Piecing Together the HIV Prevention Puzzle

AVAC Report 2009

AVAC
AIDS Vaccine Advocacy Coalition

Acknowledgments

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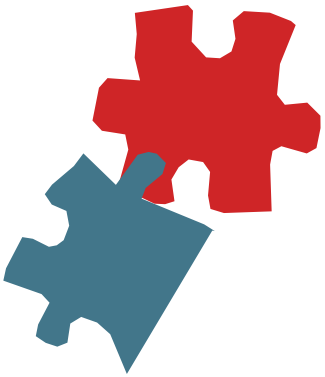


Piecing Together the Big Picture:
A letter from the Executive Director

How do we solve the HIV prevention puzzle?

No one has the answer yet. And we're still missing many of the necessary pieces. This much is clear from rates of new infections and persistently low coverage rates of proven prevention services and tools.

One portion of the puzzle can be solved in the near term by fitting together pieces we already have. These include protection of human rights; provision of safe, respectful, affordable and integrated prevention, treatment and care; sustained investments in health care infrastructure; and programs that addresses structural as well as individual risk factors. That these pieces remain jumbled is an ongoing challenge to us all.

Doing better with what we've got will fill in one portion of the puzzle. But there's also a continuing, urgent need for new pieces—new strategies—that can provide additional forms of risk reduction for people throughout their lives. The ultimate goal of biomedical prevention research on AIDS vaccines, microbicides, male circumcision, HSV-2 treatment and pre-exposure prophylaxis (PrEP), is to add some of these pieces so that someday we can complete the "big picture" of effective prevention to end the AIDS epidemic.

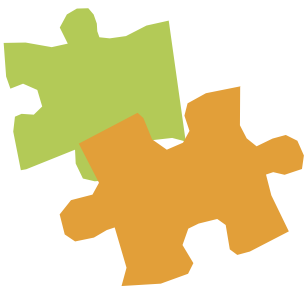
We're still a long way from that lofty goal. We're even a long way from having a single new piece of the prevention puzzle that could fit smoothly alongside any of today's proven interventions. This will hold true even if one of the current HIV prevention efficacy trials shows benefit (see page 4 for a list of 2009 trial milestones). A single positive result will trigger more research and the hard work of implementation, resource mobilization, and expanded community engagement.

In this year's *AVAC Report*, we highlight some of the ways that progress in biomedical prevention research is being made:

- Data from the Step vaccine trial are raising questions that might not have been identified otherwise (see page 32).
- Results are imminent from the Thai prime-boost vaccine trial, a study of HSV-2 treatment in HIV-positive people to reduce HIV transmission risk, an additional microbicide trial of PRO 2000 gel, and PrEP studies (see page 57).
- Research teams working with communities of gay men and other men who have sex with men in the developing world have created strong partnerships that have yielded data as well as new advocacy platforms (see page 64).

We also highlight some of the areas where there are challenges:

- The Global HIV Vaccine Enterprise still has to prove itself capable of convening the catalytic conversations among scientists, funders and donors, which many hoped it would when it was founded five years ago (see page 24).



- Enthusiasm about PrEP, and about using early initiation of ARVs in people with HIV to reduce their infectiousness, has catapulted the notion of "ARV-based prevention" into the spotlight. But the current conversation is unrealistic and pays too little attention to the major hurdles that would come with a new "ARV generation" (see page 46).
- The global epidemic in gay men and other men who have sex with men is soaring, with little action in many countries with homophobic policies, leaders, and/or cultures (see page 64).

If these lists of progress and challenges read like a jumble—with some themes repeated in both—then we've done our job. The biomedical prevention field has many of the pieces it needs to make real progress in both research and implementation in the coming years. But many of these pieces have yet to be assembled.

For example, as discussed in articles in this *Report*, we have seen only the very beginnings of conversations about how AIDS vaccine research and PrEP might fit together, and there's a need for a thoughtful look at how the rich array of AIDS vaccine research on control of HIV relates to research on prevention of infection.

"A long view is needed for the long haul of ending the epidemic."

Of course, figuring out the HIV prevention puzzle happens in the broader, global context of our times. And this year's *Report* comes at quite a time, indeed.

The great waves of consequences from the all-encompassing economic upheaval are deep, far reaching, and far from over: job losses, funding and revenue shortfalls, anxiety in non-profit and for-profit sectors alike, massive losses from bad investments and lack of growth, and ever-deepening ripple effects that underscore just how much we are all tossed around in the same small boat.

