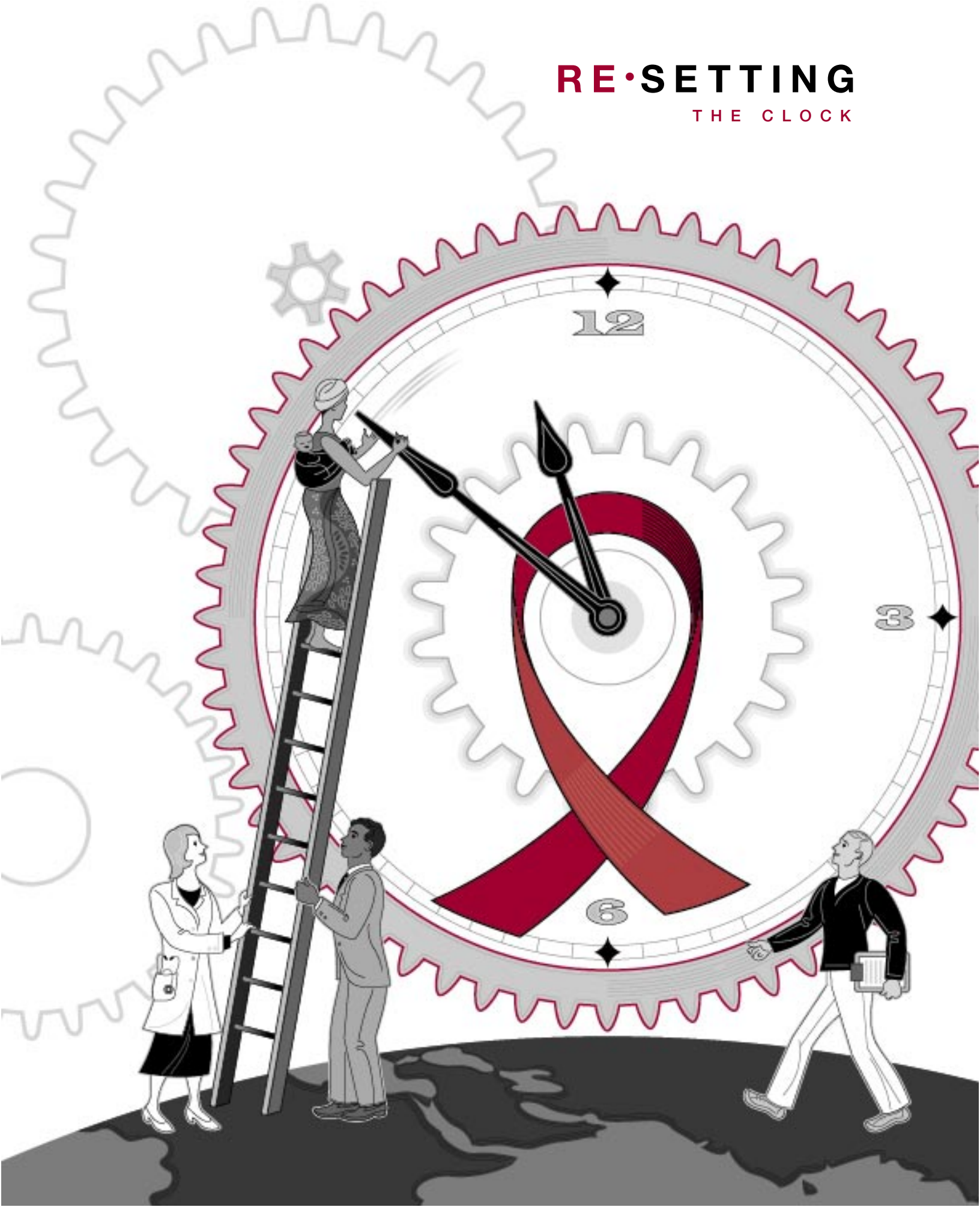
RE·SETTING
THE CLOCK



ACKNOWLEDGEMENTS

AVAC gratefully acknowledges many friends and colleagues in government, industry, academia and the advocacy community for their expertise and advice as we researched and prepared this Report.

This Report was written and edited by AVAC staff and board, and coordinated by Emily Bass, who dedicates her work to the memory of Nokulunga Mazibuko (1970-2007)—friend, mentor, and courageous activist for the rights of HIV-positive women in South Africa and around the world.

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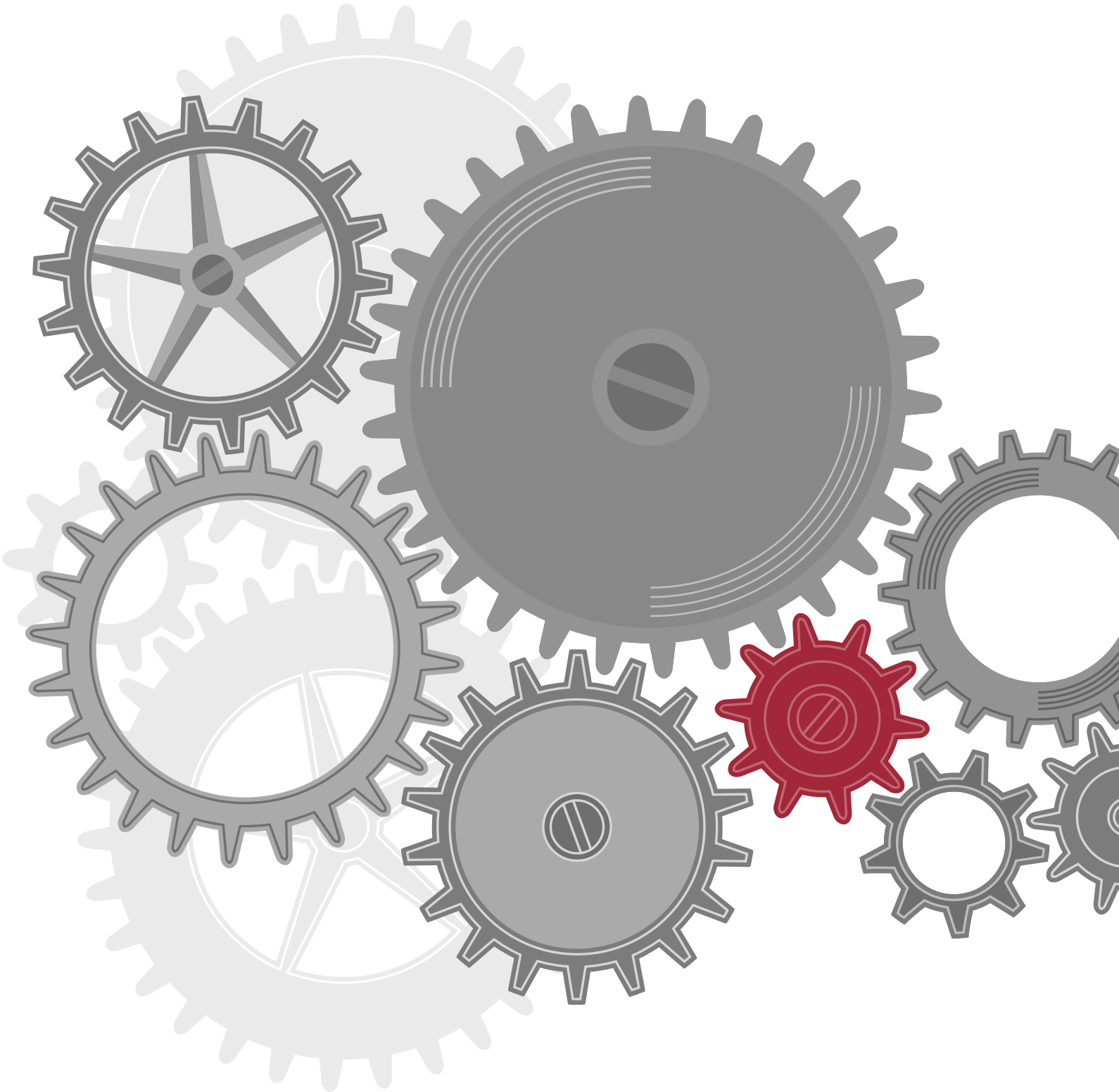


A letter from the Executive Director

AVAC'S NEW SCOPE—AND ENDURING COMMITMENT

Here at AVAC, we cannot remember an interval in HIV-prevention research that compares to the past twelve months.

The news—both good and bad—has come unceasingly. In December 2006, we confirmed that circumcision could reduce men's risk of HIV infection through vaginal sex. Just one month later, we heard that trials of the microbicide candidate cellulose sulfate would be halted because there appeared to be more infections in the active arm, than in the placebo arm. That same month, a test-of-concept AIDS vaccine trial started in South Africa. And in July, we learned that a major efficacy study of the diaphragm found no evidence that this particular cervical barrier reduced women's risk of infection.

Keeping up with these results and understanding their implications can feel like an all-consuming task. But the most critical data of all came from the report of the Global HIV Prevention Working Group, issued in June 2007, which reported absolutely abysmal rates of coverage of proven prevention strategies (see Figure 1, p.4) and provided new modeling data on how true universal access to prevention could change the epidemic (see Figure 2, p.5).

And so, when we step back from the headlines, the press releases, and the conference calls, this is what we see:

- The field of HIV-prevention research is years away from delivering even a partially-effective vaccine or microbicide.
- The response to male circumcision—itself only partially protective—reminds us, the news of such a product will be met with concern, questions, and ambivalence.
- Today's proven prevention strategies are not reaching the people who need them. Global tallies of new infections versus expanded treatment access shows that, each year, for every person who starts antiretroviral treatment, six people are infected with HIV[1]. This ratio places incredible strain on the fragile infrastructure available for HIV treatment and care.

It is a troubling and challenging state of affairs—and one that demands that all HIV-prevention advocates reexamine their messages, their mission and their goals for the next 5 to 10 years.

This is what AVAC has been doing. One decade ago, there was a sense of urgency to determine whether it would be possible to create a vaccine that provided complete prevention against HIV infection. Ten years of scientific inquiry and clinical trials have shown us just how difficult this will be[2].

An affordable and universally-deployed vaccine that provided sterilizing immunity could have a profound impact on the epidemic. This is the selling point of vaccines throughout history: they have proven potential to dramatically alter, and even eradicate, the presence of persistent and devastating pathogens—even those that thrive in poverty.

Today, we know with unfortunate certainty that it will be very difficult—and perhaps even impossible—to create such a vaccine. Nonetheless, the vaccines that are currently in clinical trials, which will almost certainly provide less than full protection, could still be important tools.

With a clear sense of what new biomedical strategies are likely to emerge over the next 10 to 15 years, our sense of urgency has also shifted. The question is no longer as simple as: can we find an AIDS vaccine? Based on the knowledge that we have now, the question is:

What needs to happen to mobilize and energize HIV-prevention activities so that the full array of today's available tools is provided to, and used by, all who need them—while sustaining commitment to and investment in vaccines and other options for the future?

[1] "Global Challenges: U.N. Officials Call on Countries to Strengthen HIV/AIDS Prevention Efforts," Kaiser Daily Health Report, 18 April 2007, accessed 19 April 2007, <http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=44316>.

[2] MI Johnston, Fauci AS. An HIV vaccine-evolving concepts. N Engl J Med 356:2073-81, 2007

The answer is: much more than is currently happening. There is not an energized, multi-layered movement for prevention at grassroots, national, regional, and global levels. There are unnecessary divisions between advocates for proven prevention and those advocating new strategies. Those of us who do advocate for prevention research have focused on specific interventions—particularly vaccines and microbicides—without investing sufficient energy in discussing the implications of other research areas such as pre-exposure prophylaxis, HSV-2 treatment, or male circumcision.

While this constitutes a state of emergency, it also holds a kernel of possibility. By building on the strong work of so many groups, we can begin to tackle these issues, build a movement, and break through false dichotomies that sap our strength and our effectiveness in winning victories for HIV prevention.

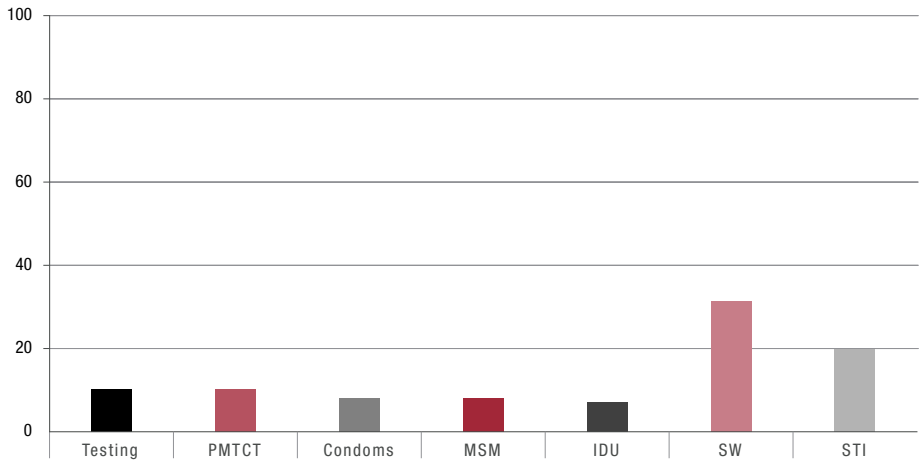
It is hard work, but it is beyond necessary. It is imperative.

As the field has grown and changed this year, so has AVAC. We have received a major grant from the Bill & Melinda Gates Foundation that will help us play a part in some of the core, transformative work that faces us all. This includes:

- Coordinated campaigns to generate political will around substantive change in approaches to and funding for proven prevention.
- Recalibration of expectations of experimental strategies. We need honesty, transparency, and unglossed reality in our communications about the long road to a partially-effective vaccine or microbicide. Anything less will cost the field credibility at a time when it needs sustained commitments.
- Development of energized and interconnected networks of global, regional, and grassroots advocates that bring passion, strategy, and clarity to an HIV-prevention agenda of the same scope and ambition as the treatment-access agenda.

The new resources are a challenge to AVAC to expand our scope without losing sight of our core principles (see p.6). The Report that you hold in your hands represents our current thinking about many key issues affecting AIDS vaccine

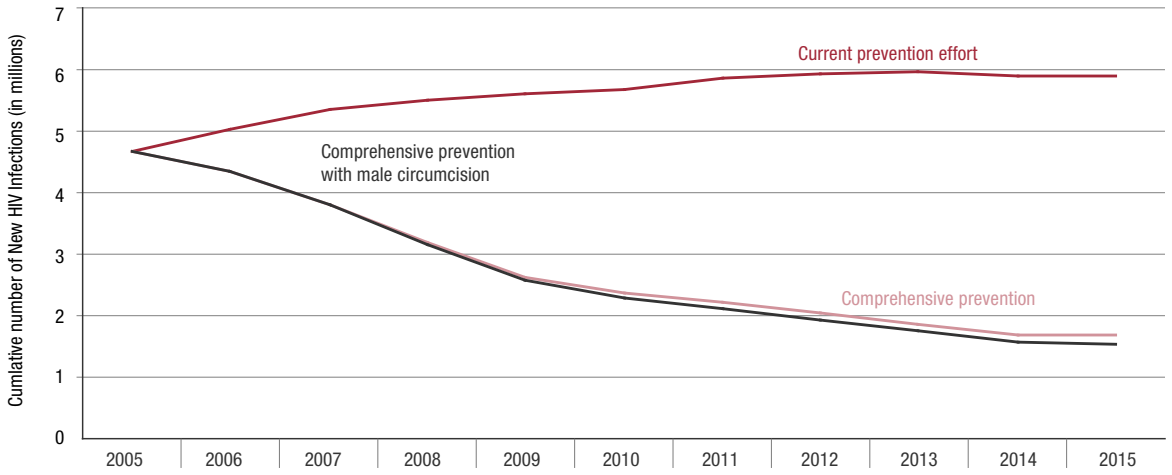
Figure 1. GLOBAL COVERAGE FOR SELECT HIV PREVENTION STRATEGIES IN 2005



KEY: PMTCT: Prevention of mother-to-child transmission; MSM: Men who have sex with men; IDU: Injecting drug user; SW: Sex worker; STI: Sexually-transmitted infection

Source: *Bringing HIV Prevention to Scale: An Urgent Global Priority* (June 2007) Global HIV Prevention Working Group.

Figure 2. GLOBAL HIV INCIDENCE WITH AND WITHOUT COMPREHENSIVE PREVENTION PACKAGE



Projections based on modelling work conducted by the Futures Group for the Global HIV Prevention Working Group.

Source: *Bringing HIV Prevention to Scale: An Urgent Global Priority* (June 2007) Global HIV Prevention Working Group.

research today. And as we move forward, we will remain committed to advocacy for an effective AIDS vaccine.

We remain committed to education, engagement, provocation, and criticism of decision-makers influencing the course of this work.

At the same time, we will strive to do more:

- More to generate a shared agenda for delivering what we have today—and searching for what might help tomorrow;
- More to raise awareness of and, where warranted, demand for new prevention strategies that may emerge in the coming years;
- More to ignite political leadership, planning, and ambition around prevention programming and research in the places where the epidemic is raging.

These are lofty goals, which we know we cannot achieve on our own. The hard and important work many groups are already doing in this arena must continue and be strengthened. Our expanded efforts will only succeed through collaboration with many partner organizations. We look forward to strengthening and sustaining these relationships. No single stakeholder can ever hope to achieve the necessary level of change alone.

The truth is this: if the cure for AIDS were a glass of clean water, the world would still be hard pressed to bring the epidemic to a halt today.

This virus thrives in places where the most basic elements of subsistence—clean water, shelter, food—are in shamefully short supply. It thrives in places where basic human rights—to dignity, health care, protection by the law—are equally scarce.

To attempt to change these realities is to attempt to change the world. We must aim this high if we hope to have any effect on HIV prevention now or in the future. The world demands it of us all.

MITCHELL WARREN, AVAC Executive Director

OUR GUIDING PRINCIPLES

Expanded access to proven prevention strategies must be taken as one of the highest priorities in the global AIDS response, along with access to treatment.

Where is the global campaign to shame governments into changing laws that compound stigma? Where is the cadre of political leaders—both male and female—who have made women's rights to education, property, and sexual and reproductive choice the centerpiece of their administrations? Why does the average man in sub-Saharan Africa have access to just three condoms per year? And why are female condoms even scarcer? **Answering these questions through sustained, substantive actions is the most immediate way to have an impact on the AIDS epidemic today.**

Biomedical strategies alone cannot solve this epidemic.

It is incumbent on all advocates for new prevention strategies to acknowledge that there will be no silver bullet. None of these biomedical interventions in current or planned trials will be quick or simple "fixes" for the epidemic. **No biomedical approach, used singly or in combination, will overcome the structural forces of poverty, gender inequality, stigma, discrimination, and human rights abuses that drive the epidemic.**

The search for vaccines and other biomedical prevention strategies is essential.

While new biomedical prevention tools will not turn around the epidemic on their own, they are critical to the global response. Prevention strategies currently under investigation will have different profiles and/or mechanisms of action from proven prevention strategies. This means that a level of risk reduction could, in the future, come in the form of a pill, an injection, or a vaginally-inserted ring. **Increasing individuals' choices for risk reduction increases the chances that a man, woman, boy, or girl will be able to find an option that works at every stage of his or her life.**

Executive Summary

Resetting the clock, this year's AVAC Report title, is inspired by the anniversary of US President Bill Clinton's 1997 speech calling for an AIDS vaccine in ten years' time. Many organizations, including AVAC, marked this anniversary—and the expiry of the original deadline—with reflection and tempered optimism on May 18 of this year.

We recognize that the title could just as easily be the punch line of a joke about the AIDS vaccine field. Here at AVAC we frequently hear—and remark—that the timeline for finding an AIDS vaccine has been "5 to 10 years" for, well, 5 to 10 years. It seems that we are always resetting the clock.

