
THE SEARCH MUST CONTINUE

AVAC Report 2008

ACKNOWLEDGMENTS

This Report was written and edited by AVAC staff and board, and coordinated by Emily Bass. We dedicate this year's Report to the thousands of individuals who have participated, are participating and will participate in AIDS vaccine and other HIV prevention trials—their ongoing and sustained dedication, commitment and enthusiasm serve as inspiration to all of us.

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TABLE OF CONTENTS

3	The Story that Must be Told: A letter from the Executive Director
7	AVAC's Top 10 Recommendations for 2008 and Beyond
9	AVAC Report 2008 At a Glance
11	Status Report: An Update on Last Year's Recommendations
13	<i>Chapter 1</i> The Whole Wide World: Global priorities around HIV prevention research
13	Our Top Priorities
21	<i>Chapter 2</i> What's (Y)our Position?: Where we stand in the post-STEP era
29	Community Input on PAVE 100: What does "GPP" say?
33	<i>Chapter 3</i> What We Know for Sure: Lessons to be learned from the STEP study
40	Towards an African-American AIDS Research Agenda: Required Reading
41	<i>Chapter 4</i> Moving Forward, Looking Back: Studying the IAVI model
46	Mobilizing Resources, Managing Expectations
52	Science Snapshot: Quick takes on next steps in the search for an AIDS vaccine
55	Time for the Enterprise to Expand its Impact
56	The Search Continues

FIGURES & TABLES

14	Figure 1 HIV Prevention Research: A Comprehensive Timeline of Anticipated Results from Efficacy Trials
17	Table 1 Ongoing and Planned PrEP Trials as of April 2008
18	Figure 2 Ongoing Trials of New Prevention Options Worldwide (April 2008)
22	Figure 3 The Era of Flat Funding: NIH and NIAID AIDS Research Funding FY 1989-2009
25	Figure 4 Losing Power: The Impact of Inflation on the Flat NIH Budget
26	Table 2 Ongoing Trials of Preventive HIV/AIDS Vaccines Worldwide (April 2008)
32	Figure 5 Why an AIDS Vaccine Is Possible
33	Figure 6 Starting the "Post-STEP" Era: A Timeline
34	Figure 7 All in This Together: Layers of the AIDS Vaccine Community
35	Figure 8 Projected HIV Prevalence By Age: US and African-American MSM
36	Figure 9 HIV Prevalence by Age Among US and African-American MSM: Current Estimates
37	Figure 10 Data on Rates of Reported Risk Behavior Among Male Volunteers in the STEP Trial
38	Table 3 Proportion of STI Prevention Expenditures Targeted at MSM in Asia
42	Figure 11 Annual Public and Philanthropic Investments in Preventive HIV Vaccine R&D from 2000 to 2006
43	Figure 12 Financing the Search
49	Figure 13 Global Distribution of Vaccine Trial Sites

Don't give up on an AIDS Vaccine LOS ANGELES TIMES •
AIDS-vaccine Trial Volunteers  **Warned of HIV-**
infection Risk BUSINESSDAY • **Warning Is Sent to AIDS**
Vaccine Volunteers *S. Africans Among Recipients*
Who May Be at Higher Risk of Contracting Virus
THE WASHINGTON POST •  **HIV vaccine trials suspended**
THE TIMES • **A pivotal moment in HIV prevention**
SEATTLE POST INTELLIGENCER • **HIV experts wrestle with**
troubling vaccine study at Seattle meeting SAN FRANCISCO
CHRONICLE • **In tests, AIDS vaccine seemed to** 
increase risk THE NEW YORK TIMES • **Too Soon to Drop** 
AIDS Vaccine Effort THE BALTIMORE SUN • **Enough**
is Enough *Instead of continuing to squander hundreds*
of millions of dollars on a futile quest for an HIV
vaccine, focus AIDS spending on prevention, testing and
treatment THE BALTIMORE SUN • **AIDS Vaccine Trials Put**
on Hold DAILYNATION •  **In Search of an AIDS Vaccine**
Rededication follows Disappointment THE WASHINGTON POST

THE STORY THAT MUST BE TOLD

A Letter from the Executive Director

The American statesman, scientist and inventor Benjamin Franklin said, “Success has many parents, but failure is an orphan.” More than two centuries later, in the age of global communications, failure is, in many instances, an orphan who makes headlines and becomes fodder for naysayers and commentators with 20-20 hindsight.

Over the past eight months, this has certainly been the case with AIDS vaccines. As the headlines on the opposite page show, the failure of Merck’s Ad5 HIV vaccine candidate (MRK-Ad5) to show any benefit in the STEP trial triggered an onslaught of media attention including editorials, blog entries, mainstream reporting and scientific commentaries—some accurate, many misinformed.

The fact that the vaccine appears to have increased susceptibility to HIV among male volunteers with pre-existing Ad5 immunity has also made news and heightened the disappointment about the trial.

The clinical trial research teams, trial sponsors, Merck, the US National Institutes of Health and the HIV Vaccine Trials Network, and their collaborators on the Phambili study in South Africa have been heroes throughout this difficult period. They have operated with a superb level of honesty, transparency and commitment to the volunteers.

That the trials were a great success cannot be said too often. Both STEP and Phambili enrolled and retained volunteers in efforts run by talented, dedicated clinical trial staff. STEP generated a clear answer about whether

the vaccine worked. It didn’t, and this is a disappointment. But this is not the end of the road.

As the Phambili principal investigator, Glenda Gray, said, “HIV is ravaging our communities, and everyone involved in Phambili has been affected by this epidemic. Our endeavors to find a vaccine must not stop; we must continue the race to find a vaccine so we can secure an HIV-free generation for the future.”

In spite of this effort, some have made these trial results the foundation of an argument that AIDS vaccine research should be halted, that the search is futile, that we are no closer to a vaccine than we were 20 years ago, and that the resources devoted to it are an exorbitant waste.

We’re all for public dialogue and debate. Everyone deserves the opportunity to voice an opinion. But the misinformation, faulty logic and revisionist history that have grown up around the STEP and Phambili studies and by extension, the field as a whole, are deeply troubling.

And so the first thing we’d like to say in this year’s AVAC Report—perhaps the most important message—is this: *enough is enough*.

It’s time to reclaim the narrative of what happened with STEP and what it means for the future of AIDS vaccines.

Bad news travels fast and misinformation has a terribly long half-life. Some of the statements that have been made this year about the futility of the search may haunt the field for years to come, in the United States—where the

statements originally appeared—and in Uganda, Kenya, South Africa, Thailand, India and the many other countries that are engaged in HIV prevention research, where they have been republished.

“It is critical that we understand that what we say today and what appears in the press may actually affect future trial conduct in Africa,” said Hannah Kibuuka of the Makerere University Walter Reed Project in Uganda.

In the pages that follow, we try to counter some of the more egregious statements made over the past months. Here are some critical points we want to state up front, loud and clear:

No one knew in advance that MRK-Ad5 was going to fail. At least one scientist has recently said publicly that he “cringed” when Merck announced its test-of-concept trials. But three years ago, when the STEP study started, the same scientist said that “Every new AIDS vaccine candidate that enters human studies brings us closer to understanding HIV and the human immune system—and to ending the worldwide AIDS pandemic.”

An editorial in a recent edition of the journal *Nature* had a similarly startling revisionist view when it stated, “Decisions to move Merck’s vaccine candidate and a previous failed candidate into clinical trials were based only partly on science. Also a factor was the field’s need to show the public that progress is being made, thereby justifying the millions of dollars it receives from philanthropists and taxpayers.”

The field has weathered some stiff controversies around whether to go ahead with other efficacy

trials, such as the gp120 study in 1994 (which didn’t proceed) and the Thai prime-boost trial that began in 2003, and is expected to reach completion in 2009. But looking back over the discussions leading up to the launch of the MRK-Ad5 test-of-concept studies, there’s no evidence or public comment that suggests there was any controversy at all.

This is a dangerous example of rewriting history. The fact is that when MRK-Ad5 was advancing into test-of-concept efficacy trials, there was strong enthusiasm and a widespread consensus in the field that this was the most promising candidate available. This didn’t mean we all assumed it would work, but it does mean that it was considered a credible candidate for testing in efficacy trials.

T-cell immunology is a rapidly evolving field. Perhaps today’s assays might have given different evaluations of the Merck candidate four years ago—but that’s scientific time travel and the reality is that the field, as a whole, was supportive of this product entering efficacy trials.

There was a rationale for attempting to induce T-cell-based immunity, and that rationale still holds true today. Cell-mediated immune (CMI) responses have been associated with long-term survival in elite controllers and have been observed in highly exposed, persistently seronegative individuals. There is evidence from the non-human primate model that a CMI response is an element of viral control in successful vaccine challenge experiments. T-cell-based vaccines are also in development for other diseases such as malaria and TB. The scientific basis for exploring this

strategy was in place before the STEP result, and the failure of a single candidate does not invalidate the evidence base that led us to where we are today. There continues to be a rationale for seeking to induce cell-mediated immune responses as one component of an effective vaccine strategy. We are not going “back to basics” and abandoning the knowledge gleaned to date. We are going forward, building on sound science—including the STEP and Phambili data.

The AIDS vaccine effort has always included basic science, preclinical work and human trials. The “post-STEP” era has prompted a flurry of calls for reexamining the priorities and scientific agendas of many research entities. In March, NIAID took up the challenge with its AIDS vaccine summit. These discussions have generated important insights about the need to continue to emphasize discovery research—aimed at answering basic scientific questions—as well as product development. But they’ve also led to a skewed story line, which portrays the field as needing to reorient to basic science in a way that it hadn’t been doing before the STEP result. As we discuss in chapter 2, the preponderance of new money going into AIDS vaccine research over the past three years has been for basic science and discovery-oriented projects.

For example, well before the STEP trial results, there was a strong emphasis on work to understand how to induce neutralizing antibodies, though all understood that this line of research would take several years to generate a viable candidate. There hasn’t ever been a point that the field was entirely focused on human clinical trials.

Just because there have been vaccine candidate failures in efficacy studies, we cannot retreat from doing future trials. Human clinical trials—both large and small—are absolutely critical for gathering much-needed information to move the field forward. It is wrong to present a false dichotomy of basic science versus human trials. It is not a matter of “either/or” but rather of using the combined strengths of basic science, animal studies and human studies as part of a sound scientific strategy.

Having said this, we must also say—as we do throughout this Report—that the introspection and course correction prompted by the Merck vaccine failure is warranted and has the potential to be highly productive.

We welcome attention to fundamental questions about vector-based immunity, host genetics, mucosal responses and correlates of protection to proven vaccines (see chapter 2).

We are in strong agreement that, given its long timeframes, the AIDS vaccine field must be funded and structured such that new and young investigators (as well as new and young advocates) consider it as a career choice.

And we are adamant that the search for an AIDS vaccine must emphasize perseverance, while simultaneously redoubling efforts to implement proven prevention and treatment efforts and to identify other new biomedical strategies like pre-exposure prophylaxis and microbicides (see chapter 1).

We also need maverick, risk-taking organizations. We salute Merck for their involvement and hope that it continues. And, as we explore in chapter 4, the International AIDS Vaccine Initiative,

a stalwart leader in the field, has the opportunity in the post-STEP era to continue pushing the envelope in its approaches to scientific challenges, clinical trial capacity, policy, preparedness and communications. The Global HIV Vaccine Enterprise, with the appointment of Alan Bernstein as its inaugural executive director, must also prove itself with dynamic leadership in this critical time.

Top-down leadership is important—so are dynamism and engagement at the grassroots level.

Benjamin Franklin also said, “Perhaps the history of the errors of [hu]mankind, all things considered, is more valuable and interesting than that of their discoveries.” And for the field to move forward we must mine the valuable lessons we now have.

The field has been disappointed, discouraged and—in all honesty—uncertain what the next ten or twenty years will hold for AIDS vaccine research. But that is the nature of the scientific

process. Every field that’s had breakthroughs has also had failures. Failure cannot be an orphan. To acknowledge failure—of a candidate—is in no way to concede overall defeat. We all now have a tremendous opportunity to learn from these disappointments and to be better for them—better, even, than we might have been without them.

AVAC remains committed and cautiously optimistic.

Onwards.



MITCHELL WARREN
AVAC EXECUTIVE DIRECTOR

IN MEMORIAM: FRANCIS MMIRO (1934-2008)

AVAC notes with sorrow the recent passing, in April, of Professor Francis Mmiro, one of the fathers of HIV prevention research in Uganda. An obstetrician/gynecologist by training, Professor Mmiro was dedicated to the fight against HIV/AIDS in his country and worldwide. He was, as one colleague described him, “a committed, brilliant and ethical practitioner,” and his passing leaves a gap in the field as well as a rich and inspiring legacy of commitment, innovation and leadership. Among his many accomplishments, Professor Mmiro served as a principal investigator of HIVNET 012, the groundbreaking study of single-dose nevirapine for prevention of mother-to-child transmission. His steadfast stewardship of pediatric AIDS vaccine research led to the launch, in 2007, of Uganda’s first pediatric AIDS vaccine trial. His intellect, generosity, humility and dedication provide a model for countless students and colleagues, and his work will live on in all of us.