The current economic downturn is adding new stress, strain, and risk. But people infected with, affected by or working in HIV/AIDS have, for more than two decades, inhabited a world bound together by a single crisis with consequences that continue to defy the imagination.

The belt-tightening of the current financial crisis demands that people invest selectively. In the next few years, it's

Figure 1 2009 Trial Milestones to Watch

1st Quarter

Results from HPTN 035, phase II/IIb trial of the vaginal microbicide BufferGel and 0.5% PRO 2000 gel for the prevention of HIV infection in women (Malawi, South Africa, Tanzania, US, Zambia, Zimbabwe)

2nd Quarter

Results from Partners in Prevention, phase III trial of HSV-2 suppression in serodiscordant couples (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia)

Launch of FEM-PrEP, phase III trial to test a once-daily dose of oral TDF/FTC in women (Kenya, Malawi, South Africa and Tanzania)

Launch of VOICE, phase IIb trial to test effectiveness and acceptability of vaginal tenofovir gel and oral TDF and oral TDF/FTC (Southern Africa)

Launch of HVTN 505, phase IIb discovery trial of the DNA prime-rAd5 boost regimen in men who have sex with men (US)

3rd Quarter

Results from Project Unity, behavioral study of different risk-reduction interventions for HIV vaccine trials (US)

Results from ALVAC-AIDSVAX, phase III trial of a prime-boost combination preventive HIV vaccine (Thailand)

4th Quarter

Results from MDP 301, phase III trial of the vaginal microbicide PRO 2000 for the prevention of HIV infection in women (South Africa, Tanzania, Uganda)

Results from CDC 4323, phase II trial to test the clinical and behavioral safety of a once-daily dose of oral TDF among HIV-negative men who have sex with men (US)

VACCINE

PRE-EXPOSURE PROPHYLAXIS (PrEP)

BEHAVIORAL

HERPES SIMPLEX VIRUS 2 (HSV-2) TREATMENT/SUPPRESSION

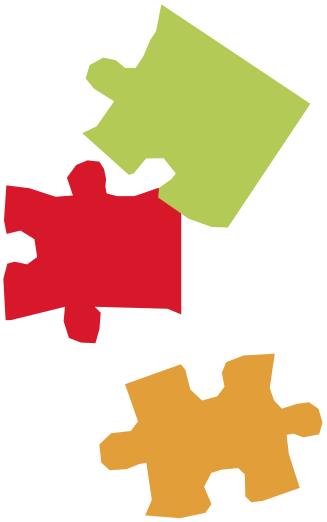
MICROBICIDE

likely that every dollar spent on the AIDS response will be subject to even greater scrutiny as budgets tighten and funders reexamine their priorities.

Against this backdrop of such urgent need and scarce resources, can AVAC realistically make the case for continued investment in HIV prevention research? To borrow one of the phrases that defined 2008: *Yes we can*. Moreover, yes we must.

A long view is needed for the long haul of ending the epidemic. Continued investment in proven prevention and prevention research is essential to safeguarding the inroads that have been made in delivering HIV treatment and care—including ARVs—to people living with HIV. The world is still far from treating every HIV-positive person who needs treatment, but progress continues to be made each day. To maintain the ground gained and continue pushing towards the goal of universal access, the rate of new infections must be slowed down. Effective prevention is the key. That's an investment argument we'd make in any year—in good economic times or bad. But we make the case this year with particular urgency based on the current context and opportunities elaborated in this year's *Report*.

To structure this year's *Report*, we took inspiration from a quotation in the 2006-2008 review of the Bill & Melinda Gates Foundation–funded Collaboration for AIDS Vaccine Discovery (*www.cavd.org*), which states that the ultimate goal "is to develop a vaccine that prevents HIV infection or disease—anything less than that can be characterized as progress, but not success."



In the first section, "Puzzling Out Progress," we report on the AIDS vaccine field, where there's an energized focus on discovery, innovation, and basic science. In the second section, "Puzzling Out Success," we turn to the implications of PrEP and other strategies in efficacy trials today. Throughout, we argue that success will depend on combination approaches: on research plus implementation; on vaccines plus PrEP, should either show benefit; and on communities plus researchers working towards common goals.

There isn't any money—or time—to waste. Funding decisions must be wise: non-duplicative to the extent possible, evidence-based yet bold, evaluable, expansive, and innovative. There is essential work happening at lab benches and clinic rooms, in legislative halls and town halls, at international agencies and community-based organizations.

