THE SEARCH MUST CONTINUE

AVAC Report 2008

AVAC
AIDS Vaccine Advocacy Coalition

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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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 futures 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 perseverence, 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

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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

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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?"

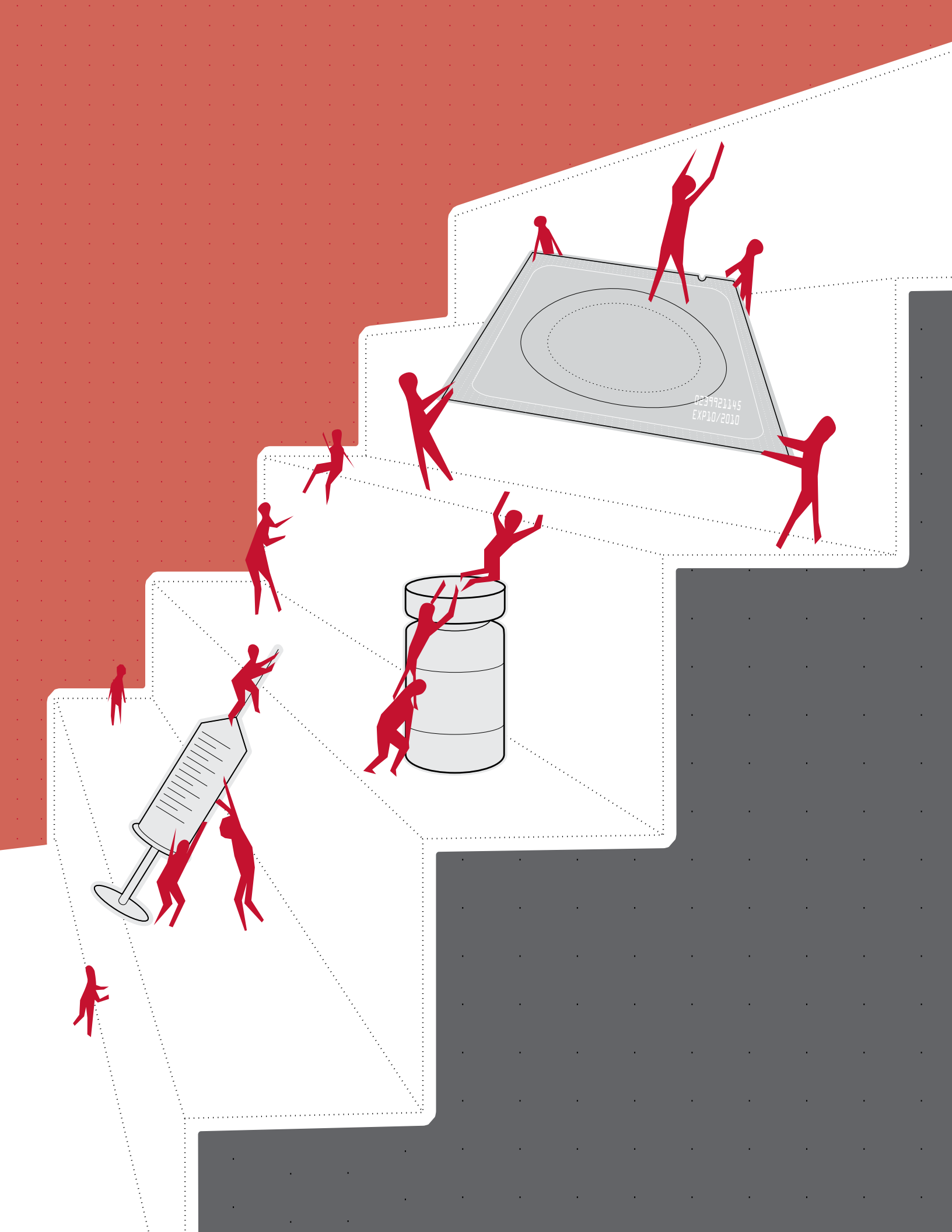
Moving Forward, Looking Back looks at the International AIDS Vaccine Initiative (IAVI) that was founded 13 years ago as a maverick leader in the search for an AIDS vaccine. As the whole field faces what to do next, this article examines the strengths and challenges of IAVI's program with an eye to what 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.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THE WHOLE WIDE WORLD