AVAC'S TOP TEN RECOMMENDATIONS FOR 2008 AND BEYOND

This year, as always, the Report has a range of suggestions for various stakeholders involved in AIDS vaccine research, and we hope you'll read through these pages to find them all. We're well aware, though, that publications and recommendations can pile up and gather dust without ever coming to life off the page.

On page 11, we've taken a look back at what happened around last year's recommendations. And below please find our top ten recommendations that we will revisit frequently in the coming year to gauge how well we and the field are doing.

- 1. Structure the field so that there are career paths for young investigators.**
(page 28)
- 2. Articulate the human discovery trials agenda and balance vaccine discovery and development.**
(page 21)
- 3. Learn from STEP and direct prevention-research resources to under-served populations.**
(page 33)
- 4. Systematically improve community engagement strategies.**
(page 29)
- 5. Watch language used to communicate expectations of prevention research.**
(page 14)
- 6. Increase community stewardship of the PrEP agenda.**
(page 16)
- 7. Engage in meaningful dialogue around male circumcision, HIV testing and gender.**
(page 16)
- 8. Prepare for results of the Thai prime-boost trial.**
(page 18)
- 9. Expand community engagement with and critique of the microbicides science agenda.**
(page 19)
- 10. Reconsider how clinical trials infrastructure is sustained and clinical research agendas are developed—in discussion led by developing country voices.** (page 19)





AVAC REPORT 2008 AT A GLANCE

Chapter 1

THE WHOLE WIDE WORLD

Who needs to weigh in on male circumcision?

Why PrEP research is a top priority

Increasing developing country leadership

Chapter 2

WHAT'S (Y)OUR POSITION

Is NIAID spending wisely?

Should the next planned efficacy trial, PAVE 100, go forward?

Are T-cell vaccines dead?

Is an AIDS vaccine possible?

Chapter 3

WHAT WE KNOW FOR SURE

Going site by site to learn from STEP and Phambili

How AIDS vaccine research must help address the African-American epidemic

Getting our messages straight

Chapter 4

MOVING FORWARD, LOOKING BACK

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

Every section in this year's AVAC Report takes on a different facet of the question that the AIDS vaccine field has faced since September 2007, when the STEP study halted immunizations: *Where to from here?*

The first chapter, **The Whole Wide World**, looks at this question in terms of the broader HIV prevention research agenda and calls for a re-direction of attention to the PrEP research agenda, implementation of gender-sensitive male circumcision programs, and implementation of Good Participatory Practice (GPP) guidelines for biomedical HIV prevention trials. The search for an AIDS vaccine has to happen in the context of creative, concerted efforts to find other strategies and to deliver what we already have.

The second and third chapters, **What's (Y)our Position** and **What We Know for Sure**, look directly at the STEP and Phambili trials and the debate that they sparked about whether the AIDS vaccine field had lost its way. Some important questions have been raised about how to strike a balance between basic science and clinical trials. As we discuss in these chapters, we believe the field must develop an agenda for human discovery trials and heed calls for more stringent criteria for advancing candidates into and through human trials. We also believe that trial sponsors must be clear about the scientific questions that a given study is asking, and what the value of the information will be for the field. Discovery trials must fit into a coordinated research agenda that has been designed to answer the question:



“What’s the suite of studies that’s needed, at this time, to help guide development of better vaccine candidates?”

Moving Forward, Looking Back looks at the International AIDS Vaccine Initiative (IAVI) that was founded 13 years ago as a maverick leader in the search for an AIDS vaccine. As the whole field faces what to do next, this article examines the strengths and challenges of IAVI’s program with an eye to what we can all learn from IAVI and what’s needed most in the future.

There are important questions that need to be asked of all the organizations in the field, not just of IAVI. As 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 we focus on IAVI because we believe its entrepreneurial history, unique identity and diverse financial support position it as a leading AIDS vaccine research organization.

Finally, our **Science Snapshot** is a quick take on some of the scientific questions and research areas demanding priority attention in the post-STEP era. We’ve included what we think are some of the most important and intriguing suggestions that have emerged in recent months. It makes for an eclectic to-do list that we’ll revisit more systematically in an upcoming publication.

STATUS REPORT: AN UPDATE ON LAST YEAR'S RECOMMENDATIONS

WHO	WHAT WE SAID LAST YEAR	WHAT HAPPENED	WHAT MUST HAPPEN NEXT
AIDS VACCINE FIELD	Focus the preponderance of new product development resources on innovative candidates.	Much of the field's attention had already turned in this direction prior to the disappointing performance of MRK-Ad5 in the STEP study.	Continue work on novel concepts and articulate the key questions for human discovery and preclinical work that have come into focus post-STEP.
	Continue to work to broaden the array of stakeholders who understand partial efficacy.	Enterprise sponsored meetings on understanding and communicating partial efficacy. AVAC convened Enterprise working group on communications.	Anticipate Thai prime-boost trial results expected in 2009 and ensure that all trials have communication plans for multiple scenarios in place.
	Explore mechanisms for an advanced clinical trial commitment to strengthen and sustain industry involvement.	STEP study result has prompted call for discovery-oriented human clinical trials, and industry may not take the lead in these.	Use innovation funds (such as the new IAVI/Gates Foundation collaboration) as a mechanism for industry engagement.
RESEARCHERS	Build trial budgets to include funding for community-wide results dissemination.	Vaccine and microbicide sites and sponsors did exemplary work in communicating unexpected research results.	Document the best practices and long-term impact of post-trial results dissemination.
	Dramatically expand awareness campaign around vaccine-induced seropositivity.	Illinois court awarded US\$5000 damages to a vaccine trial participant who was tested without consent and received a false positive diagnosis. AVAC, HVTN and others drafted resource materials on the topic.	Continue follow-up with STEP and Phambili participants; prepare for expanded education should another trial of a candidate causing seropositivity go forward.
	Pilot the Good Participatory Practice (GPP) guidelines.	Many researchers provided feedback on drafts of GPP and expressed enthusiasm for the new document.	Train staff on GPP guidelines and implement them; work with AVAC and its GPP grantees.
FUNDERS	DAIDS: Closely monitor the on-the-ground effects of its new approach to funding prevention networks and sites.	This year's events dramatically altered many sites' plans for launching or continuing trials.	Short-term solutions to site's funding needs have been found; long term follow-up and support are needed.
	Multiple funders: Consider community outreach and education fund for independent community oversight mechanisms.	Neither a fund nor an education and outreach program was created.	Developing a fund is more important than ever, given the wide range of challenging issues on in the field of prevention research.
GLOBAL HIV VACCINE	Revisit the business strategy and scientific strategic plan; develop a two-year work plan; convene focused meetings on under-discussed issues.	Inaugural executive director Alan Bernstein assumed leadership of the Enterprise in January 2008.	The recommended "to do" list is as critical as ever. (see page 52)
AVAC	Advocate standard definitions of levels of HIV care and treatment in trials.	GPP guidelines and related UNAIDS ethics document include specific language on standard of prevention and level of care in trials.	Continue to support community-level advocacy; disseminate information on approaches and outcomes for specific trials.
	Work with partners to develop clear, realistic, and consistent messages to manage expectations of new products.	Published regularly-updated comprehensive prevention timeline; developed and shared messages with partners to develop consistent messages; convened the Enterprise communications working group.	Continue current work; develop formal scenario plans in preparation for upcoming trial results.
	Work with partners to build a strong and collaborative global movement on prevention research and implementation.	Convened civil society dialogues and informal discussions on a range of issues: male circumcision, STEP, Phambili, HSV-2, PrEP and others.	Expand activity with sustained international programs.
CIVIL SOCIETY	Work in coalition to advocate for adequate, annual increases in NIH funding.	AIDS Budget and Advocacy Coalition advocated for a 15% increase for NIH AIDS research spending in FY2009.	Continue advocacy with a special focus on the new US Administration in 2009.
	Pilot the GPP guidance document.	Civil society groups worked with AVAC and UNAIDS on pilot programs.	Document experience among initial GPP pilot project is and update the guidelines accordingly.
	Support—and demand—developing country leadership on prevention.	Developing country researchers and civil society leaders played an active role in disseminating and managing negative research results.	Ensure that decisions related to PAVE 100 and other future HIV prevention trials are influenced by and responsive to these leaders.



THE WHOLE WIDE WORLD

Global priorities around HIV prevention research

IN THIS CHAPTER

Who needs to weigh in on male circumcision?

Why PrEP research is a top priority

Watch your language

This year's succession of unanticipated results in HIV prevention trials has meant that many "to-do" lists got pushed aside, or hastily revised to address emerging issues. Simply put: no one had the year that they expected, let alone the year they hoped for. In an ideal world, over the past twelve months, STEP and Phambili would have proceeded and the efficacy trial of HSV-2 for prevention of HIV acquisition would have showed at least a moderate benefit, as would the Carraguard microbicide study.

These things did not happen. Instead, there were disappointing results in all of these trials. The apparent vaccine-related effect on susceptibility to HIV infection among some recipients of the MRK-Ad5 vaccine was an additional blow. All in all, it was a difficult year, to say the least. For some treatment activists it brought to mind the 1993 Berlin AIDS conference, and its relentlessly disappointing news about AIDS treatment.

But no one gave up the search for AIDS treatment in 1993 and no one, after this year, is going to abandon the search for an AIDS vaccine. We're now well into the year after the STEP trial, and gaining perspective on this and other disappointments. It's time to look forward, not back—and to return to those "to-do" lists, which contain some items that are more important than ever.

In this section, AVAC identifies some of our top priorities for action in the coming year. This is our list, and we'd also love to hear—and collaborate on—yours. We hope you'll join our electronic "Advocates Network" and subscribe to our quarterly update, *Px Wire* (available at www.avac.org). These are both ways to contribute ideas and stay informed.

Our first charge to ourselves and to the field is to remember that AIDS vaccines are only one corner of the HIV prevention research landscape, which is itself a fraction of the world of HIV prevention and its proven modalities. When we talk about the search for an AIDS vaccine, and look for ways to explain where they fit into the broader response to HIV, it's imperative that we keep this global perspective in mind.

OUR TOP PRIORITIES

1. Watch the language used for prevention research and implementation priorities.
2. Implement, field test, and comment on new "GPP" and ethics guidelines.
3. Engage in meaningful dialogue and action around male circumcision, HIV testing and gender.
4. Prepare for the results of the Thai prime-boost vaccine trial.
5. Community engagement with and (where needed) critique of the microbicides science agenda.
6. Reconsider how sites are used and how research agendas are developed—in discussions led by developing country voices.

This means, among other things, watching our language:

- A vaccine isn't necessarily the best hope of ending the epidemic.
- A microbicide isn't a solution that's going to be easier to find than a vaccine.

- Male circumcision is neither a silver bullet nor a prevention disaster waiting to happen.

Yes, we've said all of these things. We can even make cases for many of them. But the fact is—we don't know what will work first, or when there will be positive results in any field of biomedical prevention research. And we also

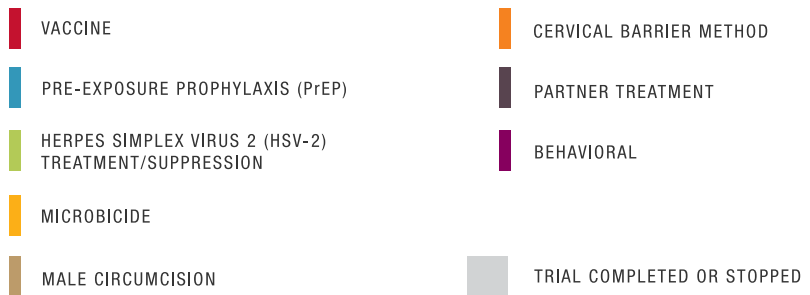
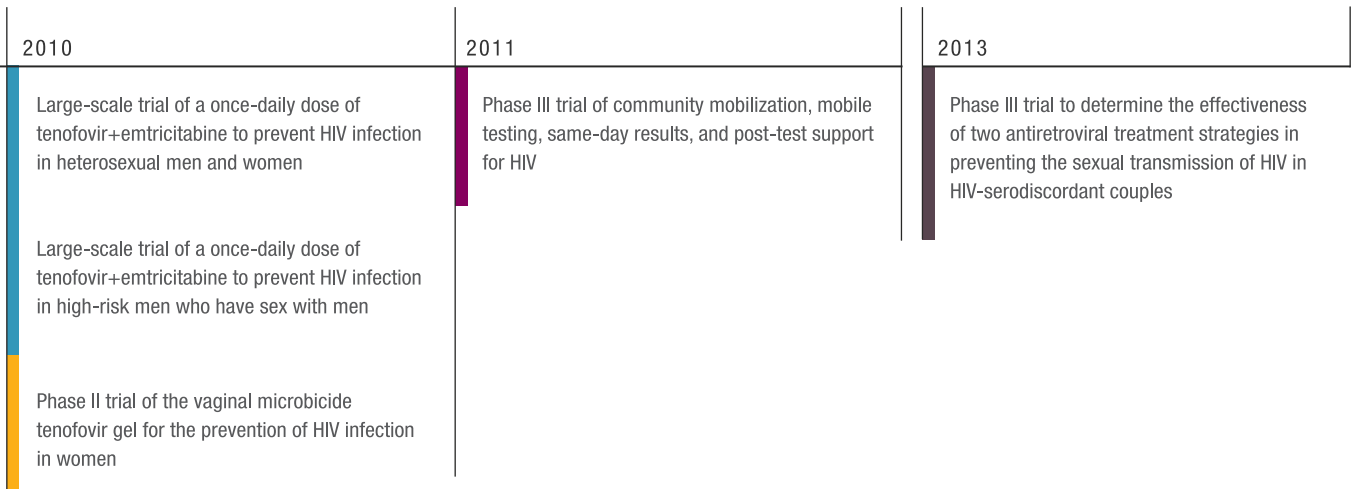
Figure 1 HIV PREVENTION RESEARCH: A COMPREHENSIVE TIMELINE OF ANTICIPATED RESULTS FROM EFFICACY TRIALS*