Subtract any piece and the picture is incomplete; the HIV prevention puzzle is as it always has been: unsolved. But we have many pieces now—and more to come very soon—so we must be sure we know how to arrange them into a coherent and meaningful picture.

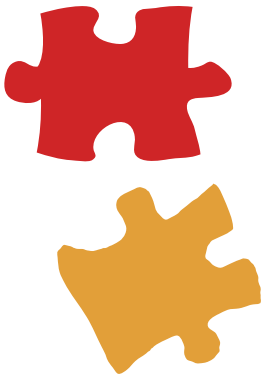
Mitchell Warren
AVAC Executive Director

In Memoriam

This year's *AVAC Report* is dedicated to Martin Delaney (1945-2009) and Lynde Frances (1947-2009), two indefatigable, irreplaceable AIDS activists who passed away in the past year.

Martin Delaney's insightful, provocative action for accelerated research on and access to AIDS treatments was based on the principle that people living with HIV and their allies can and must understand the science of AIDS treatment and prevention and be part of the decision-making processes that guide research and access. Groups like Project Inform, which Delaney helped to found in 1985, and AVAC are guided by this spirit to this day.

Lynde Francis was one of the first HIV-positive people to publically disclose her status in Zimbabwe, and the founder of The Centre for AIDS services, which has provided care, treatment and support to HIV-positive Zimbabweans for more than fifteen years. Lynde shaped lives, policies and activist agendas with deep wisdom, political savvy and articulate passion. Her leadership for women living with HIV, their families and partners had global influence and will be sorely missed by us all.



AVAC Report 2009 At a Glance

This year's *Report* covers a lot of topics. The summaries below are a guide to the main pieces of each section.

Puzzling Out Progress

Balance

Pursuing Prevention: Are there missing pieces? What might help the field balance research on virologic control with the pursuit of complete protection (see page 12)?

Planning

Fitting AIDS Vaccine Science into the Bigger Picture. What happens if there's evidence of benefit from trials of other strategies, like pre-exposure prophylaxis (PrEP) or microbicides? There will be opportunities and challenges for future trials (see page 22).

Coordination

Solving the Enterprise Equation: When is a whole greater than the sum of its parts? It's been five years since the field joined together in the collective venture of the Global HIV Vaccine Enterprise and one year since Alan Bernstein became its inaugural executive director. How well is the vision being realized (see page 24)?

Iteration

Steps to Success: The Step study's scientific contributions to the field. The trial of a candidate that failed to show overall benefit continues to yield valuable clues that can help improve next–generation approaches (see page 32).

Puzzling Out Success

Context

The PrEP Implementation Puzzle: Many missing pieces. No new prevention option will be a simple solution. Although enthusiasm is mounting about ARVs as prevention, it's essential to consider how PrEP or treatment-as-prevention of HIV-positive people to reduce infectiousness would impact health systems, human rights and current programming (see page 46).

Leadership

Part of the Solution: Setting expectations for WHO and UNAIDS. The World Health Organization and UNAIDS play essential roles as "normative agencies" offering guidance and technical and advocacy support to developing countries. What has recent experience with male circumcision taught about these agencies' strengths? What roles can they play in preparing for PrEP or other trial results (see page 54)?

Community Involvement

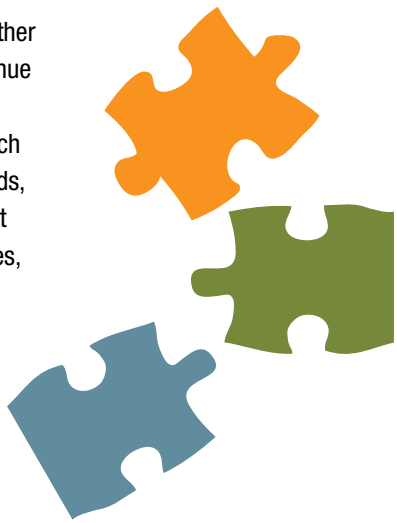
***Te queremos*—but are we ready? Taking the next step with HIV prevention research and gay men in the developing world.** Research projects can provide valuable information to guide implementation. Gay men and other men who have sex with men in the developing world have participated in a range of HIV prevention studies, and the first results from a PrEP trial may come from the iPrEx study involving gay men. What have these studies taught us, and what are the next steps (see page 64)?

AVAC's Top Recommendations for 2009 and Beyond

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

On page 8, we've taken a look back at what happened around last year's recommendations. And below please find our top recommendations that we will revisit frequently in the coming year to gauge how well we and the field are doing.