Global priorities around HIV prevention research

IN THIS CHAPTER

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

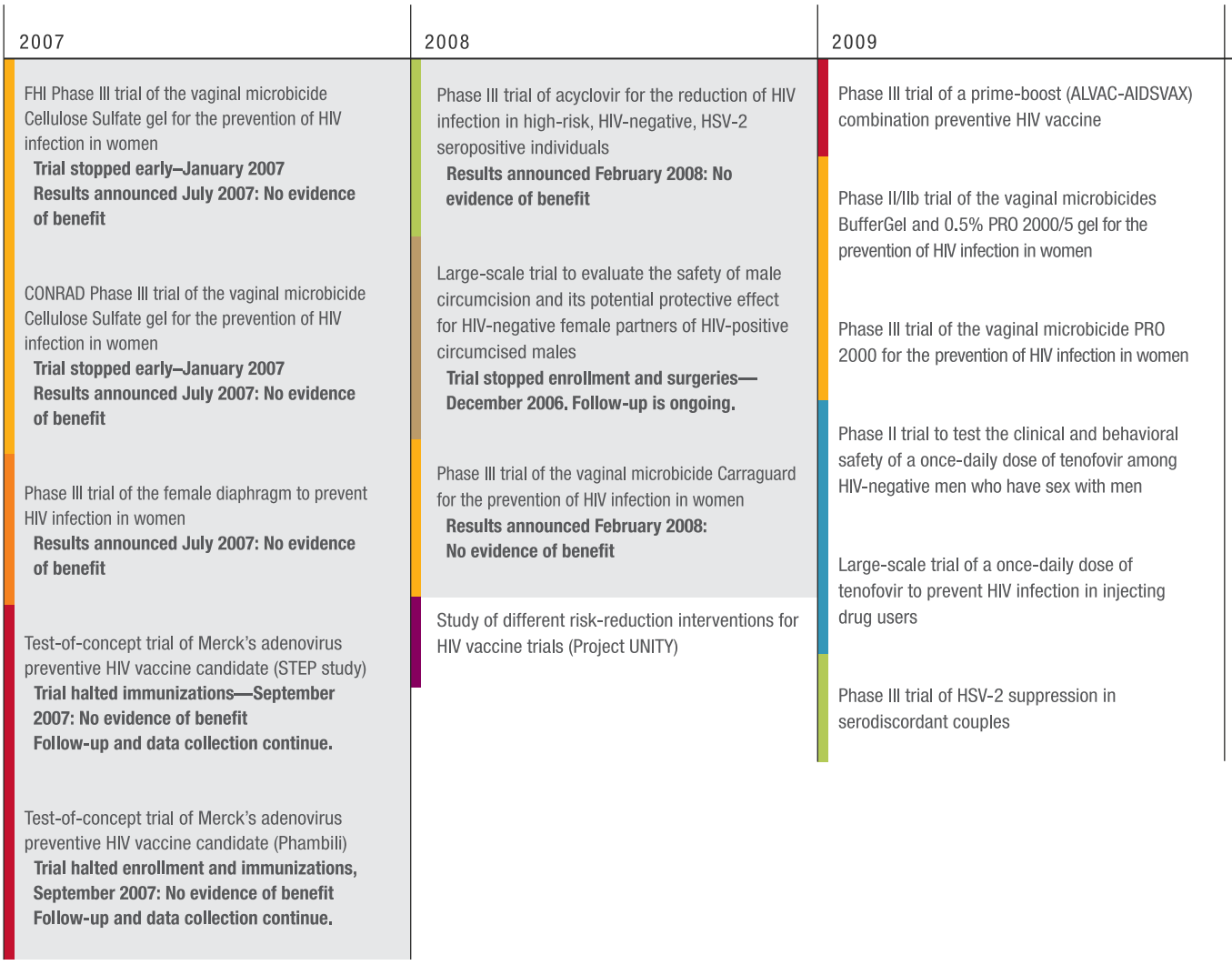
1. Watch the language used for prevention research and implementation priorities.
2. Implement, field test, and comment on new "GPP" and ethics guidelines.
3. Engage in meaningful dialogue and action around male circumcision, HIV testing and gender.
4. Prepare for the results of the Thai prime-boost 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.