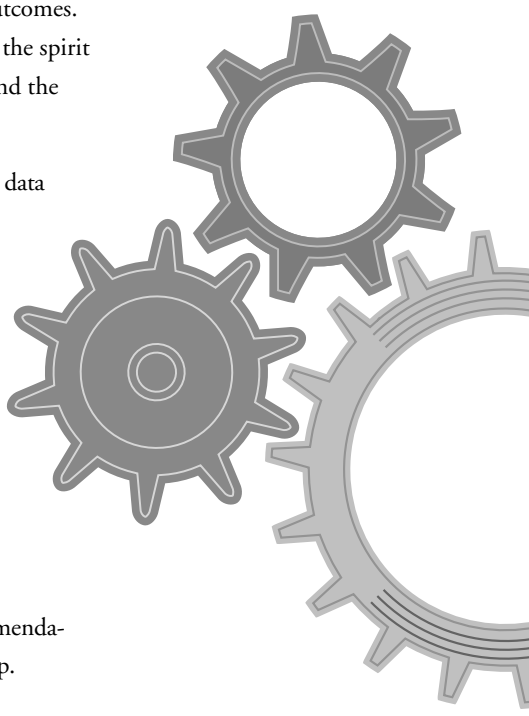
Today we argue in all seriousness that it *is* time to reset the clock. We are within two to three years of data from three test-of-concept studies of AIDS vaccines, including the ongoing Thai prime-boost study and two trials of Merck's adenovirus-based candidate. And so now is the time to set new, ambitious deadlines for developing the novel vaccine concepts and candidates that will be needed whether or not there is evidence of benefit from these first test-of-concept trials.

The three sections of this year's report outline some specific deadlines and challenges in AIDS vaccine scientific strategy, clinical trials, and the broader realm of HIV prevention. These arenas mesh like watch gears, and must function just as smoothly if the field is to proceed.

In Section 1, **New Countdowns**, we explore progress and barriers in funding and strategy-setting for the field. As we wait for the results from upcoming trials, what else do we need to be doing? What are the responsibilities of key institutions at this critical time? We've addressed these questions and returned to industry for an updated survey of private-sector work.

In Section 2, **Racing Against Time**, we turn to clinical trial issues. Here we argue that the field is already in danger of slipping behind. We mean this in several senses, including anticipating and keeping pace with clinical-trial capacity needs, reaching consensus on standards of prevention and levels of care, and solidifying communications strategies for conveying information about trial outcomes. There are also open questions about the new US approach to funding its trial networks. In the spirit of thinking globally and acting locally, we've highlighted specific examples from work around the world as a way of emphasizing issues that affect all prevention research.

In Section 3, **Wake Up Call**, we explore the critical lessons to be learned from responses to data on new approaches which could have some benefit in out-of-control epidemics. The clock is already running when it comes to implementing existing prevention approaches like male and female condoms, as well as emerging prevention strategies like male circumcision. HPV vaccine, while not an HIV prevention tool, is still an important case study. We also listen hard to what advocates from other areas of the AIDS response have to say about prevention research—since collective action is essential for improved prevention overall.



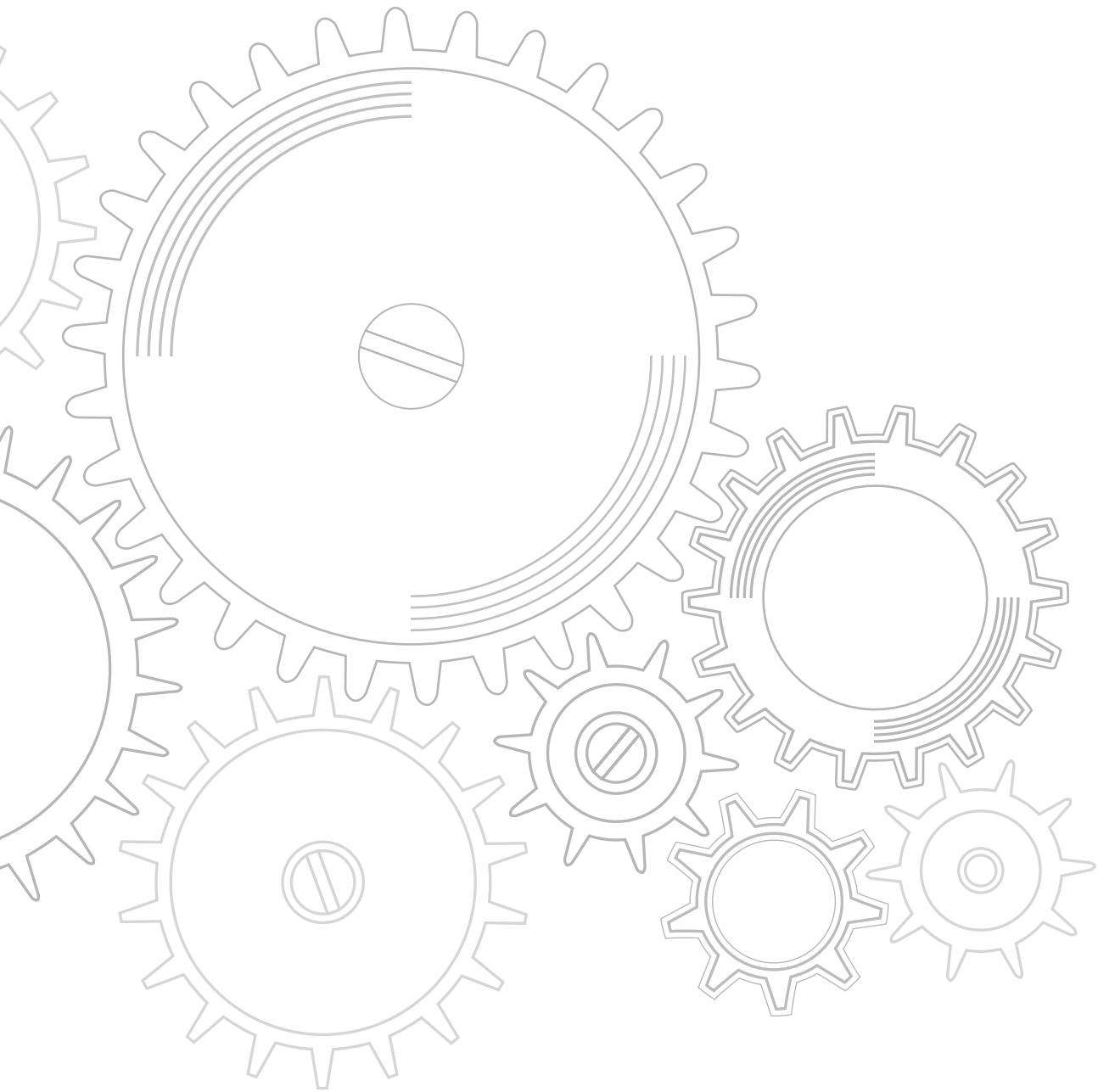
Throughout this report, we make recommendations and suggestions for key actions to be taken in the next year and beyond by different stakeholders—including AVAC. The table on page 8 provides a quick overview of many of the critical points, which are further explored in the pages that follow. In "AVAC's Status Report" on page 9, we review the recommendations we made last year to see how various stakeholders—including ourselves—measured up.

Key Recommendations

AIDS VACCINE FIELD	Focus the preponderance of new product development resources on innovative candidates including live replicating vectors and those that might induce neutralizing antibodies (page 18). Continue work to broaden the array of stakeholders who understand partial efficacy and potential qualities of current candidates (page 20). Explore mechanisms for an advanced clinical trial commitment to strengthen and sustain industry involvement (page 24).
RESEARCHERS	Build funding for community wide results dissemination into all trial budgets (page 34). Dramatically expand awareness campaigns about vaccine-induced seropositivity along with plans for long-term strategies to address the issue (page 37). Pilot the draft Good Participatory Practice (GPP) guidance document and provide feedback on its use in the field to help guide long-term implementation (page 43).
FUNDERS	US Division of AIDS (DAIDS): Closely monitor the on-the-ground effects of its new approach to funding prevention networks and sites as it is put into action, and consider alternatives if problems persist (page 39). DAIDS, Gates Foundation, European and Developing Countries Clinical Trials Partnership, and other funders: Consider community outreach and education fund that would provide additional resources to sites for maintaining and expanding innovative work, and to support independent community oversight mechanisms (page 43). All: Define and follow clear pathways for moving from efficacy results to implementation (page 51).
GLOBAL HIV VACCINE ENTERPRISE	Revisit the business strategy for the Enterprise (page 25). Publish a revised scientific strategic plan that analyzes gaps in light of current, ongoing work (page 25). Convene focused meetings on under-discussed fieldwide issues in clinical trial capacity, manufacturing and regulatory arenas, and other topics (page 25). Once hired, the Executive Director should develop and publish a workplan with a set of milestones to achieve over the next two years (page 25).
AVAC	Advocate that the broad field of HIV-prevention research finally moves beyond an ad hoc approach to defining levels of HIV care and treatment in trials—and arrives at genuine, global consensus (page 41). Work with partners to develop clear, realistic, and consistent messages about when new products might become available and what they will look like (page 51). Work with partners to build a strong and collaborative global movement on prevention research and implementation (page 55).
CIVIL SOCIETY	Work in coalition to advocate for adequate, annual increases in funding to NIH (page 16). Work to ensure that the broad field of HIV-prevention research finally moves beyond an ad hoc approach to defining levels of HIV care and treatment in trials—and arrives at genuine, global consensus (page 41). Pilot the draft GPP guidance document and provide feedback on its use in the field that can help guide long-term implementation (page 43). Support—and demand—developing-country leadership on prevention (page 51).

AVAC's Status Report—An Update on Last Year's Recommendations

	WHAT WE SAID LAST YEAR	WHAT HAPPENED	WHAT MUST HAPPEN NEXT
AIDS VACCINE FIELD	Advocate for robust, comprehensive HPV-vaccine delivery to adolescent girls and boys.	PATH launched pilot projects with four country partners. Multiple groups, including AVAC, and IAVI convened a stakeholders meeting in December 2006 and launched a call to action for cervical cancer prevention and treatment in July 2007.	HPV-vaccine rollout continues to be stymied by lack of a clear pricing structure and a dearth of commitments of sustainable financing for the developing world. The pharmaceutical industry must issue more specific information on affordable pricing structures; GAVI, UNICEF, and other funding streams must step in with financing; and advocates must move more swiftly.
	Develop a common language for talking to communities about test-of-concept trials and sequencing decisions (about when to advance candidates and/or launch additional test-of-concept trials).	Several trial sponsors developed "roadmaps" for various scenarios (impact on viral load setpoint, impact on HIV acquisition) to help discuss their upcoming studies. The Global HIV Vaccine Enterprise and WHO/UNAIDS convened a meeting to discuss upcoming trial results; a coordinating group on efficacy trial results was formed, with a communications subgroup to be convened by AVAC.	These roadmaps have increased clarity for people who are already familiar with prevention research. The vast majority of audiences still do not understand what can be expected of partially-effective AIDS vaccines. The communications subgroup and other partners must help expand awareness and understanding of the complex choices that lie ahead.
RESEARCHERS	Share outputs from research on neutralizing antibodies, adjuvants, mucosal-immunity assays, and other work in a manner that lets us understand whether and how CHAVI, CAVD, and other consortia are truly adding value to the field	In scientific publications and at meetings, scientists working in collaboratives started to share the initial data that are emerging from their work.	The Enterprise and its partners should conduct ongoing field-wide analyses to ensure wise use of resources and prompt attention to gaps and emerging issues.
GLOBAL HIV VACCINE ENTERPRISE	Reconstitute working groups on clinical trial capacity, intellectual property, manufacturing, and regulatory issues. Give these groups specific tasks to help bring these areas up to speed.	Meetings on trial design and on humoral and mucosal immunity were convened. The groups on clinical trial capacity, intellectual property and regulatory issues were not reconstituted, and limited activity happened on these topics.	Convene ad hoc expert groups to develop recommendations for Enterprise and partners on emerging and as-yet under-discussed topics.
	Take swift, transparent action to identify a new executive director.	As of August 2007, the executive director position remains unfilled. The anticipated start date for the new director is January 2008.	Preparatory work in the next six months on an updated business plan and scientific strategic plan to support the executive director when he or she steps into place.
WHO/UNAIDS	Continue to develop and regularly update guidance notes on emerging prevention interventions and technologies including HPV vaccine, couples counseling, circumcision, PrEP, and more, so that countries can plan and have dialogue even before definitive results are in.	WHO/UNFPA led consultations on HPV vaccines and released guidance documents for country-level planning. WHO/UNAIDS moved swiftly to release a discussion document on male circumcision and is continuing to develop material for implementation. WHO/UNAIDS also released new guidance on HIV testing that addresses routine testing; couple counseling was not specifically addressed.	Move swiftly to implement activities proposed for providing country- and regional-level technical assistance on male circumcision programs; continue to raise awareness of and support for HPV vaccine at country-level and within normative agencies.
	Partner with other stakeholders to convene ethical consultations on issues related to evaluation and eventual introduction of new partially-effective prevention strategies.	UNAIDS convened a consultative process to update 2000 Ethical Considerations for Conduct of HIV Vaccine Trials, with expanded coverage of trials of other biomedical prevention options.	Support additional consultations and documentation of best practices in implementing these guidelines as well as the upcoming "Good Participatory Practice" guidance document. Ensure that these and other documents, such as the guidance note on sex workers are harmonized and finalized with sufficient community input.
AVAC	Take a leadership role in developing—in consultation with multiple partners—new guidelines for "Good Community Practice."	AVAC worked with UNAIDS to convene a working group that drafted and revised Good Participatory Practice guidelines for engagement with communities in biomedical prevention trials.	Additional community consultations are still needed on the Good Participatory Practice guidelines, as well as input from groups that apply them in communities where trials are taking place.
	Support and/or convene prevention-research advocacy network that addresses emerging ethical, community, and trial design issues.	AVAC worked with partners to respond to and disseminate information about various trial results including male circumcision, female diaphragm and microbicide trials.	Stronger links need to be built between prevention research advocates and those working on implementation of proven prevention; much more capacity needs to be built for all prevention advocacy at country-and grassroots levels.

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IN THIS SECTION

- The US National Institutes of Health (NIH) is faltering in its responsibility to foster young scientists.
- As we move to a focus on “big science,” we must maintain funding for high-risk projects and innovation grants.
- The field must funnel substantial resources to innovative approaches that complement or extend current strategies —in other words, plan for life after today’s current test-of-concept studies.
- The roadmap for various scenarios from vaccine efficacy trials must be better defined and better communicated.
- AVAC Industry Survey 2007
- An update on the Global HIV Vaccine Enterprise

SECTION 1

New Countdowns

It is time to launch a countdown to ambitious deadlines for developing new vaccine concepts and candidates. These will be needed whether there is evidence of benefit from the first test-of-concept trials of adenovirus-based products or from the ongoing Thai prime-boost trial. This section identifies key responsibilities and challenges as these countdowns begin.

MORE THAN MONEY: WHAT THE FIELD NEEDS NOW

Ten years ago, one of the primary roles for AIDS vaccine advocates was to urge greater financial commitments to the field. Today, this message evokes a kind of nostalgia: it seems enviably simple compared to the concerns of 2007.

Today the field has unprecedented levels of resources. As AVAC, the International AIDS Vaccine Initiative (IAVI), UNAIDS, and the Alliance for Microbicide for Development document in our annual funding report, *Building a comprehensive response: Funding for HIV Vaccine, Microbicide and new Prevention Tools Research and Development* (August 2007, www.hivresourcetracking.org)—2006 funding for AIDS vaccine development neared the US$1 billion mark, coming in at an estimated US$933 million. This figure reflects a 23% increase from 2005 levels.

This is the latest benchmark in an upward funding trend stretching back to 2000. Between 2000 and 2006, funding from the non-commercial sector (public and philanthropic) more than doubled, from US$327 million to US$854 million. This includes a four-fold increase in European government commitments to AIDS vaccine research and development, from US$23 million to US$82 million. EUR 15 million of this money is being funneled towards Europrise, an exciting new collaborative of European scientists and two pharmaceutical companies, which launched in January 2007 with a unique focus on vaccines *and* microbicides.We hope Europe will expand its contributions to Europrise and the broader field in upcoming years.

With great resources comes great responsibility. All of the stakeholders bear a responsibility to ensure that these funds are spent wisely and that there is a broadly enabling environment for scientific progress around HIV prevention.

Here are some of the key responsibilities of various leaders in the field.

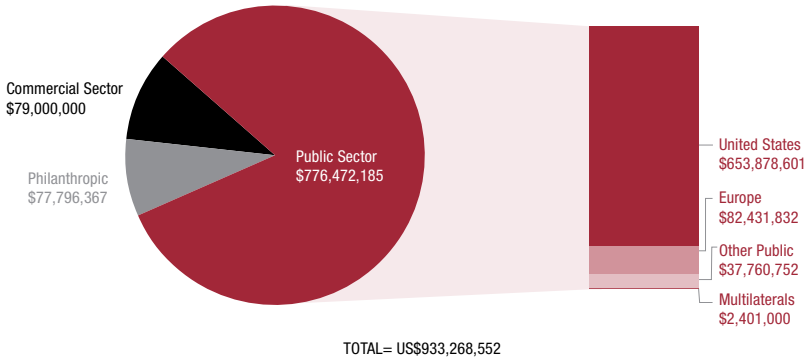
1. The Bill & Melinda Gates Foundation, Europrise, the International AIDS Vaccine Initiative (IAVI), NIH, and other research and development (R&D) funders: A responsibility to meet critical field-wide goals

The field has moved decisively towards a "big science" approach to solving key questions. In consortia such as the Center for HIV/AIDS Vaccine Immunology (CHAVI), the Collaboration for AIDS Vaccine Discovery (CAVD), and Europrise, scientists from different institutions work together, sharing samples, and combining resources in hopes of accelerating progress. In the last year, IAVI tripled funding for the Neutralizing Antibody Consortium. It is also moving more resources into its Live-Attenuated Consortium.

"Big science" is a good thing. Many of the scientific challenges around AIDS vaccine development require resources and samples on a scale that can only be met by this approach.

As we said in last year's Report, it is still early to be evaluating the merits of any of these consortia. In the coming year, AVAC will focus attention on specific workplans and outputs of various groups, and will bring an in-depth analysis to our 2008 report.

Figure 3. PUBLIC, PHILANTHROPIC AND COMMERCIAL FUNDING FOR HIV VACCINES IN 2006



Source: *Building a comprehensive response: Funding for HIV Vaccine, Microbicide and new Prevention Tools Research and Development* (August 2007) www.hivresourcetracking.org

Today, we can say that the field must not rest on its laurels. To realize the potential of the new collaboratives, additional work must be done on specific goals including the following:

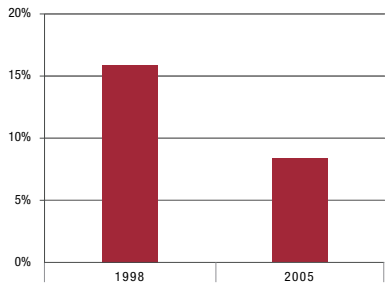
Expanding information-sharing agreements. CAVD collaboratives have broken new ground with their agreements. These should be expanded to other groups such as CHAVI, which has a healthy relationship with CAVD but no formal arrangements on sharing data or intellectual property.

Expanding work on laboratory standardization and assay validation. Important work is being done by existing programs, including the Partnership for AIDS Vaccine Evaluation (PAVE) Laboratory Working Group and others. CAVD has provided support to NIAID/VRC for a "Vaccine Immune T-cell and Antibody Laboratory." However, additional work in this arena is needed including strengthening laboratory capacity in developing countries and investing in the lengthy, costly process of validating assays that could be used across networks to compare products.

Keeping an eye on the balance between big science and innovation. Yes, big science is critical at this stage. But resources for high-risk projects are also critical, as is funding for individual investigators—including young scientists (see section on NIH responsibilities, in this section). NIAID recently modified its longstanding innovation grant program for AIDS vaccines, and it will be important to gather information on how this new program works in the future. Similarly, there is much to learn from the NIAID initiative that offers additional resources to any investigator working on B-cell related research if he or she explores potential applications to HIV vaccine research and design. The Gates Foundation, IAVI and the Wellcome Trust are also exploring a new innovation grant mechanism which could be another means of striking this critical balance.

Making sure that manufacturing capacity keeps pace with new developments. The new Canadian HIV Vaccine Initiative, the Vaccine Research Center, and other groups have helped expand capacity for clinical trial manufacturing—especially for viral vector and DNA candidates. With increasing attention going to live replicating vectors, we must ensure that capacity continues to meet the field's needs.