2007	2008	2009
<p>FHI Phase III trial of the vaginal microbicide Cellulose Sulfate gel for the prevention of HIV infection in women Trial stopped early—January 2007 Results announced July 2007: No evidence of benefit</p> <p>CONRAD Phase III trial of the vaginal microbicide Cellulose Sulfate gel for the prevention of HIV infection in women Trial stopped early—January 2007 Results announced July 2007: No evidence of benefit</p> <p>Phase III trial of the female diaphragm to prevent HIV infection in women Results announced July 2007: No evidence of benefit</p> <p>Test-of-concept trial of Merck's adenovirus preventive HIV vaccine candidate (STEP study) Trial halted immunizations—September 2007: No evidence of benefit Follow-up and data collection continue.</p> <p>Test-of-concept trial of Merck's adenovirus preventive HIV vaccine candidate (Phambili) Trial halted enrollment and immunizations, September 2007: No evidence of benefit Follow-up and data collection continue.</p>	<p>Phase III trial of acyclovir for the reduction of HIV infection in high-risk, HIV-negative, HSV-2 seropositive individuals Results announced February 2008: No evidence of benefit</p> <p>Large-scale trial to evaluate the safety of male circumcision and its potential protective effect for HIV-negative female partners of HIV-positive circumcised males Trial stopped enrollment and surgeries—December 2006. Follow-up is ongoing.</p> <p>Phase III trial of the vaginal microbicide Carraguard for the prevention of HIV infection in women Results announced February 2008: No evidence of benefit</p> <p>Study of different risk-reduction interventions for HIV vaccine trials (Project UNITY)</p>	<p>Phase III trial of a prime-boost (ALVAC-AIDSVAX) combination preventive HIV vaccine</p> <p>Phase II/IIb trial of the vaginal microbicides BufferGel and 0.5% PRO 2000/5 gel for the prevention of HIV infection in women</p> <p>Phase III trial of the vaginal microbicide PRO 2000 for the prevention of HIV infection in women</p> <p>Phase II trial to test the clinical and behavioral safety of a once-daily dose of tenofovir among HIV-negative men who have sex with men</p> <p>Large-scale trial of a once-daily dose of tenofovir to prevent HIV infection in injecting drug users</p> <p>Phase III trial of HSV-2 suppression in serodiscordant couples</p>

know that an AIDS vaccine that provided sterilizing immunity could impact the epidemic in a way that no other intervention would—this is what the history of vaccines has taught us. However we're still in the early days of our journey towards that goal and, with this in mind,

we need to be mindful of how we position vaccines in the hierarchy of potential, not-yet-identified prevention strategies as well as how they relate to current prevention and treatment.

Here are some of our other priorities:



To view this timeline online with trial details please visit www.avac.org/timeline-website/.

*The trial end-dates listed in this table are estimates. Due to the nature of clinical trials the actual dates may change. AVAC will continue to monitor the trials' progress and will update the timeline accordingly.

If you have any questions or comments regarding the information presented here please email avac@avac.org.

Implement, field test, comment on new guidelines.

In 2007, UNAIDS published two documents: the “Good Participatory Practice” (GPP) guidance on community engagement in the context of biomedical HIV prevention trials (developed in a process jointly led with AVAC), and an updated ethics guidance document (www.unaids.org). There is always a gap between theory as it’s put on paper, and practice in the real world. But both of these documents have the potential to be powerful tools for communities, sites, sponsors, and policy makers seeking to do the best possible research and ensure that there are benefits to participating in clinical research—regardless of the trial outcome. To tap this potential, the documents’ findings need to be put into action. And this takes commitment of resources. Sponsors should make it a point to train their staff on the new guidance documents. Each new trial should set aside funds and time for capacity building in the community to introduce the concept of the guidance documents and discuss how these principles relate to community concerns.

Increase community stewardship of the PrEP agenda.

By mid-2009, there could be more participants enrolled in efficacy studies of pre-exposure prophylaxis than in vaccine or microbicide efficacy trials (see table 1, page 17). The current range of trials will answer some critical questions about using ARVs as prevention including whether oral versus vaginal PrEP works better for women; how oral PrEP works in heterosexual populations versus men who have sex with men or people whose primary risk behavior is injection

drug use; how mono- versus dual-therapy works; and long-term safety and acceptability. But for all this progress, there’s still work to be done in developing community stewardship of the PrEP research agenda. This is one area that AVAC is working on in 2008, and we look forward to collaborating with others to address key issues like advance planning around cost, delivery, and access; adherence strategies and support; and how PrEP using tenofovir or TDF-FTC would work in countries where these drugs are also first-line therapy.

By mid-2009 there could be more participants enrolled in PrEP trials than in vaccine or microbicide efficacy trials.

Engage in meaningful dialogue and action around male circumcision, HIV testing and gender.

As the timeline on page 14 shows, there are no active studies of male circumcision for HIV prevention. But there is still a range of open questions—including a host of gender-related issues. In February 2008, the Rakai Health Sciences Program (RHSP) presented additional data indicating that there was an increased risk of male-to-female transmission among recently-circumcised HIV-positive men who resumed sex before wound healing. The 2006 World Health Organization and UNAIDS document on program implications for male circumcision suggests that men should be actively counseled

Table 1 ONGOING AND PLANNED PrEP TRIALS AS OF APRIL 2008					
Location	Sponsor/ Funder	Population (mode of exposure)	Intervention Arms	PrEP strategy(ies) being tested	Status/Expected completion
United States	CDC	400 men who have sex with men (penile/rectal)	1	Tenofovir disoproxil fumarate (TDF)	Fully enrolled – Ongoing 2009
Thailand	CDC	2,400 injecting drug users (parenteral)	1	TDF	Enrolling / 2009
Botswana	CDC	1,200 heterosexual men and women (penile and vaginal)	1	TDF+emtricitabine (FTC) (switched from TDF Q1 2007)	Enrolling / 2010
Peru, Ecuador, US, additional sites TBD (iPrEX Study)	NIH, BMGF	3,000 men who have sex with men (penile/rectal)	1	TDF+FTC	Enrolling / 2010
Kenya, Uganda (Partners Study)	BMGF	3,900 serodiscordant couples (penile and vaginal)	2	TDF; TDF + FTC	Planning / 2012 Anticipated start Q2/2008
Kenya, Malawi, South Africa, Tanzania (FEMPrEP)	FHI, USAID	3,900 high-risk women (vaginal)	1	TDF+FTC	Planning / 2011 Anticipated start Q3/2008
Malawi, South Africa, Zambia, Zimbabwe (VOICE Study)	MTN, NIH	4,200 sexually active women (vaginal)	3	TDF; TDF+FTC; TDF gel	Planning / 2011 Anticipated start Q4/2008
BMGF – Bill & Melinda Gates Foundation; CDC - US Centers for Disease Control; FHI – Family Health International; MTN – Microbicide Trials Network; NIH – US National Institutes of Health; USAID – United States Agency for International Development					

to learn their HIV status, but that the surgery should not be denied to men who are positive or who do not know their status. In the wake of the additional data from RHSP, the WHO and UNAIDS referred to this guidance and said that their position stands.

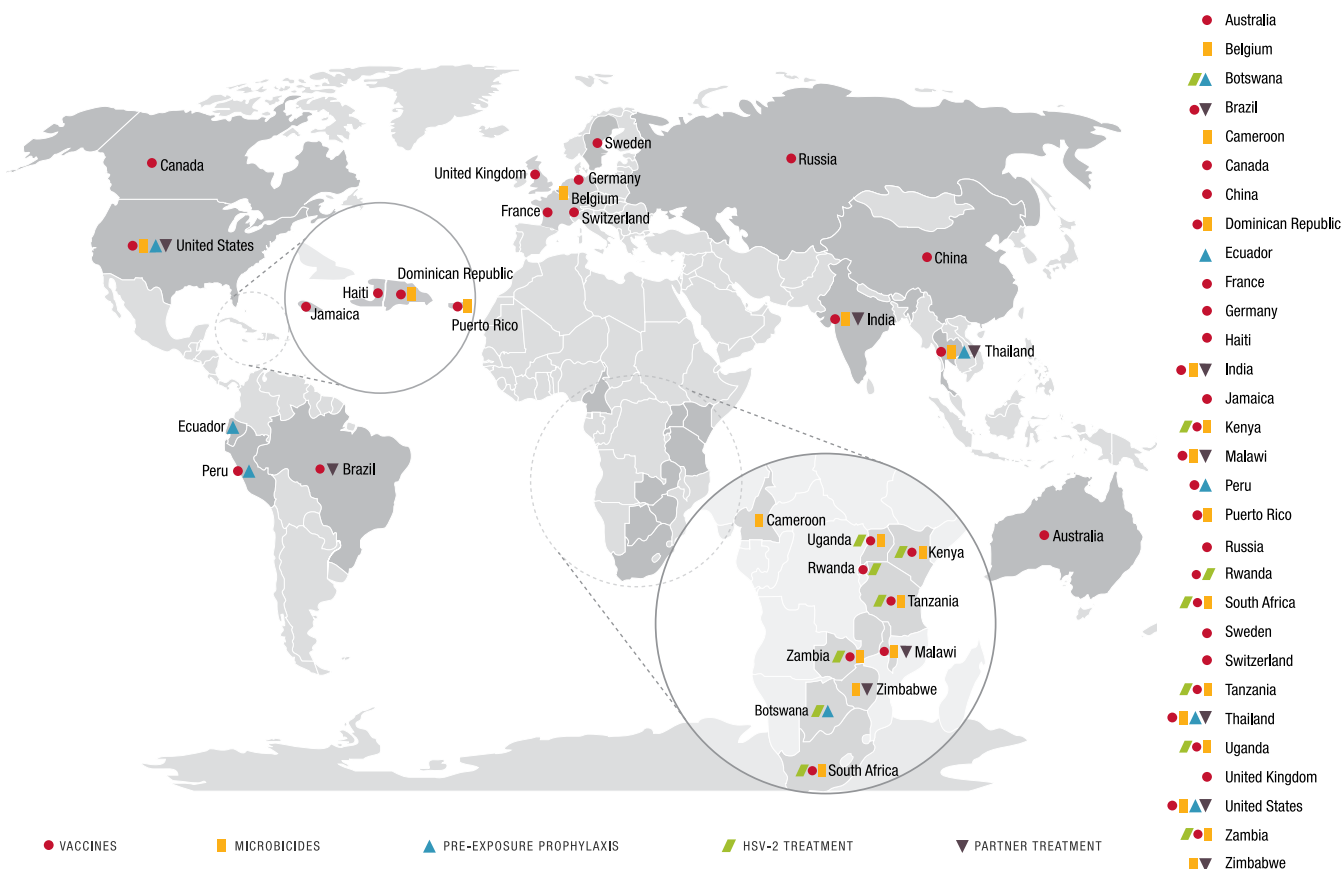
Unfortunately, this is not good enough. AVAC believes that male circumcision has the potential to be a powerful tool for HIV prevention in the context of well-designed and -resourced programs that provide counseling, testing and other services. The demand for male circumcision in some countries indicates that this could be a potential entry point for men into the health care system. But the potential for transmission to women cannot be ignored and is not sufficiently addressed in the current guidance. AVAC is working with WHO and UNAIDS to convene a meeting on gender and adult male circumcision,

and is committed to facilitating a range of civil society conversations on this topic. As programs scale up, funds should be prioritized for those services that emphasize couples counseling or voluntary testing and counseling and that have monitoring components to track reported rates of condom use, coercive sex, risk behaviors, perceptions of sexuality, and other variables over the long term. In addition, AVAC is also working with WHO and Family Health International to develop a web-based clearinghouse of information on male circumcision. Please visit our website (www.avac.org) for more information.

Prepare for the results of the Thai prime-boost vaccine trial.

As our timeline shows, the results of the 16,000-participant Thai trial of a prime-boost vaccine strategy are expected in 2009. As we’ve

Figure 2 ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE (APRIL 2008)



said previously: we cannot assume the outcome of this trial and must be prepared for either a positive or a negative result. (The vaccine combination includes a canarypox vector candidate manufactured by Sanofi Pasteur and VaxGen’s AIDS-VAX—which failed to show efficacy by itself in two earlier trials.) Should there be a positive result in this test-of-concept trial, there will be questions—similar to those first raised when the trial launched in 2003—about whether the benefit comes from the combination or the single canarypox vaccine, which has not been tested separately for efficacy. There will

also be questions about where additional supplies of AIDS-VAX would come from for additional trials and/or initial delivery, given that what is left of the VaxGen company may soon be liquidated. AVAC will publish a document in our “Anticipating Results” series to help advocates understand the issues in the run-up to the end of this trial.

