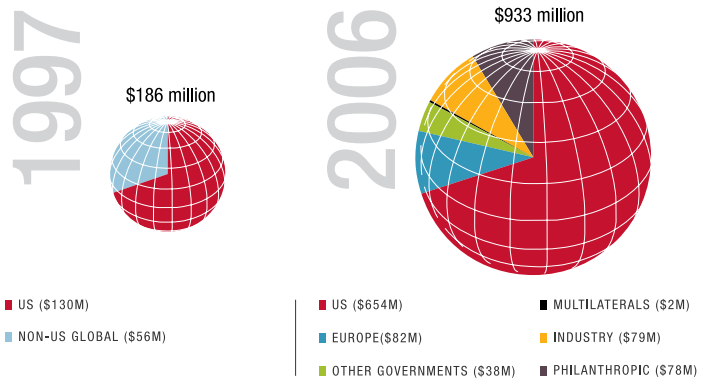
The search for an AIDS vaccine is fundamentally a scientific challenge. But looking back to the early 1990s, it becomes clear that advocacy has been critical to the field. The overall goal of advocacy is to raise awareness, advance specific agendas, and catalyze activity that wouldn't have happened otherwise. In the early 1990s, there were minimal public and private resources dedicated to the search for an AIDS vaccine; there was little pressure to move forward with clinical testing of products; and neither communities (from which trial participants are recruited) nor national governments (of countries that can choose to host trials) were engaged. All of that has changed, in large part due to advocacy, and IAVI deserves a good share of the credit.

Thirteen years ago, the Rockefeller Foundation gathered 24 leaders in the AIDS world together at Bellagio, Italy to discuss the state of AIDS vaccine research. It was a dispiriting time for

the field, with almost complete lack of attention to AIDS vaccines among advocates and policy makers. The Bellagio group recommended that "the establishment of a new global initiative would be the best way to accelerate the development of appropriate preventive HIV vaccines for those areas of the world where the virus is spreading most rapidly." The initiative was viewed as complementing, not competing with, existing national and international activities—and it soon had a name: the International AIDS Vaccine Initiative.

When our interviewees were asked to consider IAVI's advocacy work to date, their first responses were superlatives. People outside the organization told us that IAVI has "always excelled" at making the case for vaccines and has had "a huge impact." IAVI "brought the discussion to a new level that would not have been achieved by any national or global organization."

Figure 12 FINANCING THE SEARCH



Growing global resources: The funding available for AIDS vaccine research has increased but sustained financing from many sources will be needed to continue the search for an AIDS vaccine until we are successful.

IAVI's global advocacy work has taken many directions. First, IAVI has been an active communicator, driving media coverage of AIDS vaccines from almost nil before 1996, to become commonplace within the global discussion on AIDS. *IAVI Report* was launched the first year IAVI opened its doors and soon became an important reference in the field.

The organization's communications success sometimes led to exaggerated exuberance in the media, as when *Newsweek* put Seth Berkley, IAVI's President and CEO, on the magazine's cover with the headline "Can this Man Find the Cure?" Protestations that this man was not actually looking for the cure failed to impress magazine editors before they went to press. Nevertheless, Berkley must be credited for his tireless and indefatigable leadership on the issue—from the organization's inception to the present.

IAVI also brought the vaccine message to world leaders, pushing vaccines with the Clinton White House and high-profile leaders on the slopes at Davos, talking G8 "sherpas" into including vaccines in official communiqués, and convincing parliamentarians from Asia to Africa to get engaged. All that work produced more than headlines and proclamations—there is every reason to think IAVI's advocacy helped propel significant growth in public-sector investment in AIDS vaccines (see Figures 11 and 12). IAVI's work "brought a lot of funds to the field that would not have come otherwise," said Alan Bernstein, the inaugural executive director of the Global HIV Vaccine Enterprise (see box, page 55). "That has been great for the effort."

IAVI emphasizes that its advocacy work is informed by its policy research. In its first decade, IAVI invested in policy work on access, demand, and pricing, anticipating that, as one of its 2001 press releases stated, "a vaccine of at least limited efficacy will be ready within the decade." A range of publications and research papers was developed to provide an evidence base for appropriately forward-looking advocacy. With today's longer time horizons, work focused on anticipating introduction is, unfortunately, not as relevant as it once was, and now is a good time for IAVI to consider what the key policy goals—and tangible results—might be for the next five to ten years.