Figure 4. SHRINKING PERCENTAGE OF NIH VACCINE FUNDS FOR INVESTIGATOR-INITIATED RESEARCH



Bringing in new partners to fund and execute elements of the Enterprise Scientific Strategic Plan. The Enterprise has had successes and setbacks (see p.25). But the Scientific Strategic Plan remains a common reference point for the field. Additional donors should fill resource gaps identified in the plan and related documents. Partners with scientific and technical expertise should continue to align their work with Enterprise goals, providing regular updates on progress and course correction.

2. National Institutes of Health: A responsibility to foster the next generation of scientists

The overall NIH budget has been funded at a flat rate for the past three years, as the figure below illustrates. This leveling out comes after a period of consistent growth and expansion over the preceding seven years.

There is a growing chorus of groups including Families USA, the Treatment Action Group, and others who, along with leading US scientists, have sounded warnings that the current budget is failing even to keep pace with the index used to measure inflation in the cost of biological research, and that this flat-funding can significantly hamper US scientific progress on domestic and global health issues.

AIDS vaccine funding has actually fared relatively well in this climate of shrinking resources—climbing both in absolute dollars and in percentage of the overall NIH budget during each of the years of flat overall funding.

But the AIDS vaccine field does not exist in a vacuum and is not fully buffered from the negative effects of this stagnant funding. One particular concern is the chilling effect that this climate has on young investigators. In 2006, only 16.7% of new grant applications were funded. As Families USA noted in recent Congressional testimony, this 84% failure rate leaves many scientists "sitting on the sidelines, unable to develop promising ideas that could lead to an effective AIDS vaccine, improved tuberculosis treatments, and other medical interventions…"

Those grants that do get awarded are going to older scientists. The average age of investigators receiving their

Figure 6. CONSOLIDATING FUNDS FOR "BIG SCIENCE"—THE NIH EXAMPLE (2005)

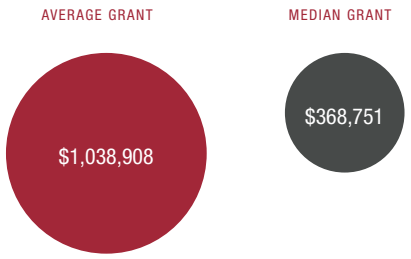
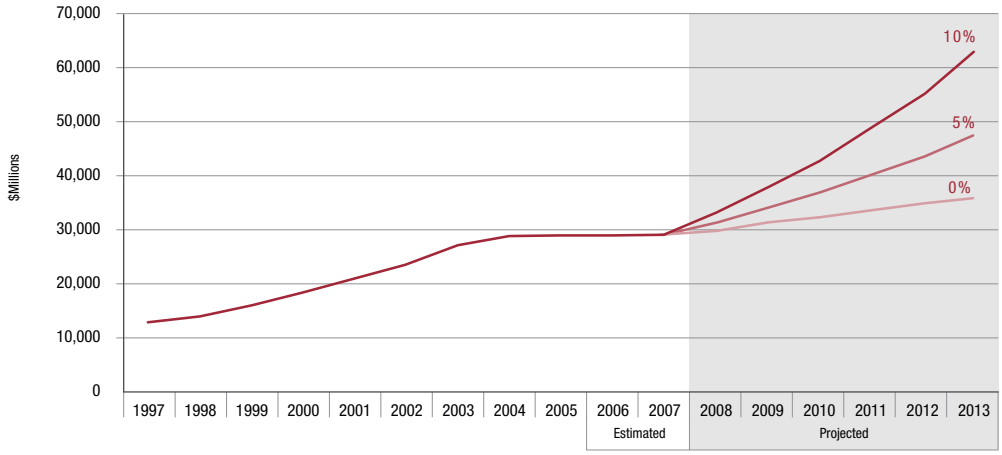


Figure 5. PROJECTING THE NIH BUDGET: 3.7% biomedical inflation plus 0%, 5%, and 10% annual increases from 2008-13



Source: Treatment Action Group—www.treatmentactiongroup.org.

first R01 has gone up significantly, indicating that many young scientists are struggling to find funds.

At the same time, NIH funding for AIDS vaccines has moved towards funding "big science"—without a compensatory balance for individual grants (see Figure 6 on p. 15). And as Figure 4 illustrates, the percentage of NIH funding for HIV vaccines awarded to individual investigators (through "R01 grants") dropped by approximately 50% between 1998 and 2005.

Simply put, big grants have gotten bigger, and small ones have gotten smaller—and harder to get.

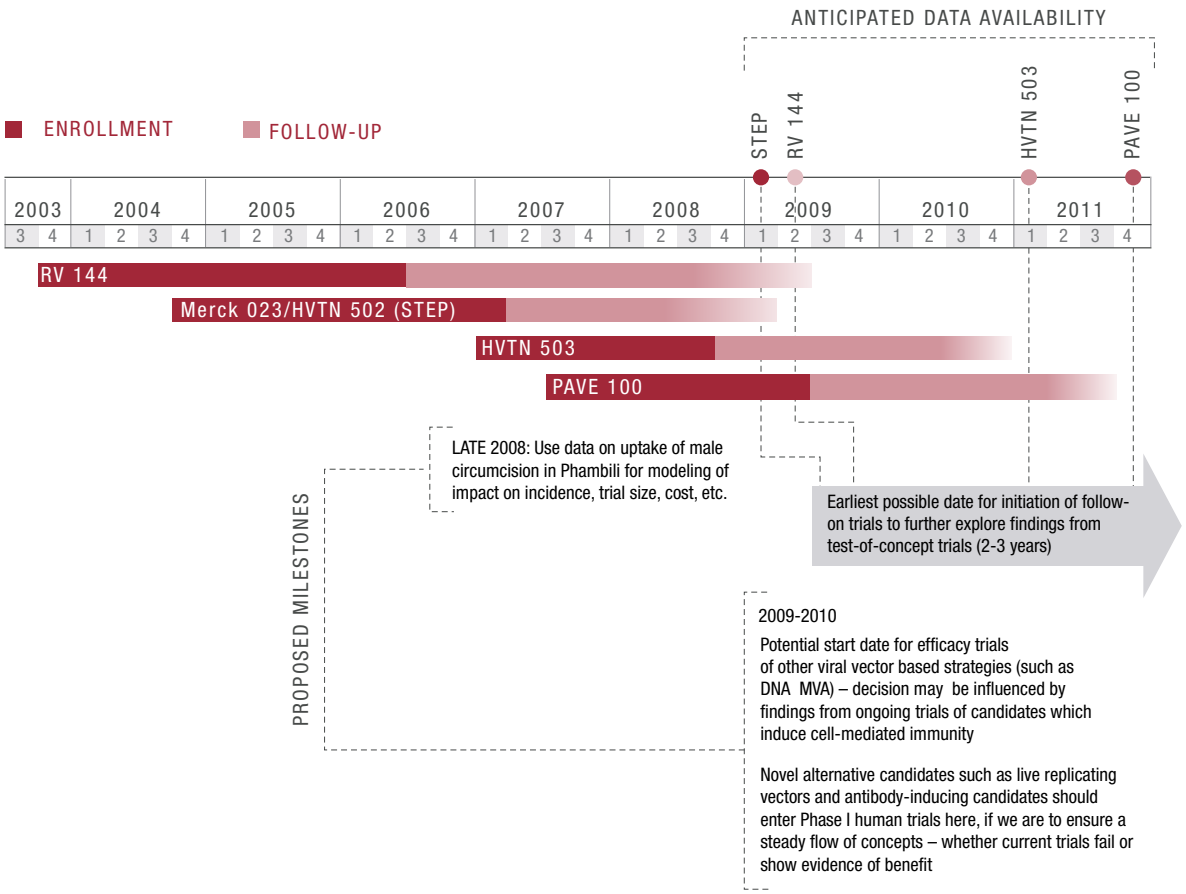
Funding big science is critical. And other entities must also step up to support young researchers. But as long as the NIH remains underfunded, the US government is not fulfilling its portion of the responsibility to support the next generation of scientists.

We are committed to working in coalition with partners to advocate annual inflationary and overall budget increases for the NIH starting in FY2008.

3. Public- and private-sector product developers: A responsibility to optimize what is now in hand—and invest in planning for life after today's test-of-concept trials

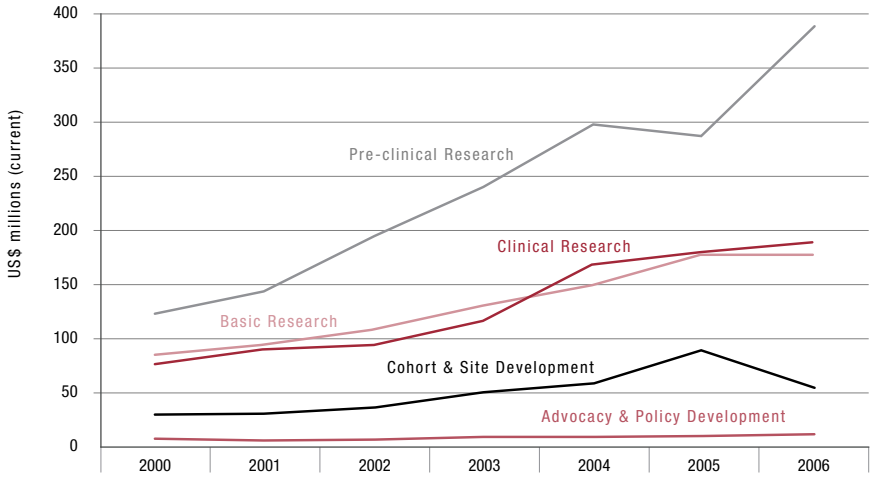
Along with the Thai prime-boost trial, which is testing a canarypox plus envelope strategy (ALVAC plus AIDSVAX), the results from the planned or upcoming studies of

Figure 7. ANTICIPATED DATA MILESTONES AND PROPOSED NEEDS FOR THE FUTURE



Source: Adapted from Alan Fix, NIAID

Figure 8. NON-COMMERCIAL FUNDING ALLOCATIONS FOR PREVENTIVE HIV VACCINE R&D BY CATEGORY IN 2000-06



Source: *Building a comprehensive response: Funding for HIV Vaccine, Microbicide and new Prevention Tools Research and Development* (July 2007) www.hivresourcetracking.org

adenovirus-based candidates will provide essential direction for the field.

These studies include Merck V520-023/HVTN 502 (the "Step study"), HVTN 503 (Phambili), and the planned PAVE 100 trial. Step and Phambili are testing Merck's candidate, called MRK-Ad5. The PAVE 100 study will evaluate a combination strategy employing a DNA prime and an adenovirus boost from the NIH's Vaccine Research Center.

Data from these studies will show whether the strategies—all of which focus on cell-mediated immunity—will either reduce susceptibility to infection or reduce viral-load set point in people who receive the vaccine and later become infected. In theory, a vaccine could even have both effects.

These studies are not designed to meet international requirements for licensure: with any new intervention, additional trials are almost always conducted after initial findings and before seeking licensure. In addition, it is still unclear how reduction of viral load will affect people's health over the long term or what level of reduction would be sufficient to win approval from the US Food and Drug Administration (FDA), European Medicines Agency (EMEA), or other regulatory authorities.

So, an initial finding indicating a benefit will lead to more studies. If there are data on viral load setpoint reduction, follow up research will ask how long the reduction lasts and whether it translates into improved health for the vaccine recipient versus a comparable individual who did not receive the vaccine. If there is evidence of an effect on risk of infection, that too will require additional follow-up studies to confirm and add detail to the observation.

The critical question is: Does the field know what to do and test next after the results from the test-of-concept trials of adeno-based concepts are released?

The answer to this question depends on whom you ask —and how you ask.

If the question is, Do we have candidates that are refinements on adenovirus, should the existing candidates show some efficacy? the answer is yes.

If the question is, Do we have candidates that do not use adeno vectors, but take other approaches to inducing cell-mediated immunity? the answer is still yes.

But if the question is, Do we have candidates—or will we have them by the time the data are available in 2009 or 2010—that take distinctly different approaches, including induction of broadly-neutralizing antibodies? the answer is, very likely not.

And if the question is, Do we have clarity on where the capacity and resources for expanded clinical trials of adeno- and next-generation candidates will come from? the answer is, not nearly enough.

The timeline on page 16 combines dates of anticipated trial results with our proposed milestones for the field. While we would like to see antibody-inducing candidates moving into phase I trials in 2009-2010, this is unlikely to happen. Safe, live-replicating vectors that employ disabled, benign viruses such as measles and adenovirus, could be another option—but only if we focus today.

While the dates we propose in the timeline may not be possible, the field should proceed as if they were, making candidates that represent true, innovative alternatives to non-replicating viral vectors that target cell-mediated immunity (CMI) a priority. And of course, we must continue the hunt for the ever-elusive candidates that might induce neutralizing antibodies, even though the science here is as challenging as ever.

We say this because, when it comes to alternative adenos, we have several options. In addition, at last count there were nearly 10 DNAs and over 5 Modified Vaccinia Ankara (MVAs) in development. Until the data are in on CMI trials, this is enough. This was the thrust of extensive discussions this year with the US committee of experts known as the AIDS Vaccine Research Working Group. Now we must ensure that, where appropriate, existing candidates are compared to one another and that key questions about manufacturing and scalability of the products we do have are answered well in advance of possible large-scale trials.

Table 1. TEST-OF-CONCEPT VERSUS PHASE III: A COMPARISON*

TEST-OF-CONCEPT STUDY	PHASE III
Designed to guide later development	Designed to license product
May use surrogate endpoint	Endpoint must be acceptable for registration
May use prototype product	Use final formulation and manufacturing process
Study population may be limited and focused	Study population must represent intended use
Smaller, faster	Larger, longer

*Source: Mark Feinberg, MD, PhD, Merck HIV Vaccine Division, HVTN Conference May 2, 2007

In short, the preponderance of the field's new resources should be focused on innovative candidates and approaches. It will likely take many years to crack the antibody problem—and the field should be honest about these timelines. At the same time, the field must move work to move truly novel candidates into early clinical trials.

4. The Enterprise: A responsibility to expand dialogue about the implications of various trial results

Over the past year, trial sponsors and leaders in the field, like Merck's Mark Feinberg, the Vaccine Research Center's Gary Nabel and Sanofi Pasteur's Jim Tartaglia, have developed presentations for the various scenarios that could emerge from their current and planned test-of-concept studies. This important effort builds on earlier discussions from other leaders in the field. It should be continued and expanded.

We must develop a field-wide view of the decision points and possible responses over the coming years. Our "road-map" on page 30 presents a broad and simplified picture of the various journeys the field may take in the near future. The range of possible scenarios raises key issues, which require field-wide discussion and planning. An April 2007 meeting co-convened by the Enterprise and hosted by IAVI

began this conversation with a look at the strengths and weaknesses of different trial designs, focusing primarily on planned and ongoing trials.

The Enterprise partners should continue to expand on the topics covered at this meeting with additional conversations that look at how results from one trial might impact on another; how trial size and design will be affected by new prevention approaches such as male circumcision coming on line; and costs and possible designs for follow-on studies to test-of-concept approaches that show impact on viral load. Some of the key questions that were raised at the April 2007 meeting and should continue to be explored include:

- What types of information (e.g., duration of protection, impact on individual health versus infectiousness) will various stakeholders (e.g., donors, regulators, developing-country decision makers and implementers, potential vaccine users) want and need about candidates with an impact on viral load or a partial effect on susceptibility?
- What types of follow-on studies will be needed to move a candidate towards potential licensure that shows efficacy on viral load setpoint?
- Should a candidate that shows an indication of benefit in Phase IIb trials become part of the placebo arm for future trials before definitive efficacy data are in?
- What needs to happen to anticipate resource needs for trials that may be significantly expanded in size and length, due to reduced incidence as new prevention technologies come on line?

MOVING BEYOND PIPELINES

When AVAC began, the world was a different place. Bill Clinton was president of the United States. The Twin Towers of the World Trade Center were standing. Gas prices in the US were $1.44/gallon.

And at AVAC, we were concerned about milestones and the AIDS vaccine pipeline.

Fast forward just over a decade. We have a new President in the United States, and we have lost the Twin Towers. Gas prices hover around $3/gallon, and the term "pipeline" conjures images of oil conduits in battle-strafed territories in Iraq, Afghanistan, and Nigeria.

The AIDS epidemic is vivid and uncomfortable, too. And it has always borrowed from the language of war. So the present connotation of "pipeline" is not a compelling reason to move away from the term in the AIDS vaccine context. The question is: Does this image describe what the field actually needs?

And the answer is no.

A pipeline is a single artery, a major source. Things flow into the pipeline and out again in a sequential manner. A certain amount of duplication and competition is a powerful catalyst for the field. But a single pipeline would imply Phase I trials of similar candidates rather than multiple, distinct approaches to the scientific question.

A pipeline is not the appropriate metaphor for what the AIDS vaccine field needs. What is needed is analogous to alternative energy sources: solar or wind power—many panels or mills gathering the energy—working separately but jointly, funneling gains into a single energy bank.

We need to be thinking in terms of concepts, not candidates, and in terms of multiple, parallel lines of inquiry proceeding at the same time, with minimal redundancy, and optimizing the resources at hand.

TODAY'S TRIAL LANDSCAPE: NOT AS SIMPLE AS I, II, II

The past few years have seen a blossoming of new terms to describe efficacy trials, including test-of-concept, proof-of-concept, and Phase IIb. More recently, IAVI has introduced a trial design it calls STOC, for "screening test-of-concept," into its plans.

Different names aside, these trial designs have a lot in common. The main components of a design, for these purposes, are the number of people enrolled, the projected incidence—or rate of new infections—in the population, and the number of HIV infections or other "endpoints" needed within the study population for the trial to have sufficient statistical power to answer its question or questions.

In general, test-of-concept trials are smaller than full-scale efficacy studies, and they may have fewer endpoints. Each of the two test-of-concept studies of Merck's Ad5 candidate aims to enroll around 3,000 people and is looking for 100-120 endpoints. However, size is not always an accurate indicator. The ongoing Thai prime-boost trial, the largest AIDS vaccine efficacy study ever undertaken, is also a test-of-concept trial, according to its investigators, who say that the data from the 16,000-person study will have to be further explored in additional, follow-up trials.

Someone hearing these numbers for the first time would likely ask: How is it possible to enroll 16,000 people and still need more data? Or to design a study that indicates that a candidate might have a benefit, but does not confirm it?

One answer has to do with incidence. The Thai study is being conducted in a relatively low-incidence population—so it has to be quite large to detect any kind of vaccine-related effect.

In the specific context of AIDS vaccines, another critical answer has to do with what we expect from the current candidates. All of the current test-of-concept studies are designed to find out whether the experimental vaccine strategies have an impact on viral load setpoint in people who receive the vaccine and later become infected. (In the course of natural HIV infection, a person's viral load climbs to a very high level shortly after infection and then drops down to settle at what is known as the "setpoint," where it can remain relatively stable for some time.) These trials are also measuring whether the vaccine strategy reduces risk of becoming infected in the first place.

The MRK-Ad5 trials are designed to detect a 0.5 log reduction in viral load setpoint in vaccine recipients, compared to participants in the placebo arm. The Thai prime-boost study is designed to detect a 0.4 log reduction.

The main reason for looking for this type of reduction is that in observational studies of natural HIV infection, lower viral setpoint is linked to slower disease progression. So a vaccine that dropped a person's viral load setpoint could help him or her remain healthier longer and possibly delay the time to starting treatment. At this point, no one knows how much of a reduction would give a clinical benefit, although natural history and animal studies suggest that it could be in the realm of 1.0-1.5 logs.

But while there is a scientific rationale for looking at viral setpoint, the truth is that we don't know whether a vaccine-induced change in viral load will be enough of a benefit to make the strategy a viable part of the HIV-prevention tool kit. At the end of these relatively brief (2-3 year) test-of-concept studies, we won't know how long this reduction in setpoint lasts or how it affects individuals' clinical outcomes (their overall health). We also won't know whether it reduces a person's likelihood of passing the virus to sexual or needle-sharing partners or to the person's children.

All of these questions will need to be explored in additional studies and in follow-up of trial volunteers from the original studies. It could take years, and significantly larger trials, to determine whether the reduction in viral load setpoint has a clear and lasting benefit.

That's one reason why these studies almost all use the term *concept.* They are an initial test of an idea: in this case, the idea that a vaccine strategy, which primarily induces cell-mediated immunity, can have a beneficial effect—either reducing risk of HIV infection or reducing viral setpoint.

