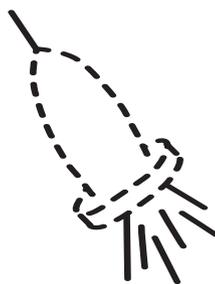
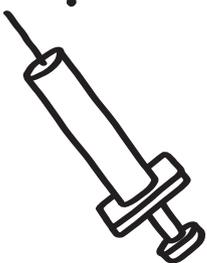


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## ACKNOWLEDGEMENTS

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## IN MEMORIAM

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### **Beth Waters Finston**

AVAC dedicates this year's Report to Beth Waters Finston, a dear friend and trusted advisor.

Beth spent a lifetime as a tireless advocate against infectious diseases. Her passion was advocacy for vaccines to prevent and treat diseases throughout the world. More than a decade ago, she was a powerful ally for the idea that a core strategy to end the AIDS epidemic is to develop a safe, effective and affordable AIDS vaccine.

She was untiring in her efforts, traveling the world to lend her intensity and expertise to companies, governmental committees and non-governmental organizations. Beth was a wise counselor, a creative problem-solver, and a relentless optimist, never ceasing to push the AIDS vaccine agenda forward, despite the scientific and political challenges.

Beth understood the power of advocacy and community engagement to push the field forward and provided visionary guidance in the formation and strategy of AVAC. She remained a close advisor and confidant to the organization's founders and directors throughout its history.

Beth was a founding member of the advisory board of the Vaccine Education Center of the Children's Hospital of Philadelphia and a member of the HIV Vaccine Communications Steering Group of the National Institute of Allergy and Infectious Disease.

A reporter for publications including the Philadelphia Bulletin, Boston Magazine and the Boston Herald in the early years of her career, Beth was a Senior Managing Director of Ogilvy Public Relations before co-founding Cooney/Waters Group, a health care public relations and public affairs company in New York City.

She continues to inspire AIDS vaccine advocacy, and she will be remembered for her dedication to conquering infectious diseases through education, sound public policy and vaccine advocacy.

## LETTER FROM THE BOARD PRESIDENT AND EXECUTIVE DIRECTOR

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AIDS at 25, HAART at 10, AIDS vaccines at 20+, AVAC at 11. This year marks a number of “anniversaries” that chart a sobering reality in the history of the epidemic.

In this year’s AVAC Report, our argument is simple: *the future is now.*

The next several years will bring a variety of scenarios that we must not encounter unprepared. Instead, the AIDS vaccine field, and the field of prevention research in general, must engage in rigorous debate, dialogue and scenario planning to anticipate the issues that the next few years will bring, and ensure that a wide range of stakeholders is informed and empowered to make decisions to compete against the virus.

Why do we say this? Why now?

*Because:*

- The next two to five years will bring results from a variety of ongoing trials, including the Thai prime-boost trial, test-of-concept studies of adenovirus-based AIDS vaccine candidates and several microbicide efficacy trials, as well as studies of male circumcision, treatment of herpes simplex virus type 2 to prevent HIV transmission or acquisition, pre-exposure prophylaxis and the female diaphragm as strategies for AIDS prevention. Each new finding means new choices, new messages, new points of convergence and necessary collaboration among trial planners, public health program designers, and communities. The time to begin anticipating and discussing these challenges is now.
- The infusion of new funding from the US National Institutes of Health and the Bill & Melinda Gates Foundation to the Center for HIV/AIDS Vaccine Immunology (CHAVI) and the Collaboration for AIDS Vaccine Discovery (CAVD) respectively, is meant to stimulate product development at the earliest stages. The fruits of these labors—in terms of products in the pipeline—will not be seen for at least two

years, based on current working plans. There is an urgent need to map out the pathway for the future: how do we ensure that there is sufficient clinical trial capacity, human resource development and community and political will for the “long haul”? How do we ensure that these new consortia generate new ideas and cross-fertilize each other?

- The AIDS vaccine field can learn valuable lessons from other fields. Recent licensure of Gardasil™, Merck’s HPV vaccine, provides the opportunity to explore issues of trial participation, access, delivery and funding for a vaccine targeted at a population that is also in urgent need of an AIDS vaccine—adolescent girls. There is no perfect model for AIDS vaccine delivery; there is also no excuse for passing up the chance to collaborate on and learn from rollout of a vital public health tool for cancer protection and sexual and reproductive health.

*AIDS Vaccines: The Next Frontiers* is AVAC’s first contribution to the scenario planning that we think is critical to the success of the field. In this year’s report, we present four chapters, each of which begins with a future scenario that imagines the world in the coming years. Each chapter is meant to raise issues, challenge assumptions, provoke debate, and provide a foundation for future vaccine and prevention research advocacy. These chapters are:

**01. AIDS Vaccine Science, Strategy and Action: The state of the field, the stakes for the future**

New infusions of funding into the field are being channeled to projects that aim to tackle one or more of the goals laid out in the Scientific Strategic Plan of the Global HIV Vaccine Enterprise. Each of the new projects aspires to greater coordination and a departure from “business as usual” in the arena of academic science and product development. How can advocates assess whether these efforts at collaboration are paying off? What are the metrics of success? And what about the areas of the plan that have not been funded to date?

## AIDS Vaccine Field

- Advocate for robust, comprehensive HPV vaccine delivery to adolescent girls and boys.
- Develop a common language for talking to communities about test-of-concept studies and sequencing decisions.

## Researchers

- Share outputs from research on neutralizing antibodies, adjuvants, mucosal immunity assays and other work in a manner that lets us understand if and how CHAVI, CAVD and other consortia are truly adding value to the field. (And don't forget to keep thinking outside of the box!)

## Global HIV Vaccine Enterprise

- Reconstitute working groups on clinical trials capacity, intellectual property, manufacturing, and regulatory issues. Give these groups specific tasks to help bring these areas up to speed.
- Take swift, transparent action to identify a new executive director.

## 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.
- Partner with other stakeholders to convene ethical consultations on issues related to evaluation and eventual introduction of new partially effective prevention strategies.

## AVAC

- Take a leadership role in developing—in consultation with multiple partners—new guidelines for “Good Community Practice”: standards that could clarify and strengthen community-researcher relationships at prevention trials worldwide.
- Support and/or convene a prevention research advocacy network which addresses emerging ethical, community and trial design issues.

\* While we make many other recommendations throughout the report, AVAC feels that these nine items are of utmost importance in the next 12 months. We'll evaluate everyone—including ourselves—by progress towards these goals.

And how will all of this go forward with the continued absence of an Enterprise chief executive? We note with concern the continued “interim” nature of Enterprise leadership, and we firmly believe that inspired leadership is increasingly vital to keeping the momentum.

We also draw your attention to the illustration of the increasingly complex field on page 14. It is our attempt to understand the new cosmology of the field at large, the Enterprise and the new funding announcements.

## 02. Reports from the Frontlines:

### Learning from last year's clinical trials

More trials, more volunteers, more reports on what works and what doesn't work in the field are needed. The past year has seen bold moves, some exciting successes, and some instructive setbacks in AIDS vaccine trials and prevention research as a whole.

There is more conversation than ever about the need to build clinical trial capacity and to ensure that communities are authentic partners in the research process. How well is this happening “on the ground” and what can we do better?

03. **The Emerging Adolescent Agenda: HPV vaccine, AIDS prevention research, and the new opportunities for reaching the young people of the world**

Two years ago, the AVAC Report 2004 examined the issue of adolescents and HIV vaccine research in its article, “The Missing Cohort.” In light of new developments, including licensure of the first HPV vaccine and steps to involve young women and men in AIDS vaccine trials, we re-visit these issues, and discuss what it will take to make these elements coalesce into an ongoing, coordinated effort to improve health and reduce disease among the world’s young women.

04. **AIDS Prevention Evolves (Again): Why we are on the verge of an era of new complexity**

Microbicides, pre-exposure prophylaxis, herpes-simplex 2 treatment, male circumcision: the list of potential prevention interventions currently under investigation is long and varied. It is our great hope that all of these show some efficacy, and that the arsenal of AIDS prevention tools expands accordingly. And if it does, this will mean new challenges for trials of AIDS vaccines, second-generation microbicides and other interventions, which may be more complicated—though no less necessary.

Why the space theme in this year’s report? Actually, it’s not the first time AVAC has had astronauts in its annual report. In our AVAC Report 1998—the second one we ever issued—photos of the moon shot were used as a fitting analogy for the search for an AIDS vaccine.

In 2006, we’re revisiting the comparison, with a new perspective born of the past years’ progress, challenges and discoveries. Our inspiration is longtime vaccine advocate Jose Esparza, who has pointed out that the search for an AIDS vaccine is a far greater challenge than sending a man to the moon. When it came down to the space race, we knew where we were; we knew where the moon was; and we knew, roughly, how to get there. It was, essentially, an engineering problem.

When it comes to an AIDS vaccine, we don’t know where the moon is—yet. But that doesn’t stop us from aiming for the heavens. As you’ll note on this year’s cover, the spacemen and rockets morph into needles and target cells in the blink of an eye. It is our hope that careful planning and execution of the goals laid out in this report will help transform the search for an AIDS vaccine into an engineering problem whose solution will change the world.

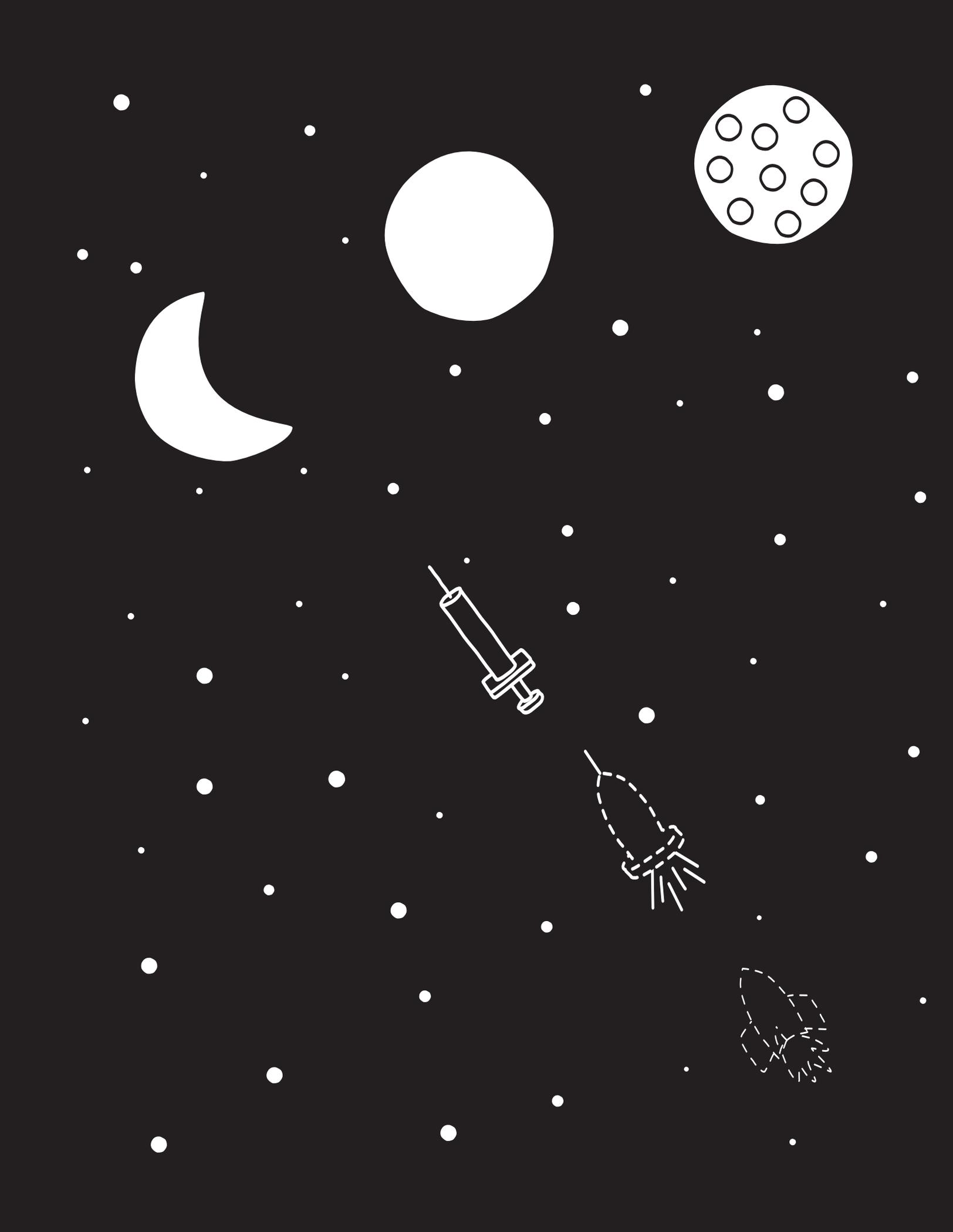
Sincerely,



Mike Powell  
AVAC Board President

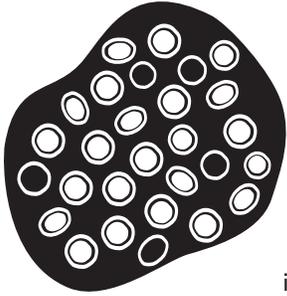


Mitchell Warren  
AVAC Executive Director



DATELINE **2009**

LOCATION **A major European city**



Dr. Delaware looks over her notes one last time. The presentation she is preparing for is an important one. As leader of a team of independent expert auditors, she has been asked by the Global HIV Vaccine Enterprise to monitor the progress of some of the major funding initiatives directed towards AIDS vaccine research in 2005-2006. For the past three years, she and her team, which includes Nobel laureates and experts from vaccinology, immunology, AIDS and other disciplines, have been able to review the budgets, data and workplans of the grantees and consortia who set out, in 2005, to answer some of the questions that have foiled the field for twenty years.

It has been a hard job by definition. The questions themselves defied easy answers and could not be molded to traditional series of interim milestones. In some instances, the milestones that were set turned out to be irrelevant; and more than once, Dr. Delaware's team recommended that the overall plan be revised and restructured with an eye to focusing on other more readily answerable questions essential to AIDS vaccine design.

Some unpredicted findings moved the field forward, as they appeared to lend themselves to swift development of candidates that could move into clinical trials.

And it has been her task to monitor all of this, to measure progress through meaningful targets, and to keep an eye on the "prize" of novel candidates moving into trials, without pursuing a full "pipeline" for its own sake.

She stacks her papers one more time. Would the field even care about her recommendations? Where potential candidates were emerging, would industry add its resources? Would the array of collaborators and consortia be willing to revisit their ways of working in the service of the field yet again?

*I hope so, she thinks as she walks out the door.*

# 01. AIDS Vaccine Science, Strategy and Action: The State of the Field, the Stakes for the Future

## I. STATE OF THE FIELD

Since its inception in 2003, the Global HIV Vaccine Enterprise has been viewed as a critical, defining element of the field's current approach to developing an AIDS vaccine. And as we look back over the past year, we focus first on what this collaborative entity has—and has not—achieved.

We start at the top: the executive position at the Enterprise secretariat. Here, the news is disappointing. In August, the Enterprise coordinating committee and Dr. Adel Mahmoud made it known that the forthright former Merck executive Dr. Mahmoud would not be taking the job (see opposite).

And so, three years after the initial article which conceived of an over-arching framework for the field, and 18 months after the publication of the Enterprise Scientific Strategic Plan, the Enterprise will be starting over in its search for a leader. This is a setback for the field, as we discuss below. And AVAC looks to the Enterprise to re-commence the search, including a swift and transparent process of reviewing the job description to ensure that it captures the roles, responsibilities and skill set needed for this entity, at this time. Acting director Jose Esparza phrased it well when he posed the question, “Does the Enterprise need a scientific leader? An ambassador? A scientific administrator?”

The Enterprise coordinating committee must answer these questions and fill the position. But we also note that as it starts the search anew, it is not starting from the same point.

In 2005-2006, two major funding initiatives began to develop agendas, plans and budgets in ways designed to execute specific parts of the shared scientific strategic plan.

Last year, the Center for HIV/AIDS Vaccine Immunology (CHAVI) was funded by the US National Institutes of Health (NIH) with a seven-year grant that aims to provide more than US\$300 million, US\$15 million of which was designated for its first year. Then in June, the Bill & Melinda Gates Foundation launched the Collaboration for AIDS Vaccine Discovery (CAVD), which provides a total of US\$287 million to 16 principal investigators over the next five years.