IAVI has always vociferously argued that a vaccine would be the most powerful tool to combat AIDS, and it has raised the profile of vaccines enormously. It's also fair to say that the organization's self-described "laser-like focus" has caused some painful burns. In the early days, it was quite possible to witness an IAVI presentation at a conference and hear little acknowledgement of the incredible potential of delivering current HIV prevention and treatment interventions more widely. The tone changed at some point, and now IAVI leaders increasingly place vaccines within the context of a comprehensive approach to AIDS.

Still, sometimes the old rhetoric dominates the message. In a December 2007 *Washington Post* op-ed, for example, IAVI pointed to the high price tag for meeting international goals to deliver AIDS prevention and treatment by 2015 to all who need it, and used it as an argument for greater investment in vaccines. Are such juxtapositions necessary in order to justify vaccine research today? After all, no level of investment will produce a vaccine before 2015, and coverage levels for current prevention and treatment interventions have only reached about 20 percent and 30 percent, respectively. The world is not in danger of over-investing in delivery of existing HIV prevention and treatment options, and there is no reason to create, or to reinforce, such a false dichotomy.

There is also the question of whether the role of product developer complicates IAVI's position as advocate. The answer probably is yes, and that's alright. IAVI's advocacy work for the field generally can be more potent because of its breadth of expertise and understanding. For example, it would be natural for the organization's advocacy and policy research on regulatory or intellectual property issues to be positively influenced by its product development work.

IAVI at its best is often an opinionated and sometimes provocative goad, with specific ideas about what needs to happen next. This is, by and large, a strength and could be critical to making headway in areas like industry incentives and HPV vaccine financing where it has created policy papers but is still working on demonstrable policy changes.

DRIVING R&D

AIDS vaccines are a prime example of the shortcomings of the modern research compact in the US: the public sector (NIH) funds the basic science that the private sector (industry) uses to develop, mass produce and bring products to market. This elegant system collapses when the science and economics of a field fail to entice industry investment, leaving new ideas to

Today the question is not so much whether we need more resources, but how to do the best possible science with the resources at hand.

languish in academic labs. As one of the original public-private partnerships, IAVI came of age hoping to bridge the breach between academic research and industry, financing development work in academia and biotechs to support work on good ideas that had not yet found a home. In the 12 years of its existence, IAVI has grappled publicly and internally with the balance between "ensuring" versus "doing"—advocacy, policy and grant-making work, versus doing those projects itself. And over the past several years, it has come to complement its "ensuring" work with an increasingly complex array of internally-initiated and managed scientific projects.

Our interviewees remarked that over the course of its evolution, IAVI developed a "thoughtful empiricism" approach of pushing forward with development and testing of a variety of candidate products, rather than focusing on basic science. "Their products haven't panned out," one person told us, "but then no one's have."

Berkley and Wayne Koff, IAVI's Senior Vice President for Research and Development, point to several achievements from IAVI's scientific program:

- The **core immunology lab** in London.
- Creation of **scientific consortia**, like the Neutralizing Antibody Consortium (NAC), and the Live Attenuated Consortium that encourage collaboration on the most difficult questions.
- **Product development teams**, including partnerships with biotechs, which brought six candidates to clinical trials.
- **Creative intellectual property** agreements with development partners that reserved rights for IAVI to make products accessible globally and inspired similar arrangements among other funding groups.

"The really important things we've done are trying to stay ahead of the curve and trying to put pressure on a field that moves too slow and has a lot of herd mentality," Berkley said. "We've sped up the process."

One anonymous IAVI staffer put it another way: "Often by annoying others and creating more competition, IAVI helped the field come out of its inertia."

Amidst today's calls for redoubled basic science work and a renewed focus on antibodies, it is worth remembering that IAVI established its Neutralizing Antibody Consortium six years ago, when hopes for cell-mediated immunity were still relatively high. As one interviewee said, "We're now at the point where people appreciate the potential role of neutralizing antibodies, but IAVI started the NAC when antibodies weren't in vogue." Several people also said the NAC has been valuable and "brought people together in a new way." IAVI's "crystallization robot" (which systematically studies crystal structures of envelope proteins) is acknowledged as one unique contribution to the field.

We also heard from individuals who perceive that IAVI believes it single-handedly transformed the world and want IAVI to temper this attitude. Others pointed out that consortia are popping up in many places and that IAVI doesn't have the corner on this market. Nor does a focus on antibodies distinguish IAVI from other research organizations working today. And one scientist warned that these efforts cannot replace product development work, saying, "The NAC is good, but it doesn't get a product developed…to do that you have to choose one thing and leave others on the back burner. It's a big risk."