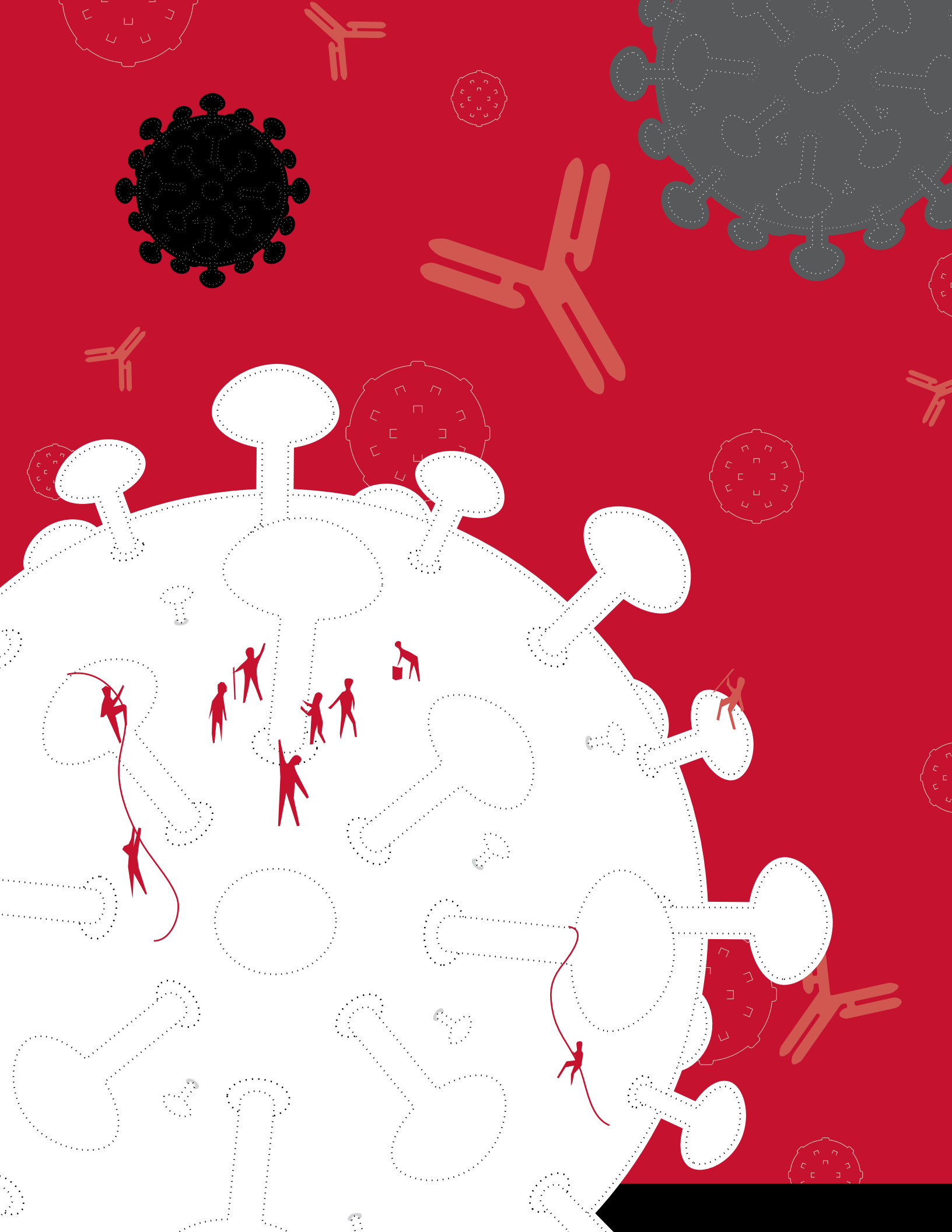
Community engagement with (and, where needed, critique of) the microbicides science agenda.

This year brought the publication of *The First 55 Steps: A Report of the Microbicide*

Development Strategy's Civil Society Working Group (<http://www.global-campaign.org/clientfiles/GCM-MDS-CSWG-FinalReport2008.pdf>). This document is described as the “missing chapter” of the original Microbicide Development Strategy (available at www.microbicide.org) which laid out specific strategic objectives for the field as a whole. This new civil society piece makes valuable specific suggestions on a range of topics and calls “insufficient investment in science-focused microbicide advocacy” one of its highest priority gaps. Like the vaccine field, the microbicide arena has had a series of candidates fail to show efficacy in trials and is advancing candidates with new approaches. These include ARV-based products, now entering efficacy trials including the VOICE and CAPRISA studies in Africa. But there’s still a vacuum of informed civil society voices and advocate-scientists examining and debating the scientific priorities for the field. This means moving from process—which is well and clearly laid out in the “missing chapter”—to product. Specific community outputs could include concrete critiques, questions and calls to action around product development agendas for the field.

Reconsider how sites are used and how clinical research agendas are developed—in discussions led by developing-country voices.

Could clinical research infrastructure be defined by the type of research question it was asking, instead of the candidate it was testing? Would the world look different if clinical research teams identified themselves and were funded based on the ability to do early-phase studies or efficacy trials or intensive investigations—rather than vaccine, microbicide or behavioral trials? These kinds of questions have started to percolate as the AIDS vaccine field considers its next steps. But to date, most of those posing the questions—and most of the audiences—have been North Americans. What’s the view from developing countries? What do research teams from sites in South Africa or Uganda or Botswana or Zambia or Kenya think would be the most useful way to categorize sites and allocate research funding? AVAC is excited that questions about priority-setting and multi-purpose sites are being raised, but we’d like to see people other than donors and North American scientists determining the answers. We’re committed to being a part of this process—but it’s one that research sponsors and other donors should be taking the lead in convening.



WHAT'S (Y)OUR POSITION?

Where we stand in the post-STEP era

IN THIS CHAPTER

Is NIAID spending wisely?

Should the next planned efficacy trial, PAVE 100, go forward?

Are T-cell vaccines dead?

Is an AIDS vaccine possible?

It's now been nearly nine months since the public announcement of the failure of MRK-Ad5, the AIDS vaccine candidate that had generated the most consistent enthusiasm throughout the field in recent years. Overall, the candidate neither prevented infection nor lowered viral setpoint, and in some individuals, receiving the vaccine was associated with an increased risk of acquiring HIV.

In the weeks and months that have followed, the phrase “more questions than answers” has all but worn out its welcome. There are, for the moment, more questions than answers about the cause of the apparent increase in susceptibility to HIV in some volunteers. There have also been more questions than answers about the best way for the field to move forward scientifically in the wake of this setback.

Some critics and provocateurs have used this opportunity to offer definitive answers to some tough questions, like “Is an AIDS vaccine even possible?” At the annual Conference on Retroviruses and Opportunistic Infections, Harvard's Ron Desrosiers raised many of the scientific issues hindering development of an AIDS vaccine. He also raised a few hackles when he flashed a slide that read “Has the NIH lost its way?” and then said that, in his opinion, the answer was

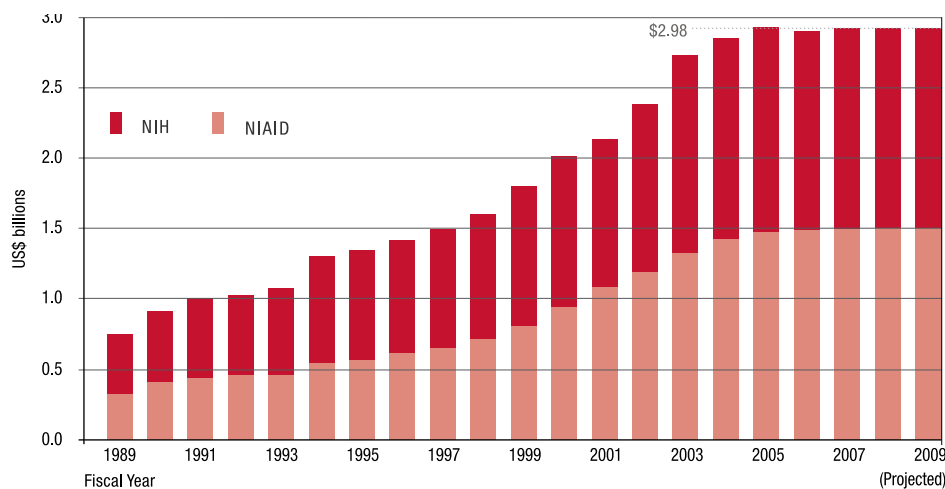
“Yes.” Everyone has—and is entitled to—an opinion. But the reality is that no one has the roadmap that will guarantee a vaccine; no one can say for certain that he or she knows the way. With that caveat, it's time to tackle some of the tough questions head on and to come up with workable answers to use as the basis for the next steps forward.

In this section, we present some of the questions and our answers. In doing so, we stress that as much as our view is informed by input from civil society around the world, we remain a US-based organization and neither claim nor want to be the only civil society voice weighing in on these critical issues. That's one reason for this article's title: we're also interested in hearing *your* position.

1) Is it time to step back from more clinical trials and instead focus on basic scientific challenges?

No. Both are essential and each informs the other. Clinical trials in humans can answer key scientific questions. These include “discovery” trials, which are not part of a product development pathway that's designed to get a candidate to licensure, and clinical trials of vaccine candidates that look safe and potentially effective based on pre-clinical studies. By choosing the best available candidates and testing them in well-designed and ethical clinical trials, we gain incremental but important insights. Discovery studies that do not test products can build out knowledge on areas like: What is the mechanism of protection of licensed vaccines? What are the characteristics of vector-specific immunity? What are the characteristics of mucosal versus systemic immune responses

Figure 3 THE ERA OF FLAT FUNDING: NIH AND NIAID AIDS RESEARCH FUNDING FY 1989-2009



Source: NIAID (http://www3.niaid.nih.gov/news/events/meetings/HIV_Vaccine_Summit.pdf)

induced by different candidates or vaccine components (vectors, immunogens, etc.)? What are the characteristics of different immunogens *in vivo*? What insert designs are best at eliciting broad responses?

The field must also continue conducting AIDS vaccine research in humans. This means developing an agenda for human discovery trials. It also means heeding calls for more stringent criteria for advancing candidates into and through human clinical trials. However, even with concerted efforts to standardize and expand the range of assays used to evaluate candidates, there's still no way of predicting with certainty what level of protection will be provided to humans. In the absence of a correlate of protection, this will always be the case. This is one reason why human clinical trials are essential.

It's also important to remember that the data looking at potential correlates of immune response and control of viral load in the STEP

trial are just beginning to emerge. While it is clear that MRK-Ad5 was not an effective vaccine, data from the trial may provide clues about the types of immune responses associated with better control of viral setpoint.

Instead of debating whether clinical trials have a role in AIDS vaccine discovery, there should be an ongoing discussion geared towards the question "What's the suite of studies that's needed, at this time, to help guide development of better vaccine candidates?" There may not be one answer that fits the agendas of all the different players in the field—and that diversity of views is a good thing. But all trials, including the proposed PAVE 100 trial efficacy of a DNA-Ad5 combination (see page 28) must be considered in light of this question.

Some movement on this front is already underway. The HIV Vaccine Trials Network (HVTN) is developing a fleet of discovery trials that its leader, Larry Corey, described to AVAC as geared towards

“filling out [our understanding] of the immunological space” in which vaccines work. This means looking at vector-specific immunity and tissue-specific responses in the mucosa, and at which antigens are optimal for which types of immune responses.

Recent meetings, like the National Institute of Allergy and Infectious Disease vaccine summit in March 2008, have also zeroed in on the criteria for advancing candidates into human trials. In order to more clearly define these criteria, work must be done to standardize some of the newer assays, like the viral suppression assay (which measures the ability of vaccine-induced T cells to inhibit HIV replication by killing HIV-infected cells *in vitro*) that has been developed by Otto Yang (University of California, Los Angeles) and taken on by IAVI, HVTN and others. More also needs to be done to define and understand the significance of polyfunctionality. (As discussed on page 55, there are multiple ways to define polyfunctionality. Studies in HIV-positive elite and viremic controllers have found that these

individuals have more T cells that produce multiple types of substances, such as IL-2, interferon gamma, TNF-alpha and others, compared with HIV-positive people with more traditional rates of disease progression.)

2) Is the National Institute of Allergy and Infectious Diseases (NIAID) spending its AIDS-vaccine related funds appropriately?

It's doing well enough—under the circumstances. A more important question: Is the United States spending its science-related funds well? Here, the answer is a resounding no. There are crises in US government research funding in many areas including physics, environmental science, and stem cell research. This context is critical. Likewise, the context for asking any question about NIAID-related funding is that the NIH has been flat-funded for the past five years (see Figure 3, page 22). When factoring in inflation, the budget has actually decreased by more than 12 percent, according to NIAID's own accounting (see Figure 4, page 25). This has a direct impact on the number of “R01” grants awarded to individual investigators.

NIAID awards applications in percentile or priority score order until a cutoff point, or payline, is reached. In the context of flat funding, the payline shifts to a smaller percentile. A healthy payline is at about the 20th percentile. Today the overall payline for scientists submitting R01s to NIAID is at the 12th percentile.

Under these circumstances, every resource allocation question receives scrutiny that is as political as it is scientific.