Both of these funding streams could have emerged and been committed without the existence of the Enterprise—and very well may have. Yet both funders credit the pre-existence of the scientific strategic plan and the principles for coordination laid out therein as having influenced these initiatives. The collaborative structures and scientific goals of CHAVI and CAVD have a common point-of-reference; and the grant-making work for each was done with an eye toward avoiding duplication, according to individuals who participated in the process.

CHAVI, for example, has already started a multi-level effort to gain a better understanding of the early immunological events that follow infection. By learning what the immune system does in the first weeks after infection and why these responses are insufficient to control infection the group hopes to shed more light on the kinds of immune responses that would be

In last year's AVAC Report, we anticipated that the Enterprise would advance into operational reality when its first executive director was to be appointed. We identified eight concrete tasks that should be the focus of the new director from the first day:

- 01 Communicate frequently and transparently.
- 02 Set policies for sharing and coordination of data and technology.
- 03 Ensure the ability to take risks.
- 04 Bring new investigators into the search.
- 05 Make the Enterprise truly global.
- 06 Involve civil society in a meaningful way.
- 07 Take on the politics and ethics of clinical trials.
- 08 Establish realistic milestones and a process for monitoring progress.

We were excited in March of this year when it was finally announced that Adel Mahmoud would be the chief executive of the Enterprise. Shortly after the announcement, Mahmoud met with the AVAC board and staff, and we were impressed. He displayed a command of the challenges, a bold willingness to address them and a commitment to ignite and fuel new scientific innovation. Mahmoud said he wanted to look at ideas that had not been explored and challenge scientists to work together more collaboratively.

At the time of his appointment, he said: "My job will be to help Enterprise partners realize the vision of the scientific plan—to identify timelines and milestones, track progress, and keep us on course to reach our ultimate goal."

The recent announcement that Mahmoud would not take up his position in September is, therefore, a disappointment.

While the Enterprise partners continue to do important work individually, and are showing signs of willingness and ability to work together in new ways, leadership matters.

In fact, it may matter more than ever. In the absence of an executive director, the Enterprise has achieved some advances, including:

- Publication of a scientific plan that lays out major issues and begins to articulate a way forward (and that now needs to be updated)
- Commitments from new funding initiatives from the Gates Foundation and the NIH that support collaborative work in the highest priority areas of vaccine discovery and laboratory standardization
- Additional Enterprise-related funding announcements from Germany, Russia and Switzerland which show promise of making the efforts more global

*(continued on page 12)*

Leadership is needed to take these initiatives to the next level. The Enterprise still needs an updated, more concrete plan, with specific timelines and milestones and a process to monitor progress, achieve accountability, and modify directions accordingly.

In the absence of a director, the Enterprise may find itself in danger of losing momentum, as it seeks to establish itself as an entity deserving of funding; and the individual players—who are collaborating now—may not agree on how best to measure progress and ensure that the new money is being spent in the best way possible.

An executive director does not have to monitor progress directly, but having someone in this role—part constructive critic, part cheerleader, part champion—will strengthen the overall endeavor and send a clear signal to multiple audiences about the importance of this undertaking.

New ventures frequently have start-up challenges—especially one like the Enterprise which has, as its core mission, a new way of doing business. And the fact that new events have taken place during the year that we were waiting for Dr. Mahmoud may help refine the job description for the next search, which we are told is already underway.

This is a critical juncture, then, for the Enterprise and its members. The ongoing search for a leader should continue with all due speed; and critical Enterprise-related activities like re-constituting working groups should happen even before the position is filled.

If this happens, then the delay—while disappointing—will have been a learning opportunity, and not a major setback for the field.

protective. This effort includes EuroCHAVI, a study of samples from progressors and non-progressors provided by several European collaborators.

Meanwhile, CAVD grants include suites of inter-linked funding for “Discovery Consortia” aimed at developing better T-cell and antibody-inducing vaccines.

And in what may turn out to be the most critical part of this initiative, the Gates Foundation provided US\$92.2 million out of the total to a set of central facilities, including a data and statistical analysis center, a mouse immunology laboratory, and laboratories for evaluation of antibody and T-cell responses.

Laboratory standardization was one critical element mentioned in the Enterprise plan, since the inability

to compare results hinders progress, and can lead to duplication.

This kind of activity would appear to embody the principle that the Enterprise is whatever its members do. And it could prompt the question: if all this happened in a year without a “head,” is there still a need for an executive director at the Enterprise secretariat?

AVAC’s answer is *Yes*. Here are three reasons why.

**01. Because there are other, still-neglected areas that require attention.**

How do we ensure that, as the field redoubles its efforts to answer fundamental questions, there is a clear path from scientific discoveries to vaccine candidates? The answer lies in attending to *all* six of

the Enterprise's priority areas: not just vaccine discovery and laboratory standardization, but also product development and manufacturing, clinical trials capacity, regulatory issues, and intellectual property issues.

Working groups on these issues have been convened and have conducted preliminary gap analysis. But more intensive work is needed. The groups should be reconstituted and given more specific assignments to address, so that they can develop clear plans to address clinical trial capacity, intellectual property (taking into account work already done by CHAVI and CAVD) and other arenas.

Engagement with industry partners is also of paramount importance and should receive attention both on these groups and in cross-cutting analysis and evaluations of the Enterprise.

Of course, ad-hoc working groups can convene themselves, issue reports and even hold cross-cutting meetings to discuss shared agendas. But this process would be greatly facilitated by a body that has authority, respect and a mandate to oversee the entire process with a respected individual as its spokesperson and head.

#### 02. **Because the Enterprise is still far from global.**

In our 2005 memo, we urged the new Enterprise ED to make the Enterprise truly global. This has not happened yet. None of the principal investigators for CAVD are from developing countries (although there are many collaborators from the developing world). Bringing in expertise and unique perspectives from countries in Africa, Asia, Eastern Europe, Latin America and the Caribbean is of vital importance. The search for an AIDS vaccine must include scientists and communities from countries where the epidemic is spreading fastest.

This is not an overnight process: making the Enterprise global means making investments in training, research funding and capacity building for scientists and clinicians from the developing world. We know that creating these opportunities is essential to addressing the health care human resource crises in these countries. The Enterprise and its ED have a critical role to play in fostering these initiatives.

#### 03. **Because monitoring and oversight are essential.**

As we look at the past year's activities, we see that there is a new level of organization in the field. In addition to the work that will continue in individual laboratories, ad-hoc collaborations, and pre-existing consortia like the IAVI Neutralizing Antibody Consortium (NAC), there are two new entities, which have their own rules of order, engagement and collaboration.

CHAVI and CAVD are focused on pre-clinical vaccine discovery efforts, including exploration of basic scientific questions that continue to challenge the field (see page 16), and funding for central facilities to support them.

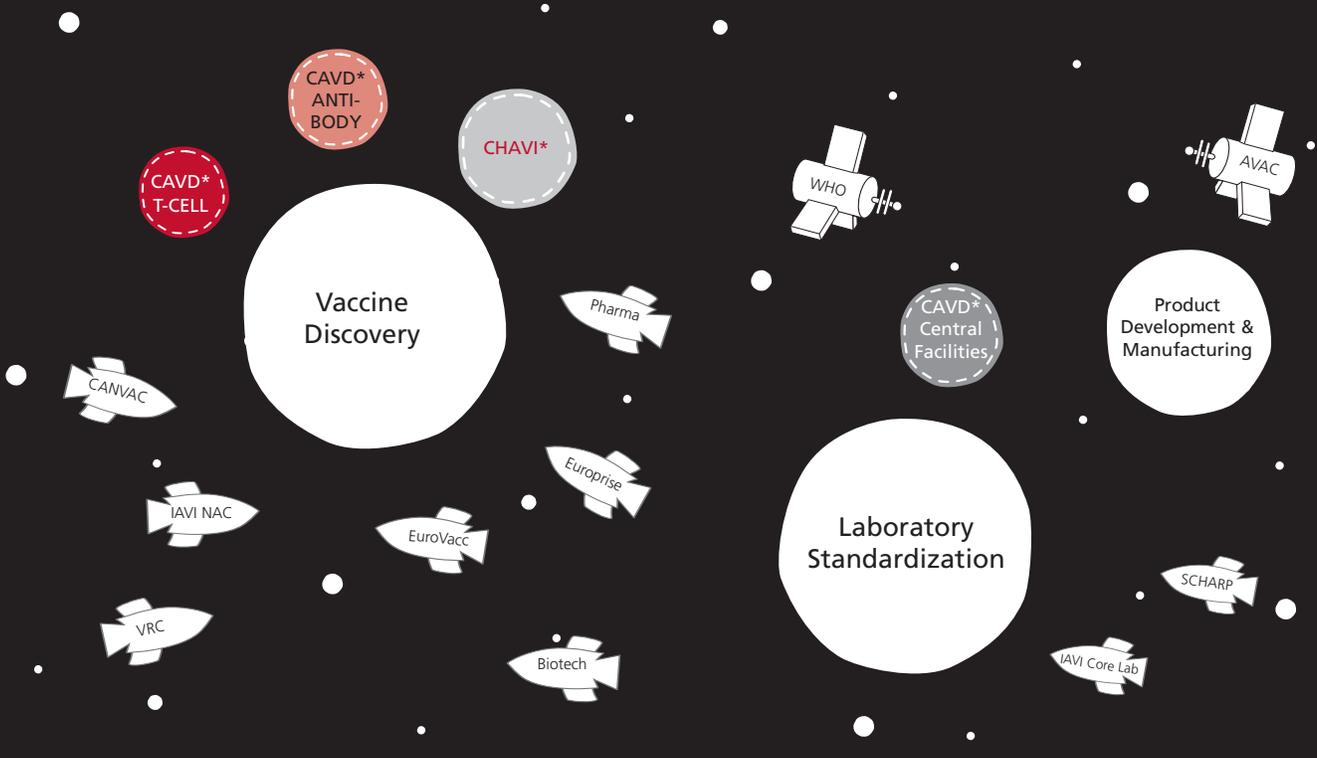
These initiatives are in their early days. They are, at the moment, *opportunities* for change. The evidence of their effectiveness, in terms of helping the field work more swiftly and efficiently than it has in the past, is still to come.

The Enterprise secretariat and, in particular, its leader can play a critical role in evaluating this evidence when it emerges over time.

There is a need for independent monitoring by an entity with high scientific caliber and a grand perspective on the field as a whole to monitor progress and determine whether money is being well spent, productive collaborations are being launched, and duplication is eliminated, while also harnessing strategic competitiveness.

This was a critique of the scientific strategic plan itself: that it lacked milestones, defined targets and timetables. We know that milestones have not always worked in the past. But defined targets need to be there: what are the answerable questions? How are they being re-framed as new data emerge from one quarter or another?

The Enterprise leadership should be in a position to provide this oversight; and it is dangerous to think that the field can now do without it.



**MAKING SENSE OF THE NEW ENTERPRISE "COSMOLOGY"**

What's going on in this corner of the sky? The six "planets" in the graphic above are the focus areas identified in the Global HIV Vaccine Enterprise Scientific Strategic Plan. CHAVI and CAVD work plans are specifically linked to these areas. Since they are the first initiatives to be connected to the Enterprise from their inception, they are represented as moons in the orbit of the Enterprise.

But the universe did not begin with the Enterprise. A wide array of projects and initiatives has been launched over the past decade or more. We've highlighted some of these projects—represented as rocket ships—and show how their trajectories relate to the Enterprise focus areas. As busy as this graphic looks, there is still work to be done: clinical trials capacity, product development, manufacturing, regulatory issues and

intellectual property issues are still being addressed by individual entities, without the coordination that has been brought to bear on vaccine discovery and standardization.

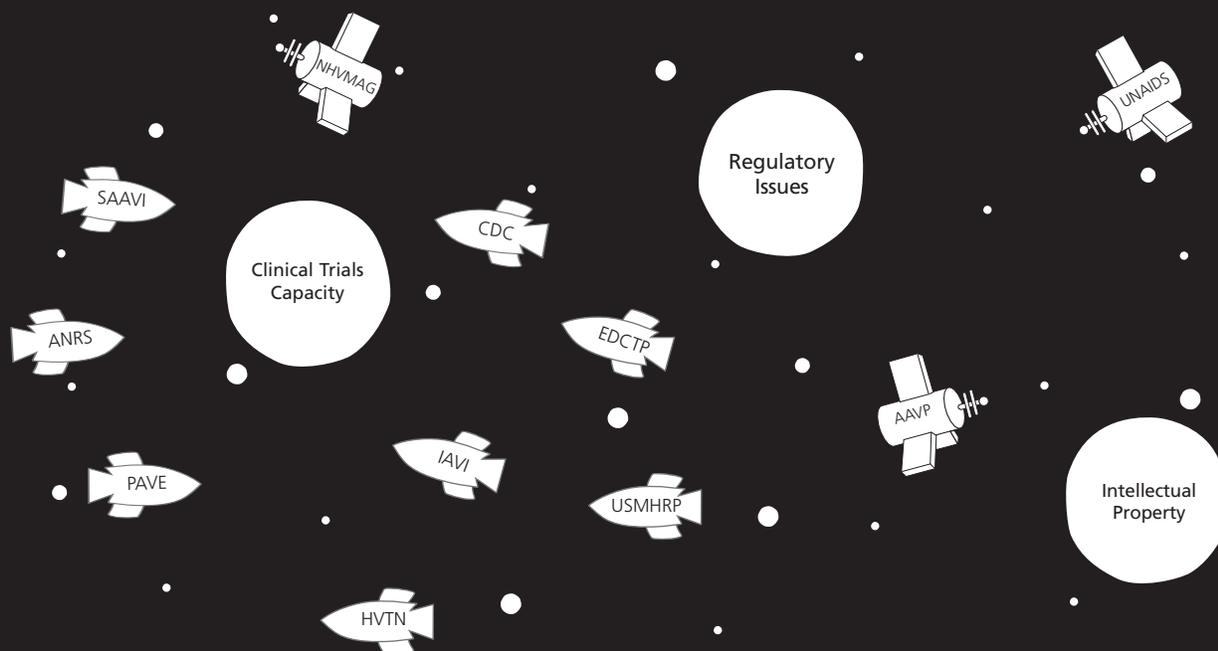
It's also important to remember that there are other critical elements of the AIDS vaccine universe which do not feature in the Enterprise cosmology at all—including social and behavioral science, policy formulation, advocacy, strategic linkages with other prevention research arenas, preparing for future access and expanded community involvement. We've included some of the groups doing advocacy work in as satellites because these entities monitor, transmit information to multiple audiences, and have an important role to play in evaluating and informing the work of the Enterprise and the field at large.

**KEY**

*\*2005-2006 New funding*

- AAVP** African AIDS Vaccine Programme
- ANRS** Agence Nationale de Recherches sur le SIDA
- AVAC** AIDS Vaccine Advocacy Coalition
- CANVAC** Canadian Network for Vaccines and Immunotherapeutics
- CAVD** Collaboration for AIDS Vaccine Discovery
- CDC** Centers for Disease Control
- CHAVI** Center for HIV/AIDS Vaccine Immunology
- EDCTP** European and Developing Countries Clinical Trials Partnership
- Europrise** European Vaccine/Microbicide Enterprise
- EuroVacc** European Vaccine Effort Against HIV/AIDS

- HVTN** HIV Vaccine Trials Network
- IAVI** International AIDS Vaccine Initiative
- NAC** Neutralizing Antibody Consortium
- NHVMAG** Nigerian HIV Vaccine and Microbicide Advocacy Group
- PAVE** Partnership for AIDS Vaccine Evaluation
- SAAVI** South African AIDS Vaccine Initiative
- SCHARP** Statistical Center for HIV/AIDS Research and Prevention
- UNAIDS** Joint United Nations Programme on HIV/AIDS
- USMHRP** US Military HIV Research Program
- VRC** Vaccine Research Center
- WHO** World Health Organization



## NEW ENTERPRISE-RELATED FUNDING STREAMS

### CENTER FOR HIV/AIDS VACCINE IMMUNOLOGY (CHAVI)

[www.chavi.org](http://www.chavi.org)

**Vital statistics:** Established in July 2005. US\$300 million over seven years from the US National Institutes of Health, support 80 investigators at 35 institutions worldwide in Year 2.