So has IAVI been able to select products and move them forward? Here, too, we heard positive answers. Some focused on the organization's decision to winnow down its crop of "me-too" DNA-MVA products. And in a twelve-month period over 2003-2004, IAVI was able to launch five trials in this tight timeframe, including the first AIDS vaccine trials to take place in Germany, India, Rwanda, and Zambia.

Another scientist summed up IAVI's major accomplishments as "taking what were leading candidates at the time, testing them and pushing them forward. Unfortunately, of course, they didn't work." Another said, "I didn't always agree with their scientific choices in candidates…but IAVI did what was considered by many to be the best science at the time." A third interviewee said that IAVI's track record on R&D has been a "mixed bag…but that has more to do with where the field is than it does about IAVI." One person concluded that IAVI's role in product development "has been more about facilitation… connecting the dots is one of the things they do really well."

MOBILIZING RESOURCES, MANAGING EXPECTATIONS

One of IAVI's core messages has always been that an effective AIDS vaccine is the "best hope" for ending the epidemic, and it has been highly successful in using its policy and advocacy to emphasize the urgent need for increased funding for IAVI and for the field as a whole. The first Bill & Melinda Gates Foundation institutional support grant of US $1.5 million to IAVI in year 1998 was followed by grants of US $25 million and US $100 million in 1999 and 2000, as well as subsequent grants to specific projects such as IAVI participation in the CAVD. Today, IAVI's operating budget is US $90.5 million. Funds for the field increased over the same time frame (see pages 42 and 43)—and many people we spoke to stressed that IAVI's advocacy for the AIDS vaccine field helped bring those resources to the table.

Today the question is not so much whether we need more resources, but how to do the best possible science with the resources at hand. And as important, how do we sustain the current investment levels for many years to come? The challenge facing all stakeholders in the field is to make and act on concrete suggestions about where money could be better spent.

These questions have been thrown into sharp relief by the STEP results which have led many in the field, including IAVI leaders, to emphasize human discovery trials, ramped up basic science and pre-clinical work. The March 25th NIAID AIDS vaccine summit focused the conversation on how US government funds might be redirected. It will be important for IAVI, like the NIH, to share its own work on reallocating resources according to the priorities of the post-STEP era.

As we gear up for the long haul, we must also continue to examine whether we're using our resources optimally—being selective and strategic about travel, meetings and conference calls and paying attention to overhead, salaries, travel budgets and staffing levels. Likewise, as the field focuses on how to do better with the resources that it already has, it must also, as we say in the first chapter, "watch its language." The "best hope" argument might not hold true about a T-cell vaccine whose primary benefit is slowing disease progression. The field must explore—and build messages around—the potential for combination strategies.

In sum, while there's some debate about whether IAVI was indispensible to various R&D initiatives that may have happened eventually with or without IAVI, there is acknowledgement that the organization has been an innovator, pursuing new approaches that sometimes yielded valuable results.

Looking forward, IAVI combines a unique array of scientific assets (like its robot and lab) and attitudes (like its results-oriented partnering with industry and its willingness to change course) that could serve the organization and the field well in the years ahead.

CONCENTRATING WHERE THE EPIDEMIC IS WORST

Today it seems obvious that AIDS vaccine research should be focused on serving the part of the world where the epidemic is fiercest, including sub-Saharan Africa. But 12 years ago, when IAVI entered the field, vaccine research efforts had largely been built around the epidemic in the developed world, with a few notable exceptions like critical early work by the World Health Organization. All the vaccine candidates at that time had been developed based on the HIV B subtype (or clade) that is prevalent in North America and Western Europe. There were few if any clinical trial sites in sub-Saharan Africa ready to test vaccine candidates targeted at the HIV subtypes in the populations most at risk of infection, and little precedent for starting Phase I safety studies of novel candidates in poor countries. Research that did take place in developing countries was, justifiably, subject to greater scrutiny for its ethical merits.

IAVI publicized the subtype mismatch as a prime example of how the AIDS vaccine field needed to be redirected to the global South, and the organization established itself as the advocate for research focused on serving people in less-developed countries. Following recommendations from the Bellagio group, the organization began developing a candidate based on subtype A, which is common in some African regions, and by 1998 had moved that DNA-plus-MVA combined strategy into human testing.