These trials leave a lot of gray areas, including questions such as, how much of a reduction in viral load is enough to warrant follow-up studies? Clearly, the answers from the first trials will prompt more questions and more years of research. There is a long road ahead of us. And if we do not communicate this reality to all of the audiences who are watching the AIDS vaccine field and wondering how their money is being spent, then we risk losing credibility at the precise moment—the end of a test-of-concept trial—when we need it the most.

THE 2007 AVAC INDUSTRY SURVEY

Twice since AVAC was formed in 1995, we have spoken with key players in the pharmaceutical and biotechnology industries about HIV-vaccine development at their companies.[3] This year, we felt it was time to conduct our survey once again. Over two months, we spoke with 11 representatives from different companies, including major industry players and small biotech firms.[4] We asked each company the same series of questions about clinical trial infrastructure, regulatory issues and incentives, and the major barriers to expanded and accelerated AIDS vaccine R&D in 2007.

What does industry involvement look like overall?

- Private-sector investment accounts for 10% of overall funding for AIDS vaccine research and development.
- The vast majority of funding comes from a handful of companies (see Table 2 on page 22), with Merck and sanofi pasteur—two companies with test-of-concept trials—committing the lion's share of the resources
- More than two-thirds of the industry programs have budgets of US$1 million or less—and most of these companies are funding their programs with resources from the NIH, while others are deriving funding from more lucrative ventures like cancer therapies or vaccines.
- Companies that are investing more significant sums tend to be concentrating on candidates that are in the mainstream of current AIDS vaccine approaches and/or are important for other programs. These include new, improved versions of concepts that were shelved. Sanofi pasteur is developing new pox-virus approaches even as the Thai prime-boost study using its ALVAC candidate moves to completion. Merck, Novartis Vaccines, GlaxoSmithKline (GSK), and Wyeth are all working on alternative viral vectors.
- The companies surveyed have a total of over 20 candidates in various stages of development. More than 50% of these candidates are in pre-clinical development.
- Just under half of the companies surveyed have candidates *only* in pre-clinical phases.

What has changed since our last survey?

- There have been advances in the broader fields of vaccine development and immunology. GSK has developed powerful new adjuvants, which are being used in its human papillomavirus (HPV) vaccine candidate, its malaria vaccine and one of its HIV vaccine projects. Wyeth is experimenting with new DNA vaccine delivery systems. Vaccines such as Merck's already-approved HPV vaccine Gardasil®, use virus-like particles and a relatively low-cost and more easily scalable production system.
- No major companies have entered the AIDS vaccine field in the past six years. Pfizer and Schering both have vaccine divisions with ongoing work that might apply to AIDS vaccines, and are among those companies that we would hope to see join the field.
- Two of the major industry players—sanofi pasteur and Merck—have candidates in test-of-concept trials. These trials are being conducted with and receive substantial funding from US government research entities.
- Public-sector partners supported Wyeth and Novartis Vaccines are moving candidates into Phase I and II trials.

What did we hear?

From an industry standpoint, the AIDS vaccine field has hardly reached the starting line. The private sector has maintained that the risks involved with AIDS vaccines are too great to warrant significant investment. With all the funding and insights of the past 10 years, we still have

[3] Past results of these interviews were published in our 1998 and 2001 Annual Reports and can be found online at http://avac.org/reports.htm.

[4] In March and April of 2007, we interviewed researchers and executives working eleven of the companies currently active in the development of HIV vaccine candidates. These companies include many of the key pharmaceutical companies in the U.S. and Europe (GSK, sanofi pasteur, Novartis, Wyeth, and Merck.). We also spoke with a number of biotechnology companies (Avant, EpiVax, GenVec , GeoVax, Juvaris BioTherapeutics, and United Biomedical).

Table 2. COMMERCIAL ENGAGEMENT IN PREVENTION HIV VACCINE R&D BY COMPANY IN 2006*
OVER US$10 MILLION
Merck & Co, Inc.
US$5 MILLION TO 10 MILLION
sanofi pasteur
Novartis International AG (after acquisition of Chiron Corporation)
GlaxoSmithKline
US$1 MILLION TO 5 MILLION
Wyeth-Ayerst Lederle, Inc.
US$25 THOUSAND TO 1 MILLION
Advanced BioScience Laboratories
AlphaVax Human Vaccines Inc.
Bavarian Nordic
Bioption AB
Crucell N.V.
Epimmune Inc.
FIT Biotech PLC
EpiVax
GenVec, Inc.
GeoVax, Inc.
Globeimmune, Inc.
Impfstoffwerk Desau Tornau GmbH
Juvartis BioTherapeudics
Maxygen, Inc.
Novavax Inc.
Progenics Pharmaceuticals, Inc.
Targeted Genetics Corporation
Therion Biologics Corporation Transgene
United BioMedical
Vical Inc.

* These estimates reflect only what the biopharmaceutical sector invests from internal resources. Most of the pharmaceutical and biotechnology companies active in AIDS vaccine research also receive substantial funding from the public sector and/or public-private partnerships.

no correlate of protection, no sign of a breakthrough on neutralizing antibodies, and no idea of a clear regulatory pathway for a vaccine that provides partial efficacy. To industry, this is a string of red lights—or at least a signal to proceed cautiously, which is what we see in all but a handful of cases.

Covering costs for clinical trials is a major concern—manufacturing, market, and pricing are reportedly of less concern. When it comes to product development, many candidates fall by the wayside in the so-called "valley of death" that separates Phase I and Phase III trials. The intermediate stage includes Phase II testing and "process development"—the term used for developing manufacturing processes that can supply efficacy trials and, potentially, initial introduction. These steps are both riskier and costlier than Phase I testing. Getting through this stage depends on having human results that meet, exceed, or differ from those demonstrated for products already in Phase III. Many respondents indicated that funding for this stage is particularly hard to secure. While these concerns have been raised in past surveys, they are particularly acute in light of NIH funding limitations.

In contrast, few of the companies surveyed said that they were concerned about maintaining intellectual property rights, market size, or downward pressure on pricing. What industry is willing to discuss publicly does not necessarily reflect all actual concerns—but the lack of immediate emphasis is worth noting.

Programs rely on NIH and other public-sector funds. Basic research in the biotech industry, and some in the pharmaceutical industry, is still heavily financed by the NIH. Most companies that receive NIH funding for part of their pre-clinical or clinical-trial programs expressed concern about whether this funding would be available—and at what levels. We have heard these concerns but need to pay close attention to them. Today, small biotech firms are engaged in important scientific work on adjuvants and delivery systems. They are on the frontlines of some of the newer technologies such as proteomics and gene expression analysis.

These small companies need additional capital incentives for applying their innovations to AIDS vaccines, if the field is going to learn about the potential applications of these new approaches without delay. "Usually a small biotech firm that has an adjuvant which everyone wants to take a look at has one half-time business person dealing with all the requests," said one product developer/researcher from a public entity.

Little interest has been attracted by advanced market commitments. In June 2005, the G8 Finance Ministers agreed that an advanced market commitment (AMC) could be potentially a "powerful mechanism to incentivise research, development and the production of vaccines for HIV, malaria and other diseases." AMCs, which provide funds to procure vaccines that meet certain benchmarks, have been suggested as a way of guaranteeing a market for

Table 3. INDUSTRY HIV VACCINE INVOLVEMENT 2007*

COMPANY	VACCINE CONCEPT	STATUS
AlphaVax	Venezuelan Equine Encephalitis (VEE) vector	Phase I
Avant	Virus-like particles	Pre-clinical
Aventis Pharmaceuticals	Lipopeptide	Phase II
Epimmune	Protein	Phase I
EpiVax	Epitope mapping	Pre-clinical
GenVec	Adenovector technology	Preclinical
GeoVax	DNA/MVA vector	Pre-clinical
GlaxoSmithKline Biologicals	Protein	Phase I
	Measles vector	Pre-clinical
	Non-human primate adenovirus vector	Pre-clinical
	DNA with adjuvant	Phase I
Juvaris Biotherapeutics	Inactivated simian immunodeficiency virus	Pre-clinical
Merck	Adenovirus vector	Phase IIB
	DNA	Phase I
Novartis Vaccines	Alphavirus vector	Phase I
	Live adenovirus vector	Pre-clinical
	Tat protein	Phase I
	DNA/Protein	Phase II
Sanofi Pasteur	Canarypox (ALVAC)/ AIDSVAX.	Proof of concept efficacy trial
	DNA /vaccinia virus (NYVAC)	Phase I
	Canarypox (ALVAC)/peptide	Phase I
Therion	MVA vector	Phase I
	Fowlpox vector	Pre-clinical
United Biomedical	Peptide	Pre-clinical
Wyeth	DNA plasmid cytokine	Phase I
	Vesicular stomatitis virus (VSV) vector	Pre-clinical

* This table represents a selection of the industry and biotech work on AIDS vaccines taken from interviews and public records. Additional companies working in the field are listed in table 2. AVAC welcomes updates and additions. Please send them to avac@avac.org.

an HIV vaccine. Yet, from what we heard from industry, the distant promise of an AMC is hardly sufficient to draw them into the search for an AIDS vaccine, since it does not provide support for clinical trials or pre-clinical development.

What must happen next?

We cannot, by force of will or advocacy, generate a breakthrough that will eliminate the scientific uncertainty for industry or the field at large. But we can address some of the barriers to ongoing involvement. Here are some suggestions:

- Explore an advanced clinical trial commitment. More immediate than an AMC, it would be an incentive package that guarantees funding for intermediate and large-scale trials of candidates that meet certain criteria—such as immunogenicity, or correlates of protection—once they are identified.

- Expand the pool of public-sector venture capital. When IAVI started, its goal was to move money quickly to smaller entities with promising concepts. More than 10 years later, it's a fully-fledged product developer all its own. But funds still need to be available for small programs that are taking innovative approaches to AIDS vaccines or other ancillary technologies. IAVI and the Gates Foundation are among those exploring such initiatives—and we encourage their launch soon.

- Follow the new money. Right now, the world economy is awash with private capital and easy credit, some of which is being used to take public companies private. There is some anxiety, based partly on US economic performance, about whether this climate will persist. However, there is still reason to consider: Could a similar form of diversification of risk and use of private equity be harnessed for the good of public health? Perhaps an amalgam of for-profit and philanthropic investment could combine the advantages of private foundations with the venture-capital incentive of high-risk/high-reward? We're not sure what form this could or should take, but we at AVAC are very willing to explore such possibilities with elected officials and wealthy investor consortia to begin to brainstorm about some sort of new mechanism for doing well while doing good.

A CALL TO ACTION FOR THE GLOBAL HIV VACCINE ENTERPRISE

AVAC Report 2007 identifies a number of challenges facing the field, which will be most effectively addressed by collaborative work.

These include:

- The need to foster innovation and independent work, particularly of young scientists, along with "big science";
- The need to sustain industry involvement;
- The need to anticipate how current vaccine trial results and developments in other prevention fields will influence the size, cost, and goals of future AIDS vaccine clinical trials;
- The need to build better bridges between the AIDS vaccine field and other research and implementation arenas.

We are not alone by any means in calling for greater collaboration. The Global HIV Vaccine Enterprise was founded precisely to create a coordinated response to enduring challenges in the field.

The Global HIV Vaccine Enterprise was proposed in an article authored by 24 leaders in HIV vaccine research and published in *Science* magazine in June 2003[5] (for a timeline of select Enterprise activities to date, see p. 27). The Enterprise was envisioned as a group of independent entities united by a shared commitment to finding an AIDS vaccine. In February 2005, this commitment was further defined with the publication of a Scientific Strategic Plan, which laid out core directions for the field, in *PLoS Medicine*.[6]

Six working groups involving more than 120 participants from 15 countries contributed to this plan, which aimed to provide a blueprint for coordinated work throughout the field. The working group topics were: vaccine discovery, laboratory standardization, product development and manufacturing, clinical trials capacity, regulatory issues, and intellectual property. The goal of each working group was to provide roadmaps and recommendations for the field as a whole and to identify areas where new or realigned strategy and funding would be likely to improve outcomes.

AVAC'S ENTERPRISE UPDATE AT A GLANCE
AREAS OF PROGRESS
Increased funds flowing into research and selected other areas such as manufacturing and clinical trials aligned with the Enterprise Scientific Strategic Plan
Increased sharing of data and samples through formal agreements at groups like CHAVI and CAVD
Increased understanding of genetic determinants of viral control and slower disease progression from CHAVI
Creating a supportive environment for collaborative work on clinical trials like PAVE 100
AREAS WHERE THE CLOCK IS STILL TICKING
Invigorated field-wide analysis and decision-making on critical topics related to clinical trials, regulatory issues and intellectual property
Ongoing analysis of how activities in the field are (and are not) filling identified gaps
Follow up on head-to-head trials, assay standardization and other areas requiring even greater collaboration
Development of a clear independent voice distinct from the Gates Foundation

[5] Klausner, RD, Fauci AS, et al: "The need for a global HIV vaccine enterprise." Science 300:2036, 2003

[6] Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise: "The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan." PLoS Medicine: January 18, 2005 doi:10.1371/journal.pmed.0020025

In the two years since the Plan was published, the Enterprise has had several important accomplishments. The NIH-funded Center for HIV/AIDS Vaccine Immunology (CHAVI) and the Gates-funded Collaboration for AIDS Vaccine Discovery (CAVD) are new collaborative research efforts that unite major players in the field with unique agreements on data and sample sharing, all with the goal of overcoming some of the toughest scientific challenges.

Both CHAVI and CAVD take a "big science" approach to solving enduring problems. In July 2007, CHAVI announced one of the first findings from its work: the "host genetics team," which is led by David Goldstein (Duke University), published findings from its genome-wide association study. This involved close analysis of nearly 500 DNA samples from HIV-positive people, chosen from a pool of more than 30,000 samples.

Analysis of these samples identified human genes that appear to play a role in how well individuals control HIV and/or remain healthy, without disease progression, in the absence of antiretroviral therapies. This scale of analysis would not have been possible without CHAVI's collaborative muscle, and CHAVI, in turn, is clearly aligned with the Enterprise and its goals.

Likewise, members of the Partnership for AIDS Vaccine Evaluation, or PAVE, have told AVAC that formation of the Enterprise solidified the collaborative spirit that has brought the NIH, Centers for Disease Control and Prevention, the US Military HIV Research Program, and the International AIDS Vaccine Initiative (IAVI) together to evaluate the Vaccine Research Center's (VRC) DNA-Ad5 vaccine strategy in the planned PAVE 100 trial.

There are also positive signs that new players are getting involved to tackle gaps specifically identified in the Scientific Strategic Plan. In February 2007, Canada joined with the Gates Foundation to launch the Canadian HIV Vaccine Initiative, which includes a program on manufacturing that is closely aligned with the needs outlined in the plan. Also recently, the European and Developing Countries Clinical Trials Partnership (EDCTP) and the Gates Foundation launched a joint call for proposals to support capacity building in developing countries.

But for all of these accomplishments, the Enterprise has yet to fulfill its promise.

From its inception, the Enterprise has always made it clear that it was to be the sum of its parts, relying on various partner groups to align their plans with the Scientific Strategic Plan and implement activities towards achieving goals laid out in the shared plan. CHAVI, CAVD, IAVI, Europrise, and others have played key roles in this work.

But the Enterprise has also, at least in theory, promised to be a whole that is *greater* than the sum of its parts. As various players align their work with specific goals, the Enterprise should provide a mechanism for assessing progress and making course corrections if needed. Of course, each research group must measure its own progress against relevant milestones and make course corrections accordingly. But there is also a need for field-wide analysis.

As an example, a recently published report co-funded by the Gates Foundation and IAVI calls for improving the research and development decision-making process and states that "investments in the availability of and use of common procedures across labs, and possibly in head-to-head comparisons of leading candidates" could enhance field-wide decision making on which candidates advance to larger scale trials[7].

[7] HIV Vaccine Research and Development: Modeling the Path to Speedier Success (2006), International AIDS Vaccine Initiative and the Bill & Melinda Gates Foundation. Available at: www.iavi.org

At present, there is no formal mechanism to move valid field-wide recommendations such as this one into practice—yet it clearly warrants further exploration and refinement. (In the absence of established correlates of protection, it may not make sense for trials to limit themselves to common procedures—but a core set of shared assays could indeed help improve decision-making.)

The Enterprise's own progress report, published in August 2007, further highlights the need for work to translate recommendations into actions. Its first section summarizes ongoing work in the field; its second covers the key recommendations from three meetings held to address enduring scientific challenges. And yet the reader who was using this document as an introduction to the Enterprise would be hard-pressed to understand whether and how the entities cited in the first section were taking up the recommendations made in the second section.

While this may be a matter of developing a better format for the progress report, it also speaks to the deeper need for the Enterprise to provide updates that refer back to the gaps identified in the plan and so help to track progress from where partners started, to where they are today. The Report does not do this; we look forward to an updated Scientific Plan—which is scheduled for completion in the near future.

This is critical because there has been limited activity in three of the six areas identified in the original plan: clinical trial capacity, regulatory issue considerations, and intellectual property issues.

There is a need for ad hoc groups that bring together key stakeholders in each of these areas to consider emerging challenges. These meetings don't need to consider all the possible ramifications of a given topic. They need to be targeted and tailored to key challenges, be they questions

Figure 9. GLOBAL HIV VACCINE ENTERPRISE TIMELINE 2003-07*

2003	2004	2005	2006	2007
Enterprise concept paper published in *Science*	6 Working groups convened: vaccine discovery, laboratory standardization, product development & manufacturing, clinical trials capacity, regulatory issues, intellectual property	Scientific strategic plan published in PLoS medicine	Announcement that Adel Mahmoud would not assume role as Enterprise Executive director	Meetings held on topics including trial design, humoral and mucosal immunity
Airlie House meeting to develop Enterprise concept		Stakeholders meeting, London	Gates Foundation announces grants for CAVD	Enterprise publishes first report on its activities
		NIH awards for CHAVI to Duke University		
		Funders' Forum, London		

* Adapted from Global HIV Vaccine Enterprise: Report of Activities 2005-2007 (2007)

about how changes in standard of prevention will impact trial size, funding, and capacity needs, or how lack of clarity on international intellectual property might cause roadblocks for future product development.

The Enterprise is well-positioned to convene such groups, and its initial scientific plan suggested that these would be key areas of work. If that has shifted, then the plan should be updated accordingly—the key to the success of the Enterprise is not to be all things to all people, but to be clear about its role and goals.

Hiring an executive director should accelerate progress on these goals. A leader who has a strong and, where necessary, challenging voice could help to initiate discussions on specific high-priority topics and follow through on key recommendations that emerge from these and other meetings. He or she could help to move the Enterprise into a second phase—one that uses the collaborative spirit and initial work of the first two years as the foundation for an expanded, ambitious scope of work.

A new executive director could also help the Enterprise to develop an identity that is distinct from the Gates Foundation. The Foundation has housed a small Enterprise secretariat since 2005, which has worked energetically to move the Enterprise forward.

In its next phase though, the Enterprise should move in a more independent direction. The global perception that the Gates Foundation has "taken care" of investments in HIV-prevention research is false, yet persistent. With a strong director at the helm, the Enterprise secretariat will be able to tackle fundraising, if needed, and, we hope, to be both a critical and a unifying voice.

AVAC sees four critical action areas for the Enterprise and its incoming Executive Director in 2008:

1. Implement collective planning and decision-making on product candidate advancement

The AIDS vaccine field faces multiple, critical decisions about which products to move forward and when. Though there has been discussion for years about the need for head-to-head trials of candidates, it has not happened.

2. Translate Enterprise 2007 report recommendations into specific action plans

The current report on the Enterprise summarizes activities in the field and makes recommendations for filling gaps in some critical areas. The updated Scientific Strategic Plan should place these recommendations into the "big picture" of Enterprise activities and identify new or persistent gaps.

3. Address clinical trial capacity issues

There is a clear need for resources and strategic thinking around clinical trial capacity development, including expanding infrastructure and human resources (scientific leadership from developing countries, counselors, laboratory technicians, recruitment staff, and others). The EDCTP plays part of this role, but a single entity working alone cannot solve the global issues. In 2008, the Enterprise should convene focused discussions on clinical trials to develop a strategic plan and operational action recommendations.