**Overall goal:** To define the enabling technology for HIV vaccine development by determining correlates of protective immunity at mucosal surfaces in acute HIV-infected (AHI), and exposed uninfected (EU) individuals.

**Specific initial studies:** (1) Determine the molecular and virologic characteristics of the transmitted virus; (2) Define the genes that determine viral load levels in AHI individuals; (3) Define the genes that determine protection; (4) Define the genes that determine protection in EU and AHI individuals; (5) Determine T cell, B cell and innate immune responses to the transmitted virus at the mucosal surface in AHI and EU individuals; (6) Develop vectors and adjuvants that are capable of inducing protective immune responses to the transmitted virus at mucosal surfaces. Use data from studies 1-6 to design and test novel immunogens for induction of optimal mucosal anti-HIV immune responses.

### COLLABORATION FOR AIDS VACCINE DISCOVERY (CAVD)

[www.cavd.org](http://www.cavd.org)

**Vital statistics:** Launched in July 2006. US\$287 million over five years from the Bill & Melinda Gates Foundation. Funding will support 16 research consortia, with more than 165 investigators from 20 countries.

**Overall goal:** To overcome major scientific obstacles facing HIV vaccine research, and accelerate the development of an effective vaccine that could help bring the global AIDS epidemic under control.

**Specific initial studies:** The 16 grants are organized into eleven vaccine discovery consortia (five neutralizing antibodies discovery consortia and six cellular immunity discovery consortia) and five central laboratory and statistical service facilities. The neutralizing antibody consortia include grants for novel vaccine design using HIV-2, synthetic molecules incorporating key regions of HIV into protein "scaffolds," research on additional types of neutralizing antibodies in animals and humans; as well as studies of the V-3 loop region of HIV, and innate and adaptive immunity. The cellular immunity consortia include grants to optimize existing strategies, such as pox virus and adenovirus vectors; as well as studies of candidates which target dendritic cells, and adjuvants to enhance T-cell vaccine performance. Central facilities include three laboratory networks for evaluating the immune responses elicited by vaccine candidates, a research specimen repository, and a data and statistical management center.

**WHAT DOES AN EFFECTIVE AIDS VACCINE NEED TO DO?**

The broad consensus—based on fundamental principles of vaccinology as well as years of observations of long-term non-progressors, highly-exposed persistently seronegative individuals, and non-human primate studies—is that an effective AIDS vaccine will need to stimulate two key types of immune responses.

The first type is responses that induce broadly-neutralizing antibodies, which are capable of binding to HIV and blocking it from infecting target cells. To be effective, these antibodies must be able to neutralize different HIV strains.

The other type is cell-mediated immune responses, which can destroy cells that have already been infected with HIV, effectively eliminating the viral “factories” that drive infection.

We know what we need in theory. But we still don’t know how to determine whether we’ve found it. The search for “correlates of protection” (measurable indices of whether or not a candidate is effective) and “surrogate markers” (early clinical endpoints—markers of disease progression), continues, and without this information it is difficult to answer this question, or the one that follows directly from it, below.

**HOW DO WE BUILD VACCINES THAT CAN DO WHAT WE NEED THEM TO DO?**

The ultimate goal is a vaccine or vaccine combination that induces broadly neutralizing antibodies and potent cell-mediated immunity against HIV. So how do we do this? The answer is still: we are not sure. We do not know how many antigens need to be in the vaccine. Should there be multiple antigens (i.e., a range of synthetic fragments of HIV genetic material)? Is there an optimal number? What types of vaccine designs will optimize both the potency and longevity of the induced immune response, since we want to develop vaccines that provide lasting protection, ideally for years after the immunizations have been delivered? Antigens are one piece of this; vectors and adjuvants are also critical; and the field still lacks information about optimal forms of various vectors that have been tested extensively in various Phase I trials; likewise there is still a tremendous amount to be learned about how to use adjuvants to the best advantage in AIDS vaccine design.

**WHAT, EXACTLY, DOES THE VACCINE TARGET “LOOK” LIKE?**

We know, in broad strokes, that an ideal vaccine needs to induce immune responses that block HIV from infecting cells and destroys cells that have already been infected. But HIV has a tremendous amount of genetic variability, and there is some indication that the strains that are transmitted most frequently have some specific traits that may make them more efficient at establishing infection. What are these defining traits exactly? Should a vaccine be targeted against the viruses? How relevant is this for prevention of infection in injection drug users?

## II. STATE OF THE SCIENCE

Everything that we've talked about so far falls under the rubric of science management. That's one part of the picture. The other part, of course, is the science itself. When we look back over the past year's developments it isn't a matter of seeing what CHAVI or CAVD did—and it never will be. Exciting breakthroughs can come from anywhere, and frequently emerge from individual scientists who have gone out on a limb, exploring possibilities that are left unexplored, by their peers.

### Continuing importance of mucosal immunology; and a continuing lack of validated assays to measure it

Last year we called for expanded research on mucosal immunology. There is more attention being paid; CHAVI has added a mucosal immunology discovery team, led by Robin Shattock of St. George's Hospital Medical School at the University of London. The findings of researchers like Daniel Douek (Vaccine Research Center) have provided further rationale for this area of inquiry.

This year, for example, Douek reported on preservation of central memory cells in the gut mucosa of a group of 10 men who received post-exposure prophylaxis with ARVs after exposure to HIV. Three of the men had evidence of anti-HIV antibodies in their blood but no sign of infection, and Douek hypothesizes that preservation of gut mucosal immune responses may be an indicator of protection against HIV.

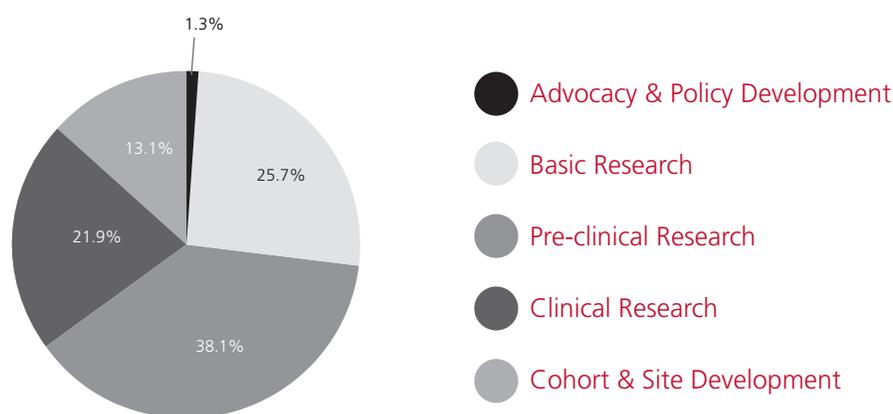
Biopsies such as those used in Douek's study are invasive, complicated and unfeasible for large-scale trials and the field has yet to identify a reliable surrogate marker for mucosal immune responses. We welcome the ongoing interest in developing mucosally-targeted interventions and learning more about immune events at the mucosa. **We urge that this work continue with an additional emphasis on developing practical assays to measure mucosal immunity in the field.**

### Central memory cells as correlates of protection

At scientific meetings and in journals Norman Letvin (Beth Israel Deaconess Medical Center) and Douek

FIGURE 2

NON-COMMERCIAL FUNDING ALLOCATIONS FOR PREVENTIVE HIV VACCINE R&D BY CATEGORY IN 2005



Source: HIV Vaccines and Microbicides Resource Tracking Working Group, *Adding It All Up: Funding for HIV Vaccine and Microbicide Development, 2000 to 2005*, August 2006, [www.hivresourcetracking.org](http://www.hivresourcetracking.org).

presented data suggesting that central memory T-cells could be a correlate of protection. Memory T-cells are a subset of the immune repertoire that mounts the most rapid responses to invading pathogens. As their name suggests, they are the keepers of the immunologic “memory” of diseases that have been encountered before. Central memory cells, when triggered, can rapidly begin dividing to fight the disease if it reappears.

Memory T-cells have a specific “phenotype” thought to be indicated by particular receptors on the cell surface. Past HIV vaccine trials have looked at vaccine-induced HIV-specific T-cells overall, but have not looked at memory cells in particular. Letvin has presented data suggesting that HIV-specific memory T-cells could potentially be used as a measure of vaccine protection by measuring cells with these receptors. However these measurements require new and expensive technology.

These data have prompted excitement: VRC head Gary Nabel says that the Partnership for AIDS Vaccine Evaluation (PAVE), the collaborative effort

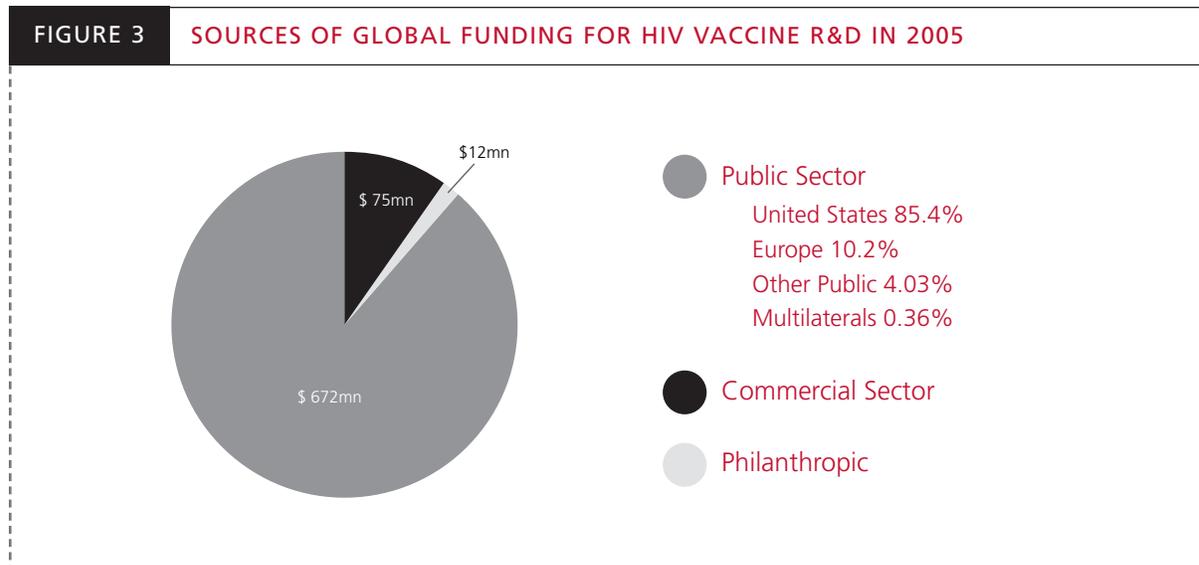
currently evaluating the VRC’s DNA-Adenovirus based combination, is considering using central memory T-cells as a correlate of protection in the planned test-of-concept study known as PAVE 100.

As intriguing as these findings are, there are still many unanswered questions. Can an assay that measures memory in the peripheral blood (as opposed to the mucosa) be developed and validated for widespread use, given that mucosal memory—which is harder to measure—may be the determining factor?

**In the next year, as the PAVE 100 protocol is finalized, we call for expert consultation about the potential benefits and challenges of using memory cell responses as a correlate of protection—including analysis of how these data should be collected in other trials and over time.**

**New approaches to adjuvants and enhancing immune responses**

Data presented this year from ongoing work on toll-like



Source: HIV Vaccines and Microbicides Resource Tracking Working Group, *Adding It All Up: Funding for HIV Vaccine and Microbicide Development, 2000 to 2005*, August 2006, [www.hivresourcetracking.org](http://www.hivresourcetracking.org).

- In 2005, total global investment in preventive HIV vaccine R&D was approximately US\$759 million.
- Between 2000 and 2005, public and the philanthropic investments more than doubled from US\$327 million to US\$684 million.
- During the last six years, European funders have increased their commitment to preventive vaccine R&D three-fold from US\$23 to US\$69 million. In 2005, R&D continued to grow outside of the US and Europe with contributions from countries such as Brazil, Canada, India, South Africa and Thailand totaling US\$27 million.
- The public sector, particularly in developing countries where trials are planned or are underway, provides considerable non-financial support through staff and facilities. These non-cash contributions are not trivial and have grown considerably over the last six years.
- In 2005, R&D expenditures were predominately on basic and pre-clinical research, which accounted for approximately 64% of the funds spent. In comparison, support for clinical trials accounted for 22%, cohort and site development 13%, and advocacy and policy development 1%.
- As of July 31 2006, preliminary public sector and philanthropic commitments for 2006 equaled US\$781 million, a 14% combined increase for these two sectors over 2005. This increase may not be sustained in subsequent years, as it reflects significant new investments by the Bill & Melinda Gates Foundation and the US National Institutes of Health.
- Although investment in preventive HIV vaccines increased in 2005, the Global HIV Vaccine Enterprise estimates that US\$1.1-US\$1.2 billion is needed annually to speed the search for a safe, effective HIV vaccine.

receptors (TLR) and dendritic cells suggests that targeted stimulation can increase the immune response. Given that HIV also targets dendritic cells (which stimulate TLRs), it remains to be seen whether this will be a useful strategy for fighting HIV infections. Juliana McElrath (Fred Hutchinson Cancer Research Center) is leading a team from industry, biotechnology and academia that, with support from CAVD, will seek to develop and understand the mechanism of these specific biological signalling mechanisms, which could be used with a variety of vaccines.

**In the next year, we look to see evidence that promising findings from adjuvant research feed into design of next generation products, with safety, regulatory, and intellectual property issues for new potential adjuvants addressed promptly.**

#### **New targets for neutralizing antibodies**

Neutralizing antibodies (NAbs) that block the activity of HIV remain one of the most elusive goals in the search for an AIDS vaccine. This year's scientific conferences focused on the potential target area

TABLE 1	ANNUAL INVESTMENTS IN PREVENTIVE HIV VACCINE R&D BETWEEN 2000 AND 2005 (current US\$ millions).						
	*The 2006 estimates represent disbursements and firm commitments made as of July 31,2006.						
	2000	2001	2002	2003	2004	2005	2006
<b>PUBLIC SECTOR</b>							
US	272	314	376	463	516	574	663
Europe <sup>A</sup>	23	32	39	44	57	69	26
Other <sup>B</sup>	10	12	21	24	28	27	10
Multilaterals	2	2	2	2	2	2	2
<b>Total public</b>	<b>307</b>	<b>359</b>	<b>436</b>	<b>532</b>	<b>602</b>	<b>672</b>	<b>704</b>
<b>PHILANTHROPIC SECTOR</b>							
<b>Total philanthropic</b>	<b>20</b>	<b>7</b>	<b>112</b>	<b>15</b>	<b>12</b>	<b>12</b>	<b>77</b>
<b>Total non-commercial investment</b>	<b>327</b>	<b>366</b>	<b>548</b>	<b>547</b>	<b>614</b>	<b>684</b>	<b>781</b>
<b>COMMERCIAL SECTOR</b>							
Pharmaceutical companies	-	-	-	-	59 (range 47-71)	64 (range 52-76)	
Biotechnology companies	-	-	-	-	9 (range 7-11)	9 (range 9-13)	
<b>Total commercial</b>	<b>-</b>	<b>-</b>			<b>68</b> (range 54-82)	<b>75</b> (range 61-89)	
<b>Total global investment<sup>C</sup></b>					<b>682</b>	<b>759</b>	

<sup>A</sup> This figure includes funding from the European Commission

<sup>B</sup> Other includes all national public sector funding apart from funding from the US and Europe

<sup>C</sup> Commercial sector investments were estimated for selected years in the series

known as the membrane-proximal external region (MPER) of gp41 (an area of HIV that is instrumental in docking on and infecting cells). Monoclonal antibodies that bind to conserved epitopes in the MPER neutralize primary HIV isolates from different clades. At the Conference on Retroviruses and Opportunistic Infections, Michael Zwick (Scripps Research Institute) was among the speakers who discussed MPERs and narrowed down the specific epitopes in the region that induce potent antibodies. Like other NAb-inducing sites, MPERs may be “masked” by the outer coating of lipids that surrounds HIV. Another potential drawback is that these antibodies

may be poly-specific, meaning that they could bind to targets other than HIV, causing an auto-immune reaction in the body. Barton Haynes (Duke University) has received grants from CHAVI and CAVD to pursue separate but related projects in this area.