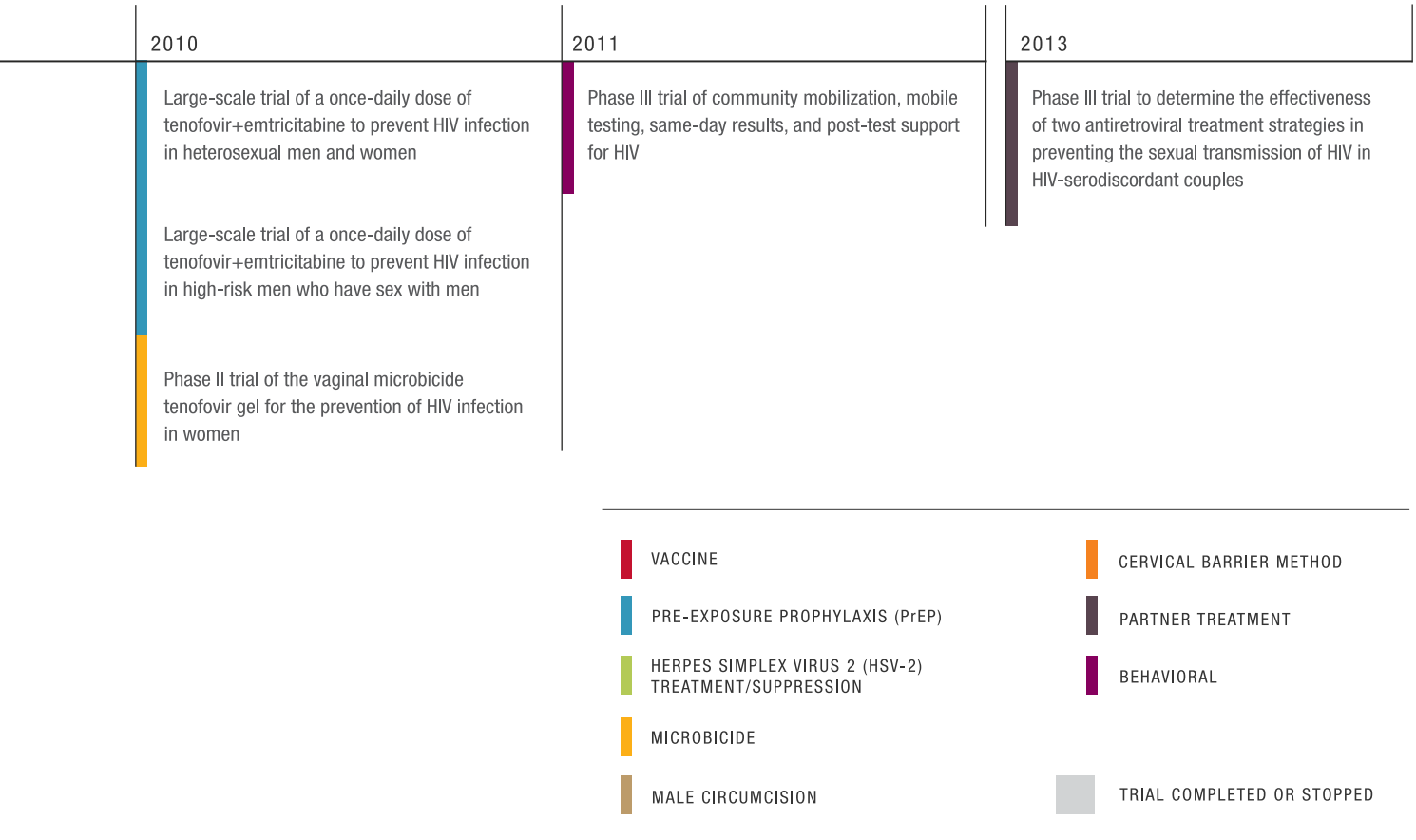
Yes, we've said all of these things. We can even make cases for many of them. But the fact is—we don't know what will work first, or when there will be positive results in any field of biomedical prevention research. And we also