4. Engage a broader range of community stakeholders

AVAC has been committed to working with the Enterprise since its inception, attending the Airlie House meeting in 2003 and contributing to development of the Scientific Strategic Plan. But we do not and cannot represent the full

scope of community issues and perspectives for the world. The Enterprise should ensure representation from all key constituencies and community stakeholders and should actively support capacity building for prevention research advocacy worldwide.

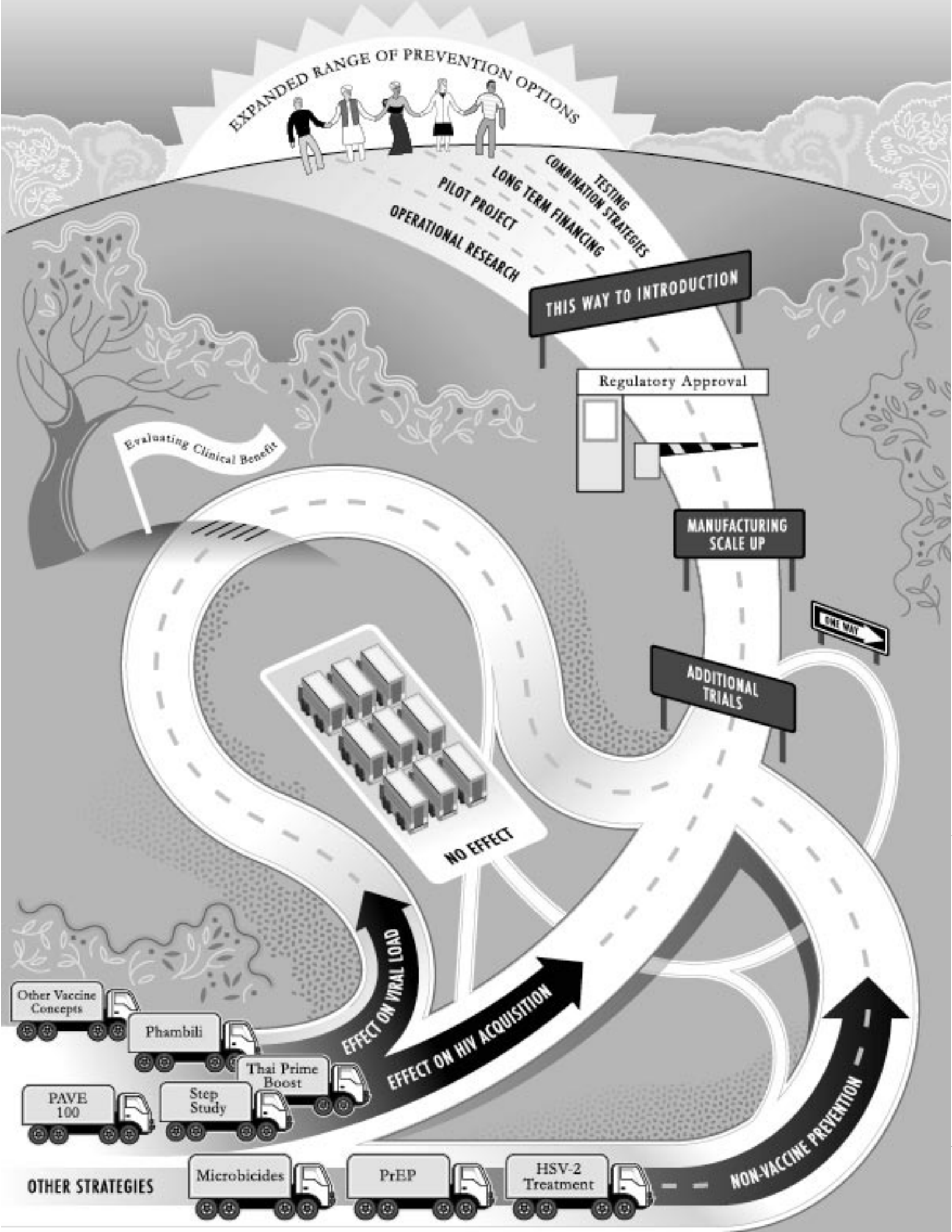
AVAC recognizes the tension in our own role as watchdog of both the Enterprise and the Gates Foundation, given that we receive funding from both the Enterprise secretariat and the Gates Foundation. We are a member of the Enterprise, and Bill Snow, a co-founder and board member emeritus of AVAC is on the Enterprise coordinating committee. We recognize the challenges this brings to our work and we are committed to independence of thought and advocacy. We are all learning as we go.

The newly-published Enterprise report tells us that it will be January 2008 when the Executive Director takes on the job. It takes time—often a year or more—for a new leader to get up to speed, develop a plan of action, and find the right staff.

AVAC believes that the vaccine field cannot afford to wait another year for the Enterprise to run on all cylinders. Therefore, we call on the Enterprise partners and the interim secretariat to start getting ready for the incoming director. Specifically:

- Begin the preparatory work to revise and publish an updated scientific strategic plan including a gap analysis and recommendations to the partners, the new leadership, and the science strategy committee.
- Consult key stakeholders to identify high-priority, under-discussed topics in the areas of clinical trial capacity, manufacturing, and intellectual property; and to convene focused meetings to consider specific questions and generate recommendations that can be used to inform the ED's first year of work.
- Develop an Enterprise business plan with specific milestones for the next two years, including a transparent process for monitoring timelines and results. The incoming ED should review, modify, and publish this during the first quarter of 2008.

The Enterprise was conceived as a global collaboration to add strategy and urgency to the search for an effective AIDS vaccine. While a single leader cannot and should not be the sole focal point of the endeavor, the time is well past for this critical effort to have an independent voice, a face, an outspoken champion. AVAC looks forward to collaborating with the Enterprise leadership in communicating the growing urgency of the need for a vaccine and in instituting policies and practices to ensure that research and development, and trial processes are continually improved and accelerated.


EXPANDED RANGE OF PREVENTION OPTIONS
TESTING COMBINATION STRATEGIES
LONG TERM FINANCING
PILOT PROJECT
OPERATIONAL RESEARCH
THIS WAY TO INTRODUCTION
Regulatory Approval
Evaluating Clinical Benefit
MANUFACTURING SCALE UP
ONE WAY
ADDITIONAL TRIALS
NO EFFECT
EFFECT ON VIRAL LOAD
EFFECT ON HIV ACQUISITION
Other Vaccine Concepts
Phambili
Thai Prime Boost
PAVE 100
Step Study
NON-VACCINE PREVENTION
OTHER STRATEGIES
Microbicides
PrEP
HSV-2 Treatment

HIV PREVENTION ROADMAP

The road to expanded biomedical HIV prevention options is long and winding. As the pathways for the vaccine trials show, even if we get an initial finding of efficacy, there will be twists and turns of additional trials and long-term follow-up of volunteers to better understand the initial findings. As other new prevention strategies move down their own routes, we can expect paths to cross, leading to potentially more complicated trial designs—and, we hope, more options for slowing the spread of HIV.

IN THIS SECTION

- Vigilance is needed to ensure that new funding structures for NIH-funded trial networks do not harm critical site-level functions
- An urgent call to action to address vaccine-induced seropositivity
- Strong activities related to communication of trial results and unforeseen developments
- One vaccine trial site's response to male circumcision data and its implications for the prevention standard of care

SECTION 2

Racing Against Time

HIV-prevention research is a field of long timelines. It is also one of immediate needs. While it will likely be two years before we get results from ongoing vaccine-efficacy trials, time is not on our side. In the arena of clinical trials, there are several areas where we are already—or soon to be—racing against time.

BUILDING GLOBAL APPROACHES ON LOCAL EXPERIENCES

This section takes the phrase "think globally, act locally" to heart. Like so many others, it can ring hollow if it isn't backed up with action. So, in the following section, we've used specific local examples as the starting point for exploring themes of global relevance.

Communication

Cellulose sulfate: Conveying bad news

On January 31, 2007, phones began ringing in the United States, the United Kingdom, Ghana, India, and around the world. The callers included advocates, communications officers, scientists, and lawyers. All were grappling with the Data and Safety Monitoring Board (DSMB) recommendation that Phase III trials of the microbicide candidate cellulose sulfate (CS) be stopped, due to preliminary evidence that there were more HIV infections among women trial participants using the experimental gel, versus those who were using the placebo gel.

The news that there is even a *potential* for harm associated with an experimental product of any kind is always bad. In the case of the microbicide field, it brings home the need to continue to refine and explore measures of safety, so that products that may increase risk of infection are weeded out before they reach efficacy trials.

However, as bad as the news appeared to be on cellulose sulfate[8], there are encouraging aspects to the events that followed. An interdisciplinary group including advocates and the trial team developed communication strategies that enabled clear and consistent messages about the DSMB recommendation to be communicated directly from the trial staff to developing countries and trial communities.

Execution of these strategies meant securing legal permission to share the results with communities and countries, even as the company involved in the study announced the findings to its shareholders. Such sequencing of disclosure is unusual in products developed by publicly-traded companies, but sets an important precedent for prioritizing communications with communities over or alongside the interests of shareholders.

The rapid response to the CS results was an example of the benefits of well-coordinated communication around clinical trial outcomes. Initial inaccurate press reporting in South Africa accused of using women as "guinea pigs." A strong response from civil society, including the Treatment Action Campaign, and from sites involved in CS and trials of other microbicide candidates, helped to clarify the findings, activate collection of gel samples, and make important distinctions between CS trials and ongoing studies that did not have safety issues.

Key principles from this experience:

- **Collaborate with advocates before the trial results are made public to ensure consistent messaging.**

[8] A subsequent close examination of results of the Phase III studies of cellulose sulfate (CS) found no statistical difference in safety or efficacy results between the group using cellulose sulfate and the group using a placebo product in either the CONRAD or the FHI trial, although there were more seroconversions in the CS arm of the CONRAD study. Overall, these data confirm that CS gel is not effective against HIV infection.

- **Give priority access to breaking news on trial outcomes to audiences in the trial host country—particularly trial communities.**
- **Provide transparent explanation of what is known and not known about results—whether they are good or bad.**
- **Ensure communication between neighboring research sites to minimize the impact of results from one trial on the conduct of another.**

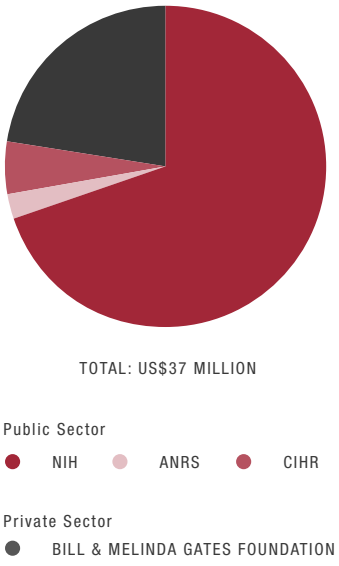
Male circumcision: Community-based results dissemination

Clinical trials may do excellent work on community outreach when they are launching a study. But when the study is finished, do they expend the same energy on disseminating and discussing the study results with the trial communities? Often, the answer from the community perspective is, No.

This year, the trial team responsible for the male circumcision study in Kisumu, Kenya developed an approach that deserves careful consideration as a model for future research. The report on the dissemination program presented this rationale: "In particular, since young men comprise the study population and are at a high risk of contracting HIV, it seemed especially important to inform youth of the protective effect of male circumcision and to caution them that since circumcision is not 100% protective, they still need to follow safe sex practices."

Activities launched in the months immediately following the announcement of the trial findings included sponsorship of football (soccer) matches, organization of community meetings, and the delivery of lectures to an array of stakeholders, health authorities, and prevention partners. At the football matches, the trial team provided T-shirts for the players and gave fliers to spectators detailing, in lay terms, the results of the trial along with safer-sex reminders. In addition, information was shared orally during half-time breaks. A total of 38 teams participated in 21 matches and reached an estimated 6,730 people. Stakeholder meetings reached more than 1,000 people.

Figure 10. TOTAL INVESTMENTS (2001-07*) IN RESEARCH ON MALE CIRCUMCISION FOR HIV PREVENTION[9]



*The 2007 estimates represent actual disbursements and firm commitments made as of June 30, 2007.

In addition, trial participants were informed of trial results when they came to the site or were reached at their homes. Each volunteer was provided with a simple, written explanation of the results which site staff also discussed with them.

The team documented questions and concerns related to the trial, which will be used to inform follow-up programming and expansion of male-circumcision services.

Like informed consent, documentation of results dissemination is best practiced as an ongoing process—not a one-time event. However the early, transparent, and proactive response at the Kisumu site is an important initial element. The price tag for this extensive effort was less than 1% of the overall trial budget, and yet its importance cannot be over-emphasized.

Disseminating trial results needs to happen in all trials and at all stages of development. The AIDS vaccine field should take note of these approaches.

[9] Building a Comprehensive Response: Funding for HIV Vaccine, Microbicide and New Prevention Tools Research and Development (July 2007). www.hivresources.org

Key principles to take forward in future trials include:

- **Develop and fund a results-dissemination plan. This should be a standard part of all trial planning—and not an ad hoc activity as the trial draws to a close.**
- **Use multiple media channels to translate results for trial participants and the broader community.**
- **Document participants' questions about and understanding of the trial results following dialogue with site staff.**
- **Plan for follow-up and ongoing exploration of community understanding of research results as scale-up begins.**

Expanding the standard of prevention in trials to include new proven strategies

In late 2006, while the world was anticipating the results from Kenyan and Ugandan trials of male circumcision for HIV prevention, South African principal investigators on the Phambili vaccine trial decided to move ahead by offering male circumcision to trial participants. The leaders of the Phambili trial, also known as HVTN 503, decided to offer the intervention to all enrolled male trial participants on the basis of the evidence from the South African trial of male circumcision for HIV prevention, which took place in Orange Farm and showed that circumcision substantially reduced men's risk of HIV infection via vaginal sex.

ENGAGING AFRICAN-AMERICANS IN HIV-PREVENTION RESEARCH: 17 PERCENT IS NOT GOOD ENOUGH

The numbers are growing too familiar. And yet they bear repeating: African-Americans make up 13% of the US population and more than half the HIV infections in this country. AIDS is the leading cause of death for black women aged 25-34 years[10]. Rates of HIV in some communities of color tell a tale of an unchecked epidemic that resembles or outstrips what is seen in sub-Saharan Africa. This is particularly true for poor and drug-using women and men who have sex with men.

Logic and ethics tell us that the prevention resources and prevention research dollars deployed in America should focus on where the epidemic is most severe. It should be easy to measure this: Are we seeing rates of new infections going down? Is funding for HIV-prevention education high enough so that *all* issues and identity groups are reached?

And we must also ask, Are the resources of the HIV-prevention research enterprise being optimally used to contribute to an effective response to this particular epidemic? A recently published review found that African-Americans accounted for 17% of the total in all Phase I and Phase II studies sponsored by NIAID from 1998 to 2002.[11] Low rates of enrollment in large-scale trials will not give statistically significant answers on vaccine effects in non-white subgroups. This happened in the VAXGEN study of an AIDS vaccine candidate, and could happen again in future trials.

Clinical trials should aim to enroll participants in proportions that reflect the groups hardest hit by the epidemic. That means African-Americans should be close to, if not over, one-half of participants in prevention trials. This takes work with and by communities: a broad acceptance of and commitment to prevention research is necessary before members of any community will consider enrolling in trials in large numbers.

It is also a matter of equity. In a setting of scant US resources for comprehensive, evidence-based, prevention programming and caps on NIH research dollars, we must be certain that the work that is done in the US reflects the needs and priorities of women and men of color.

In the coming year, AVAC will conduct a systematic analysis of the contributions of the HIV-prevention research field in addressing the African-American AIDS epidemic. We will use this analysis as the basis for advocacy in collaboration with other groups looking at this critical issue.

[10] WISQARS Leading causes of death reports, 1999–2004. Available at:http://webappa.cdc.gov/sasweb/ncipc/leadcaus10.html. Accessed July 27, 2007.

[11] G. Djomand et al. Enrollment of racial/ethnic minorities in NIAID-funded networks of HIV vaccine trials in the United States, 1988 to 2002. Public Health Rep. 2005 Sep-Oct;120(5):543-8.

Guy DeBruyn, one of Phambili's South African principal investigators, says that this circumcision trial, completed in 2005, provided a sufficiently compelling rationale for male circumcision in the South African context. He says,"For any study, part of planning is thinking about what could potentially be considered standard of care for prevention during the period when the trial is ongoing." Anticipating that the other trials would also find a protective benefit and foreseeing logistical challenges in adding the offer of male circumcision after the vaccine study was underway, the Soweto-based team decided to change the protocol. All men enrolling in the vaccine study were counseled about and offered a referral for male circumcision.

Since there were no points of service for adult male circumcision in the trial vicinity, the Soweto site had to build local capacity. The Soweto team worked with a quasi-private "wellness clinic" linked to the trial site and supported by funds from the US Agency for International Development and the President's Emergency Plan for AIDS Relief (USAID/PEPFAR). Until the South African government develops its policy on male circumcision (see Section 3 for more on this issue), the services cannot be set up in public-sector clinics. Clinicians from the Orange Farm trial trained local providers to perform the procedure, which is offered free of charge to all men who enroll in the Phambili trial. By late June, 11 out of the 65-70 men enrolled to date had opted for the procedure.

Phambili is the first example of a trial to take such a step and it is an ad hoc effort. At the moment, there is no official policy on or funding for inclusion of male circumcision in standard of prevention for trial participants at HVTN or IAVI, for example. However leaders at both entities say that if and when countries develop national policies, local trial sites will likely follow the Soweto lead in offering referrals.

In the South African case, the trial site team decided to add the offer—and build local capacity—before a government strategy was approved. This step was taken in a country where trail-blazing physicians—including Glenda Gray and James McIntyre of the Soweto site—and powerful activist communities have worked to spur a government to action on treatment access. In other settings, sites may not want to move ahead of governments.

Where epidemic conditions suggest that male circumcision could reduce incidence, can trial protocols omit the procedure simply because of government inaction? And when governments *do* develop a policy, is it sufficient to offer referrals without also building capacity at the first points of service?

These questions require careful consideration at the national and international levels.

Today, our position on male circumcision as part of the standard of prevention for biomedical HIV-prevention trials is as follows:

AVAC believes that the field of HIV-prevention research should be in the vanguard of implementing new, proven prevention strategies. Where epidemiology and rates of circumcision suggest that the procedure could reduce individual and community incidence, there is an ethical obligation on clinical trial sites to work with local and national partners to make the procedure available to participants and the broader community. This offering should follow recommendations from WHO/UNAIDS guidance documents on the subject, placing emphasis on abstinence until wound healing, couples counseling where feasible, and counseling about the need to continue using condoms and other risk-reduction strategies. Where government policies are still in formation or do not exist, trial administrators should partner with health ministries to ensure that trial-initiated services inform and are in line with the national approach as it is developed.

AVAC is committed to facilitating and participating in discussions on this issue, which will reemerge whenever data from other prevention trials become available, and to learning from the perspectives of other stakeholders.

SHIFTING STANDARD OF PREVENTION AND CLINICAL TRIAL CAPACITY: FORECASTING THE FUTURE

There are problems, and then there are "high-quality" problems—situations that we are glad to have to tackle, but which require careful troubleshooting nonetheless.

One high-quality problem, which may emerge soon, is how to budget for and conduct trials as the standard of prevention shifts and expands.

In clinical trial settings in sub-Saharan Africa, male circumcision drops HIV-negative men's risk of acquiring HIV by 60 percent. As mentioned previously, the Phambili vaccine trial in South Africa is already offering male circumcision to its participants, and we hope others will soon follow. The procedure is not mandatory, of course. But if there is high uptake and appropriate counseling, then incidence should go down in the study population.

When incidence goes down, trial size goes up. When size increases, so do the cost and the length of the trial. The numbers of additional volunteers and sums of money needed to adjust for decreased incidence may be substantial.

Recent years have already provided many examples of how lower-than-expected incidence, slower-than-expected recruitment, and regulatory delays can change trial timelines and sometimes shut down specific sites.

These unavoidable scenarios will be complicated further by data from new biomedical prevention studies, which could prompt changes in standards of prevention for both countries and clinical trials, and affect the behavior of individuals and populations.

Any time incidence goes down, it is a good thing. And any combination of strategies that does this should be embraced and widely deployed. At the same time, the AIDS vaccine field should take active steps to anticipate what it will need to meet this challenge.