**With multiple laboratories working on MPERs, this area of research is an ideal test case for the field’s ability to work collaboratively and additively, sharing information and avoiding redundancy. In the next year, we will look to outputs from the various groups to measure both scientific progress and process within the field.**

### III. THE STAKES FOR THE FUTURE

Fundamentally speaking, the stakes for the future are exactly the same as they have ever been: an AIDS vaccine is an essential tool for slowing the spread of this epidemic and failure to act swiftly, efficiently and in harmony will be measured in a heartbreaking toll of lives.

But as always there are new forces at work, and so we can also say this. In the next one to two years, the soundness of the vision behind CHAVI, CAVD and the Enterprise will be tested. It cannot fairly be tested in terms of the numbers of scientific breakthroughs or new candidates that emerge in 10, 12 or 18 months. These are long-term problems and one of the strengths of the new grants is that they do not have unrealistic timeframes for the results.

Nevertheless, the strength of the vision can still be measured by the field's ability to pose answerable questions; to assign well-funded, well-resourced teams to tackle these questions; to minimize duplication of efforts between these teams; and to ensure that there is rapid sharing of data, scientific platforms, and reagents across the field as needed and where appropriate.

It will also be measured by the progress that the Enterprise secretariat makes towards articulating its role and finding the appropriate structure and staff.

Now is the time to use this opportunity—without delay. The prolonged hiring process sends a signal of disorganization about the field to outside observers and potential allies. The job for all of us, including AVAC, is to continue to communicate clearly with

multiple constituencies about the state of the science, the organizational structures that have been proposed to make it work better, and, most importantly, the pace of progress towards our ultimate goal of changing the face of the epidemic forever.

#### With this in mind, AVAC commits to:

- Critical analysis of CAVD and CHAVI funding looking at transparency of granting procedures; duplicative versus additive funding; and optimizing of linkages across programs and consortia where possible and needed
- Work in collaboration with developing country scientists and initiatives including AAVP, SAAVI and others to develop a concrete proposal for achievable targets for increasing developing country leadership in new and existing consortia in the field
- Hold the Enterprise secretariat and its members accountable for proceeding swiftly with organizational activities in other critical areas including regulatory, intellectual property, clinical trials capacity, manufacturing process development and scale-up
- Work with the Enterprise to ensure that the job description of the Enterprise executive director is reassessed, that a transparent process is put in place to select a new slate of ED candidates and that the position is filled with deliberate urgency
- Serve as an active partner and, where needed, a leader in engaging civil society in dialogues about the direction, scope and vision of the Enterprise

TABLE 2

TRIALS OF PREVENTIVE HIV/AIDS VACCINES WORLDWIDE (AUGUST 2006)

PROTOCOL #	START DATE	SPONSOR, FUNDER, DEVELOPER	TRIAL SITE(S)
<b>PHASE III</b>			
RV 144	Oct-03	USMHRP, MoPH Thailand, Aventis, Vaxgen	Thailand
<b>TEST-OF-CONCEPT</b>			
HVTN 502/Merck 023	Dec-04	DAIDS, HVTN, Merck	US, Canada, Peru, Dominican Republic, Haiti, Puerto Rico, Australia, Brazil, Jamaica
<b>PHASE II</b>			
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
HVTN 204	Sep-05	DAIDS, HVTN, VRC, Vical, GenVec	US, Brazil, South Africa, Haiti, Jamaica
ANRS VAC 18	Sep-04	ANRS, Aventis	France
<b>PHASE I/II</b>			
RV 172	May-06	NIH, WRAIR, VRC	Kenya, Uganda, Tanzania
C060301	Feb-04	FIT Biotech, IAVI	Finland
<b>PHASE I</b>			
VRC 011	Apr-06	NIAID, VRC	US
HVTN 065	Apr-06	DAIDS, HVTN, VRC, GeoVax	US
IAVI D001	Feb-06	IAVI, Therion	India
HVTN 064	Jan-06	DAIDS, HVTN, Pharmexa-Epimmune	US, Peru
HVTN 068	Feb-06	DAIDS, HVTN, VRC	US
HIVIS 02	Jan-06	Karolinska Institute, Swedish Institute for Infectious Disease Control, WRAIR	Sweden
IAVI V001	Nov-05	IAVI, NIAID, VRC	Rwanda, Kenya
RV 158	Nov-05	WRAIR, NIH	US, Thailand
HVTN 063	Sep-05	DAIDS, HVTN, Wyeth	US, Brazil
HVTN 060	Aug-05	DAIDS, HVTN, Wyeth	US, Thailand

VACCINE(S)	# OF VOLUNTEERS	CLADE
Prime: canary pox viral vector with <i>env</i> and <i>gag-pol</i> Boost: Env protein (gp120 subunits)	16,402	B, A/E
Adenovirus vector with <i>gag, pol, nef</i>	3,000	B
AAV2 (adeno-associated virus type 2) vector with <i>gag, pol, ΔRT</i>	91	C
Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>	480	B A, B, C
5 lipopeptides with CTL epitopes from <i>gag, nef, pol</i>	132	B
Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>	324	B A, B, C
DNA vaccine with <i>nef, rev, tat, gag, pol, env</i> , CTL epitopes	28	B
DNA vaccine with <i>gag, pol, nef + env</i> or Adenovirus vector with <i>gag, pol + env</i>	60	A, B, C
Prime: DNA plasmid with <i>gag, pro, RT, env, tat, rev, vpu</i> Boost: Modified vaccinia Ankara (MVA) vector with <i>gag, pol, env</i>	120	B
Modified vaccinia Ankara (MVA) with <i>env, gag, tat-rev, nef-RT</i>	32	C
Recombinant protein vaccine with <i>gag, pol, vpr, nef</i> and DNA vaccine with protein containing T-helper epitopes from <i>env, gag, pol, vpu</i>	120	B
Adenovirus vector with <i>gag, pol + env</i> or DNA vaccine with <i>gag, pol, nef + env</i> followed by adenoviral boost	66	B A, B, C
Modified vaccinia Ankara (MVA) viral vector with <i>env, gag, and pol</i> to volunteers from HIVIS 01	38	A, E
Prime: DNA vaccine with <i>gag, pol, env</i> Boost: Adenovirus vector with <i>gag, pol, env</i>	104	A, B, C
Modified vaccinia Ankara (MVA) viral vector with gp160, <i>gag</i> and <i>pol</i>	48	A, E
Prime: Genevax Gag-2692 +/- IL-15 DNA Boost: Genevax Gag-2692 + IL-12 DNA or IL-15 DNA	120	B
Prime: Genevax Gag-2692 +/- IL-12 DNA adjuvant Boost: DNA plasmids with <i>gag</i> or RC529-SE and GM-CSF with <i>env, gag, nef</i>	156	B

TRIALS OF PREVENTIVE HIV/AIDS VACCINES WORLDWIDE (AUGUST 2006) *continued*

PROTOCOL #	START DATE	SPONSOR, FUNDER, DEVELOPER	TRIAL SITE(S)
HVTN 054	Apr-05	DAIDS, HVTN, VRC	US
VRC 008	Apr-05	NIAID, VRC	US
N/A	Mar-05	Changchun BCHT, Guangxi CDC	China
HIVIS 01	Feb-05	Karolinska Institute, Swedish Institute for Infectious Disease Control, Vecura	Sweden
EuroVacc 02	Feb-05	EU, Imperial College London, UK MRC Clinical Trials Unit, EuroVacc	UK, Switzerland
N/A	Feb-05	St. Jude, NIH	US
RV 156	Jan-05	NIAID, HVTN, VRC, USMHRP, Makerere U.	Uganda
IAVI C002	Jan-05	IAVI, ADARC	US
HVTN 059	Oct-04	HVTN, SAAVI, Alphavax	US, South Africa, Botswana
HVTN 055	Sept-04	DAIDS, HVTN, Therion	US, Brazil
HVTN 056	Apr-04	DAIDS, HVTN, Wyeth	US
HVTN 050/Merck 018	Jan-04	NIAID, HVTN, Merck	Thailand, Brazil, Haiti, Puerto Rico, South Africa, US, Malawi, Peru
HVTN 049	Dec-03	DAIDS, HVTN, Chiron	US
HVTN 044	Dec-03	DAIDS, HVTN, VRC	US
IAVI A001	Dec-03	Columbus Children's Research Center, Indian Council of Medical Research, National AIDS Control Organization, IAVI, Targeted Genetics	Belgium, Germany, India
B011; RV 138	Jul-02	WRAR	US

KEY

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  
 NIAID National Institute of Allergy and Infectious Diseases

NIH National Institutes of Health  
 SAAVI South African AIDS Vaccine Initiative  
 UMMS University of Massachusetts Medical School  
 USMHRP United States Military HIV Research Program  
 VRC Vaccine Research Center  
 WRAR Walter Reed Army Institute for Research  
 ZEHRP Zambia Emory HIV Research Project

VACCINE(S)	# OF VOLUNTEERS	CLADE
Adenovirus vector with <i>gag, pol + env</i>	48	B A, B, C
Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>	40	B A, B, C
Prime: DNA vaccine Boost: recombinant adenovirus vector	49	C
Intramuscular or intradermal injections of plasmid DNA. with HIV genes <i>env, rev, gag, and RT</i>	40	A, B, C
Vaccinia vector with <i>gag, pol, nef, env</i>	40	C
Recombinant HIV-1 multi-envelope DNA plasmid vaccine with <i>env</i>	6	A, B, C, D, E
Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>		B A, B, C
Modified vaccinia Ankara (MVA) vector with <i>env/gag-pol, nef-tat</i>	48	C
VEE (Venezuelan equine encephalitis) vector with <i>gag</i>	96	C
Prime: Modified vaccinia Ankara (MVA) viral vector with <i>env, gag, tat, rev, nef, pol</i> Boost: Fowlpox viral vector (FPV) with same genes as prime	150	B
Conserved CTL epitopes from <i>gag, nef</i> and helper T epitopes from <i>env, gag</i> in adjuvant (RC329-SE), with or without cytokine (GM-CSF)	96	B
Adenovirus vector with <i>gag</i>	435	B
Prime: DNA vaccine with <i>gag, env</i> attached to microparticles Boost: Env protein (oligomeric gp140) + adjuvant (MF59)	96	B
DNA vaccine with <i>gag, pol, nef + env</i> with or without cytokine (IL-2) adjuvant	70	B A, B, C
AAV2 (adeno-associated virus type 2) vector with <i>gag, pol, ΔRT</i>	50	C
Canarypox viral vector with <i>env, gag, pol</i>	36	B



DATELINE **2011**

LOCATION **Kiev, Ukraine**

Masha, a study nurse at a clinical trial site in Kiev, is sixty-three years old. This makes her nearly a statistical anomaly in a part of the world that has seen life expectancy decline as health care services faltered in post-Soviet Union times.



It also means that she can remember when the first prevention research sites were established in her city; and how long it took to establish trust with the injection drug users, commercial sex workers and migrants; and how it was yet more difficult to establish a community advisory mechanism that brought leaders from these socially-stigmatized groups together with scientists and clinicians to discuss those first protocols.

In those days, she never thought the clinic would be in the position it is in now: having to turn down protocols because the site is already functioning at capacity.

She thinks back over the past few years: as part of an international trials network, Masha and her team have recruited volunteers for a follow-up test-of-concept study of a candidate that showed some efficacy in preventing heterosexual transmission.

Initially, volunteers wanted the vaccine regardless, and said that it would be unethical to have placebo-controlled trials. However, after community educators talked about the statistical uncertainty around the result, and about the different modes of transmission of HIV, these attitudes changed, and the study was launched.

But now there are several new candidates that have emerged as a result of basic science initiatives that were launched in 2006. No one knows whether these new strategies will work, but there is excitement about the animal study data; Masha has picked up the optimism of her colleagues at scientific meetings. She's been hoping that their site could start a safety trial of one of these candidates sometime soon.

But at a meeting today, the team looked at its resources and its plans for the year and decided it couldn't be done. The site has been supported for its trial-specific activities, but not for overall growth and expansion that would allow it to easily add another study. And the resources are stretched too thin on the test-of-concept trial already.

How did this happen, Masha wonders? And is it the case elsewhere in the world? Or was there an organized effort to build trial site capacity in line with the anticipated needs as new candidates emerged? She hopes so—just as she hopes that the studies that do happen include injection drug users and their partners. It's a position she would rather not be in: she cannot help test the hypothesis at her own already over-taxed trial site. Instead, she will have to wait and find out.

## 02. Reports from the Frontlines: Learning from Last Year's Clinical Trials

As we look back on this year's clinical trials of new prevention technologies, we are struck by a field that is teeming with activity and yielding insights at an invigorating rate.

Taking stock of this activity means taking a step back: lessons are coming from AIDS vaccine trials, but they are also coming from microbicide studies and from the array of other new prevention research endeavors discussed in greater length in chapter 4. This is especially true for areas of community involvement, ethical discussions, infrastructure, staffing and capacity building.

But there are also issues that are specific to AIDS vaccine trials. These include decisions about which candidates move forward into trials; how to sequence trials (of the same candidate and of candidates in the same class) and related investments in manufacturing; and selection of study endpoints, particularly for vaccines that might work by reducing the severity of disease progression.

This year brought developments on both fronts—some new, some familiar but newly-urgent, and some open questions. Taken together, they serve as signposts for where the field should (and should not) be heading in the coming years.

### Calculated risks in trial sequencing

Last year we reported that the STEP study, a test-of-concept of Merck's adenovirus candidate, which is being run by Merck and the National Institutes of Health HIV Vaccine Trials Network (HVTN), doubled its enrollment from 1500 to 3000.

Even with the size increase, the single trial remains a test-of-concept which will, at best, give an indication of whether there is a trend towards efficacy that would then be re-confirmed in subsequent trials.

This year, Merck and the HVTN decided to begin preparations for a second test-of-concept trial which is known as HVTN 503. This trial is planned for South Africa and will test the same candidate, and include a possible study among adolescents (see chapter 3).

This decision is a risk, in that HVTN 503 will go forward before any conclusive data have been analyzed from the ongoing STEP study. More precisely, it is a calculated and exemplary risk. Merck's Ad5 vaccine is the lead candidate at the moment. The sequencing of the STEP and 503 means that we will minimize any delay in gathering additional data, should STEP indicate that the candidate has some efficacy.

HVTN 503 will also shed light on whether a vaccine that is based on epitopes that are conserved across clades but based on a single subtype (B) is immunogenic and effective in the South African setting, where subtype C predominates.

In the best-case scenario, where both trials show efficacy, there will be important lessons to learn about how to explain these sequencing decisions to various audiences. And in a situation where there is indeterminate or no efficacy, the field will have an opportunity to re-orient itself to new directions, based on the data.

FIGURE 4

COUNTRIES CONDUCTING PREVENTIVE AIDS VACCINE TRIALS (AUGUST 2006)



With the stakes as high as they are in the epidemic, a gamble on positive results is the right decision. This is the kind of forward-looking risk-taking that the field needs and should embrace.

At the same time, we must prepare for the ethical questions that may arise when and if a product that shows signs of efficacy in a test-of-concept trial is moved into a phase III study.

Various community constituencies have questioned whether a placebo-controlled trial of a product showing indications of benefit can be justified, and this concern needs to be addressed immediately.

**Moving forward with a collaborative trial**

The Partnership for AIDS Vaccine Evaluation, or PAVE, has continued its work on a collaborative trial of the Vaccine Research Center’s (VRC) DNA prime/Adenovirus-vector-based boost vaccine strategy. The three-part phase II trial of the combination has begun in the Americas, where the sites are being run

by the HVTN; in East Africa, where the International AIDS Vaccine Initiative (IAVI) and the US Military HIV Research Program (USMHRP) are running sites; and at HVTN sites in South Africa.

PAVE is testament to the fact that entities with different organizational cultures, funders, protocols, and approaches to everything from assays and blood draw procedures to precise definitions of adverse events can work together on a single trial. “This required a lot of negotiation and several inches of paperwork to arrive at a compromise,” says Assistant Director for HIV/AIDS Vaccines at NIAID, Peggy Johnston. “What is underestimated is the amount of time [that collaborations take].”

The VRC candidates contain *env* genes from multiple subtypes—another potential strategy for a vaccine that is effective around the world. Conducting trials in multiple regions is a critical first step to testing this hypothesis. A trial with the geographic spread of the current Phase II could not have easily been conducted

The Division of AIDS of the National Institutes of Health (DAIDS) houses various networks that fund assorted HIV/AIDS-related clinical trials across the world—and is the largest funder of vaccine and other prevention studies in the world.