1. **The AIDS vaccine field** needs to expand its understanding of what HIV vaccines need to do, leading to more predictive measurement and novel and substantially improved next-generation candidates (see page 12).
2. **Biomedical prevention researchers and sponsors** must work with transparency and broad input to plan collaboratively for trials that might take place if PrEP or any other emerging strategy shows efficacy. A comprehensive research agenda needs to be developed that addresses questions such as what's possible in terms of evaluating combination strategies, and how decisions about shifting standards of prevention may be made (see page 22).
3. **The Global HIV Vaccine Enterprise** needs to demonstrate its value through timely publication of an updated Scientific Strategic Plan by early 2010 and improved leadership on critical emerging issues (see page 24).
4. **The HIV Vaccine Trials Network** needs to develop a suite of easy-to-understand materials that add depth and detail to available documents regarding HVTN 505, a planned test-of-concept trial of a prime-boost regimen developed by the US Vaccine Research Center (see page 38).
5. **WHO and UNAIDS** need to marshal their technical and advocacy resources to provide global leadership in preparing for pre-exposure prophylaxis (PrEP) should it show benefit for HIV prevention. The first step is developing, securing funding for, and implementing a jointly coordinated work plan, similar to the one used to prepare for results from the Ugandan and Kenyan trials of male circumcision for HIV prevention (see page 54).
6. **Stakeholders exploring PrEP and the use of ARV treatment to reduce infectiousness** in HIV-positive people need to add specificity around financial, health care infrastructure, and human rights implications of using ARVs for prevention (see page 48).
7. **Prevention research stakeholders from all arenas** need to embrace and execute an agenda, with bold, measurable milestones and targets, which focuses on the expansion of HIV testing and counseling as the cornerstone of implementing male circumcision and any new ARV-based prevention strategy, if one is identified (see page 48).
8. **Governments around the world** need to respond to the HIV prevention needs and priorities of communities of gay men and other men who have sex with men, as they continue to have high prevalence and be at highest risk. Data from prevention trials and research projects are helping to articulate these needs, but effecting change will be difficult without broad support and significant policy changes, which do not yet exist (see page 64).



Status Report

An update on last year's recommendations

1. Structure the field so that there are career paths for young investigators.

There's progress in this area from the HVTN, the Global HIV Vaccine Enterprise, and public health leaders outside the field. It will now be critical to monitor the impact of new initiatives aimed at addressing this issue.

2. Articulate the human discovery trials agenda and balance vaccine discovery and development.

The AIDS vaccine field has had a year of focused, nuanced conversations and presentations of new data and directions (see page 12). The Step trial has helped generate questions we might not have otherwise known to ask (see page 32). These developments should help shape the next Scientific Strategic Plan of the Enterprise (see page 24).

3. Learn from Step and direct prevention research resources to under-served populations.

In 2008 the US Centers for Disease Control and Prevention released revised estimates of the US AIDS epidemic, which underscore the severity in populations of gay men of color and of African Americans. The incidence from Step told a similar story. Far more needs to be done in terms of targeted spending and appropriate programs to address this crisis.

4. Systematically improve community engagement strategies.

There have been mixed results this year. AVAC and UNAIDS have worked with partners to disseminate the *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials.* There are strong partnerships between research teams and communities of gay men and other men who have sex with men in the developing world (see page 64). However, there are also ongoing questions from the broader community about the HVTN 505 vaccine trial (see page 38).

5. Watch language used to communicate expectations of prevention research.

It depends on whom you listen to. Enthusiasm about pre-exposure prophylaxis research, or PrEP, can sometimes produce overly optimistic forecasts of results (see page 46). The vaccine field has done a strong job of recalibrating expectations, though work still needs to be done around explaining discovery research. The microbicide field and its allies grappled with the challenge of an indeterminate finding with the results of the HPTN 035 trial, which showed a non-statistically significant trend toward protection with one candidate (PRO 2000).