Data on rates of uptake of male circumcision from the Phambili trial should be collected and used in preliminary models that forecast changes in trial size and impact on incidence for future studies. We need price tags and size estimates for trials that might take place in 10 or 15 years. This is the only way to ensure that clinical trial capacity investments will be sufficient.

Active, transparent, and expanded activities to address vaccine-induced seropositivity

Early in 2007, a young American woman participant in the Step study of Merck's Ad5 AIDS vaccine candidate visited her regular physician for hormonal contraception. The woman requested that the doctor not perform an HIV test—explaining that she was a participant in a study of a vaccine candidate that induced antibodies that could cause positive results on standard diagnostics for HIV infection. Unaware of these studies and unwilling to cooperate with his patient, the doctor performed the HIV test—and subsequently informed the woman that she was infected with HIV. Distraught, she reported this to the trial site, which performed more sensitive tests showing that the woman was HIV-negative. The "false positive" had been the result of a vaccine-induced immune response.

This woman's experience prompted concern among trial staff, the network, and community advisory boards—and dramatically illustrates the issues and potential harm of vaccine-induced seropositivity.

Most standard diagnostics for HIV look for the presence of antibodies to HIV envelope genes (env). MRK-Ad5 does not contain env. However, immunization does cause unusual or uncommon patterns on Western Blot tests—which lab technicians may interpret as a positive test result.

The planned test-of-concept study PAVE 100 is a study of DNA-adenovirus-based combination strategy with a multigene DNA prime and an adeno candidate that both include *env*—meaning that HIV-negative participants who receive the experimental vaccine could have test results that look exactly like those for people who are infected with HIV.

This is not a new issue. Informed-consent protocols for all trials of these vaccine candidates discuss the potential for vaccine-induced seropositivity. And all enrolled participants are counseled on an ongoing basis to seek HIV testing only from the trial site—which is equipped with diagnostics that can distinguish between HIV infection and vaccine-induced immune responses.

At present, US sites for the Step study are working on additional local education and outreach campaigns with community-based organizations funded through the NIAID HIV Vaccine Research Education Initiative (NHVREI).

But these activities are not sufficient. The burden of addressing this issue should fall on product developers and trial sponsors, who should commit resources to developing, field-testing, and scaling up information campaigns specific to the various contexts in which the trials take place. These campaigns should take into account local approaches to testing, including routine and mandatory testing protocols that may severely limit participants' ability to determine whether and when they are tested. It is therefore not enough to simply ask vaccine participants to avoid other testing sites, or to provide broad assurances that trials will provide support for harm associated with false positives during or after the trial.

Community groups, such as those funded by NHVREI, can help develop and disseminate these messages and should receive additional funding to do so. They should not be using their own funds, which are limited at best.

Responsibility also lies with public health authorities advocating for routine testing in health care settings, including the US Centers for Disease Control and Prevention and the World Health Organization. While there are potential benefits of expanded testing, there are also real issues with ensuring that all individuals—including vaccine trial participants—retain the right to refuse testing.

There are additional challenges after the trial is over. The site could offer testing to verify or rule out HIV infection as long as the site continues to operate. But even then, participants may move far away and be unable to travel back.

The field has started to respond to this issue. NIAID recently held a two day meeting on the issue, and has put forward a "request for proposals" (RFP) for work on alternative diagnostics that would only detect HIV infection, and would not give a positive result for vaccine-induced immune responses. The US Military HIV Research Program has committed approximately US$1 million for this fiscal year and FY2008 to further explore the issue, looking at nucleic acid testing as one strategy for diagnosing true HIV infection.

This attention is fully warranted and perhaps even overdue. PAVE 100, which will likely launch in the next 12 months, plans to enroll approximately 8,500 people in sites around the world, including several countries like Kenya, Uganda, and South Africa, where routine HIV testing is rapidly expanding in health care settings.

We look to Merck, the US Military HIV Vaccine Research Program, HVTN, the PAVE partners, and all other product developers with candidates to build on their current efforts to accomplish the following:

- **Dramatically expand awareness campaigns about vaccine-induced seropositivity, targeting testing facilities and laboratory technicians in the vicinity of trial sites.**
- **Disseminate concrete plans for strategies to address the issue, shared with and informed by communities where trials will take place.**
- **Ensure rapid, well-funded action on feasibility of novel diagnostics that do not detect antibodies to AIDS vaccines, such as the next-generation EIA assay from Abbott, which does not contain *env*, and the HIV-SELECT test developed specifically for this reason by Hanna Golding at the US Food and Drug Administration (FDA).**
- **Evaluate pilot mechanisms to address participants' long-term needs (including specific forms of testing and verification of trial participation) after the trial has finished.**
- **Create a shared registry for tracking and capturing individuals' adverse experiences.**

Figure 11. COUNTRIES WITH AIDS VACCINE TRIALS (AUGUST 2007)

NEW NIH FUNDING STRUCTURES: THE JURY IS OUT

While there have been many instances of creative, exciting, and informative activity on clinical trials this year, we end this chapter with a note of caution regarding the new funding structure for National Institutes of Health sites funded through the Division of AIDS (DAIDS). This includes sites participating in the HIV Vaccine Trials Network (HVTN), the HIV Prevention Trials Network (HPTN), the Microbicide Trials Network (MTN), the IMPAACT (which studies parent-to-child transmission), and the Adult AIDS Clinical Trials Group.

Last year saw the end of a process in which all of the existing networks submitted applications for renewed funding—and new networks also applied for NIH support. All of these networks receive their NIH funding through DAIDS.

When the dust had settled on a long and at times controversial process, NIH-funded prevention networks included the HVTN and the HPTN, which were re-funded, as well as the newly created Microbicides Trials Network (MTN), and the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) group, whose focus includes prevention of parent-to-child transmission of HIV and testing of vaccines in adolescents. The Adult AIDS Clinical Trials Group was also re-funded.

With new funding came new approaches to delivering it. In the past, sites have received fully-funded budgets that were not tied to specific performance indicators. The bulk of the money for prevention research trials was allocated to the sites and the network coordinating centers, leaving a relatively small balance at DAIDS. These two conditions meant that money—sometimes large amounts—went to sites that recruited few patients or sometimes were not even involved in trials at all. It also meant that DAIDS had limited flexibility to move funds in response to emerging data or urgent needs.

The new funding structure is designed to address both of these issues and to create an environment in which sites can participate in trials from multiple networks. (In NIH jargon, this is known as being a "pluripotent site.")

Under the new system, sites apply to participate in various trials. When a site is selected for a specific trial, it receives an allotment of core funding, the sum of which varies by site and depends on location, trial population, and type of trial that is being conducted. The sum is supposed to cover trial planning, initiation, and the recruitment of the first 20 volunteers into the study. Sites are then reimbursed on a per-participant basis for the remainder of the trial. In the past, sites have received full funding, regardless of their performance at recruiting.

In theory this new approach leaves DAIDS with a larger pot of money to use as a cross-network advisory board sees fit. As all DAIDS' available funds are presently committed to research, this pool of funds will only become available as current studies finish up, and remaining funds return to DAIDS for redistribution—i.e., for trials of emerging interventions that show promise but require additional investigation.

The new funding system also allows sites to participate in multiple types of trials, in theory a way to maintain capacity with fewer gaps as one study ends and another begins.

Flexibility at the central and site levels, and performance-based funding are excellent principles. DAIDS should be commended for implementing them.

However, at the moment, there are different views on whether the current system will achieve the desired ends.

On the one hand, experienced leadership say that it was time to overhaul a system in which too much money was spent with too little return. They also point out the important efforts that have been made to tailor the introduction of the system to the needs of various networks. With HVTN in particular, NIAID anticipated that challenges might emerge and permitted the core of operations to redirect some of NIAID funding to the site level.

However, in these early days, experienced sites working under the new system have reported serious problems in overall planning, retention of key trial staff, and maintenance of community outreach and education activities. The resources HVTN core has shifted have helped to cover some of these shortfalls, and more of the kinks in the system may be worked out over time.

At this stage, it is important to monitor the effects of the new approach to see if sites' negative experiences persist, and, if they do, to react swiftly with changes that could help the system achieve its entirely laudable aims.

Based on what we have heard (all of the site staff we interviewed requested that their comments remain unattributed), the following issues should be tracked:

• **Provision of core funding that is sufficient to cover sites for the real time it takes to get a trial started.** Clinical trials are, by definition, unpredictable. Delays in the regulatory and ethical-approval processes can keep sites in a holding pattern for months after they were scheduled to start recruitment. Core funding that could comfortably cover a site for three months of preparation and start-up stretches very thin after six or nine months of unpredictable delays. **What to look at:** Site reports on funding gaps due to postponed trial launch—and documentation of how these gaps affected infrastructure, if at all.

• **Stability of staffing, especially for community outreach, education, and recruitment.** Sites have told us that the per-participant recruitment approach makes it difficult to plan ahead financially and, that in this climate of uncertainty, staffing levels are difficult to maintain. We heard particular concerns about hiring and retaining enough recruiters. One individual told us, "It is difficult to know what the budget is for the year and thus hard for me to say we can afford another recruiter or counselor." Understaffing community education can slow recruitment and lead to the loss of experienced workers who may seek jobs with less uncertainty and greater financial stability. **What to look at:** Rates of site staff turnover and desired versus actual staffing levels.

• **Recruitment of hard-to-reach populations.** Around the world, HIV incidence is highest among populations who can be hard to recruit and retain in clinical trials. This

NOT THERE YET: A CALL FOR GLOBAL CONSENSUS ON STANDARD OF PREVENTION AND LEVEL OF CARE

The lack of international consensus on trial sponsors' obligations regarding HIV treatment for individuals and communities involved in HIV-prevention trials continues to harm the field and jeopardize its trials. The overwhelming majority of ongoing microbicide and vaccine trials have stated policies in which the sponsor commits to ensuring access to antiretroviral medications to individuals who seroconvert. However, these policies are untested in the field. Ongoing studies have had relatively few seroconversions. (This is expected: as an example, fewer than 250 seroconversions are expected in the two test-of-concept trials of Merck's vaccine, combined.) There have been no published reports evaluating how the system met the needs of individuals diagnosed during trials and who did progress to the point of starting antiretroviral therapy (ARVs). For individuals who are newly-diagnosed and do not qualify for ARV, it should still be possible to document the degree to which they were (or were not) linked to facilities providing other essential elements of care such as opportunistic-infection prophylaxis including cotrimoxazole, treatment for sexually-transmitted infections, TB diagnosis and treatment, and positive prevention.

We must move beyond an ad hoc approach, to a genuine consensus. The revised UNAIDS guidelines on ethical conduct of HIV-prevention trials provide a framework for these discussions. The guidelines distinguish between the "standard of prevention" that trial sponsors are ethically obliged to provide to all participants, and the "level of care" for seroconverters, of which ARVs is one component. This guidance document provides a strong foundation for all future work in this area.

In addition to addressing what will be provided to participants, trials must deal forthrightly with what will and will not be made available to community members who do not or cannot enroll in trials. For example, if male circumcision is made available via a trial-supported referral center for participants, the procedure should be free and high-quality for all community members in the surrounding area. Trial sponsors do not have to shoulder the financial burden for all service provision, but should work with local partners to build the needed systems. This has been done in several settings.

University of San Francisco researchers Nancy Padian and Bernard Lo provided an excellent, succinct statement on this obligation regarding ART treatment in a recent article in *AIDS*, stating, "Providing antiretroviral therapy (ART) to participants who seroconvert during HIV-prevention trials in developing countries is an ethical expectation. Promising treatment to the few seroconverters widens disparities within a resource-poor country and would be unjust. Such an assurance should be done in a way that also improves access to ART for others in the country."[12]

We agree, and broaden this statement to include a full range of prevention services and treatment offerings.

[12] B. Lo, N. Padian, and M. Barnes. (2007). The Obligation to Provide Antiretroviral Treatment in Prevention Trials. AIDS, 10: 1229-1231.

Table 4. TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE				
Country	PrEP	Herpes Suppression	Microbicides	Vaccines
AFRICA				
Botswana	•	•		
Cameroon			•	
Kenya			•	•
Malawi			•	•
South Africa		•	•	•
Tanzania			•	•
Uganda			•	•
Zambia		•	•	•
Zimbabwe		•	•	•
ASIA				
China				•
India			•	•
Thailand	•			•
AUSTRALIA				•
			•	•
EUROPE				
France				•
Sweden				•
Switzerland				•
Russia				•
United Kingdom				•
LATIN AMERICA & THE CARIBBEAN				
Dominican Republic				•
Haiti				•
Jamaica				•
Puerto Rico				•
NORTH AMERICA				
Canada				•
United States	•	•	•	•
SOUTH AMERICA				
Brazil				•
Peru	•	•		•

includes poor, marginalized, and criminalized groups in every country. Experienced sites say it takes time, consistent staff, and ongoing community outreach to build the trust that's needed to make a trial possible. If the new system does lead to scaled-back staffing or shorter contracts for some key staff, this type of ongoing work may be more difficult to perform. On the positive side, the DAIDS system does offer higher reimbursements for harder-to-reach populations. **What to look at:** Percentage of trial participants from hard-to-reach high risk groups such as poor, drug-using African American women, and gay men of color in the United States.

Any change to an established system is bound to raise complaints and concerns, and it may be that DAIDS and the networks will be able to work out some of these initial issues. But with an upcoming vaccine trial involving 8,000-plus persons (PAVE 100) and the real possibility of increasing trial size as interventions like male circumcision start to bring down incidence in some communities, now is not the time to be taking chances with site capacity.

We hope that DAIDS will work with networks to gather the types of information listed above, and to respond to emerging issues.

Experienced sites have also said that they preferred an earlier system in which they predicted how many individuals they feel they will be able to recruit in a given year and fund them accordingly—with additional resources for recruitment over and above the initial target.

The question of how to ensure sufficient funding for quality community outreach and education is one which cuts across all networks. DAIDS and other trial sponsors could consider community outreach and education funds separate from trial budgets that would provide additional resources to sites for maintaining and expanding innovative work. For NIH-funded research, the cross-network coordinating Community Partners Group could take a leadership role in establishing such a fund and in ensuring that its allotments are well spent, so that they speed recruitment and contribute to the success of ethical trials.

WANTED: INPUT ON GOOD PARTICIPATORY PRACTICE GUIDELINES

Over the past year, AVAC has worked closely with UNAIDS and a group of activists, advocates, and HIV-prevention research trial staff from around the world on a new draft guidance document called *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials.*

This document aims to provide a systematic framework for stakeholders in HIV-prevention research to implement and evaluate community engagement in clinical trials.

The tool has been through one round of revisions and comments and is currently being widely circulated in revised draft form. Comments received by the end of September will be incorporated into an updated version, which will be released for use in the field.

The publication of this document is the beginning, not the end, of the process. We hope that wherever you live and whatever your relationship to HIV-prevention research, you will explore the document, use it, adapt it—and above all share your comments on how it could be improved or how it is helping you in the work that you do.

For more information contact gpp@unaids.org.

Table 5. TRIALS OF PREVENTIVE HIV/AIDS VACCINES WORLDWIDE (AUGUST 2007)

Protocol #	Start Date	Sponsor , Funder, Developer	Trial Site(s)	Participants #	Vaccine(s)	Clade
PHASE III						
RV 144	Oct-03	USMHRP, MoPH Thailand, Aventis, Vaxgen	Thailand	16,402	Prime: canarypox viral vector with *env* and *gag-pol* Boost: Env protein (gp120 subunits)	B A/E
TEST-OF-CONCEPT						
HVTN 503 (Phambili)	Feb-07	SAAVI, HVTN	South Africa	3,000	Adenovirus vector with *gag, pol, nef*	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 *gag, pol, nef*	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 *gag, pol*, ΔRT	C
HVTN 204	Sep-05	DAIDS, HVTN, VRC, Vical, GenVec	US, Brazil, South Africa, Haiti, Jamaica	480	Prime: DNA vaccine with *gag, pol, nef + env* Boost: Adenovirus vector with *gag, pol + env*	B A, B, C
ANRS VAC 18	Sep-04	ANRS, Aventis	France	132	5 lipopeptides with CTL epitopes from gag, nef, pol	B
PHASE I / II						
EV 03/ANRS Vac20	June-07	European Commission, ANRS	UK, Germany, Switzerland, France	140	Prime: DNA vaccine with *env* plus *gag, pol, nef* Boost: NYVAC-C	C
HIVIS 03	Dec-06	MUCHS, Karolinska Institute, SMI, Vecura, USMHRP	Tanzania	60	Prime: HIVIS DNA with *env, gag, rev*, RT Boost: MVA-CMDR with *env, gag, pol*	A, B, C, A, E
RV 172	May-06	NIH, USMHRP, VRC	Kenya, Uganda, Tanzania	324	Prime: DNA vaccine with *gag, pol, nef + env* Boost: Adenovirus vector with *gag, pol + env*	B A, B, C
PHASE I						
DVP-1	May-07	St. Jude's Children's Research Hospital	US	20	Prime-boost regimen with *PolyEnv, EnvPro, EnvDNA*	A, B, C, D, E
VRC 012	May-07	NIAID, VRC	US	35	HIV-1 adenovirus vector vaccine VRC-HIVADV027-00-VP: dose escalation and prime-boost with an HIV-1 adenovirus vector vaccine, VRC-HIVADV038-00-VP	A
DHO-0586	Oct-06	ADARC, IAVI	US	8	ADMVA with *env/gag-pol, nef-tat*	C
HPTN 027	Oct-06	Makerere University, Johns Hopkins University	Uganda	50	Canarypox viral vector with *env* and *gag-pol*	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 *gag, pol, nef + env* or Adenovirus vector with *gag, pol + env*	A, B, C
HVTN 065	Apr-06	DAIDS, HVTN, VRC, GeoVax	US	120	Prime: DNA plasmid with *gag, pro, RT, env, tat, rev, vpu* Boost: MVA vector with *gag, pol, env*	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 *env, gag, tat-rev, nef-RT*	C

Protocol #	Start Date	Sponsor , Funder, Developer	Trial Site(s)	Participants #	Vaccine(s)	Clade
PHASE I						
HVTN 064	Jan-06	DAIDS, HVTN, Pharmexa-Epimmune	US, Peru	120	Recombinant protein vaccine EP-1043 with *gag, pol, vpr, nef* and DNA vaccine EP HIV-1090 with protein containing T-helper epitopes from *env, gag, pol, vpu*	B
HVTN 068	Feb-06	DAIDS, HVTN, VRC	US	66	Adenovirus vector with *gag, pol + env* or DNA vaccine with *gag, pol, nef + env* followed by adenoviral boost	B A, B, C
HIVIS 02	Jan-06	Karolinska Institute, Swedish Institute for Infectious Disease Control, USMHRP	Sweden	38	Modified vaccinia Ankara (MVA) viral vector with *env, gag,* and *pol* to volunteers from HIVIS 01	A, E
RV 158	Nov-05	USMHRP, NIH	US, Thailand	48	Modified vaccinia Ankara (MVA) viral vector with gp160, *gag* and *pol*	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	156	Prime: Genevax Gag-2692 +/- IL-12 DNA adjuvant Boost: DNA plasmids with *gag* or RC529-SE and GM-CSF with *env, gag, nef*	B
*Env*DNA	May-05	St. Jude's Children's Research Hospital	US	6	Recombinant HIV-1 multi-envelope DNA plasmid vaccine with *env*	A, B, C, D, E
VRC 008	Apr-05	NIAID, VRC	US	40	Prime: DNA vaccine with *gag, pol, nef + env* Boost: Adenovirus vector with *gag, pol + env*	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 *env, rev, gag,* and *RT*.	A, B, C
EuroVacc 02	Feb-05	EU, Imperial College London, UK MRC Clinical Trials Unit, EuroVacc	UK, Switzerland	40	Vaccinia vector with *gag, pol, nef, env*	C
IAVI C002	Jan-05	IAVI, ADARC	US	48	Modified vaccinia Ankara (MVA) viral vector with *env/gag-pol, nef-tat*	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
HVTN 055	Sept-04	DAIDS, HVTN, Therion	US, Brazil	150	Prime: Modified vaccinia Ankara (MVA) viral vector with *env, gag, tat, rev, nef, pol* Boost: Fowlpox viral vector (FPV) with same genes as prime	B
HVTN 050/Merck 018	Jan-04	NIAID, HVTN, Merck	Thailand, Brazil, Haiti, Puerto Rico, South Africa, US, Malawi, Peru	435	Adenovirus vector with *gag*	B
HVTN 049	Dec-03	DAIDS, HVTN, Chiron	US	96	Prime: DNA vaccine with *gag, env* attached to microparticles Boost: Env protein (oligomeric gp140) + adjuvant (MF5	B
*Env*Pro	Jun-03	St. Jude's Children's Research Hospital	US	9	Recombinant Purified HIV-1 Envelope Protein Vaccine	D
PolyEnv1	Oct-97	St. Jude's Children's Research Hospital	US	18	Polyvalent Vaccinia Virus-HIV-1 Envelope Recombinant Vaccine	B, 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