Many people now believe the clade issue was over-simplified and that effective products will ultimately need to address more than clade to adequately deal with the genetic diversity of HIV. Even if that proves true, it seems clear that IAVI's advocacy and research investments brought needed attention to the priorities of the global South. A critical element of that success was the organization's ability to find a rich new vein of financing for vaccine research. "One of our greatest innovations was to try to make research funding sensitive to the needs of developing country scientists," said Berkley. "We were able to get development agencies to change their rules so that they could fund research, which allowed capacity building and long-term support." IAVI went directly to international development agencies of governments in the US, Canada, and Europe and made the case for investment in research and development, securing grants from eleven governments as of 2008.

These funds helped support IAVI's country-level programs, which cover a spectrum of activities—from parliamentarians' meetings to cohort building to media trainings—and are unique among the major sponsors of vaccine trials.

With country programs in India, Kenya, South Africa, and Uganda and more focused efforts underway in Brazil, China, Rwanda, and Zambia, IAVI has established strong partnerships with policy makers, civil society leaders, and local clinical research teams. IAVI staff members work on equal footing with the Kenya AIDS Vaccine Initiative, the Uganda Virus Research Institute and others.

In collaborating to launch AIDS vaccine projects in developing countries, IAVI occasionally trod on the toes of organizations with established projects. One interviewee said, "Clearly IAVI has made a huge difference, but it's important not to forget those who were toiling away for years" building research teams and establishing cohorts in developing countries. Here, as in other areas of its work, IAVI's ability to move swiftly and decisively sometimes raised concerns for existing, established groups working in the same settings.

These critiques notwithstanding, IAVI has consistently used its resources to build an enabling environment for AIDS vaccine research, and its pioneering work on partnering with developing countries was the area of greatest consensus in the interviews for this article. One researcher described it as "maybe the best approach to cohort development and setting up sites internationally." Another said IAVI's clinical infrastructure work "has been at the top of the field…they built infrastructure, trained people." Several people noted favorably that IAVI sites are designed with a focus on readiness for efficacy trials, in addition to smaller-scale studies.

"One of our greatest innovations was to try to make research funding sensitive to the needs of developing country scientists."

—SETH BERKLEY, IAVI

These efforts provide a strong foundation for work still to come: as we discuss on page 29, there's been a notable absence of meaningful community input into discussions of the PAVE 100 protocol, with a scant handful of African scientists (all sponsored by the Department of Defense) present at the December meeting of the NIH's AIDS Vaccine Research Subcommittee that discussed the study, and few community representatives actively participating in protocol-related discussions.

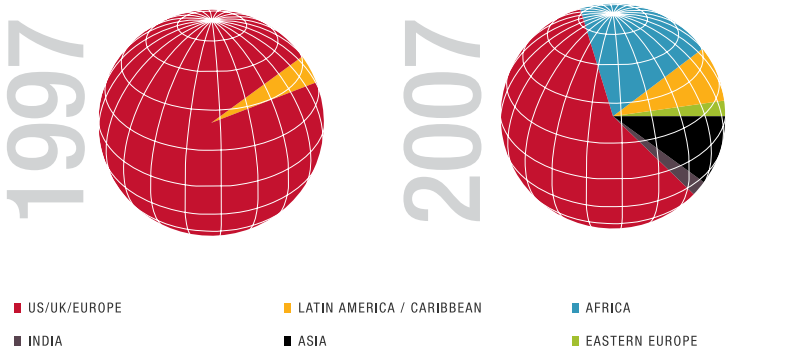
IAVI can work with its strong country-level collaborators to fill the gaps in developing country participation that emerged during this year's unanticipated and relatively fast-moving decision-making process. For many trials, some of the key discussions happen on conference calls, which can be a challenging environment for community representatives. While it is important to support community participation in protocol calls, this cannot be the only channel; there must be supplementary approaches to information sharing, caucusing, and group

feedback. What's the best way to disseminate complex and incomplete information to community representatives—including, but not limited to, community advisory board members—so that they're able to follow evolving discussions? Is there a sample strategy that can be developed based on recent events? In answering these questions, IAVI can make a major contribution.

LONG-TERM INVESTMENTS IN THE SCIENTIFIC FUTURE

In the mid-1990s, IAVI was a leading voice of the empiricists, arguing that if more vaccine candidates could be moved off the shelves and through testing more quickly, then the search for an AIDS vaccine could be accelerated. The failure of IAVI (and all other) candidates has forced the organization (and many others) to focus resources on basic science and preclinical work aimed at addressing some of the fundamental obstacles to developing effective vaccines.