Recommendation: Develop institution-specific and field-wide agendas to address the question of which key discovery studies that should go forward in humans. NIH, Europrise, IAVI, the Bill & Melinda Gates Foundation, and others should all look at their portfolios in light of this question, and should develop and share plans in a process that could be convened by the Global HIV Vaccine Enterprise. Plans may change and ideas may vary. The need isn't for a homogenized approach but for one that is flexible, comprehensive, and supported by work from all stakeholders. This could also set in motion the process of standardizing some of the newer assays.

US investment is critical because at the moment, the US government is the source of roughly 80 percent of all funds directed towards AIDS vaccine research worldwide. Other governments and funding agencies should commit funds to increase the overall resource pool, as well. In 2006, for example, donations from Europe constituted just 10.6 percent (US \$82 million) of all public, philanthropic and commercial spending on AIDS vaccines (see www.hivresourcetracking.org). This is proportionally low compared to US funding and should be remedied through EU and individual government support to Europrise and other initiatives. The Canadian government has committed CA \$111 million over five years to support its Canadian HIV Vaccine Initiative (CHVI). Should the Government of Canada increase its support for the initiative, the Bill & Melinda Gates Foundation has pledged to contribute up to US \$40 million towards this effort. CHVI has a strong focus on manufacturing issues and could cover costs of manufacturing high-quality GMP lots of critical reagents for small studies of promising ideas. It will be important to monitor both this gap and the CHVI program in the coming years.

It's also important to look at how NIAID is apportioning its AIDS vaccine related funds. In FY 2007, 47 percent of extramural funds (grants given to scientists working outside the NIH system) for AIDS-vaccine research went to discovery work, 11 percent to preclinical work, and 38 percent to clinical research. As this break-down illustrates, the majority of NIAID funds are already going to discovery and preclinical work. Post STEP, there have been a number of calls for NIAID to shift funding priorities away from clinical trials and toward basic science and discovery. But the balance is already tipped in that direction, both at NIAID and across the field. US \$200 million of the \$273 million

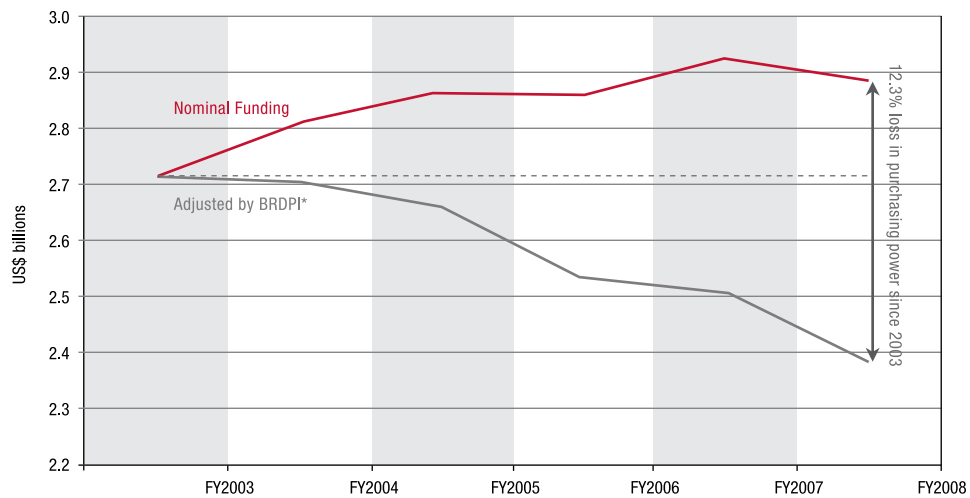
AVAC joins other AIDS organizations in supporting the legislation proposed by US Senators Charles Schumer and Hillary Clinton that would increase NIH funding to \$3.4 billion in FY2009, a 15 percent increase. This is a first step towards redressing years of neglect.

Collaborative for AIDS Vaccine Development (CAVD) grants funded by the Bill & Melinda Gates Foundation has also gone to basic science and discovery work.

The issue is not whether there should be more basic science and fewer clinical trials, but what kind of clinical trials in humans are needed most at this time. Likewise, the question is not whether more basic science funding is needed, but whether there's an appropriate balance between consortia and individual laboratories.

The extramural funding includes a grant of up to US \$300 million over seven years to support the Center for HIV/AIDS Vaccine Immunology (CHAVI). This is different from traditional NIH funding which goes to investigators who come up with their own proposals. CHAVI funds went to a consortium of investigators from Duke University, the Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, Oxford University, and the University of Alabama-Birmingham, led by Dr. Barton Haynes of Duke. This consortium, and a range of other collaborators including IAVI, have so far used the funds to explore characteristics of transmitted viruses and early events in infection. Under CHAVI grants, teams of investigators from different institutions work together, pool samples, share data and address questions at a scale that's not possible when individual laboratories go it alone. The CAVD grants also work on a consortia-style model.

Figure 4 LOSING POWER: THE IMPACT OF INFLATION ON THE FLAT NIH BUDGET



* The Biomedical Research and Development Prince Index calculates inflation for scientific research
Source: NIAID (http://www3.niaid.nih.gov/news/events/meetings/HIV_Vaccine_Summit.pdf)

The shorthand for these consortia and collaborations is “big science.” It’s a model that aims to harness the muscle of collaborative work to take on some of the enduring challenges facing the AIDS vaccine field. But while a laboratory run by an established researcher who is tied into consortia-style projects may be an excellent proving and training ground for young scientists, it is not a clear stepping stone for an emerging talent to become independent and establish his or her own laboratory.

The issue is not whether there should be more basic science and fewer clinical trials, but what kind of clinical trials in humans are needed most at this time.

The desires to work with greater autonomy and to head one’s own laboratory are natural and necessary—ambition and competition have fueled science throughout the years. At the NIAID vaccine “summit” in March, many audience members and presenters voiced concern about the lack of opportunities for young scientists who may look elsewhere if the future in AIDS vaccine research appears too constrained or, frankly, doomed. In the context of current peer review systems and constrained funding, young scientists cannot afford failure. Preliminary promising results are often the *bona fide* for securing a grant. They may also be deterred by the fact that a single failed trial prompted a slew of doomsday editorials about the entire field, not to mention a scientific summit at NIAID. There need to be mechanisms which support young scientists interested in entering a field that is high risk and undoubtedly requires persistence. These could include longer-term awards (seven years as opposed to the standard five-year NIH

Table 2 ONGOING TRIALS OF PREVENTIVE HIV/AIDS VACCINES WORLDWIDE (APRIL 2008)

Protocol #	Start Date	Sponsor, Funder, Developer	Trial Site(s)	# of Participants	Vaccine(s)	Clade
PHASE III						
RV 144	Oct-03	USMHRP, MoPH Thailand, Aventis, Vaxgen	Thailand	16,402	Prime: canarypox viral vector with <i>env</i> and <i>gag-pol</i> Boost: Env protein (gp120 subunits)	B A/E
TEST-OF-CONCEPT						
The two trials that follow, HVTN 503 and 502, stopped enrollment and immunizations, September 2007. Follow-up and data collection continue. For more information visit: http://avac.org/vax_update.htm .						
HVTN 503 (Phambili)	Feb-07	SAAVI, HVTN	South Africa	801	Adenovirus vector with <i>gag, pol, nef</i>	B
HVTN 502/ Merck 023 (Step study)	Dec-04	DAIDS, HVTN, Merck	US, Canada, Peru, Dominican Republic, Haiti, Puerto Rico, Australia, Brazil, Jamaica	3,000	Adenovirus vector with <i>gag, pol, nef</i>	B
PHASE II						
IAVI A002	Nov-05	Children's Hospital of Pennsylvania, Columbus Children's Research Center, Indian Council of Medical Research, National AIDS Control Organization, Targeted Genetics Corp.	South Africa, Uganda, Zambia	91	AAV2 (adeno-associated virus type 2) vector with <i>gag, pol, ΔRT</i>	C
HVTN 204	Sep-05	DAIDS, HVTN, VRC, Vical, GenVec	US, Brazil, South Africa, Haiti, Jamaica	480	Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>	A, B, C
ANRS VAC 18	Sep-04	ANRS, Aventis	France	132	5 lipopeptides with CTL epitopes from <i>gag, nef, pol</i>	B
PHASE I / II						
EV 03/ANRS Vac20	June-07	European Commission, ANRS	UK, Germany, Switzerland, France	140	Prime: DNA vaccine with <i>env</i> plus <i>gag, pol, nef</i> Boost: NYVAC-C	C
HIVIS 03	Dec-06	MUCHS, Karolinska Institute, SMI, Vecura, USMHRP	Tanzania	60	Prime: HIVIS DNA with <i>env, gag, rev, RT</i> Boost: MVA-CMDR with <i>env, gag, pol</i>	A, B, C A, E
RV 172	May-06	NIH, USMHRP, VRC	Kenya, Uganda, Tanzania	324	Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>	B A, B, C
PHASE I						
N/A	Apr-08	IPCAVD, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Crucell	US	48	Recombinant adenovirus serotype 26 (rAd26) vaccine	A
HVTN 070	Oct-07	NIAID, HVTN, UPenn/Wyeth	US	120	PENNVAX-B alone, in combination with IL-12, or with 2 different doses of IL-15	B
HVTN 072	Aug-07	NIAID, HVTN, VRC	US	17	DNA and Adenovirus 5 or 35 vectors, all with <i>env</i> in varying prime-boost combinations	A
HVTN 071 [As of Sept 07 enrollment and vaccinations have been discontinued]	Jul-07	NIAID, HVTN, Merck	US	35	Adenovirus 5 vector with <i>gag, pol, nef</i>	B
DVP-1	May-07	St. Jude's Children's Research Hospital	US	20	Prime-boost regimen with <i>PolyEnv, EnvPro, EnvDNA</i>	A, B, C, D, E
VRC 012	May-07	NIAID, VRC	US	35	HIV-1 adenovirus vector vaccine VRC-HIVADV027-00VP: dose escalation and prime-boost with an HIV-1 adenovirus vector vaccine, VRC-HIVADV038-00-VP	A
HVTN 067	Apr-07	NIAID, HVTN, Pharmexa-Epimmune, Bavarian Nordic	US	108	DNA Vaccine EP-1233 and recombinant MVA-HIV polytope vaccine MVA-mBN32, separately and in a combined prime-boost regimen	B A, B, C, D, E, G

Protocol #	Start Date	Sponsor, Funder, Developer	Trial Site(s)	# of Participants	Vaccine(s)	Clade
PHASE I						
DHO-0586	Oct-06	ADARC, IAVI	US	8	ADMVA with <i>env/gag-pol, nef-tat</i>	C
HPTN 027	Oct-06	Makerere University, Johns Hopkins University	Uganda	50	Canarypox viral vector with <i>env</i> and <i>gag-pol</i>	B
C86P1	Sep-06	SGUL, Richmond Pharmacology, Novartis Vaccines	UK	31	Prime: HIV gp140 with LTK63 Boost: HIV gp140 with MF59	B
VRC 011	Apr-06	NIAID, VRC	US	60	DNA vaccine with <i>gag, pol, nef + env</i> or Adenovirus vector with <i>gag, pol + env</i>	A, B, C
HVTN 065	Apr-06	NIAID, HVTN, GeoVax	US	120	Prime: DNA plasmid with <i>gag, pro, RT, env, tat, rev, vpu</i> Boost: MVA vector with <i>gag, pol, env</i>	B
HVRF-380-131004	Mar-06	Moscow Institute of Immunology, Russian Federation Ministry of Education and Science	Russian Federation	15	VICHREPOL with polyoxidonium adjuvant	B
IAVI D001	Feb-06	IAVI, Therion	India	32	Modified vaccinia Ankara (MVA) viral vector with <i>env, gag, tat-rev, nef-RT</i>	C
HIVIS 02	Jan-06	Karolinska Institute, Swedish Institute for Infectious Disease Control, USMHRP	Sweden	38	Modified vaccinia Ankara (MVA) viral vector with <i>env, gag, and pol</i> to volunteers from HIVIS 01	A, E
RV 158	Nov-05	USMHRP, NIH	US, Thailand	48	Modified vaccinia Ankara (MVA) viral vector with gp160, <i>gag</i> and <i>pol</i>	A, E
HVTN 063	Sep-05	DAIDS, HVTN, Wyeth	US, Brazil	120	Prime: Genevax Gag-2692 +/- IL-15 DNA Boost: Genevax Gag-2692 + IL-12 DNA or IL-15 DNA	B
HVTN 060	Aug-05	DAIDS, HVTN, Wyeth	US, Thailand	144	Prime: Genevax Gag-2692 +/- IL-12 DNA adjuvant Boost: DNA plasmids with <i>gag</i> or RC529-SE and GM-CSF with <i>env, gag, nef</i>	B
<i>EnvDNA</i>	May-05	St. Jude's Children's Research Hospital	US	6	Recombinant HIV-1 multi-envelope DNA plasmid vaccine with <i>env</i>	A, B, C, D, E
VRC 008	Apr-05	NIAID, VRC	US	40	Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>	B A, B, C
N/A	Mar-05	Changchun BCHT, Guangxi CDC	China	49	Prime: DNA vaccine Boost: recombinant adenovirus vector	C
HIVIS 01	Feb-05	Karolinska Institute, Swedish Institute for Infectious Disease Control, Vecura	Sweden	40	Intramuscular or intradermal injections of plasmid DNA with HIV genes <i>env, rev, gag, and RT</i> .	A, B, C
EuroVacc 02	Feb-05	EU, Imperial College London, UK MRC Clinical Trials Unit, EuroVacc	UK, Switzerland	40	Vaccinia vector with <i>gag, pol, nef, env</i>	C
RV 156 A	Nov-04	NIAID, HVTN, VRC, USMHRP, Makerere U.	Uganda	30	VRC-HIVADV014-00-VP alone or as a boost to VRC-HIVDNA009-00-VP	A, B, C
IAVI C002	Jan-05	IAVI, ADARC, University of Rochester	US	48	Modified vaccinia Ankara (MVA) viral vector with <i>env/gag-pol, nef-tat</i>	C
HVTN 050/ Merck 018	Jan-04	NIAID, HVTN, Merck	Thailand, Brazil, Haiti, Puerto Rico, South Africa, US, Malawi, Peru	435	Adenovirus vector with <i>gag</i>	B
<i>EnvPro</i>	Jun-03	St. Jude's Children's Research Hospital	US	9	Recombinant Purified HIV-1 Envelope Protein Vaccine	D