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

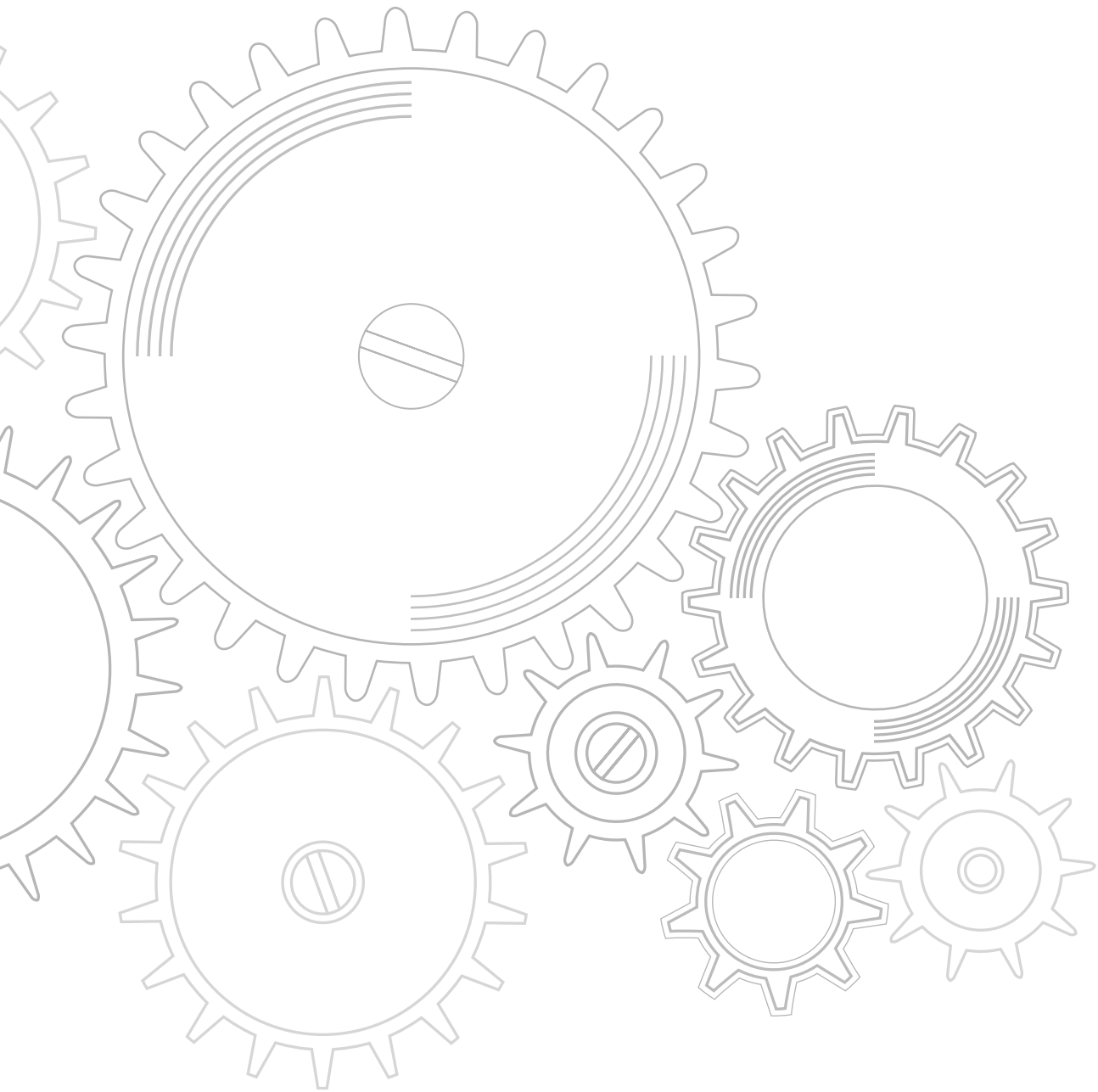
SMI: Swedish Institute for Infectious Disease Control

UK MRC: United Kingdom Medical Research Council

USMHRP: United States Military HIV Research Program

VRC: Vaccine Research Center

ZEHRP: Zambia Emory HIV Research Project




3

IN THIS SECTION

- Responses to male circumcision, HPV vaccine—and the lessons for AIDS vaccines
- Steps towards “implementation activism” on new strategies
- Critical thoughts on prevention research advocacy from other arenas of the AIDS response

SECTION 3

Wake-up Call

The clock is already running when it comes to implementing existing prevention approaches like male and female condoms, as well as emerging prevention strategies like male circumcision. HPV vaccine, while not an HIV prevention tool, is still an important case study. It is time to respond to the alarming rate of new infections—and to forge better links between various prevention arenas, in order to build momentum for effective change.

CAUTION AND CURIOSITY: WHY AREN'T WE STRIKING THE BALANCE WHEN IT COMES TO NEW PREVENTION TOOLS?

For many years, the AIDS vaccine and microbicide fields have been convening meetings and writing white papers exploring the issues that would arise in the event that an effective product was identified. Many hours and many thousands of dollars have been put towards these conversations about important, but wholly theoretical, issues.

Recently, AVAC has participated in discussions about the familiar topics of access, acceptability, and social and cultural implications of new interventions. But this time, discussions were definitely not theoretical. In the case of male circumcision for HIV prevention and of the HPV vaccine to prevent cervical cancer, the interventions have arrived—bringing issues that are all too real.

The responses to both of these interventions should provide a wake-up call to the AIDS vaccine field—and to all other stakeholders in HIV-prevention research.

While neither is a perfect model for the introduction of an AIDS vaccine or a microbicide, both HPV vaccine and male circumcision are test cases for global action on future biomedical HIV-prevention strategies.

It has now been more than six months since the data from the male circumcision trials were released. Over that period, some important steps have been taken:

- WHO/UNAIDS issued a document with recommendations on male circumcision.
- PEPFAR has allocated US$10 to 15 million in new money for countries to pilot and scale-up male circumcision.
- Some countries including Uganda, Kenya, and India have taken steps to convene national committees to review the implications of the data.

These are all critical steps in the path to country-level decision making around any new strategy. At the same time, what has been disappointing is the notable lack of urgency that has surrounded this activity. The scope of work and timeframe for findings from some of the national committees are poorly defined. And there have been no public statements from either developing-country governments or civil society groups regarding the need to rapidly assess and, if appropriate, introduce this strategy as part of a comprehensive response to the epidemic and the acknowledged crisis in prevention.

Some caution is certainly appropriate, since we do not yet know the full risks of implementing adult male circumcision on a large scale in resource-constrained areas where a wide range of health care providers and healers will be involved in these procedures. We also do not know how circumcision of HIV-positive men affects the likelihood that they will transmit to their partners, or how to effectively introduce male circumcision so that it complements, and does not detract from, other prevention strategies. There

are also major gaps in information about how male circumcision rollout might affect gender dynamics and women's ability to negotiate condom use. We also do not know about the protective benefits, if any, of male circumcision in the context of anal sex.

But these unanswered questions are not insurmountable obstacles. They are opportunities for advocacy. If the impediment is a gap in knowledge, then let us hear clear demands for these questions to be answered. AVAC developed its own statement on research priorities around male circumcision (available at: http://aidsvaccineclearinghouse.org/pdf/MC/AVAC_MC_scientific_statement.32807.pdf) and is eager to work with partners to further refine it and move it forward as an advocacy tool.

Instead of clear calls to understand the appropriateness of this new strategy as part of the AIDS response in different settings, there are a multitude of cautionary and sometimes outright skeptical voices.

Consider, for example, the statement jointly released by the African Council of AIDS Service Organizations (AfriCASO), Network of African People Living with HIV/AIDS (NAP+), and Society for Women Against AIDS in Africa (SWAA), which reads

The three community networks hereby acknowledge circumcision as a comprehensive care package. [sic]

However, the community members hereby demand:

No diversion of resources from other treatment, care and prevention interventions to circumcision. We cannot afford to lose resources that would otherwise go to universal access to start parallel circumcision intervention. We need to be assured that there will be extra funds for this intervention.

Circumcision must be implemented in the context of universal access. In other words, targets must be set within the universal access framework.

No vertical programmes should be implemented. Circumcision should be implemented as part of a holistic approach to treatment, care, prevention and testing and should include transformational sexuality counseling, and access to condoms. In other words, circumcision must not be presented as an end in itself but part of a prevention and care consortium.

Monitoring: the potential negative effects of circumcision programmes should be monitored, especially the way in which women are treated sexually as a result of men having undergone circumcision.

HIV+ men should not be discriminated against or turned away from circumcision programmes; this could lead to further stigma and discrimination.

This is a strong statement. It succinctly identifies issues that are critical to the implementation of male circumcision. All of the cautionary elements are warranted and must be attended to if male circumcision is to be a success.

And yet, there is a lack of curiosity or even enthusiasm about this new finding, in spite of its potential benefits as a new prevention tool.

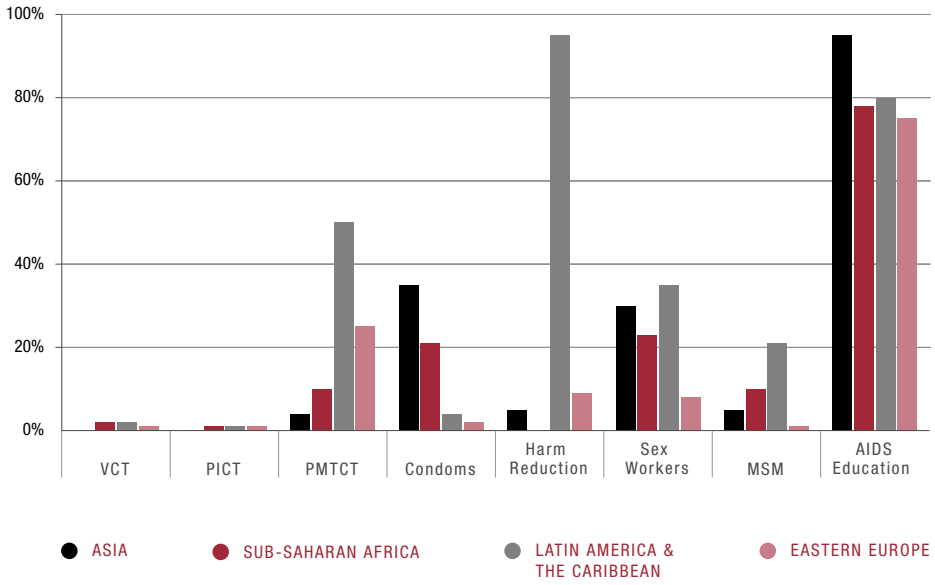
At this year's South African AIDS Conference, local health professionals made a call for circumcision and were greeted with skeptical public remarks from health minister Manto Tshabalala-Msimang. In one news story, prevention researcher Glenda Gray said, "I am surprised there is no action on male circumcision. Where are the male activists?" In the same article, one of Gray's colleagues noted the "deafening silence" around the intervention[13].

And so, while there are plenty of voices saying, "*If* it is done, male circumcision must be done well," there are very few voices saying, simply and firmly, "Male circumcision *must* be done."

Male circumcision has robust supporting data, shows a high level of efficacy, and is a one-time procedure. In contrast, a vaccine is unlikely to have three tightly corresponding efficacy trials (as male circumcision did) before it goes to licensure. And it will probably be many years before we find a single shot that offers 60% reduction in individual risk (as male circumcision has been shown to provide).

[13] Blandy, F. Doctors urge mass circumcision for AIDS-hit South Africa. *Agence France-Presse.* Available at http://www.aegis.com/news/afp/2007/AF070616.html. Accessed July 31, 2007.

Figure 12. COVERAGE OF ESSENTIAL PREVENTION SERVICES*



* *"Bringing HIV Prevention to Scale": An Urgent Global Priority* (June 2007). Global HIV Prevention Working Group

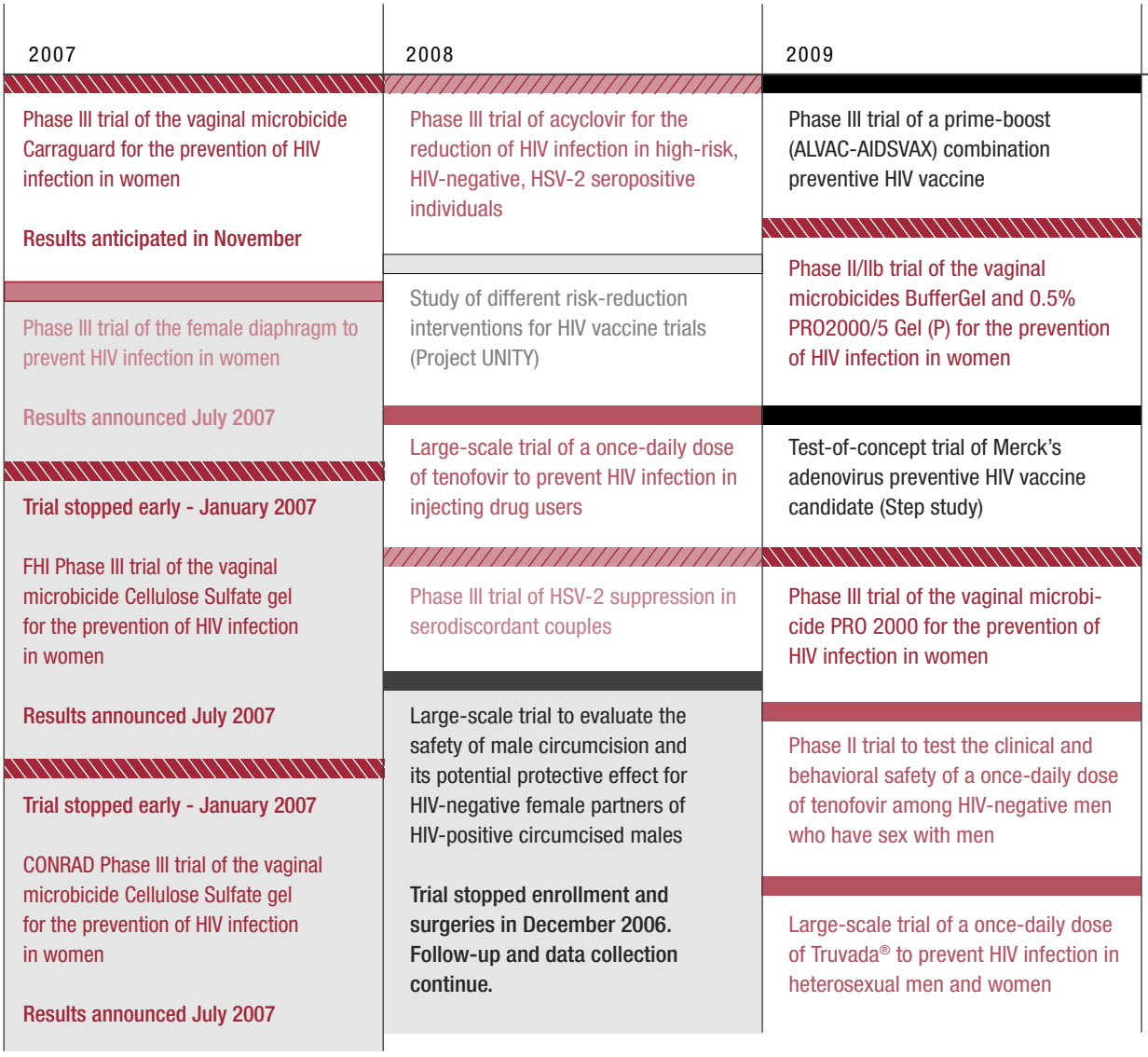
What is happening now with male circumcision and, to some extent, with HPV vaccine (see p.54) can and will happen repeatedly with other partially-effective interventions currently under investigation including vaccines, microbicides, pre-exposure prophylaxis (PrEP), and HSV-2 treatment (see timeline p. 52-53), unless we take this opportunity to learn from experience and take the following actions:

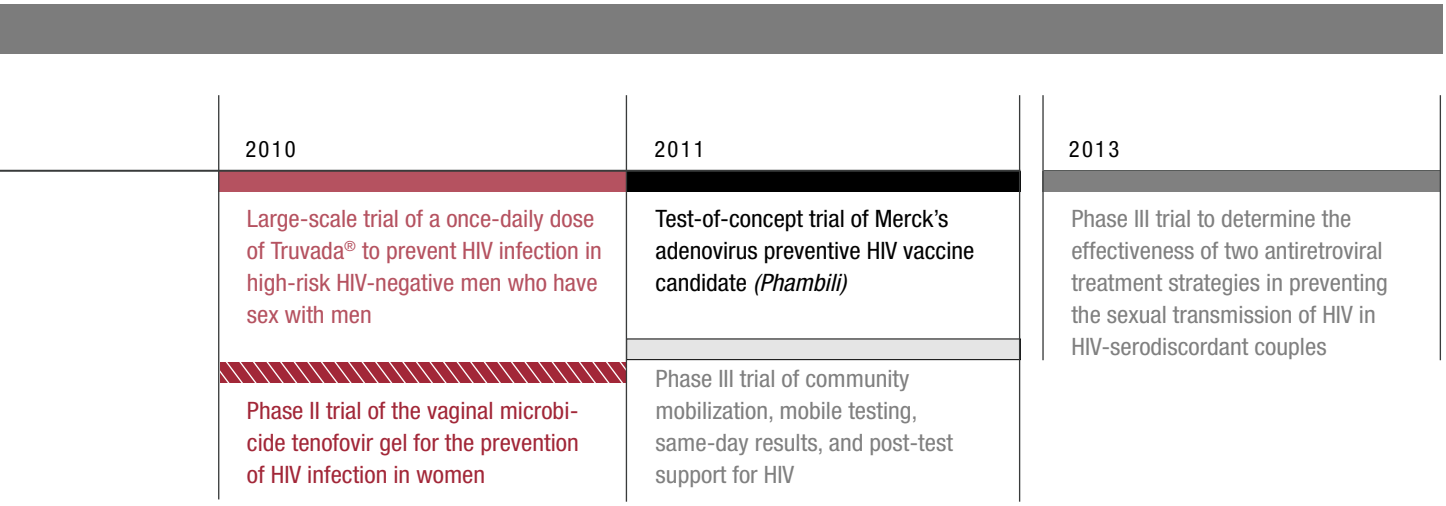
• Define and follow clear pathways for moving from efficacy results to implementation. Groups that fund and conduct clinical trials lack the expertise and the resources to move to programmatic implementation. And yet, the gap between WHO/UNAIDS guidance and developing-country action must be filled by a better and more coordinated response from a range of stakeholders. This means clear expectations about the timelines for national consultative processes, collective planning around operational research, and proactive outreach to civil society groups before national plans are developed.

• Support—and demand—developing-country leadership on prevention. Implementation of new prevention findings should take place in the context of strengthened national prevention programs. These must be created and owned by developing countries. They should be ambitious, innovative, and forward-looking with regard to incorporation of new prevention approaches if and when they are identified. Without this flexibility, countries may be bound by five-year plans that do not reflect the latest available information on either the epidemic or the tools available to fight it.

• Improve understanding of partial efficacy. Male circumcision reduces men's risk of infection during vaginal sex by up to 60%. The first-generation microbicide trials are powered to detect efficacy of 33%, and the current test-of-concept AIDS vaccine studies (see Section 1) are looking for effect on viral load in people who receive the vaccine and become infected. There are compelling arguments, including mathematical models, that say that partially-effective interventions will have an important impact on specific epidemics—particularly when combined. And yet, most of the world sees partial efficacy as a half-empty glass: an intervention that is not worth investing

Figure 13. HIV PREVENTION RESEARCH: A COMPREHENSIVE TIMELINE OF EFFICACY TRIALS*





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

HPV VACCINE: WORRYING DELAYS AND CHALLENGES TO ROLLOUT

It has been just over one year since Merck announced the licensure of Gardasil®, its quadrivalent vaccine that blocks infection with four strains of human papillomavirus that can cause genital warts and cervical cancer.