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



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

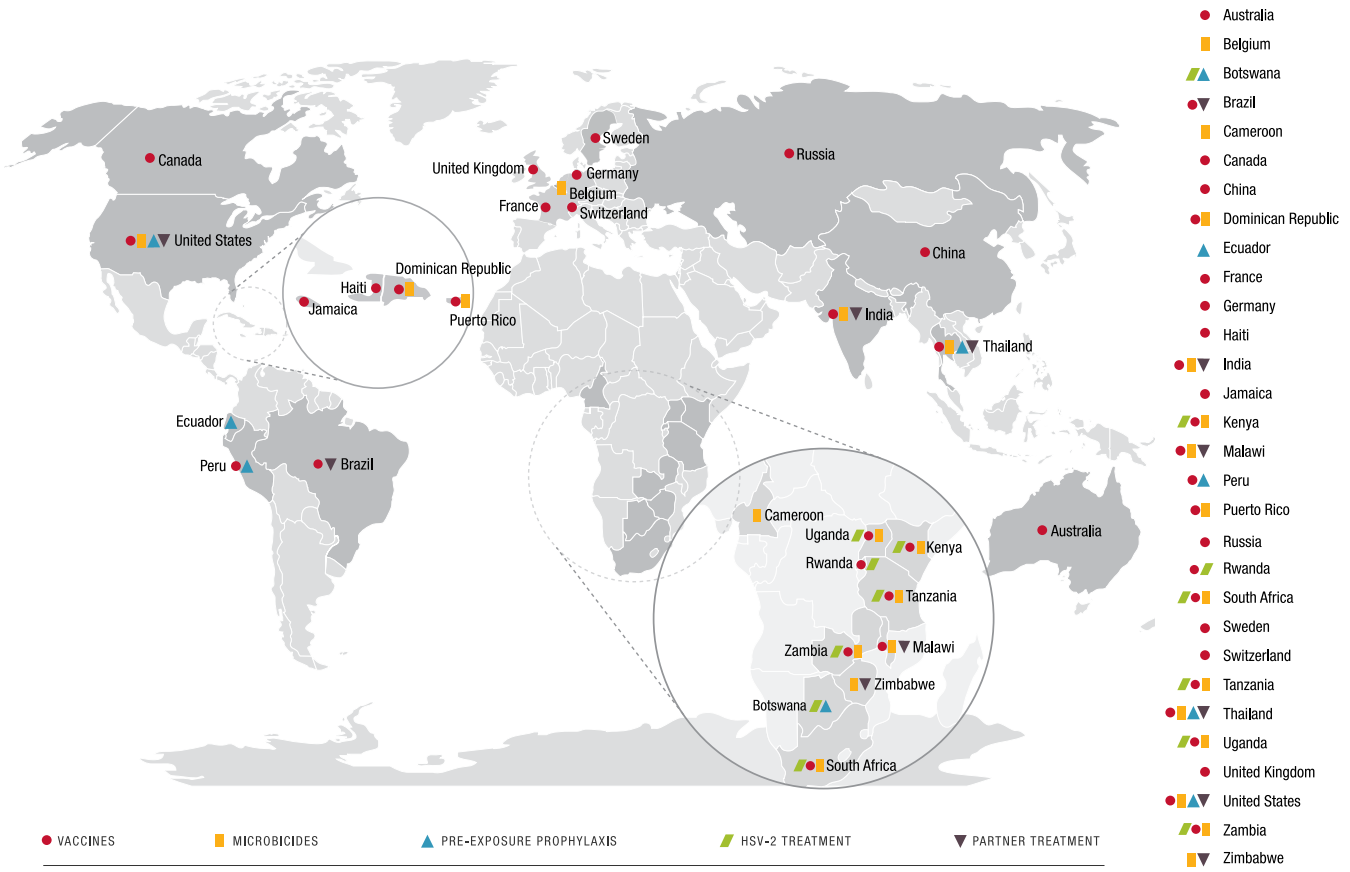
to learn their HIV status, but that the surgery should not be denied to men who are positive or who do not know their status. In the wake of the additional data from RHSP, the WHO and UNAIDS referred to this guidance and said that their position stands.

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 AIDSVAX—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 AIDSVAX 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.