ABL: Advanced BioScience Laboratories
ADARC: Aaron Diamond AIDS Research Center
ANRS: Agence Nationale de Recherches sur le Sida (France)
DAIDS: Division of AIDS
HVTN: HIV Vaccine Trials Network
IAVI: International AIDS Vaccine Initiative

IPCAVD: Integrated Preclinical/Clinical AIDS Vaccine Development
MoPH: Ministry of Public Health
MUCHS: Muhimbili University College of Health Sciences
NIAID: National Institute of Allergy and Infectious Diseases
NIH: National Institutes of Health
SAAVI: South African AIDS Vaccine Initiative

SGUL: St. George's, University of London
SMI: Swedish Institute for Infectious Disease Control
UK MRC: United Kingdom Medical Research Council
USMHRP: United States Military HIV Research Program
VRC: Vaccine Research Center
ZEHRP: Zambia Emory HIV Research Project

For an updated list of trials visit www.avac.org/research.htm.

grant, or a grant along the lines of Howard Hughes Foundation awards that give six years of funding for scientists establishing independent laboratories). Europe should implement similar strategies through Europrise, and the Bill & Melinda Gates Foundation could explore a parallel process of extending grants to young scientists in the developing world.

3) Should a revised version of PAVE 100 go forward?

News about the STEP study generated a lot of discussion about whether human clinical trials of AIDS vaccines should continue. No study received more attention than the PAVE 100 trial, a planned efficacy study of a combination strategy developed by the NIH Vaccine Research Center (VRC). One of the components of the VRC strategy uses an adenovirus serotype 5 (Ad5) vector that is similar, though not identical, to the Ad5 vector used in the Merck trials. PAVE 100 was scheduled to start in the Americas just days after the announcement that the Merck studies would halt immunizations and there has been considerable discussion about whether, and in what form, the trial might take place in the new “post STEP” era.

Current discussions about a revised PAVE 100 protocol are focusing on a test-of-concept trial that proposes to enroll only Ad5 seronegative men who have been circumcised. (Vaccine recipients in this group were at not at increased risk of HIV infection in the STEP study.)

A vaccine which showed benefit in such a restricted population wouldn't be appropriate for widespread use. If PAVE 100 shows efficacy, this precise regimen most likely won't move forward to pivotal licensure trials. A positive

NIAID and other funders should look at its funding allocations in light of the need to provide avenues for young scientists and scientists from outside the AIDS vaccine field to be involved. The goals of these programs should be specific. Young scientists are important—provided they're working in a context where the key questions are articulated, where risk-taking is rewarded, and where there's both coordination and openness to non-traditional thinking.

finding would be used to help design vaccine candidates that don't have the potential safety issues that appear to have been associated with the Ad5 vector in certain subpopulations. (We don't know whether the VRC strategy would have the same safety profile as the 3-dose MRK-Ad5 strategy, and the redesigned PAVE 100 trial will not tell us about this because of its restricted enrollment criteria.)

An initial proposed approach to PAVE 100 entailed two separate but closely-integrated trials known as PAVE 100A and PAVE 100B. “A” would have enrolled men who have sex with men in the Americas. “B” would have enrolled heterosexual populations in sub-Saharan Africa. Because of the high rates of Ad5-seropositivity in the potential participating African countries, many otherwise-eligible volunteers would have been screened out.

In March, IAVI, one of the original PAVE collaborators decided not to participate, stating, “From a practical standpoint, the new exclusion criteria for PAVE 100B [...] limit the number of participants and speed with which IAVI could enroll from our existing cohorts in Africa, and to generate additional cohorts from which to recruit would require a huge increase in resources.”

COMMUNITY INPUT ON PAVE 100: WHAT DOES “GPP” SAY?

“GPP” is short for *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials* (www.avac.org/gpp.htm). Developed in a collaborative process convened by AVAC and UNAIDS, this document identifies minimum elements of good practice for community engagement in HIV prevention trials.

GPP was published in 2007, and its true value will only be determined by testing it in the field. AVAC is using GPP principles to guide our analysis of consultative processes regarding the proposed PAVE 100 trial. As we went to press, the process had not yet included sufficient community input based on these guidelines. Plans were underway to expand community consultations. AVAC welcomes these developments and offers these suggestions for specific principles or activities identified in GPP that should be put into place by PAVE collaborators.

- The core GPP principle of “more transparency” states, “The principal investigator should strive to provide clear, comprehensible and timely access to trial-related information for communities affected by research.”

A proposed PAVE protocol was presented at a public meeting in December 2007 and has been the basis for ongoing discussions. While the protocol hasn’t been finalized, key elements could be used in community consultations in many settings.

- The section on Protocol Development identifies the following as “essential steps in all circumstances:
- “Clear transparent communication about the kinds of input that the community can and cannot have incorporated into a protocol based on the circumstances of the trial...
- “Opportunities created—and facilitated—for community advisory groups and/or mechanisms to provide input into study design mechanisms such as selection criteria, recruitment....”

So far, it has been unclear when and how community would be able to provide input into the critical conversation about whether PAVE 100 should go forward. A plan for gathering these viewpoints should be put forward and implemented.

The other PAVE collaborators with potential sites in Africa have also taken these issues into serious consideration. At press time, the primary focus was on a PAVE 100 study in the Americas. (For additional resources and updates visit www.avac.org)

And so the question remains: should PAVE 100 go forward in any form?

AVAC’s answer is a conditional yes. A trial could be designed and conducted to provide a relatively quick and clear answer about whether the VRC candidate has any benefit in protecting against

infection or reducing viral load setpoint. Information about whether the vaccine does provide any kind of protection could in turn help guide future vaccine design efforts.

At this moment, our answer is conditional because some of the critical issues related to community acceptability of this trial have not been addressed. As noted at the beginning of this chapter, AVAC is a small civil society organization that cannot and should not speak for the wide array of communities that may be asked to participate in this trial.

Is a trial that tests a candidate that almost certainly would not advance to licensure studies acceptable to communities? STEP and Phambili were also test-of-concept in that they were designed to provide an initial idea of vaccine efficacy. If there had been a clear benefit, additional larger trials would have been launched to learn more. If PAVE 100 shows efficacy, the strategy most likely won't move forward to pivotal efficacy trials. Communities need to be engaged and have input on what this means to them.

This boils down to questions like: What are community attitudes towards and questions about a test-of-concept trial of a candidate that will not move forward to further large-scale studies? What are community attitudes about a trial whose exclusion criteria (Ad5-seropositive people and, possibly, uncircumcised men) mean that the results will be hard to generalize? How do communities which were asked to participate in STEP feel about potentially being recruited for PAVE 100?

Right now, there's scant information to help answer these questions. And yet, the systems exist. For example, the NIH HIV Vaccine Research Education Initiative program has a robust network of experienced partners connected to an array of communities who were asked to participate in STEP and who may participate in PAVE. Every one of these partners could hold a consultation using a standardized discussion tool and feed these results into the decision-making process. The NIH HIV/AIDS Network Coordination office "Community Partners" program is another potentially valuable mechanism for gathering input. These conversations can and, in our

reading of the GPP document (see page 29), must happen before a firm decision is made about proceeding with the trial.

NIH representatives have said that the proposed PAVE trial will answer important scientific questions even though it is not part of a product-development pathway for the current VRC strategy. Still, there needs to be a set of next steps that flow from whatever the data are. We'd call that a research pathway—and would like to see one before a final decision is made on whether PAVE 100 goes forward.

4) Is it possible to preserve clinical trial site capacity even when clinical trials are postponed?

Yes—but it may mean that AIDS vaccine trial sites have to work on other important areas like male circumcision, pre-exposure prophylaxis, other vaccine research, microbicides, epidemiological studies, or act as training sites or centers of excellence to build research capacity of other sites. It may also mean that funding structures need to reexamine how allocations are made for outreach and education, since these critical activities—which are often tied to specific trials—must continue and be expanded to address the questions and issues arising at a community level as a result of postponed or cancelled trials and disappointments like STEP, Phambili, Carraguard and others.

There are some signs that this is happening. At press time, IAVI was working with the clinical research teams that are its partners to consider various alternative projects. Some of the teams that were planning to conduct PAVE 100 are now considering conducting TB vaccine trials, making

Communities that may be targeted for PAVE 100 must have the chance to consider whether the trial is a priority and what the questions are in the wake of the STEP study, and to ask for and consider additional information that might help inform their thinking. AVAC can help support consultations on this topic. NIH and the PAVE collaborators should work through multiple mechanisms including NHVREI, Community Partners, and other structures to solicit this critical feedback.

plans for Phase I studies, and looking for ways to use site capacity to help train newer research teams. HVTN leader Larry Corey told AVAC that it was focusing on additional Phase I studies (see page 22) and would collaborate with the HPTN on work to determine whether cohorts of high-risk women could be enrolled for future vaccine or prevention trials in the US and the Caribbean.

These are promising steps, but they are also incomplete. Phase I trials require types of infrastructure and staffing levels that are different from what is needed for efficacy trials. If there is no efficacy trial for two or three years, then some of that infrastructure, including experienced staff and prepared communities, may be lost. Yes, some sites may end up conducting other studies—the new NIH funding structure for trial networks allows for sites to explore and apply to participate in a range of research studies. But is this sufficient? Probably not, especially when it comes to maintaining community education and outreach programs, which have been shown to thrive with consistent staff and sustained relationships with communities. As the human clinical trials agenda is revamped and reconsidered, priority needs to be placed

on maintaining community outreach and education staff and capacity.

As we discuss in the first chapter, the broader HIV prevention research arena is dealing with a range of opportunities including how to introduce male circumcision and how to manage disappointments such as lack of efficacy in recent microbicide, diaphragm, and HSV-2 trials. Trial sites and the structures that fund them must be prepared, logistically and financially, to find new and innovative ways to adapt to unforeseen circumstances. They need research agendas that can be flexible enough to respond to the evolving HIV prevention landscape. Financing should go where it can do the most good in the short-term and also aim to ensure that trial capacity that exists today is maintained for the long term.

5) Are T-cell vaccines dead?

No, not by a long shot. As we discuss at greater length in our “Science Snapshot” (page 52), the failure of a single candidate, Merck’s MRK-Ad5, in no way spells the end to the notion that a vaccine can be developed to generate cell-mediated immunity that blunts viral replication and slows disease progression. The arguments that supported T-cell vaccine development in the past remain relevant. The MRK-Ad5 vaccine stimulated a subset of the many types of T-cell responses that can be induced by a vaccine. There is still a whole range of open questions that are relevant, and a whole body of data suggesting that potent T cells can play a role in controlling infection. This is the basis for the ongoing T-cell work funded by CAVD, CHAVI, IAVI, and Europrise. The recent NIAID AIDS vaccine summit identified additional key research areas

around T cell vaccines, as did this year's Keystone AIDS vaccine meeting. AVAC will be looking in greater detail at the scientific agenda for both T-cell and antibody-based vaccine strategies and discovery work in the coming months, and we will issue a separate report on this topic.

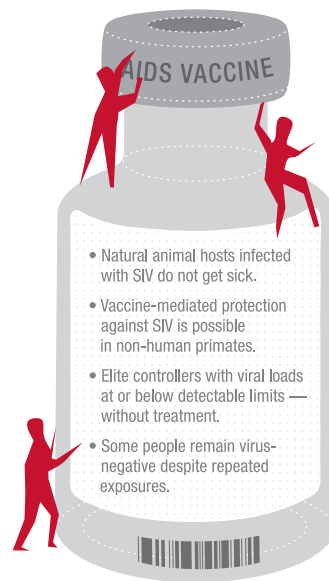
6) Is an AIDS vaccine possible?

Yes, an AIDS vaccine is possible. We have no secret insights, no crystal ball, no scientific breakthrough waiting in the wings to put behind this statement. But the world must continue to operate as though the answer is yes because the indicators are still there, and still good (see Figure 5). We just don't understand them well enough as yet.