The vaccine is an important tool in its own right. Globally, HPV-related cervical cancer affects some 470,000 women annually and kills 270,000. Cervical cancer is the leading cause of cancer death among poor women in sub-Saharan Africa, where screening and treatment services are rarely available.

AVAC Report 2006 discussed the many ways that HPV vaccine was relevant to the field of AIDS vaccines. Effective delivery of this existing tool has much to teach us about how to reach adolescents and school-age children, who might also be targets of an eventual licensed vaccine.

One year later, there has been some progress. July 6, 2007 saw the launch, in Nairobi, Kenya, of a global call to action to accelerate access to cervical cancer screening and treatment—including but by no means limited to the vaccine (for the text, see www.cervicalcanceraction.org).

At the same time, Merck and GlaxoSmithKline (GSK) (which also has an HPV vaccine in development) have yet to clarify their pricing structure for these vaccines in the developing world. One year ago, the companies were saying that they were committed to radical price reductions. More recently, Merck has stated that it will make the vaccine available "at cost."

But these promises are not enough to prompt developing countries to action—with limited resources, multiple priorities, and concerns over sustainable financing, a broad commitment to lowered prices is simply not enough. By the same token, industry insists that demand estimates from poor countries are essential to clarifying the price structure.

This stalemate is leading to worrying delays. Merck and GSK must put a precise figure to their "at cost" commitments and clarify how a tiered pricing structure might be used. At the same time, developing-country stakeholders and middle-income countries must work to make HPV vaccine access a front-burner issue.

The United States has seen Merck backpedal from initial work toward making the vaccine mandatory for school-age children. Many other immunizations are mandatory for school attendance and there is a strong rationale for immunizing school-age girls before their age of sexual debut. However, there has been resistance on many fronts—from conservative groups worrying about the vaccine promoting sexual promiscuity, states that may be worried about the logistics and politics of introducing the vaccine, and communities' concerns about a new vaccine—when long-term data on safety and protection do not yet exist.

And yet, if steps are not taken to address all of the issues—cost, community concerns, pricing, and many more—in developing and developed countries, then the story of HPV vaccine runs the risk of being the next chapter in the history of how effective vaccines have failed to reach the people who need them most for decades after their discovery.

in. Investments must be made in communications, pilot projects, and expanded modeling to ensure that findings of partial efficacy are translated to potential public-health benefits.

• Improve collaboration and communication between prevention-research advocacy groups and groups working on implementation of HIV treatment, proven HIV prevention, sexual and reproductive health, and other issues. The major advances in approaches to AIDS treatment and care have come as a result of highly-mobilized activist groups demanding accountability from governments and donors. Right now, these groups are largely focused on implementing existing strategies—leaving prevention-research advocacy to a handful of groups. When it comes to implementation, we all need to be working together. Those on the prevention-research side must demand increased access to what already exists. Those on the implementation side must consider the possibilities of new strategies—without dismissing them outright.

AVAC is committed to working in partnerships with other groups to achieve these goals. It is clear that there are major gaps in the translational work needed to turn communities, civil society groups, policy-makers, and political leaders into champions of new interventions.

In the coming year, AVAC will document responses to male circumcision data—and other studies as they come online—to identify best practices and gaps in countries where the trials have been taking place.

There is also a need for new funds and a coordinated operational-research agenda to answer questions about interventions as they come online.

Donors and developing-country governments need to work jointly to develop an operational-research agenda around male circumcision and ensure full support for relevant WHO/UNAIDS work plans.

As these questions are being answered, advocates, communities, organizations of medical professionals, and HIV/AIDS organizations must begin to mobilize demand for innovative, comprehensive service provision of new and old prevention approaches. Yes, there are caveats and infrastructure challenges. But this has been true with every biomedical element of the AIDS response: from antiretroviral (ARV) treatment, to prevention of mother-to-child transmission (PMTCT) programs, to condom distribution. These are partial solutions and often more flawed than they should be. But prior experience and past failures cannot be used as an excuse for abandoning new findings when they emerge. They are, more than anything, a clarion call to do better.

To begin to develop common ground on advocacy for new prevention strategies, AVAC will work in the coming year, to convene dialogues among groups working in multiple disciplines and countries. Our emphasis will be on countries where research has taken place and on bridging the gap between prevention-research advocates and advocates working on service delivery and access to proven strategies.

We acknowledge that the prevention-research arena must earn the trust and support we are calling for. Biomedical strategies will not succeed without structural changes to poverty, gender-based violence, discrimination, and other pervasive social ills. One-shot interventions will not solve problems in communities that lack basic health care.

If we are to stem the global tide of new infections and improve on the deplorable rates of service delivery shown on page 51 we must build comprehensive prevention programs that provide existing services well *and* can accommodate new emerging strategies as they come on line.

There is a well-documented gap between clinical trial results and public-health programs. This can be bridged by advocacy, new financial commitments, and innovative programs that are informed and owned by the communities where they are being introduced. As male circumcision and, to a lesser extent, HPV vaccine illustrate, without these contributions, this gap can also turn into an abyss. When this happens, the benefits of new strategies—including future, first-generation AIDS vaccines—may be dramatically reduced or lost outright to all.

COMPREHENSIVE HIV PREVENTION: TURNING OUR FAVORITE RHETORIC INTO REALITY

The AIDS epidemic has spawned its own vocabulary—an alphabet soup of acronyms and abbreviations and a kaleidoscopic array of catch phrases for strategies and approaches. The danger with any of these phrases is that they will be used so often as to become meaningless—or they will be used in policy documents without being put into practice.

This year, the phrase most in danger of becoming empty before it has even been tested in the field is "comprehensive prevention package." AVAC has used it throughout its documents, as have many others in the field. What do we mean by it? UNAIDS has developed this definition, which we have reprinted below.

Components of Comprehensive HIV Prevention

In assembling a national HIV prevention plan, each country should prioritize access to proven prevention strategies, tailoring the targeting and scale-up of HIV prevention to particular national circumstances and needs. The roster of proven HIV prevention approaches includes a range of measures:

Preventing Sexual Transmission

- Behavior-change programs (to increase condom use, delay initiation of sexual behavior in young people, and reduce the number of partners)
- Condom promotion
- HIV testing
- Diagnosis and treatment of sexually transmitted infections (STIs)
- Adult male circumcision

Preventing Blood-Borne Transmission

- Provision of clean injection equipment to injection drug users
- Methadone or other substitution therapy for drug dependence
- Blood safety (including routine screening of donated blood)
- Infection control in health care settings (including injection safety and universal precautions)

Preventing Mother-to-Child Transmission

- Primary HIV prevention for women of childbearing age
- Antiretroviral drugs
- Breastfeeding alternatives
- Caesarean delivery (in the case of high maternal viral load)

Social Strategies and Supportive Policies

- HIV awareness campaigns (including mass media)
- Anti-stigma measures
- Gender equity and women's empowerment initiatives
- Involvement of communities and HIV-infected individuals
- Visible political leadership
- Engagement of a broad range of sectors in HIV awareness and prevention measures
- Legal reform to create an environment supportive of HIV prevention (such as laws decriminalizing needle possession)

EXPLORING RESPONSES TO TODAY'S NEW PREVENTION INTERVENTIONS

As the foregoing section described, many advocates in the civil society arena have greeted the new findings in HIV prevention with far more caution than enthusiasm. Why the ambivalence? For this year's AVAC Report, we asked impartial observer and longtime AIDS reporter, Anne-christine d'Adesky to conduct interviews with more than a dozen leading AIDS activists and advocates to learn their views of the prevention-research landscape. In the article that follows, she reports on her findings.

In 2006, there were 4.3 million new infections, spanning every region of the world. HIV incidence has increased in the past two years, according to UNAIDS, which estimates that less than one in five people at risk for HIV infection have access to basic prevention services, and only one in eight who wants access to HIV testing can get it.

Equally sobering is that for every one person started on effective antiretrovirals in a given year, there are six new HIV infections. These statistics have human faces: poor women, people living in conflict zones, refugees, children, men working in mines far away from home.

The potential of prevention strategies to make a global impact on the AIDS epidemic is also huge: with universal access to existing prevention strategies some 28 million new infections could be averted between 2005 and 2015, saving US$24 billion in associated treatment costs.

But while there is strong consensus on the need to improve prevention everywhere, there is a great range of opinion on how to do it. And outside of the relatively small world of advocacy for HIV-prevention research, many veterans of the fight for treatment and prevention view new biomedical strategies with ambivalence.

In multiple conversations a set of core concerns emerged:

- **New prevention may divert resources from existing strategies.**
- **Biomedical advances may detract attention from context-specific, structural issues that contribute to vulnerability to HIV/AIDS.**
- **Emerging partially-effective methods may be difficult to introduce in effective ways and without causing confusion and abandonment of other prevention methods.**
- **Leadership is lacking in the prevention field and—according to some—there is a sense that prevention-research advocacy groups may be too closely aligned with researchers.**

These issues look and sound different in different communities; not all of them were voiced by all of the individuals interviewed. But taken together, they constitute a bracing wake-up call for the field of prevention research. Below is more of what we heard.

Concerns around implementation and messaging

"The information as such is really exciting and promising," said Asia Russell of Health GAP, a US-based group dedicated to expanding access to HIV treatment and improved healthcare worldwide, referring to the evidence that male circumcision can reduce risk of HIV infection among HIV-negative men. "But what are also clear are the sorts of challenges that will exist at the level of implementation and at the community, in scaling up, to assure effective and ethical access."

In a breath, Russell ticked off a litany of concerns, "It's everything from ensuring voluntary access by men to the technology, to structural concerns around safe deployment—literally training health care providers, both professional and paraprofessional—to unanswered

questions about how women benefit from this technology, and also these unanswered scientific questions." She warned, "There's a risk of doing more harm than good" to vulnerable groups, if such issues aren't addressed.

The notion that new prevention strategies—particularly partially-effective ones—could do more harm than good echoes throughout conversations on different experimental options.

"Until we get an effective vaccine against the HIV virus itself, caution must be exercised at all times while promoting [experimental] interventions that [may] provide very little protection," says Milly Katana, a Ugandan AIDS activist and former representative of NGOs from the Global South on the board of the Global Fund to Fight AIDS, Tuberculosis and Malaria.

> *"Until we get an effective vaccine against the HIV virus itself, caution must be exercised at all times while promoting [experimental] interventions that [may] provide very little protection,"*
>
> —Milly Katana, Ugandan AIDS activist

Prevention-research advocates acknowledge obstacles to rolling out new strategies in a way that strengthens service provision of existing interventions. Likewise, considerable thought has been devoted to communication strategies that emphasize the limitations, as well as the potential benefits, of existing interventions.

And yet the current dialogue around male circumcision and future strategies suggests that, to some extent, this work has not translated into a common agenda that encompasses research and implementation of prevention and treatment.

Lack of leadership

"Prevention is struggling to find its place in the global response to HIV/AIDS," says Katana. "Whereas WHO [World Health Organization] is now clearly taking leadership on treatment, it is not clear who is leading on prevention. Efforts are spread out between UNAIDS and UNFPA [United Nations Population Fund]. The gap is, from time to time, filled by self-seeking individuals, groups and organizations."

Questions about the motives for groups conducting and advocating for research are real ones. Outside observers sometimes miss distinctions between organizations working in the tight community of prevention research. For example, some activists do not distinguish AVAC and AMAG [African Microbicides Advocacy Group] from the groups sponsoring the trials and developing the candidates.[14]

"I think there is a larger issue which is, 'Who is really leading the advocacy movement right now, period?'" said Judy Auerbach, PhD, Director of Advocacy at the San Francisco AIDS Foundation. "Globally, there is AVAC and the Global Campaign for Microbicides, and various technology-specific or strategy-specific [groups]." Turning to the US, she added, "It would be very hard for you and me to name the leading organization in the states around domestic advocacy. There is CHAMP [Community HIV/AIDS Mobilization Project] and other groups, but it is very hard to say who is at the helm of prevention advocacy. I think we have to define who the *we* is…is there an identifiable leadership?"

Despite over 25 years of prevention activism, there is no clearly-defined prevention movement with a comprehensive agenda and clear global messages. Rather, there is a smaller flotilla of single-topic advocacy and scientific groups that have pushed forward various issues related to global prevention, and have done so admirably in the face of resistance by

[14] Here at AVAC, we are well aware that receiving major support from the Bill & Melinda Gates Foundation, which also supports research, can be seen as complicating our role as a field-wide watchdog. We are committed to our independence and an uncompromising advocacy agenda; we welcome suggestions, constructive criticism, and allies in our work.

the Bush administration, which has emphasized abstinence over evidence-based prevention strategies.

In practice, this has meant that some groups have focused on accelerating HIV-prevention research while others have worked on safeguarding and expanding access to proven prevention. Prevention-research advocacy efforts have been further diluted among different strategies: microbicides, vaccines, etc.

Today, these efforts are weakening the broader AIDS response. On the prevention-research side, the development of constituencies for vaccines and microbicides has left other interventions like male circumcision or, potentially, HSV-2 treatment, without vocal groups of informed advocates.

On the implementation side, groups that have focused on proven prevention are among the most cautious when it comes to embracing new interventions, in part because they have been worn down by years of fighting the Bush administration's policies and funding cutbacks.

Tensions between structure and science

Gregg Gonsalves is a veteran, openly HIV-positive activist who recently moved to South Africa after years of working in New York City, another early epicenter of AIDS. He is concerned that technology is driving the current prevention agenda—and steering it in the wrong direction.

"My big concern here is the collapsing of HIV prevention into medical/technological 'fixes,'" said Gonsalves. "Climate change is possible—that is, changing the climate of risk of HIV infection is possible, but not if we think that we have to wait for a vaccine or microbicide, or that a condom or circumcision alone is going to change the reality of people's lives or how resources are distributed in countries. I think we can mobilize people around HIV prevention, but it first and foremost has to be about mobilizing them around issues that confront them on a daily basis."

By the same token, there is concern that emphasis on structural factors will detract from immediate responses. A recent communiqué from the International Sex Workers Project and a range of other signatories slammed UNAIDS for issuing a draft guidance note on HIV and sex work that suggested that structural responses and improved HIV prevention should receive equal resources. It said, "If HIV resources are used to address issues such as the feminization of poverty, women's lack of access to credit and education and 'constructions of masculinity,' fewer resources will be available to address the immediate drivers of HIV—client demand for unprotected sex, violence and lack of access to condoms, information and health care."

Gender issues

Turning specifically to male circumcision, another major area of concern was how it would be rolled out in varying communities and what the specific impact would be on women.

"It is good news, but it is no panacea," agrees Louise Binder, a leading HIV-positive Canadian activist, about male circumcision. "It is another prevention method that will require male consent. It is not going to work 100% of the time, so another method will be required, and will men agree to that?" On the plus side, she added, "At least it is low cost and a one-time procedure. It may save some women's lives in communities where women cannot negotiate anything to do with safer sex but (male) circumcision is acceptable."

Her remarks strike at the heart of why some feminists and HIV-positive women are openly suspicious of the global public-health embrace of male circumcision—compared to their years fighting to push microbicide research forward. "There are important ramifications for women of this policy shift and these research findings," said Tyler Crone of the Athena Network, a global coalition focused on gender dimensions of HIV and AIDS. "I am concerned about the lack of attention being paid to gender inequity in these discussions."

"This is an ethical question," said Dr. JoHanna Kehler, Director, AIDS Legal Network in Cape Town. "Aren't we setting people up for [false perceptions of] safety [such as] 'Now I'm circumcised, now I am no longer at risk.'"

Where to from here?

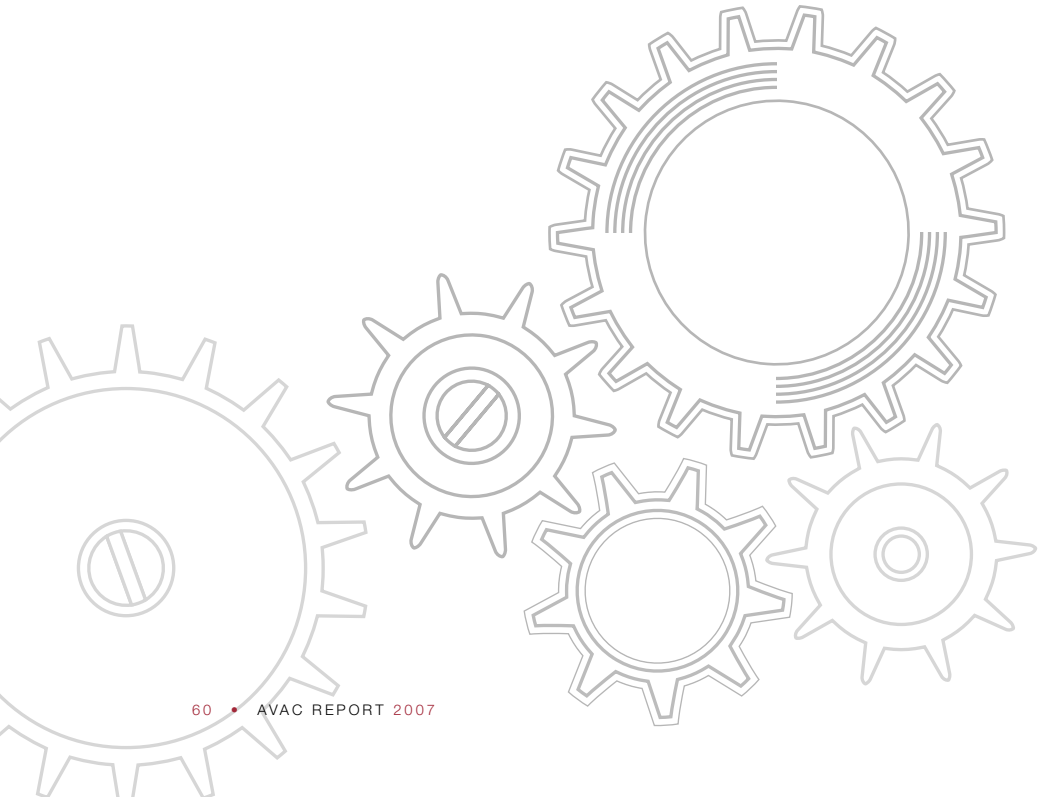
Distinctions between different facets of the AIDS response exist in electronic discussion forums and international conferences. But they largely vanish on the ground—where prevention, treatment, and care are all equally important, and where the need for food, schooling, and legal protections almost certainly outweighs the perceived need for new biomedical strategies on any given day.

> *"My big concern here is the collapsing of HIV prevention into medical/technological 'fixes,'"*
>
> —Gregg Gonsalves, AIDS activist

And yet, HIV-prevention research must continue—on the ground—and the results of new trials must be translated into action—on the ground—where the findings warrant it. Resources are needed for what works and for what may work. Structural issues must be considered, as must supplies of existing essential prevention commodities like male and female condoms—which are absent from the vast majority of prevention programs.

To get beyond distrust and dichotomies, advocates from many arenas must work together to develop a common platform of issues around prevention and prevention research. This means dealing with identity and constituency politics in a straightforward way. This means men's groups advocating for male circumcision and for methods women can use; microbicide advocates who include vaccines, pre-exposure prophylaxis (PrEP), and HSV-2 treatment in discussions of female-initiated strategies; women's groups who recognize that well-designed male circumcision programs could help reduce women's risk; and prevention research advocates who explore both the successes and the failures of past trials.

Some groups and individuals are already exploring opportunities for shared agendas with allies in a range of fields. But the conversation needs to be broader, more diverse, and even more honest about areas of disagreement and discomfort. The AIDS epidemic in 2007 demands nothing less of those who are committed to bringing it to an end.



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 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 new prevention technologies.

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 the AIDS vaccine field and mobilize political, financial and community support for AIDS vaccine 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 toward the development of an HIV/AIDS vaccine and makes recommendations for actions in the coming year, AVAC publishes the AIDS Vaccine Handbook and operates the AIDS Vaccine Clearinghouse (www.aidsvaccineclearinghouse.org), a comprehensive and interactive source of AIDS vaccine information on the internet.

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