All of the AIDS-related clinical trial networks funded by DAIDS have time-limited funding from grants, which generally last five years. This year, as part of the ongoing “recompetition” process, DAIDS considered applications from existing and proposed networks, all seeking funding for the next seven years.

The six networks were announced in June and will each address a different priority: vaccines (HVTN); microbicides (MTN); other prevention research (HPTN); maternal, pediatric and adolescents (IMPAACT); strategic initiatives (INSIGHT); and therapeutic clinical trials (ACTG.)

Clinical trial sites and research organizations around the world were able to apply to one or more of these networks, and so could potentially work with multiple networks at the same time doing different types of studies. Under this arrangement, DAIDS—which has its own, increased centralized budget for trials activities—offers a lump sum to a site, which covers core operations for all of the networks that it is working with. Each network then funds the direct protocol and study operations costs for the site. Sites were free to apply to as many networks as they liked, and the networks could approach promising sites as well.

This arrangement is one strategy for realizing the vision of “pluripotent” or multifunctional sites which can do multiple types of research simultaneously or in sequence. It’s a vision that has gained a lot of traction in conference-room conversations about clinical trial-site capacity. In theory, it offers a cost-effective approach to maintaining sites, using trained staff and infrastructure effectively, and ensuring that there is less “down time” between trials.

But how does the reality look on the ground?

As a first step towards answering this question, AVAC spoke to seasoned investigators in South Africa about how their sites are faring under this system.

At press time, most sites were waiting to hear the outcomes of their applications, and most had applied to more than one network, in hopes of broadening from areas of proven experience (be it prevention of mother-to-child transmission, ARV delivery, vaccines or microbicides) into newer activities.

Overall, we heard good news and some cautionary notes. There was broad consensus that multi-tasking was a cost-effective approach, but there was also concern that some essential activities might be under-funded. Most sites also felt that they would need to find additional funding resources for trial-related activities from a limited local and international pool.

Staffing was a major concern. Because staff funding is often related to specific protocols, salaries have to be apportioned across different projects and sometimes even different funders, as no single funder is really prepared

to support entire, long-term staff structures. Instead, they prefer to pay for part of an individual staffer's time. The result is a juggling act, which can sometimes fall short. One investigator, who, like many interviewed, asked to speak anonymously, said that this could become a "huge problem." Another site reported losing a fairly senior and experienced investigator as a result.

Another area of concern was capacity development—the catch-all phrase which includes developing, training (and re-training) staff; maintaining and expanding infrastructure; and building and sustaining strong relationships in the community and at multiple levels of government and the media.

Here, too, human resource issues loom large. "Capacity development will need further funding from the outside," says Glenda Gray of the Perinatal HIV Research Unit at the Chris Hani Baragwanath Hospital in Soweto. "No one is willing to pay to develop scientists or researchers. We will need to be innovative to ensure that capacity development occurs."

Gita Ramjee of the South African Medical Research Council says that the sites that are best positioned to become multifunctional are ones that already have strong capacity, raising the question of whether and how new, additional capacity can best be developed. "The [DAIDS] funding will be for research within clinical trial sites with trained staff and infrastructure," she says.

Other areas of concern include long-term and essential issues of social marketing and communication about the site's activities, HIV research and services such as counseling, testing or treatment. Community mobilization, recruitment and retention are also time- and labor-intensive and can be under-funded through protocol-specific budget lines, as well.

"The big issue is that funding occurs on specific protocols, so money only flows when you are enrolling or have activated a protocol. There is very little money to develop sites' community relations. Sometimes it can take up to 18 months to get real community buy-in and no one is prepared to pay for the preparations sites need to do before trials are started," says Gray.

Balanced against these concerns is the over-riding sense that working with the NIH is a truly collaborative exercise, and that there are many benefits—from training opportunities and infrastructure development to information exchange with colleagues in other countries—that come from working within the DAIDS networks.

Given the range of trials that are ongoing or planned for the coming years, it will be critical to build on these strengths and to pay close attention to unmet needs, including ongoing community work, development of new sites, and expanded relationships with existing treatment and care infrastructure. Addressing these issues is critical to making the idea of multifunctional sites a credible and sustainable reality.

"But," says Gavin Churchyard, a principal investigator at Aurum Health Research, which is working in South Africa's mining communities, "our complaints are small in comparison to the good work being done with the networks and the NIH. It is mostly a very positive experience."

FIGURE 5

ESTIMATED NUMBER OF ADULTS AND CHILDREN NEWLY INFECTED WITH HIV, 2005



by any single partner, since each has focused its efforts in a particular region. For this reason, PAVE’s work to date and in the planned PAVE 100 trial (whose test-of-concept protocol is in collaborative development) is a strong example of where collaboration is a wise and necessary choice for moving forward.

#### Trouble-shooting in the Thai Prime-Boost Trial

In late 2005, the Thai Prime-Boost trial of Sanofi Pasteur’s ALVAC vCP1521 and VaxGen’s AIDSVAX enrolled its last volunteer, reaching its target number of 16,402 volunteers from Chon Buri and Rayong provinces in Thailand; all immunizations were completed at the end of July 2006.

One of the most important lessons to be learned from this trial—aside from the simple statement: it can be done—is that collaborative trouble-shooting can help address problems that emerge after the trial is underway. In the early part of 2006, the trial was seeing worryingly low retention rates of 88 to 90 percent says Nelson Michael, a principal investigator from the USMHRP.

The low retention rates (which reflect per protocol attendance at study visits) were attributed to higher-than-expected levels of migration from the rural provinces where the study population was drawn from, to the capital city of Bangkok.

To address this issue, the trial team worked with the Thai Ministry of Public Health (which has provided clinic space for the trial site activities) to add study site facilities to clinics in the Bangkok area and to train outreach teams to help trace volunteers who do not return for follow-up. As of July 2006, retention was up to 95 percent—a sign that the intensified and collaborative strategy had worked, says Michael.

Sharing experience of problem solving is essential: while trial administrators may be reluctant to air their issues in public forums, making case studies of where issues arose and were addressed will only improve future endeavors. While we cannot conduct trials simply for the sake of this type of information, we should make every effort to gather and disseminate it widely.

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**RECOMMENDATION:** Ensure that the various strategies for current trials and plans for future ones are shared at a meeting of a reconstituted Enterprise Clinical Trials Working Group, to ensure that lessons are learned, capacity needs are anticipated, and decisions about when and how to conduct and sequence trials are not made in a vacuum by any single sponsor.

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### Addressing the issue of vaccine-induced seropositivity

Many AIDS vaccine candidates include synthetic viral components that can cause a positive reaction in standard HIV diagnostic tests (which look for antibodies against the virus, rather than the virus itself). This phenomenon of “vaccine-induced seropositivity”—in which an uninfected volunteer tests positive for HIV antibodies—is a challenge that the field has faced, in theory, for several years.

But until recently, the issue has garnered little attention: trials were small enough to allow case-by-case attention to volunteers; or the candidates did not induce responses that made seropositivity an issue. The current Ad5 candidates may be changing this. Both the Merck and the VRC candidates are significantly more immunogenic than previous candidates. Most HIV tests detect antibodies generated against *env*. Merck’s Ad5 candidate does not contain *env*; the VRC’s candidate does.

The seeds of a solution may lie in the work of Hana Golding of the US Food and Drug Administration, who this year published a paper about HIV SELECTEST, a new assay that identifies antibodies against sequences of HIV that are not part of most current HIV vaccine trials.<sup>1</sup>

This is welcome news. But it is only a first step. Issues of regulatory approval, cost, manufacturing capacity, and existing testing algorithms at national and site level must be addressed before SELECTEST can be considered a complete solution.

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**RECOMMENDATION:** Develop a timeline with milestones for validating SELECTEST as a useful tool for addressing vaccine-induced seropositivity, securing approval, and moving to widespread, affordable access where needed.

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### Pregnancy

At the biannual Microbicides 2006 meeting in Cape Town, South Africa, much attention was given to higher-than-expected rates of pregnancy among women volunteers, particularly in the five ongoing efficacy trials of six products that are being conducted in multiple sites in sub-Saharan Africa and elsewhere. Sites are reporting rates of pregnancy as high as 64 pregnancies per 100 person-years.

These rates of pregnancy come among volunteers who are counseled about the need to use contraception and avoid pregnancy for the period of immunization; the data are ample evidence that these messages cannot overcome many other factors affecting women, including inability or unwillingness to use hormonal contraception or other highly-effective methods.

In some instances, women may decide to join the trial if they are planning to get pregnant, since the general level of medical care is greater than that available to the general community.

Since women who remain pregnant cannot continue using the study product (none of the candidates in development have undergone sufficient reproductive toxicity screening), they are removed from the active study protocol, although they continue to be followed up. This means a lower sample size and, by extension, the potential for reduced statistical power in the trials.

There are multiple options for addressing this challenge, from expanding the study cohort once the trial is underway, to enhancing on-site delivery of contraception, to targeting post-partum women, who may be most interested in family planning to space children.

<sup>1</sup> Human Immunodeficiency Virus (HIV) Vaccine Trials: a Novel Assay for Differential Diagnosis of HIV Infections in the Face of Vaccine-Generated Antibodies. *Journal of Virology*, Mar. 2006, p. 2092–2099.

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**RECOMMENDATION:** AIDS vaccine trial planners and advocates should actively engage the issues related to pregnancy, contraception, and women’s reproductive choices that have been highlighted by recent microbicide trials. AIDS vaccine trials historically have enrolled fewer women than men in many parts of the world. Addressing these issues in consultations with communities, local health authorities and international advocates could prove to be an important step towards facilitating women’s participation in these trials.

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### Making investments to reaching the “right” populations

The past year brought reports from scattered trial sites—including microbicide studies in Ghana and Nigeria, and a behavioral intervention among injection drug users in Russia—of instances in which the incidence among trial volunteers was lower than expected or predicted by study planners, with the result that the site lost its statistical power to answer the study question.

These reports underscore the need to invest the time and energy required to reach the right populations for prevention trials: those who are at high-risk of infection and therefore in high need of new interventions.

In many instances, the same factors that contribute to individuals’ vulnerability to HIV infection also present challenges from a trial planner’s perspective. High-risk women in the United States—who remain largely overlooked in many arenas of prevention research—are one example. AIDS continues to spread among poor women, often with substance-abuse problems, whose addictions can lead to homelessness, incarceration, and instability that complicate follow-up.

The key to addressing these issues is building relationships with communities of potential AIDS prevention trial volunteers. This takes time, energy, and an authentic commitment to creating an environment of mutual trust at every level—from the study team and the clinic space, to the attitudes of political, community and media leaders.

It also requires that sites take a context-specific approach to their recruitment efforts. In the case of the STEP study, each site has developed its own approaches, which range from street-based campaigns using former commercial sex workers to internet-based campaigns for San Francisco’s gay men to outreach to individuals who test HIV-negative at a voluntary counseling and testing center in Haiti. Successful sites have also been able to build trust by responding to rumors circulating in the community: when word went around in San Francisco that the vaccine candidate might contain live HIV, the site developed a simple ad campaign focusing solely on this issue—and saw its outreach numbers jump.

This approach appears to be working. As of mid-2006, the STEP study had met its target for recruiting high-risk volunteers, and was, if anything, exceeding its projected rate of “events,” says Mike Robertson of Merck.

“We emphasize to our sites that since this is an event-driven study, it’s not just about getting bodies through the door [to enroll]...but to focus on getting high-risk people,” Robertson explains. An event-driven study is one in which enrollment and follow-up continues until a threshold number of events—in this case, new infections—have occurred. In other trial designs, a specified number of people are followed for a pre-determined amount of time.

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**RECOMMENDATION:** Document and disseminate best practices in innovative epidemiological survey techniques to identify “hotspots” of incidence recognizing that this is an on-going process; fund and support projects for the resource-intensive work of reaching and retaining particularly vulnerable groups.

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### The need for consensus on “good community practice”

This item is last on this list but is first among AVAC’s own priorities. As we look at the state of the field and the array of scientific, ethical and logistical questions that are being raised by current trials in multiple fields,

we feel more strongly than ever that a consensus on “good community practice” is long overdue. This new “GCP” would be a universal document that would help the scientific community and communities “in the field” ensure that every trial that is initiated meets agreed-upon criteria for substantive and sustainable engagement with the issues.

**In the next year, AVAC commits to playing an active role in developing a draft set of “GCP” guidelines.**

To do this, we will start by engaging in dialogue with a wide array of stakeholders including researchers, community members, service providers and international decision makers. We began this process with a skills-building session in Toronto, and we are already using the insights and ideas from that initial collaborative step to move the process to the next level.

**Putting it all together**

From closely-spaced test-of-concept trials, to collaborative efforts, to trouble-shooting in the largest AIDS vaccine trial to date, the field is experimenting with different ways of working to evaluate candidates. At the same time, other research endeavors are providing relevant findings about reaching and working with various communities.

We must plan today with an eye towards the issues that will emerge in the future. Decisions about trial sequencing will only get more complicated as data from other prevention trials emerge (see chapter 4).

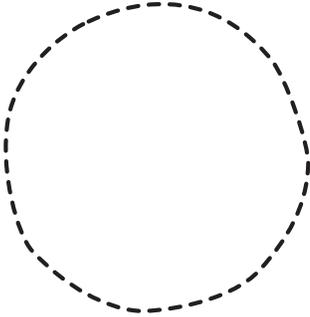
Nor will it be easy to interpret the data from the current test-of-concept trials—even if it is positive. The Merck candidate is being evaluated in trials that look at viral set point. But the field lacks validated endpoints for vaccines that aim to prevent disease progression. (It takes too long and would raise ethical issues to track infected volunteers without treatment over time; yet viral set point or peak may or may not be a useful indicator of a vaccine’s impact on long-term health outcomes.) VRC head Gary Nabel says that PAVE is considering memory cells as a surrogate marker of efficacy. This, too, has yet to be validated.

And so we must plan now so that we have capacity, community buy-in, and clear pathways to evaluate candidates that show different kinds of efficacy in initial trials. At the same time we must also plan for the time, several years from now, when a new generation of candidates begins to emerge from CHAVI and CAVD initiatives. Will capacity be there? Will communities be engaged and willing to participate in the full sequence of trials—from Phase I through efficacy—once again?



DATELINE **2010**

LOCATION **Kamwokya Trading Center, Kampala, Uganda**



Jackie has lived in the same small house for her entire life. She remembers when her mother died there and when her father's second wife arrived and later gave birth to twins. She remembers how one of the twins, a girl, grew sick and died before her second birthday, and how soon after that her father and her stepmother learned that they were both infected with HIV.

All that happened five years ago, before Jackie was six years old. Now Kato, the twin who survived, is fat and happy. So, too, are his mom and dad. They started getting ARVs from a family clinic that receives money from the US government. The same clinic gave Jackie her first HIV test, back when she was the age that Kato is now, and found out that she did not have the virus.

Jackie likes the clinic. It helped the people in her family, and it also helped her. One of the nurses there talked to her parents about a program just for girls. It wasn't a program for people with HIV. It was just a place to go one afternoon every month to play games and sing songs and sometimes to learn more about how girls can be healthy at every age.

Jackie started going to the program after her parents said it was alright. She made some friends and learned about how to eat healthy foods and why it is important to drink clean water, even if it means walking an extra kilometer when the local well is contaminated. She even got a vaccine, which the nurses explained would help protect her against a kind of cancer that some women got later in life.

Today Jackie is thinking about the clinic. She is walking back to the house carrying a bright yellow gerry can of water in each arm. Kato is playing in the packed-dirt yard where the local women brew *marua*, the strong alcohol that men in the neighborhood like to drink late into the night.

It is the sight of the women that makes her think about the clinic. They've started talking to her more than they did when she was a young girl, and they've told her to be careful walking around, even when she goes to the latrine at night, because their customers have said how pretty Jackie has become.

Jackie puts down her gerry cans and thinks. There is already one girl in their class who has fallen pregnant and had to stop school. That girl got the vaccine too, so Jackie knows it won't protect them against everything. But maybe the girls' program would have something else that could help her? She likes how the people there listen, and how she can go there and know that her parents will not disapprove.

But will the program be able to give her advice about how not to fall pregnant? About how to avoid that virus which is inside her step-mother and father? Jackie has heard that they are doing experiments in her country to try to find a vaccine that might block HIV. Could she be one of the people to go into that experiment? She'd like to, she thinks, and decides that she will go to the clinic tomorrow, just to ask.