The AIDS vaccine we believe is possible is not necessarily one that provides sterilizing immunity—the holy grail of complete protection. It could be a vaccine that reduces viral load or protects against some modes of exposure but not others. Moreover, when we look at elite controllers—those who are infected and maintain low or undetectable viral loads for many years—we see evidence that the immune system can control the virus. We believe it is possible that a vaccine can create this immune profile, even if it may be a long way off.

Will an AIDS vaccine be possible in the next ten, twenty, thirty years? In the lifetime of a physician who saw the first AIDS cases on the wards in the 1980s? Maybe not. Or in the lifetime of an infant being born today, perhaps one who is being protected from HIV infection through the use of antiretrovirals for prevention of

Figure 5 WHY AN AIDS VACCINE IS POSSIBLE



parent-to-child transmission? We hope so. We wish the time horizons were shorter and hope we will figure out how to abbreviate them in the future. In the meantime, we must be as clear about the long haul of this endeavor as we are about its merit. Looking across the world at rates of new infections and at the human costs and dismal coverage of proven prevention strategies, we still say: We need an AIDS vaccine, no matter how long it takes.

WHAT WE KNOW FOR SURE

Lessons to be learned from the STEP study

IN THIS CHAPTER

Going site by site to learn from STEP

How AIDS vaccine research must help address the African-American epidemic

Getting our messages straight

We may never have all the answers.

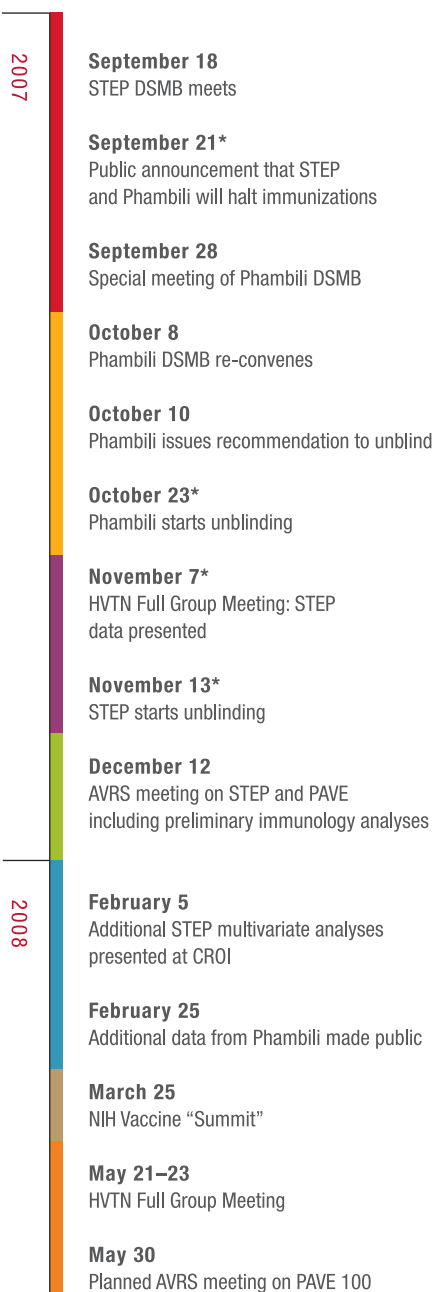
Even after the data are fully analyzed, there are many things we may never know for sure.

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 possibility 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.

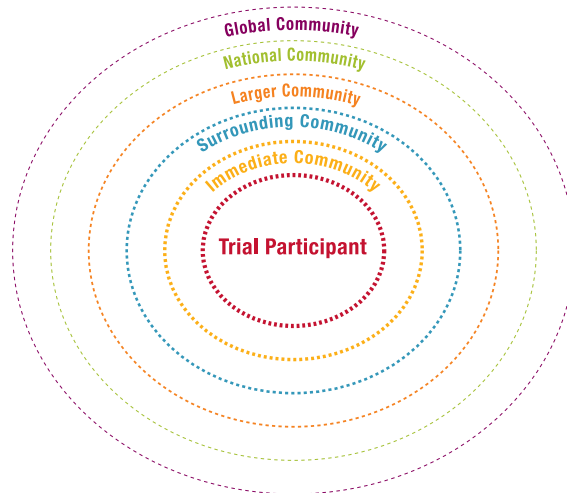
ACTION 2

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, colleagues 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.

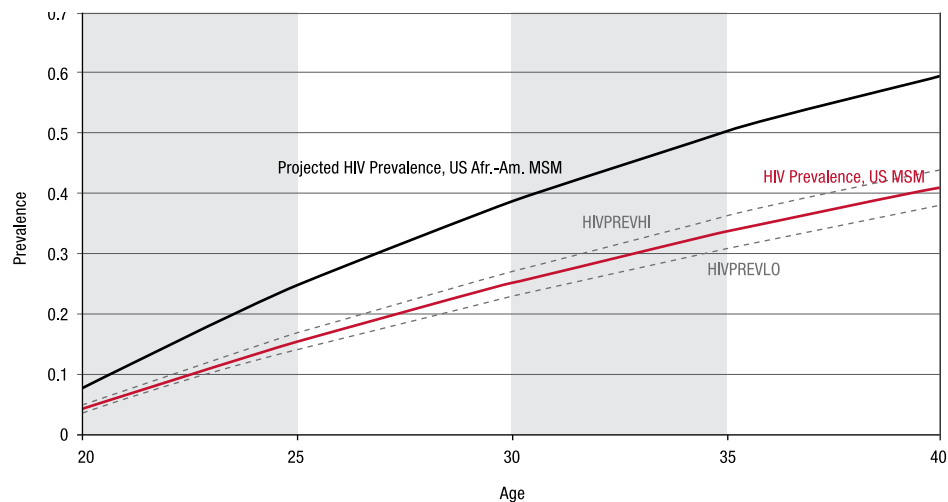
Looking ahead, the PAVE 100 partners need to do far more to facilitate community input into discussions and decisions about the redesigned protocol. Community involvement in the discussions around protocol revisions has been inadequate—with limited participation from even the community representatives 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.

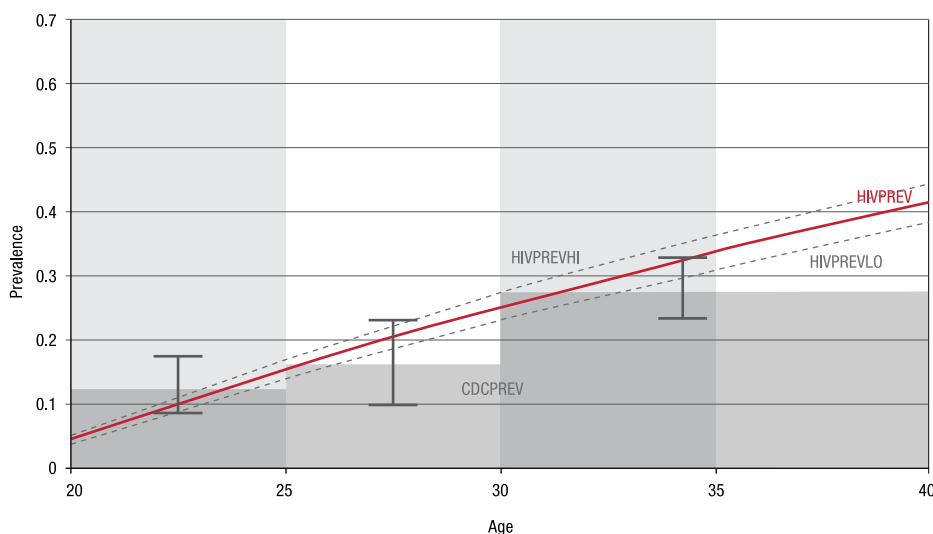
Looking at MSM from the Americas, Australia and the Caribbean in the STEP study, the incidence data confirm the severity of the global epidemic. All of the questions about possible

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

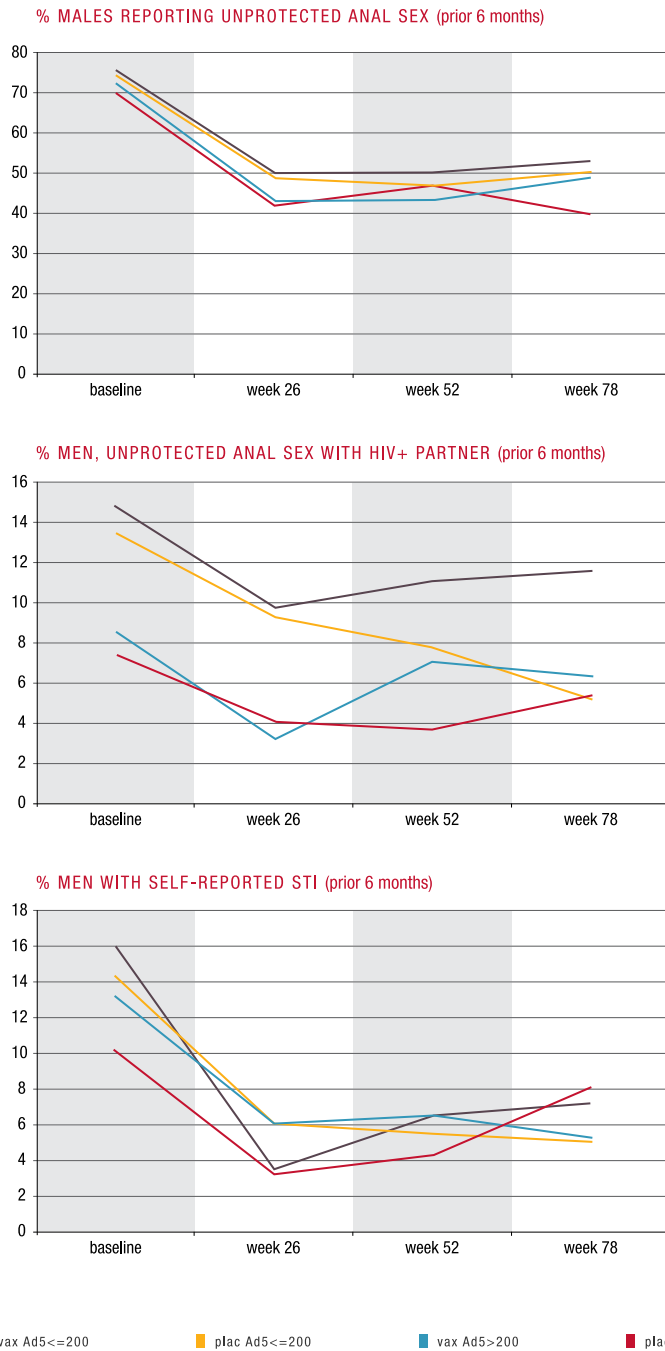


Current estimates of HIV incidence and prevalence in the US are imprecise, but the best available data show the toll HIV is taking on MSM in general and African-American MSM in particular. How will this look in 20 years? See Figure 8. The confidence intervals are derived from CDC data, see citation below.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

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. Millett’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

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

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.

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.

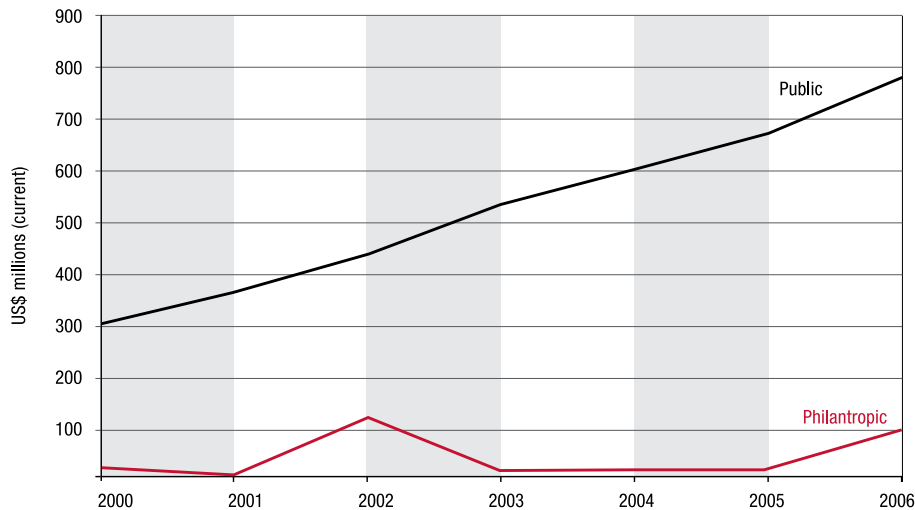
But when it comes to models that are worth considering for what they've accomplished, and what they might contribute to the future of the field, the International AIDS Vaccine Initiative (IAVI) tops the list. One of the world's first “public-private partnerships”—a term that has since morphed into “product 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.

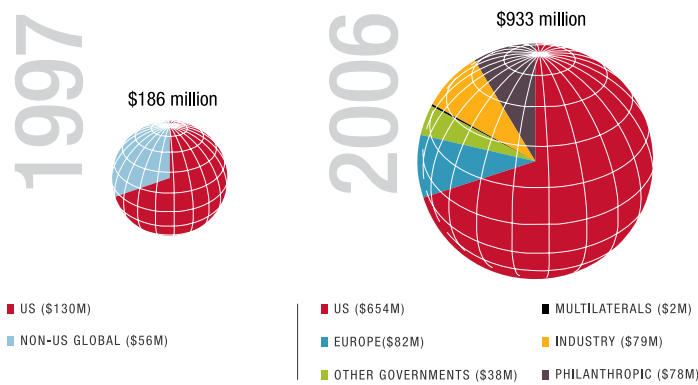
When our interviewees were asked to consider IAVI’s advocacy work to date, their first responses were superlatives. People outside the organization told us that IAVI has “always excelled” at making the case for vaccines and has had “a huge impact.” IAVI “brought the discussion to a new level that would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

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.”