Figure 13 GLOBAL DISTRIBUTION OF VACCINE TRIAL SITES



A global endeavor: In the past ten years, capacity for conducting AIDS vaccine trials has expanded around the world.

"The pendulum at IAVI has moved from all product development to at least 50-50 discovery and development now," said IAVI's Koff. "The goal is to solve the major scientific problems impeding vaccine discovery and translate this information to get a better generation of candidates." That change in emphasis has also led to a new way of doing business, from using most of the product development budget to contract out with biotechs and academic labs working on products, to building major research functions inside the organization. In 2007, IAVI and the Bill & Melinda Gates Foundation launched an innovation grant fund that is the first to target biotechs working outside the AIDS vaccine field. Other components of the new paradigm include expanded activity by the NAC and the LAC, and a preclinical pipeline that IAVI says includes half of the new vectors under development field-wide.

IAVI has long worked in partnership with many entities—and it is forging new ones. In April, it announced a joint venture with CHAVI that will include collaborative immunological studies and assay standardization, as well as work focusing on understanding newly-transmitted viruses, and the impact of human genetics on HIV control.

In addition to the collaborative work, IAVI is also expanding its in-house capacity. The AIDS vaccine development laboratory in Brooklyn, New York, which adds industry-style capabilities and expertise to IAVI's product-development work, is one example.

The new in-house model may make sense on paper, but can IAVI pull it off? Two researchers interviewed for this article questioned whether the organization has the financial resources or breadth of expertise across vaccine design and development to lead the field to new products. One worried that, "seeing what it takes to develop a product and guide it through all the steps makes me wonder…the resources needed are hundreds of millions a year, not millions a year."

Koff says critiques like these misconstrue IAVI's new direction. "We are not the 'A to Z'—the fully integrated biotech company…we've decided to tackle a few problems in discovery and development…but we do want to run the organization with the discipline of a biotech."

Even those who raised concerns about the ability of IAVI to lead on product development admitted that with the extremely limited industry engagement in the field, all willing and smart players are welcome. Only time will tell whether IAVI's new approach pays off. One person noted that there are several "innovation funds" today and no one knows which, if any, will yield results. Regarding IAVI's focus on different vectors at the new lab: "It's a risk. Will it add value? The jury is out." Another researcher said IAVI's new directions represent smart, if not transformational, thinking: "Maybe they are not ahead of the game now, but they are focused. They can direct research more effectively than some others." A third said that moving more work in-house is "a bold move, a gamble. And I wouldn't criticize them for gambling."

PLAYING WELL WITH OTHERS?

In our off-the-record conversations about IAVI, the word "arrogant" often came up. From its inception, the organization set itself apart from the field, aiming to work more quickly than others and bulldoze through roadblocks. It's also been accused of overzealous self-promotion and disparaging the efforts of others. IAVI has long distinguished itself from major research institutions like NIH, which many say can't be as swift or flexible as a non-governmental organization like IAVI. The organization generated considerable controversy in AIDS research circles when it successfully sought an earmark for itself in the US federal budget, thereby obtaining upwards of $25 million over four years. This was for research outside of the NIH review process, which allocates most of the US research dollars.

IAVI and its partners can help fill the gaps in developing country participation that emerged this year.

Though IAVI's collaborations on clinical research were highly praised, several interviewees in the field hoped IAVI would demonstrate greater willingness to collaborate with others. "I wish they were more open and communicative," said one researcher. "They seek their own council… from a scientific view they are a bit too insular," said another.

Many would argue that IAVI's single-minded drive is much needed in a field that is too often mired in self-criticism, risk-aversion, copy-cat research, and a general sense of malaise. But the organization's sense of independence also means it is not always perceived as a neutral player representing the field generally. Part of the genesis of the Global HIV Vaccine Enterprise was a sense that an impartial organization was needed to coordinate, plan, and convene players across the field. In the early days, IAVI would have been an obvious candidate for that role, but not today. That is not a criticism at all; IAVI evolved to meet the challenges and fill the gaps it found.

WHERE TO FROM HERE?

The vast majority of people we spoke to for this article gave IAVI high marks for the groundbreaking work it's done to date. Now, with the page turning to a new chapter in AIDS vaccine development, IAVI has the potential to remain one of the field's great assets—provoking, promoting, partnering with developing countries, and taking risks. By the nature of its multi-functional, comprehensive approach, IAVI has something to contribute to all of the major challenges facing the field in the near- and mid-term. None of these challenges are unique to IAVI. But all of them are areas where IAVI has the opportunity to make unique contributions. We look forward to them.