### 03. The Emerging Adolescent Agenda: HPV Vaccine, AIDS Prevention Research, and the New Opportunities for Reaching the Young People of the World

Two years ago, in 2004, the AVAC Report examined the issue of adolescents and HIV vaccine research in its article, “The Missing Cohort.” Then, we pointed out that there were compelling reasons to include adolescents in HIV/AIDS vaccine trials, and that their absence from most studies of new biomedical interventions for HIV/AIDS prevention was an obstacle to progress in the field.

Two years later, in 2006, adolescents, particularly girls and women, remain at great risk of HIV infection and other sexual and reproductive health problems. When compared with male counterparts, they are disproportionately more likely to be HIV-infected before they celebrate their sixteenth birthday. And in several countries, marriage is actually an HIV risk factor for young women, even those who practice fidelity—one of the pillars of the PEPFAR prevention policy.

Nor can we forget the needs of adolescent boys and young men. In the United States, for example, some of the highest rates of new HIV infections are found in young men of color who have sex with other men. This was true two years ago, and it is true today.

So why is AVAC re-visiting the issue of adolescents in this year’s report? The answer is simple: even though the alarming statistical backdrop has remained the same, some important things have changed.

In June 2006, Merck received FDA approval for Gardasil™, its vaccine against human papillomavirus (HPV). This vaccine, which prevents infection with the HPV strains that cause cervical cancer, was found to have superb efficacy in trials of 20,000 young women around the world. The vaccine is currently licensed for use in young people up to age 26, and is likely to be most effective in pre-adolescents or adolescents before the age of sexual debut, when HPV exposure occurs. Also in June, the Bill & Melinda Gates Foundation announced a US\$27.8 million grant to the Program for Appropriate Technology in Health (PATH), which will oversee pilot HPV vaccine introduction projects in India, Peru, Uganda and Vietnam.

There are also new developments on the AIDS prevention front. As South Africa gears up for HVTN 503, a study of the Merck adenovirus-based candidate, it is planning for a nested substudy of the vaccine in adolescents—the first AIDS vaccine trial of its kind. Meanwhile, there are illuminating findings coming from microbicide trials which have enrolled women as young as 16 years of age.

Taken together, these developments add up to increased momentum in the field. But the elements of a nascent immunization program for adolescent girls, and an expanding knowledge base about how to ethically enroll adolescents in HIV prevention trials, will

not automatically coalesce into an ongoing, coordinated effort to improve health and reduce disease among the world's young women and men.

There is still much work to be done on the advocacy front. And so AVAC is revisiting the adolescent issue in this year's report with the goal of identifying steps that we and others can take to ensure that the promise of current events is realized in concrete changes in the future.

### **Laying a foundation for the future: HPV vaccine delivery**

AVAC believes that the licensure and plans for introduction of HPV vaccine are among the most important events to happen in the HIV/AIDS vaccine field this year. Of course there are important differences between HPV vaccines and potential AIDS vaccines (see Table 3), and HPV vaccines do not offer a perfect model for AIDS vaccine delivery—at this point, there is no such thing. However, taking an active interest in careful planning and implementation of delivery strategies for HPV vaccines—including honest, open analysis of what does and does not work—may be the single best step we can take to plan for access to an AIDS vaccine in the future.

*Here are four important reasons why:*

- **The same populations that need HPV vaccine the most also need HIV vaccines and other new prevention strategies.** Adolescent girls are at disproportionate risk for HIV infection in many parts of the developing world. In addition, adolescent boys and young men, particularly men who have sex with men, are also at high risk of HIV and must not be overlooked as a critical target population for enhanced, innovative adolescent health and wellness programs.
- **HPV vaccine presents a unique opportunity to develop a delivery infrastructure that reaches a population at grave risk for HIV/AIDS and other sexually-transmitted diseases.** An adolescent delivery platform for HPV vaccine could be enhanced or expanded to include HIV/AIDS vaccines, microbicides, male circumcision and other HIV/AIDS prevention interventions as they are identified.

- **Ensuring rapid access to HPV vaccine in high-need developing countries will upset the long-standing paradigm of delayed introduction of novel vaccines in developing countries.** It took twenty years from licensure to see widespread introduction of hepatitis B vaccine in the developing world. This is one of the many shameful examples of delays in distributing life-saving vaccines where they are needed most. AIDS prevention advocates can do more than make promises that AIDS vaccine access will not be business as usual. With HPV vaccine there is a concrete opportunity to make good on these commitments and, in the process, to build regulatory capacity at national and international levels.
- **HPV vaccine introduction requires careful messaging around scope and duration of vaccine-related prevention, screening and care for women who are already infected, and the need for continued condom use, irrespective of receipt of the vaccine.** Sound familiar? These are some of the key messages that will need to be conveyed to multiple audiences and in multiple contexts as part of the introduction of any partially effective HIV prevention intervention (see chapter 4). Getting them right in the context of HPV vaccine is critical for the program and, arguably, for multiple inter-related fields that will be speaking to the same target populations for many years to come.

**There are several steps that the AIDS vaccine field can take to optimize the potential benefits of HPV—both as a stand-alone intervention and in relation to HIV prevention:**

- **Advocate for international and national financing commitments to ensure widespread access to the vaccine in resource-poor settings.** The Global Alliance for Vaccines and Immunization (GAVI) has yet to determine whether or not it will finance developing countries' purchase of HPV vaccines. The HIV/AIDS prevention field can and should contribute to a strong "investment case" for this vaccine to be presented to the GAVI board, and should also lend support to groups lobbying for tiered-pricing and other strategies to make this high-priced vaccine (in the US, Gardasil™ will

**TABLE 3**

**HPV VACCINE AND HIV VACCINES: HOW DO THEY COMPARE?**

KEY SIMILARITIES	KEY DIFFERENCES
<p>New vaccine designed to prevent a sexually transmitted infection.</p>	<p>HPV vaccine can be—and is being—positioned as an “anti-cancer” vaccine, which can potentially distance it from the more sensitive world of sexually transmitted infections and sexuality, especially for girls and young women.</p>
<p>HPV vaccine requires three immunizations; AIDS vaccines currently in development also require a series of patient visits.</p>	<p>Burden of disease is very different—HPV is a significant public health problem for women and accounts for substantial morbidity and mortality with some 500,000 new cases diagnosed and 250,000 deaths each year. However, no where near the scale of the HIV/AIDS epidemic.</p>
<p>For maximum individual and public health impact, both vaccines are ideally delivered to young people before sexual debut (i.e., 10-13 years of age). This group is not currently reached effectively by health or social services.</p>	<p>Low levels of awareness of cervical cancer in many settings, even among health professionals and policy makers. Even in settings where there is some overall awareness, little knowledge of association between HPV and cervical cancer.</p>
<p>Both vaccines have the potential to raise complex social and familial concerns about behavioral disinhibition, “promiscuity” and so forth.</p>	<p>For AIDS, especially in high prevalence and incidence settings, pervasiveness of educational messages—and impact on families and people—mean people will likely be more aware and willing to consider being vaccinated against HIV than against HPV which is relatively unknown on its own or in connection with cervical cancer.</p>
<p>A young woman’s ability to access an HPV—or AIDS—vaccine will be influenced by many interlocutors— policymakers, providers, parents, and peers. In some settings, the actual people—in research, regulatory agencies, or ministries— may be the same.</p>	<p>AIDS has very vocal constituency and commitment and leadership at the highest levels; HPV will need to build constituency and political will.</p>
<p>Partial efficacy—although the HPV vaccine has been hailed as “nearly 100% effective” that is only against the four targeted strains of HPV. In effect this means that even with perfect coverage, it will potentially be able to prevent around 70% of cervical cancers.</p>	
<p>HPV vaccine was developed in the absence of a validated animal model or correlates of protection. Industry acted on a breakthrough (generation of virus-like particles).</p>	

cost approximately US\$360 for three injections) widely available.

HPV vaccine was also one of the products mentioned as a candidate for the G8’s proposed vaccine financing initiative. At the G8 meeting in July, the world leaders failed to reach consensus on this initiative; at subsequent meetings and in other forums, the

AIDS vaccine field should lend its voice and its expertise to strong calls for public financing, which would make this vaccine available and affordable from Appalachia (the region with one of the highest rates of cervical cancer in the United States) to Tanzania (one of the highest rates of cervical cancer in the world, according to the World Health Organization), and all points in between.

- **Document and learn from HPV experiences with clinical trials and pilot introduction programs.** The four pilot projects being undertaken by PATH will provide critical lessons about HPV vaccine delivery. These projects will examine a range of operational and political questions with the aim of informing and promoting favorable HPV vaccine policy at the global level. Each country involved (India, Uganda, Peru and Vietnam) is using a different model, and the PATH project includes a research and documentation effort to learn from these models, which will explore issues such as school- versus community-based delivery programs, feasible and acceptable target populations, community information needs, and prospects for financing of vaccine purchases and delivery. The Ugandan project has a stated objective of learning lessons in preparation for an HIV/AIDS vaccine. This is an objective that should be embraced by the AIDS prevention field as a whole.
- **Collaborate on advocacy and communication campaigns at every level.** From a public health perspective, new vaccines are often embraced as a “silver bullet”—the complete solution to stopping a given disease. For HPV vaccines and, in all likelihood, for AIDS vaccines, this description does not apply. Cervical cancer develops years after infection with HPV (just as symptomatic AIDS often develops years after infection with HIV). This means that the public health impact of these vaccines in terms of reduction of deaths or cancer incidence will not be seen for several years. Nor will the vaccine protect women who have already been exposed or who live in places where there are cancer-causing HPV strains in circulation that are not targeted by the vaccine. Here, too, there are key similarities with HIV/AIDS vaccines and other potentially partially effective interventions. In any country where there is an HPV program, there is the potential—if not the imperative—for AIDS prevention research advocates to collaborate, ensuring that there are harmonized messages that manage expectations about HPV vaccines today, and lay the foundation for the introduction of future partially effective interventions.

### Next Steps: AIDS Prevention Research Reaches Out to Adolescents

The AIDS prevention field can learn from HPV. It can also learn from its own experiences. After several years of discussing whether it would be possible to enroll adolescents into trials, there are fresh examples of innovative work with adolescents coming from within the field.

One exciting example comes from the Phase III trial of Carraguard, a microbicide candidate developed by the US-based Population Council. Trial sponsors recruited young women 16 years and older for its three trial sites in South Africa. The trial protocol was approved by the South African Medicines Control Council as well as the ethics review boards at the University of Cape Town, University of Limpopo/Medunsa Campus, the Medical Research Council, South Africa, and the Population Council.

In order to inform young women about the trial, the study staff members who conduct community outreach, first requested permission to speak at local schools. After receiving permission from schools’ administrations, the study staff held meetings at schools to disseminate information about the HIV pandemic and different prevention methods individuals can employ to protect themselves from infection. The trial was also discussed, and interested students were invited to visit the study clinic to receive more information. Clinic hours were expanded to accommodate student schedules should they choose to volunteer and so that formal information sessions and regular appointments could be scheduled when school is not in session.

One of the key issues for adolescent enrollment in prevention trials is whether or not parental consent should be a pre-requisite. In the Carraguard trial, two of the three ethics review boards initially approved the enrollment of young women (16-17 years old) with or without parental consent letting the participant decide whether or not she wanted to inform her parents. Ultimately, during the trial, the third ethics committee changed its stance and approved enrollment without parental permission. Young women who attend

information sessions are encouraged by study staff to bring their parents or guardians if possible. Women who are abstinent are encouraged to remain abstinent. However based on data collected in the trial to date, it is clear that 16-17 year-olds in the trial population are sexually active and at risk for HIV, thereby underscoring the need for their participation in this and future trials.

More insights could come from the planned proof-of-concept South African trial of the Merck adenovirus vaccine candidate that will include a sub-study of adolescents. The study, HVTN 503, proposes to enroll adolescents at sites around the country.

The study is designed to determine safety and immunogenicity in the adolescent population; however, there is a potential that the data from this sub-study may also be included in the final analysis of the larger Phase IIb trial. In preparation for the study, investigators in Cape Town and Soweto surveyed South African mothers and found that almost 90% were willing, or probably willing, to have their children participate.

AVAC welcomes these developments and encourages the field to take the following steps to ensure that we continue moving in the right direction.

To do this we must gather, discuss and disseminate information on some of the critical issues related to adolescent participation in research. These include:

- Parental informed consent: when is it mandatory; when is it optional; who decides?
- Social harm, stigma and subsequent access to care for adolescents identified as HIV-infected during the screening process
- Ongoing information/counseling needs for adolescent participants to address potential misconceptions about the protection/benefit that might come from experimental product
- Assessing the impact of trial participation on school or work attendance, sexual activity and other risk behaviors

The AIDS vaccine field, along with other partners in AIDS prevention research, should also continue

to call for, participate in and learn from country-level activities designed to clarify the regulatory environment around enrolling adolescents in clinical trials and delivering licensed products to adolescents. In May 2006, the US Food and Drug Administration (FDA) issued *Development of Preventive HIV Vaccines for Use in Pediatric Populations*, a guidance document designed to help trial sponsors and product developers understand FDA expectations and requirements. This document is a vital step forward, and AVAC is proud to have worked with the Elizabeth Glaser Pediatric AIDS Foundation and other groups to advocate for its publication.

But there are still unanswered questions, particularly for adolescents. The FDA guidance does not address how Institutional Review Boards (IRBs) should approach potential approval of trials enrolling adolescents. Here, one critical issue is identifying or clarifying the circumstances under which research on HIV vaccines in adolescents or infants could be approved as “presenting the prospect of direct benefit” to those adolescents and infants under DHHS §46.405 or FDA §50.52.

There is also a need to understand the risks that the IRBs will consider, including effects such as behavioral disinhibition and stigma.

The FDA does not have the monopoly on regulatory decisions around the world. It is vital to support country-level processes, such as the ones that have taken place in South Africa and Botswana, where legal precedents on age of consent for everything from marriage to HIV testing have been researched as part of an effort to clarify the environment for clinical trials.

The broader AIDS prevention research field should incorporate plans for gathering data on adolescents and children into product development plans. The field is seeking to coordinate its activities more than ever before (see chapter 4). Questions about safety and efficacy in adolescents should be identified and prioritized as part of the product development pathway for all candidates. This does not mean that all vaccine candidates should be tested in adolescents to start off

In the United States, the past year's discussions over HPV vaccine have underscored the current climate of discomfort, and political disincentive, for talking openly about sex. HPV is transmitted by skin-to-skin contact, primarily during sexual intimacy. Yet the desire to distance the vaccine from sex—and to focus solely on the less-stigmatized disease of cervical cancer—has led to some high-flying verbal gymnastics. One prominent researcher speaking on Capitol Hill suggested to a packed room of staffers that skin-to-skin HPV transmission didn't necessarily mean sexual transmission. It could also be sports related: "Think of wrestling," she said.

When we talk about HPV vaccine or HIV vaccines or any other intervention that has to do with young women's and men's lives and bodies, we should not be thinking of wrestling. Every country will make its own decisions about how to position and describe HPV vaccines. But no country or community should lose sight of the need to ensure that young women receive accurate and age-appropriate information about their lives and their bodies. This means discussing their right to education, employment opportunities, family planning and yes, sexual pleasure. It means telling the truth about the effectiveness of condoms in preventing the spread of HIV and ensuring that interventions that can prevent diseases are provided when they should be, with appropriate information and follow-up to ensure that the public health impact is maximized and personal risk of stigma and discrimination are minimized, if not eliminated.

with, but it does mean that all product developers should have a plan for when and how they will gather information about this critical population.

### Continuing the fight

It is far too soon to claim any victory at all when it comes to the fight to safeguard the health and well-being of the world's young people. But we at AVAC are heartened by signs that more and different stakeholders are entering the fight with the understanding that it is essential to any long-term progress in public health worldwide. We will hold ourselves accountable to doing our part to maintain this momentum, both by working towards implementation of recommendations made throughout this chapter and by taking on the following activities ourselves.