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 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 indispensable 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

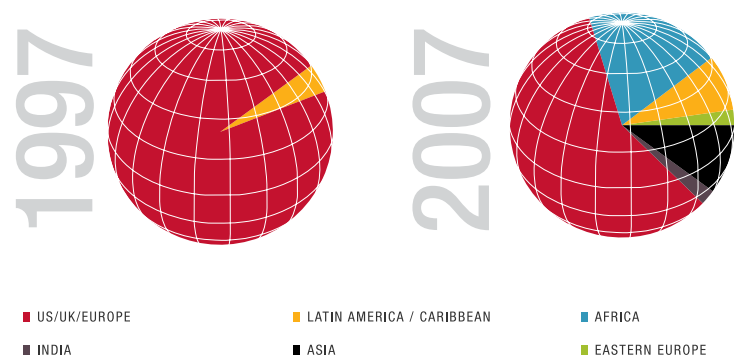
In the mid-1990s, IAVI was a leading voice of the empiricists, arguing that if more vaccine candidates could be moved off the shelves and through testing more quickly, then the search for an AIDS vaccine could be accelerated. The failure of IAVI (and all other) candidates has forced the organization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

“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.

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 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

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

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.

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.



SCIENCE SNAPSHOT: QUICK TAKES ON NEXT STEPS IN THE SEARCH FOR AN AIDS VACCINE

This year's AVAC Report heads to press in a flurry of editorials and articles opining, often gloomily, about the possibility of finding an AIDS vaccine. Much of this mainstream media coverage was prompted by the NIH Vaccine Summit which was billed as the first step in reorienting the US government's spending and priorities in the post-STEP era.

AVAC hopes and anticipates that there will be concrete changes coming out of the Summit and related meetings to be held in the coming months, and that organizations like IAVI (see page 41), Europrise and the Global HIV Vaccine Enterprise will contribute to an even broader discussion and set of shared activities.

Over the coming year, AVAC will track what's been suggested and see what's actually come from these more recent conversations, as well as take a closer look at what's coming out of the "big science" consortia like CAVD (the multi-million-dollar Gates Foundation initiative), the IAVI consortia on neutralizing antibodies and replicating vectors, and the NIH-funded CHAVI. Each of these has promised broader, well-funded and more systematic approaches to some of the field's most intractable scientific challenges. As they approach two to three years of activity, we can fairly start to look at what CHAVI and CAVD teams have delivered thus far. One challenge is figuring out how to evaluate and monitor such discovery efforts, since they don't

lend themselves as readily to milestones or signal achievements, which are the most straightforward metrics of success.

These are quite complex topics, so we've decided to publish the results of that work in a separate in-depth report during the coming year, before our next annual report. For this Report, we decided to put together a brief snapshot of some of the most important or intriguing suggestions that have emerged from those efforts. It's an eclectic and admittedly incomplete list, which we'll be able to revisit more systematically in the future.

ORGANIZING FOR FUTURE WORK

- Standardize assays in emerging areas: single-cell proliferation, mucosal immunity, viral suppression.
- Fund and coordinate more systematic animal-model work with the goals of: meeting the need for a wider range of well-characterized antigens, immunogens and challenge viruses; standardizing where appropriate; addressing animal shortages and funding issues for primate facilities; and working, where possible, toward agreement about which models are useful for which types of questions. There also needs to be further exploration and some level of resolve in the ongoing debate over using animal models as a gatekeeper for advancing candidates into clinical trials.



- Define a suite of human discovery trials that would be most valuable for moving the field forward, and which would support several parallel approaches to key challenges or questions.
- Use an annual meeting such as the October AIDS Vaccine conference in Cape Town for a public, town hall-style forum to review the scope of ongoing work and assess implications and gaps. Some questions, prompted by the March summit, include: What do primate researchers and Phase I clinical trialists need to do to optimize each other's work? What are human discovery studies yielding in terms of insights for product development? What are new insights into immunogen design—and is the field acting on them? Such a meeting should be linked to responsive funding. If a “natural” collaboration emerges that needs additional support, there should be a pool of funds for the group to draw on.
- Make sure that each funding entity does most what it does best. NIH, AmfAR, the Gates Foundation, IAVI and others have strengths and “sweet spots” when it comes to fueling different types of research such as investigator-initiated, innovation-oriented or orphan projects. There doesn't need to be turf carved out, but it would help for entities to play to their strengths and collaborate so that no corner is overlooked.

- CHAVI, CAVD and other consortia like IAVI's groups could productively be more systematic, strategic and open about how they assess progress. Going “forward to basics” means recognizing that the clear, measurable milestones of product development simply don't apply here. Given the unpredictability of discovery-based work, it's far from clear what the best criteria are for evaluating success, especially since repeated failure may even be a good measure of potential future success.

EXPANDING THE OVERALL EFFORT

- Follow the outcomes of the Europrise example, which is creating a PhD “school” that trains graduate students and places them in laboratories of participating Europrise scientists, so that outreach to young scientists starts early.
- Look for novel funding incentives that would support young scientists' work in established scientists' laboratories. Can grants to seasoned investigators have plus-ups or designated budget lines for new scientists? Perhaps more important, cultivate independence by strengthening funding structures for first-time or R01-naive investigators.

AREAS FOR NEW OR INTENSIFIED INVESTIGATION

- “Immunogens, immunogens, immunogens”: Where are the antibody-inducing immunogens? What types of inserts should be used in vaccines





to induce effective immune responses? What can be learned about immunogen design by studying human responses to proven vaccines?

- Continue work on defining what constitutes an effective T-cell response and on standardizing measures of this. This work should consider T-cell qualities like memory phenotype, proliferative ability, *in vitro* control of HIV replication, homing to mucosal tissues, interaction with innate immunity, and support for B-cell immunity.
- Probe B-cell regulation: HIV-positive people don't generate neutralizing antibodies in real time against their virus. Instead, antibodies isolated at any given time point can neutralize virus isolated from the same person at earlier timepoints. Viral genetic variability means that HIV is always one step ahead of naturally-generated antibodies. So researchers are beginning to ask whether this delay reflects not only the molecular trickery HIV uses to hide Env from the immune system, but perhaps also something about the B-cell immune response itself. Are the right kinds of neutralizing antibodies actually made, but the cells that produce them switched off? Might it be possible to manipulate B-cells to be better responders to HIV? Might that manipulation occur at the site of infection? At Keystone, Quentin Sattentau

(Oxford University) presented data on stimulating antibodies through vaginal delivery of adjuvants and antigens. Other insights may come from an ongoing clinical study on neutralizing antibody responses in HIV-infected people with certain B-cell defects. More complete answers will take extensive research into how antibodies against HIV are made and how these pathways are regulated—research that's beginning, but still sorely needs expertise from researchers already expert in B-cell regulation.

- Don't rest with the current definition of polyfunctionality. As Rafick Sekaly wrote in a recent article¹: "The term polyfunctionality might also imply more than just the induction of CD8+ and CD4+ cells that produce multiple cytokines; it could also reflect an integrated immune response that includes different types of T cells (Th1 and Th2), B cells, and other innate immune cells, including dendritic cells and natural killer (NK) cells."
- Look at factors that may increase T-cell resistance to HIV infection. For example, the VRC has data showing that production of MIP-1 beta by CMV-specific memory CD4 T cells is associated with greatly reduced susceptibility to HIV. Can this type of response be preferentially induced with an HIV vaccine candidate?

¹ Rafick-Pierre Sekaly, "The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development?" *The Journal of Experimental Medicine* 205, no. 1 (2008), <http://www.jem.org/cgi/content/short/205/1/7>.

TIME FOR THE ENTERPRISE TO EXPAND ITS IMPACT

For each of the past three years, AVAC has devoted a portion of its annual report to addressing the executive director of the Enterprise—before one had been identified, after the first candidate was offered the position, and then again as the search continued. Our core recommendations remain the same since we first published them in 2005:

1. Communicate frequently and transparently.
2. Set policies for sharing and coordination of data and technology.
3. Ensure the ability to take risks.
4. Bring new investigators into the search.
5. Make the Enterprise truly global.
6. Involve civil society in a meaningful way.
7. Take on the politics and ethics of clinical trials.
8. Establish realistic milestones and a process for monitoring progress.

Our sense of urgency has only intensified with the appointment of Alan Bernstein as the inaugural director at the beginning of the year. As he finds his bearings and conducts the necessary “listening tour” and introductory meetings, we have been impressed with his openness and honesty. We look to him now to articulate the critical milestones for the rest of 2008 and beyond.

We need an updated scientific plan; we need a convening entity that uses the members’ professed “moral” commitment to collaboration to its best advantage. We hope the Enterprise will not become sidetracked by issues of fundraising, but instead focuses on better use of existing resources. And there’s still a lot of work to be done around building scientific and clinical-trials literacy as a foundation for real community engagement. Here, too, the Enterprise has a critical leadership role to play.

- Hone understanding of *in vivo* neutralization. For HIV and most other viruses, neutralization is defined (and measured) by an antibody’s ability to block virus from entering (and then replicating in) cultured cells. But for HIV, it’s emerging that neutralization and protection don’t necessarily go hand-in-hand: several new studies have found antibodies that protect macaques against the simian immunodeficiency virus (SIV), but don’t neutralize virus in the standard laboratory test. So the issue of defining the right responses takes on a new twist: what, exactly, defines a protective antibody? If classical neutralization isn’t the whole story, does it need to block virus from crossing the mucosal layers that line the genital tract—a key step in sexual transmission? Or block virus transmission from one type of cell to another? Over the next year, CHAVI researchers will systematically look at which of four antibody functions (or which combination) is most relevant to protection in macaques—one first step in answering this important question.
- Increase complementarity of Phase I and discovery studies in humans and trials in non-human primates, so that data from either discipline informs the other in real time, and so that there’s information on a given question coming from both non-human primates and humans.



THE SEARCH CONTINUES. IT MUST.

What's the best way to end a Report from a year that's been by turns disappointing, frustrating, heartbreaking and inspiring—in terms of individual and collective ability to face difficult situations?

With appreciation.

For the integrity, honesty, and faith that so many different stakeholders have brought to these difficult times.

These stakeholders range from volunteers who, on learning that the STEP and Phambili trials would halt immunizations, asked, “When is the next trial?” to senior scientists like the University of Alabama’s Beatrice Hahn who made clarion calls for funding the next generation, to the study nurses at sites from Cape Town to Lima to San Francisco who explained difficult data and disappointing news to participants.

Appreciation, too, to leaders who reiterate to skeptics near and far that the search for an AIDS vaccine cannot, under any circumstances, be abandoned. Dazon Dixon Diallo, Tony Fauci, Zackie Achmat, Glenda Gray and many, many others around the world have been stalwart on this front throughout this year.

To you and many other stakeholders, we say: Thank you. The search continues.

ABOUT AVAC

Founded in 1995, the non-profit AIDS Vaccine Advocacy Coalition (AVAC) seeks to create a favorable policy and social environment for accelerated ethical research and eventual global delivery of AIDS vaccines and other HIV prevention options as part of a comprehensive response to the pandemic. This work is guided by the following principles:

- Translate complex scientific ideas to communities AND translate community needs and perceptions to the scientific community.
- Manage expectations.
- Hold agencies accountable for accelerating ethical research and development.
- Expand international partnerships to ensure local relevance and a global movement.
- Ensure that policy and advocacy are based on thorough research and evidence.
- Build coalitions, working groups and think tanks for specific issues.
- Develop and widely disseminate high-quality, user-friendly materials.

AVAC FOCUSES IN FOUR PRIORITY AREAS:

1. Develop and advocate for policy options to facilitate the expeditious and ethical development, introduction and use of AIDS vaccines and other HIV prevention options.
2. Ensure that rights and interests of trial participants, eventual users and communities are fully represented and respected in the scientific, product development, clinical trial and access processes.
3. Monitor HIV prevention research and development and mobilize political, financial and community support for sustained research as part of a comprehensive response.
4. Build an informed, action-oriented global coalition of civil society and community-based

organizations exchanging information and experiences.

A major part of AVAC's work is to translate complex scientific ideas to communities through the development and wide dissemination of high-quality, user-friendly materials. In addition to our annual Report, which analyzes progress in the field and makes recommendations for actions in the coming year, AVAC publishes the *AIDS Vaccine Handbook*, maintains the AIDS Vaccine Clearinghouse (www.aidsvaccineclearinghouse.org) and PrEP Watch (www.prepwatch.org) as comprehensive and interactive sources of information on the internet, and publishes *Px Wire*, a quarterly update on HIV Prevention Research (www.pxwire.org).

We also manage the Advocates' Network, an electronic network for organizations and individuals interested and involved in AIDS vaccine and HIV prevention research advocacy. Please join us by visiting <http://aidsvaccineclearinghouse.org/network.htm> or e-mail avac@avac.org.

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