### AVAC Commits

- At AVAC, we have been working to articulate a pathway for IRB approval and to promote research to identify and mitigate risks to adolescents arising

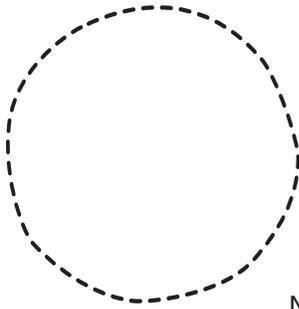
from trial participation. We will continue to do this through ongoing consultations with key stakeholders, and by publishing a background paper.

- We will actively participate in collaborative efforts to build a constituency for HPV vaccines. We are one of the co-conveners of the "Stop Cervical Cancer: Accelerating Global Access to HPV Vaccines" conference to be held in December 2006. There, we will work with policy makers, funders, and experts from adolescent health, sexual and reproductive health, cancer prevention and other arenas to develop a joint platform for action.
- We will lead and support efforts to solidify and systematize documentation of experiences with enrolling adolescents in clinical trials and reaching them with services, including HPV vaccine. We will seek out and act on opportunities to feed this information into policy frameworks, impact-modeling exercises, and country-level discussions.



DATELINE **2013**

LOCATION **Sub-Saharan Africa**



Principal Investigator Wilhemina X is the head of a center of research excellence in a sub-Saharan African country where prevalence has stabilized at an estimated 10 percent and incidence continues to be high among adolescents, young married women, internally-displaced people and other high risk groups.

For the past several years, her center has participated in vaccine trials, including early safety studies of *Vaxino*—an experimental AIDS vaccine candidate that showed unprecedented levels of immune responses in human volunteers in Phase I and Phase II trials.

Now, the time has come to evaluate *Vaxino* in efficacy trials. PI Wilhemina's site is one of those considered for inclusion in the multi-site trial. She is profoundly hopeful that her country will be included. It is a great opportunity to use the expertise and capacity of her team. And having lost a sister and several cousins to HIV/AIDS, she is personally aware of the disease's impact on women, and on the limitations of current prevention options, particularly for married women.

PI Wilhemina and her team have been working hard to prepare for the study. They have conducted community outreach activities to explain the trial and its questions, and have held dialogues with medical professionals, politicians and community leaders about the implications of identifying a vaccine candidate that might reduce the risk of HIV infection without completely preventing infection. They've also discussed the ethical and practical dimensions of the prevention, treatment and care provided to trial participants, their families and their communities.

In the midst of this activity, results are released from a microbicide efficacy trial that was also conducted in Wilhemina's country. The trial showed that the candidate is partially-effective; similar studies have had the same finding in other parts of the world. The WHO has yet to approve the product, but Wilhemina's country is a priority for rollout of an expanded access program, pending full regulatory approval.

On a conference call, Wilhemina and her colleagues discuss the implications of this development. If her site is included in the *Vaxino* trial, and the microbicide is available, there may be an ethical obligation to offer it to all trial participants. This means the site will have to recruit twice as many individuals as originally anticipated. It also means the site would be offering a different standard of prevention care than that provided at other locations, where the microbicide is not yet available.

The investigators consider their options: introduce the microbicide as part of the protocol in all countries, invest the resources needed to set up a nested sub-study of the combination strategy at Wilhemina's site, or exclude the site and move forward with the original protocol—the most efficient and least expensive option.

"What do you think?" an investigator asks PI Wilhemina.

She stays silent for a moment, weighing the options. The site has been gearing up for this trial for two years. This is the moment they have been waiting for. On the other hand, the network will have to scramble to find resources to fund the expansion of the trial site—and an answer could come more swiftly from another country where the microbicide is still not available on a national level. Then again, Wilhemina is concerned that population-level efficacy of the microbicide may be lower than what was observed in the highly-controlled clinical trial setting—and holds firm to her hope for identifying a vaccine for her country.

She takes a deep breath and begins to speak.

## 04. AIDS Prevention Evolves (Again): Why we are on the verge of an era of new complexity

What do AIDS prevention and the theory of evolution have in common?

One answer is that both have come under fire from right wing Christian fundamentalists in the White House and Capitol Hill.

Another is that one of the tenets of AIDS prevention, and evolution, is that things get more complex over time.

Both of these answers are of great importance today. 2006 brought a number of reports about how US government policies have threatened implementation of AIDS prevention and sexual and reproductive health services. Demanding that the interventions that we know to work—condoms, clean needles, mother-to-child transmission prevention—are made widely available is a top priority for every prevention advocate.

The issue of increasing complexity is also timely and highly significant. The next two to three years will bring the release of data from an array of studies including male circumcision, microbicides, AIDS vaccines, pre-exposure prophylaxis (PrEP) and treatment of HSV-2 infection (see Figure 6). These data will indicate whether any of these strategies provide protection against HIV infection.

Here, the key word is *indicate*. While data from some of these studies may give definitive answers about whether or not an intervention works, other studies have been deliberately designed to provide preliminary answers, which will need to be confirmed in further studies. One example of this is the ongoing “STEP” study of the Merck adenovirus-based AIDS vaccine candidate (for more on this, see chapter 1). This test-of-concept trial will give an early indication

of whether or not the vaccine candidate is effective. But no matter what, more studies will need to be done. Still other studies may yield data that are indeterminate or statistically hard to analyze.

Even when the data are clear-cut, they are expected to demonstrate only a partial efficacy. None of the interventions under study are going to be the silver bullet that provides complete protection against HIV infection for everyone under every circumstance. And so there are going to be additional challenges as the field works to provide clear messages about these new interventions to multiple audiences.

The field is on the verge of an era of increased complexity and, potentially, increased confusion. Will this result in progress (à la evolution) or chaos? AVAC believes that the answer depends on the willingness of various stakeholders to begin discussing and dissecting some of the key issues that will arise as data emerge from these new studies. This has already started in the context of circumcision. We believe that more efforts like these are needed, and on a larger scale. Here are some of the areas where attention is needed today:

### ETHICS

We start our list with ethics because in the face of data that are indeterminate or preliminary—and so require confirmation in additional studies—consensus on ethical issues will be of paramount importance.

Take, for example, the hypothetical case of a microbicide “X,” which reduces the risk of HIV infection by 30 percent among women volunteers who used the product consistently and correctly in the context of a prevention trial. In many instances, product developers

**TABLE 4 TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE (AUGUST 2006)**

Country	Male Circumcision	Female Diaphragms	PrEP	Herpes Suppression	Microbicides	Vaccines
<b>AFRICA</b>						
Benin					•	
Burkina Faso					•	
Botswana			•	•		•
Cameroon					•	
Ghana			•			
Kenya	•			•		•
Madagascar					•	
Malawi					•	•
Nigeria					•	
Rwanda				•		•
South Africa		•		•	•	•
Tanzania				•	•	•
Uganda	•			•	•	•
Zambia				•	•	•
Zimbabwe		•		•	•	
<b>ASIA</b>						
China						•
India					•	•
Thailand			•			•
<b>AUSTRALIA</b>						
Carlton, Victoria					•	
Sydney						•
<b>EUROPE</b>						
Belgium					•	•
Finland						•
France						•
Germany						•
Sweden						•
Switzerland						•
United Kingdom						•
<b>LATIN AMERICA &amp; THE CARIBBEAN</b>						
Dominican Republic						•
Haiti						•
Jamaica						•
Puerto Rico						•
<b>NORTH AMERICA</b>						
Canada						•
United States			•	•	•	•
<b>SOUTH AMERICA</b>						
Brazil					•	•
Peru			•	•		•

might then proceed with a second or even third efficacy trial to confirm the initial findings and to gather more information about how the product works in different populations with different HIV risk factors.

Suppose, now, that another microbicide or vaccine trial is being launched in the same country or region where the first study was conducted. Should microbicide “X” be included in that study, even if it has yet to be licensed and made available for widespread use? Scientists and trial planners might argue convincingly that this would be premature. But would communities see it the same way? Perhaps. But in the context of a broader array of prevention tools, it will be essential to use dialogue and consultation to define research questions that are relevant to scientists *and* communities.

At issue is how different communities interpret the state of equipoise (the technical term for a state of being equally balanced; or, not knowing the answer to a scientific question). This issue has already emerged in the context of PrEP trials, where some community advocates have asked why trials of mono- and duo-therapy for PrEP are happening at the same time.

As Susan Buchbinder, director of the HIV Research Section at the San Francisco Department of Health and a principal investigator on the STEP study (see chapter 2), explains, “There may be differences between ‘scientific’ equipoise and ‘community’ equipoise.”

There will also be ethical issues when the data are clear-cut, and a strategy is deemed effective. How will the poorest and most vulnerable populations be guaranteed swift access to these interventions? There will be an inevitable delay as manufacturing capacity is scaled up and individual countries deliberate over regulatory approval, financing and delivery. During this gap period, trial sites will face many specific questions, including:

- Can/should research sponsors wait until a product or strategy that shows efficacy in clinical trials is licensed, before considering it as part of an add-on trial of other interventions (see “Trial Design” section)?
- Once an intervention is licensed, should trial sites add it to volunteers’ prevention package regardless of whether it is adopted by the country as part of a national program—or will this provide undue inducement for volunteers to enroll?
- Couple-, family-, and community-oriented voluntary counseling and testing (VCT) all have potential to increase VCT impact on prevention; yet these interventions compromise the confidentiality of the trial volunteer, which is central to ethical conduct of all research. Is there a role for trial sites in expanding availability of enhanced VCT to larger community?
- If ethical obligations related to any or all of above questions slow or prevent effective AIDS vaccine trials, in spite of overwhelming need for this research, what are the ethical consequences, if any, of this type of delay?

As with many other realms of research-related ethics, there are no black-and-white answers to these questions—at least for the moment. But it should be possible to reach consensus on some of the critical issues by engaging and educating various audiences, constituencies and groups of decision-makers. AVAC commits to working with partners in various forums to initiate and inform these dialogues.

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#### **ETHICS RECOMMENDATION:**

Convene WHO/UNAIDS/Civil society-sponsored ethical consultations on issues related to introduction and evaluation of new partially-effective prevention strategies

Develop an infrastructure that will allow for ongoing review of these issues, so that consultations are not held at a single time point, but can be revisited and updated on a regular basis

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**TABLE 5** CONSIDERATIONS FOR USE OF A PLACEBO VERSUS AN ACTIVE CONTROL\*

	YES	NO
Is there effective treatment?	•	
Does the treatment affect survival or irreversible morbidity in the population to be studied?	•	
Is "effective" treatment accepted uniformly as standard treatment?	← Active control in all studies	Placebo control where doubt exists →

\* Adapted from Ellenberg et al. *Annals of Internal Medicine* 2000; 133: 464-470

### TRIAL DESIGN

Right now, all of the prevention trials that are being conducted address more or less the same question: Does this strategy decrease the risk of HIV infection more than the standard prevention package provided by the study? Or, more simply put: Does it have an added benefit?

The standard prevention package also looks more or less the same for most of these studies. It includes: risk-reduction counseling, condoms or clean needles or both (depending on the study population), and treatment for sexually-transmitted infections.

But as data are released from these studies, prevention trial planners may find themselves posing new questions and revisiting the components of a given study's prevention standard of care.

#### New Trial Questions

"Knowledge begets knowledge," astronaut John Glenn said. "The more I see, the more impressed I am—not with what we know—but with how tremendous the areas are as yet unexplored." And when a new AIDS prevention intervention is identified, it will bring as many new questions as it does answers: Is a second-generation candidate better than a first generation candidate—and if so, how much better? Is a combination of strategies—for example, a vaccine plus a microbicide—better

than either one on its own? Or: What is the overall public health impact of a package of interventions? To answer a different question, you need a different trial design. And a scenario in which there are one or more partially-effective "first generation products"—as well as a pipeline filled with as-yet untested second generation candidates will add complexity to the work of trial planners and product developers.

This is a welcome challenge since it would only emerge in the context of evidence that one or more strategies has some level of efficacy. "I would give anything to have my life be more complicated," says Benoit Masse, chief statistician for the newly-formed Microbicide Treatment Network (MTN), who, along with colleague Steve Self at the Statistical Center for HIV/AIDS Research and Prevention (SCHARP), is exploring the trial design issues that could arise when one or more partially effective interventions are identified.

But as welcome as this challenge might be, it must still be addressed with careful, coordinated planning. The ethical consultations recommended above are one aspect of this planning. It is also important to begin to explore the different trial designs that might be employed to get answers about new candidates, and to take steps to ensure that communities, political leaders and other audiences understand the rationale behind these various studies and the questions that they can (and cannot) answer.

TABLE 6

PRESENT AND FUTURE PREVENTION TRIAL DESIGNS

QUESTION POSED/ANSWERED BY THIS TYPE OF TRIAL	DESCRIPTION	STATISTICAL AND OTHER CONSIDERATIONS
Trial type: <b>ADD-ON TRIALS</b>		
Does adding experimental intervention “x” to the existing standard of care have a significant benefit (i.e., reduction in risk of transmitting or acquiring HIV)?	Most prevention trials use this strategy, i.e., <i>adding on</i> an experimental vaccine to proven interventions like condoms and clean needles and measuring any change, in incidence. In the future, add-on trials might involve a vaccine added on to a partially effective microbicide.	Sample size smaller in general than non-inferiority trials (see below); unable to provide answers about individual components of a given intervention.
Trial type: <b>SUPERIORITY TRIALS</b>		
Is one intervention better than another of the same type or category (i.e., an experimental microbicide/vaccine versus a partially effective microbicide/vaccine) when each is added to the current standard of care?	Trials that determine whether one intervention is more effective than another.	Sample size smaller in general than non-inferiority trials (see below) and similar in size to current Phase IIb/III trials; must be willing to drop intervention that might be ‘non-inferior’ to a partially effective intervention.
Trial type: <b>NON-INFERIORITY TRIALS</b>		
Is one intervention better or non-inferior than another of the same type or category (i.e., an experimental microbicide/vaccine versus a partially effective microbicide/vaccine) when each is added to the current standard of care?	Trials that determine whether one intervention is more, or at least as effective (within a certain margin) than another.	Can be very large (hundreds of thousands of people), particularly if the proven product has only low to moderate efficacy. Sample size for these trials is primarily determined by the anticipated magnitude of the effect of the new candidate and the size of the “non-inferiority” margin. If a first-generation candidate has a low level of efficacy (30-50%) then the non-inferiority margin will have to be small since the new intervention efficacy cannot get too close to, say, 20%.

**QUESTION POSED/ANSWERED  
BY THIS TYPE OF TRIAL**

**DESCRIPTION**

**STATISTICAL AND OTHER  
CONSIDERATIONS**

Trial type: **FACTORIAL DESIGN**

How do several different experimental strategies interact with each other and with the current standard of care?

Factorial trials can have multiple arms. For example, a 4-arm trial might test the following combinations:

- 1) Experimental microbicide + placebo
- 2) Experimental vaccine + placebo
- 3) Experimental microbicide + experimental vaccine
- 4) All placebo

Factorial clinical trial designs allow an assessment of interactions among the interventions.

Sample size can be smaller than with superiority trials, but it is usually difficult to predict favorable conditions for efficiency; potential efficiency gains should be weighed against potential loss of power under possible scenarios. (See Green et al. in *Journal of Clinical Oncology*, 20(16), 2002.)

Trial type: **COMMUNITY-LEVEL TRIALS**

How does a specific package of care provided to an entire community affect HIV incidence and prevalence in a population?

Randomization of communities to receive different interventions. Already being used to evaluate two VCT strategies, it could be adapted to evaluate various prevention "packages" including a range of components. Community randomized trials typically allow the assessment of direct and indirect effects of an intervention.

Provides a "real world" picture of the combined impact of an array of services. Because the measurement is at the population-level (incidence and prevalence), these large trials could be less expensive than superiority trials of a similar size which measure individual impact (a given individual's risk of HIV infection). They could not be used for licensure of a single product (similar to add-on trials). Also, in today's global environment, it may be increasingly difficult to find two comparable communities which do not have some degree of "cross talk" (knowledge of/access to what is happening in the neighboring site) which could complicate data analysis.

Work of this kind has already been done in Thailand around the ongoing prime-boost trial. The study tests a combination that includes AIDS-VAX, a candidate that failed to show efficacy when it was tested alone. If the ongoing trial does show some efficacy, it may be difficult to determine whether that is the result of the vaccine combination or solely of the ALVAC vCP1521, which is the other component of the prime-boost strategy.

More of this kind of work will need to be done on this front as various situations arise. Table 6 describes some of the different types of trial designs which might be employed to answer various questions.

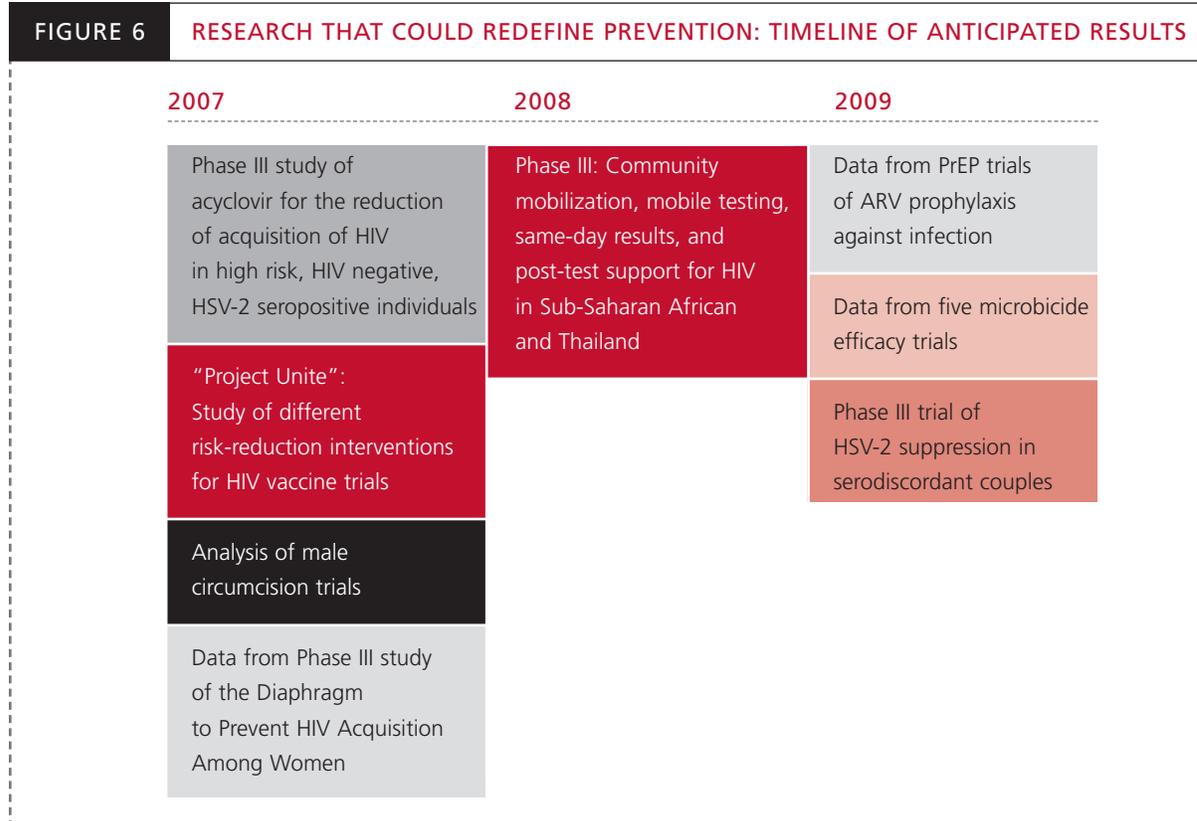
### A New Standard of Prevention?

The field must also plan for the scenario in which a new intervention is proposed as part of the standard of prevention services and interventions for trial volunteers. Such an intervention would then be

added to the package provided to volunteers in both the active and the placebo arm.

In some cases, there could be a clear-cut argument for adding this intervention. If, for example, treatment of HSV-2 in HIV-uninfected people slashes the risk of HIV infection, then this could become part of the standard of care for all prevention programs in a relatively short amount of time. After all, the drug acyclovir is already on the market and approved for exactly this use.

But here again, the field should also be planning for confusion. What if circumcision shows a high level of efficacy in protecting men against HIV infection? A trial site could not require that all of its participants be circumcised, but should it offer the service on site? How much counseling time should be devoted to helping men and their partners make this decision?



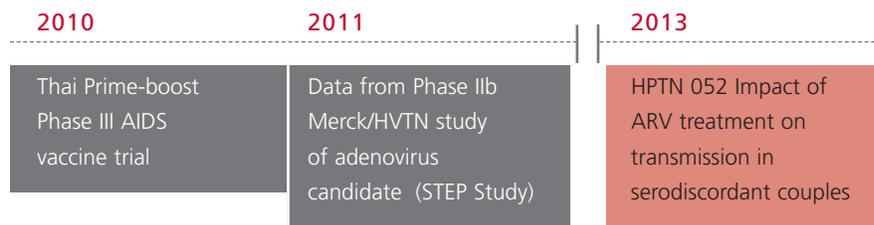
Or, what if one of the first-generation microbicides shows a low to moderate level of efficacy among women in serodiscordant relationships? Would it be ethical to conduct a placebo-controlled trial of another candidate in commercial sex workers, or should all trials going forward provide the first generation microbicide as an “active control”?

The above question is particularly difficult to answer prior to regulatory, licensing and manufacturing issues being addressed. During the limbo period prior to approval by the FDA, EMEA or other national regulatory authorities, how should these decisions be made? And in a situation of limited manufacturing capacity and finite quantities of product, should trial participants be prioritized to receive it?

The list of hypothetical situations and open questions is long. But given that we are likely to have several years to consider and prepare for them, we should use this time well. This means exploring how decisions about including a new product as an “active control” in a trial or in a country’s standard of care might be made.

Ben Masse and Steve Self have proposed the diagram in Table 5 as a starting point for these deliberations, but it’s important to note that these decisions will vary from country to country—especially in the period before so-called “normative” agencies like the World Health Organization, UNAIDS or PAHO have made decisions on a global or a regional scale.

In making these decisions, country- and community-level stakeholders (both policy makers and opinion leaders) will need a range of information including:



### The strength of the data from the efficacy trial

- Is it conclusive? If so, for which populations? Are additional confirmatory trials needed? Does the level of efficacy meet community expectations—for example, is a 30% efficacious product or intervention desirable in all settings in the same way that, say, an 80% efficacious intervention might be?

### The safety profile of the candidate

- Is the population in which product was evaluated similar in risk profiles, background disease, etc., to the one in which it might be used as an active control?

### Community input

- What are the perspectives of potential trial participants, political leaders, and medical professionals?

### Product availability

- Is there sufficient manufacturing capacity and supply to meet immediate and long-term needs? Is it licensed in the country where it would be used? Is it approved by international regulatory agencies?

It is important to plan for and discuss situations in which trial sponsors decide not to include a newly-identified intervention as the active control in a particular trial. This will not be the first time that such decisions were made; and they have drawn controversy in the past, as with the Ugandan study HIVNET 012, which compared the efficacy of single-dose nevirapine in mother-to-child transmission (MTCT). In that study, the control arm received a modified short course of AZT, which had shown efficacy in a recent Thai trial, rather than the extended regimen then used in the US and elsewhere in the developed world.

The world has changed dramatically since these early trials. ARVs are becoming increasingly available in resource-poor settings, and some MTCT programs have now expanded to MTCT-Plus, which provides combination treatment to the mother, father and children as needed after delivery. But future prevention

trials are still likely to face challenging decisions about *what* to add to the general standard of prevention care—or to the trial protocol—and *when* to add it. It will be absolutely critical that stakeholders on all levels contribute to the dialogue and decision-making process.

Adding an active control to a trial has an impact on the size and cost of the study. A new, additional effective intervention will ideally lower incidence in the trial population, thereby requiring larger numbers of participants and/or additional sites.

Depending on the trial design selected, the size of these trials could grow to greatly exceed that of current studies. Budgets for various trial networks, including the MTN and the HVTN, may be impacted by these findings—since most financial projections do not take into account the adjusted trial sizes suggested by early projections.

Large trials enrolling tens and hundreds of thousands of people are not unheard of, and have been conducted for other vaccines, like the Salk Polio vaccine, which was tested in hundreds of thousands of US children in the 1950s. More recently, the Merck HPV vaccine was tested in upwards of 20,000 young women. However, none of these interventions is a direct analog to HIV prevention, and much preparation is needed to ensure that there is capacity and political will for such trials to be done.

Getting regulatory guidance on the types of trial design that will be considered for licensure of a product is also important. If an add-on trial finds efficacy in a combination microbicide-vaccine, for example, where one component of the combination has not been tested on its own, how will the final product be licensed? This question will also be raised if there is an efficacy finding from the Thai prime-boost trial. Even though such questions may still be several years in the future, it is imperative that discussions among trial planners, funders, communities and regulatory authorities start now to avoid future confusion and delay.

It is also important to note that the majority of the new interventions currently under study are being evaluated for the prevention of sexual transmission of HIV. PrEP, HSV-2, and vaccine trials are all enrolling heterosexuals and men who have sex with men; and there is growing attention being paid to the issue of testing rectal microbicides in men who have sex with men. PrEP is also being studied in injection drug users, but this is the exception rather than the rule.

Cohorts of IDUs might therefore be recruited and ethically enrolled in trials that focus on efficacy of new interventions in preventing injection-related HIV transmission. But if these trials are to happen, it is critical that prevention-research sponsors and their partners in government and international health agencies do a better job of delivering proven interventions such as clean needles, syringe exchange sites, and drug replacement therapy using buprinorphine or methadone to trial participants. Twenty-five years into the epidemic, these proven interventions are still out-of-reach, if not illegal, in the vast majority of countries where injection drug use is driving the epidemic, and there is an urgent need to address this gap, both in the context of trials and on a broader policy level.

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### **TRIAL DESIGN AND PLANNING RECOMMENDATIONS:**

A series of expert consultations on trial design- and planning-related issues, with results widely-disseminated to prevention research stakeholders

Regulatory guidance from FDA, EMEA and other authorities about trial designs that can be used for licensure applications of candidates and/or combination strategies

Develop a coordinated advocacy agenda designed to document best practices and improve prevention services offered to IDU cohorts

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### **VOLUNTEER COUNSELING AND TESTING AND RISK REDUCTION FOR VOLUNTEERS**

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All volunteers in prevention trials receive intensive risk reduction counseling as well as condoms and, in some instances, clean needles. These are provided at every study visit. As a result, volunteers often receive a higher standard of prevention care and support on a more regular basis than is available to or accessed by the general community.

But while there is general consensus about the high-quality and standard of VCT and risk-reduction counseling in the context of vaccine trials, there is surprisingly little research evaluating the efficacy of these trial-specific interventions.

Nor is there any common mechanism for quality assurance or control that could be used to evaluate or review services at the time of site initiation or throughout a trial.

There are some analogies from outside the AIDS vaccine field. The “Explore” study recently completed in six U.S. cities was the first trial to prospectively evaluate the impact of two different risk reduction interventions on HIV incidence in MSMs. This trial enrolled 4295 men and followed them for more than four years. Ultimately, it found no significant difference in HIV infection rates between the two arms.

The “Explore” experience underscores the reality that it can be very difficult to gather definitive data on the different behavioral interventions. But there is still a need to improve our understanding of what constitutes quality risk-reduction counseling for trial volunteers.

Dr. Beryl Koblin and her team at the New York Blood Center are attempting to answer this question in the context of high-risk women, through a study

called UNITY, which is comparing two different types of HIV risk-reduction and vaccine-education interventions in high-risk women in New York City. The women will be offered hepatitis B vaccine as a surrogate for an AIDS vaccine. The trial will measure levels of comprehension about key aspects of vaccine research and number of unprotected vaginal and anal sex acts in the two arms.

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#### **VCT AND RISK REDUCTION COUNSELING**

**RECOMMENDATION:** Develop a fully-funded and coordinated research agenda geared towards defining the effects of various risk-reduction counseling strategies in context of HIV/AIDS vaccine trials

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#### **REGULATORY AND IMPLEMENTATION ISSUES**

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If a new intervention is identified, it will not automatically be adopted by all countries at the same time. As experience with HPV vaccine is showing, initial introduction may be in specific pilot countries; other countries may conduct cost-benefit analysis and determine that the value added by the new strategy—particularly one that is only partially effective—is not sufficient to justify the costs of introducing it at a country level.

Situations in which a new intervention has not been introduced as part of a national program, or is only available in select pilot sites, present a unique challenge to trial planners. “One of the questions you have to ask at a site and a country level is: ‘At what point would a research team have to say there is enough evidence for this to be [part of the trial] standard of care?’” says Helen Rees principal investigator at the Reproductive Health Research Unit in Soweta, South Africa. “Can a research team put in a prevention standard of care that is not programmatic in the country? At what point does that become a perverse incentive?”

These decisions bear strong similarities to the debates around provision of ARVs as part of the treatment

standard of care for prevention trial volunteers and communities. Here, sponsors are already grappling with questions like: What happens if ARVs are not widely available in the community or at country-level? What kinds of strategic partnerships can be leveraged to expand access to a given service, so that inequities between volunteers and their communities are minimized?

As trial sponsors face these decisions, so, too, do countries. And here there is an important role to be played by the World Health Organization in issuing and updating guidance notes on specific interventions. Given the planning and logistical requirements of introducing new prevention approaches, these documents should, in some instances, be issued before or at the same time as results from confirmatory trials are released.

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#### **REGULATORY AND IMPLEMENTATION**

**RECOMMENDATION:** Regularly-updated WHO guidance notes on new and emerging prevention interventions including male circumcision, PrEP, HSV-2 treatment, couples counseling, enhanced VCT to support country-level decision making about adding new interventions to national programs

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#### **COMMUNICATIONS AND ADVOCACY**

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The foundation for all of these action items is a clear and coordinated communications effort that conveys consistent messages about partial effectiveness, evolving standards of care and the need for trials of multiple prevention interventions—even after first-generation strategies have been identified. This effort can build on the strong work to date done by the microbicides and vaccine fields. But it must go further: in an era where there is a partially effective microbicide or vaccine, or PrEP intervention, the boundaries between the fields will all but vanish. It is incumbent on all prevention-research stakeholders to coordinate and prepare for this convergence.

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## COMMUNICATIONS AND ADVOCACY

**RECOMMENDATION:** Form a prevention research advocacy network that brings together stakeholders from all the various fields and regions to discuss communications and messaging strategies and to share best practices from around the world

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## THE AIDS VACCINE ADVOCATES' CHALLENGE

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In just a few years, the context for conducting prevention trials may be dramatically different from what it is today. But one thing is certain: there will still be a need for a safe, effective and affordable AIDS vaccine as an element of a comprehensive prevention package. Just as effective family planning programs rely on providing women with a “menu” of options for different times and situations in their lives, so, too, must AIDS prevention continually aspire to identifying a complete array of strategies and choices.

Given the history of vaccines as the most powerful tool for ending epidemics that the world has ever known, it is absolutely imperative that these trials continue to be prioritized and conducted, with the goal of identifying candidates with ever-increasing levels of efficacy. One reason for this is that challenges

of conveying the realities of partial efficacy will always be many—and hard to overcome.

AIDS vaccine advocates have a critical role to play in ensuring that research continues with speed and the highest ethical standards. To help contribute to this, AVAC commits to:

- **Create clear, user-friendly materials explaining the consequences of findings from trials of various interventions including circumcision, HPV vaccine, HSV-2 treatment, PrEP, microbicides and vaccines**
- **Support and/or convene a prevention research advocacy network that facilitates and disseminates results from expert consultations on cross-cutting ethical, community and trial design issues**
- **Develop, field-test and update initiatives to expand comprehension of partial efficacy and its implications for public health and future trial design**
- **Advocate at WHO level and elsewhere as appropriate for guidance notes on relevant topics**

Future AVAC Reports and publications will measure our progress on these goals and provide updates on the state of the field in achieving research milestones, while also providing excellent prevention services for every population, every place in the world.

## ABOUT AVAC

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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 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 CURRENTLY FOCUSES IN FOUR PRIORITY AREAS:

01. Develop and advocate for policy options to facilitate the expeditious and ethical development, introduction and use of AIDS vaccines and other new prevention technologies.
02. 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.
03. Monitor the AIDS vaccine field and mobilize political, financial and community support for AIDS vaccine research as part of a comprehensive response.
04. 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 that 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](http://www.aidsvaccineclearinghouse.org)), a comprehensive and interactive source of AIDS vaccine information on the internet.

### FOR MORE INFORMATION ABOUT AVAC'S PROGRAMS AND PUBLICATIONS OR TO BECOME A MEMBER, PLEASE CONTACT US AT:

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