6. Increase community stewardship of PrEP agenda.

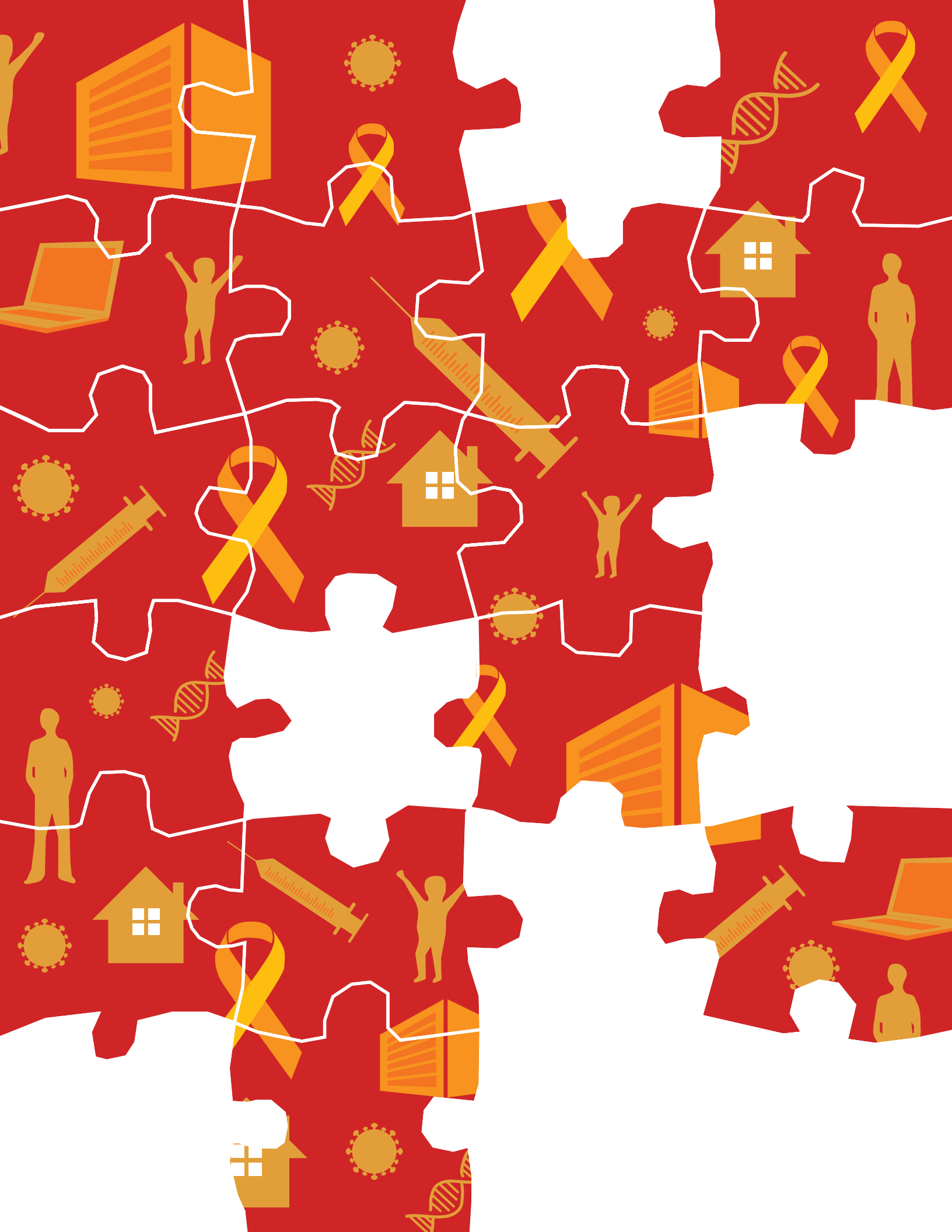
The expansion of interest in PrEP has been exciting to watch and be a part of. There are increasingly strong constituencies in the developed and developing world, and in specific communities like gay men and other men who have sex with men. Much more needs to be done, though, to grasp what PrEP would mean for health care infrastructure, financing, testing, and other issues (see page 46).

7. Engage in meaningful dialogue around male circumcision, HIV testing and gender.
WHO/UNAIDS published its report from the June 2008 meeting on male circumcision and implications for women; AVAC published its report on a complementary, civil society consultation that preceded the WHO meeting. Both are available at *www.malecircumcision.org*. On the ground, there's still a vacuum of accurate information about women's and men's experiences with rollout.

8. Prepare for the results of the Thai prime-boost trial.
The trial sponsors have developed a comprehensive dossier in anticipation of results, which includes different communications messages under different scenarios. AVAC is preparing a publication in its "Anticipating Results" series to help advocates understand the trial, which will present results in September.

9. Expand community engagement with and critiques of the microbicides science agenda.
The Microbicide Media and Communications Initiative hosted three meetings for advocates and communications experts to clarify issues and priorities around ARV-based microbicides. And there's growing discussion about the similarities and differences between PrEP (oral ARVs) and topical ARV-based microbicides. But the distinctions are still blurry, and there's need for more clarity on science topics and possible trial-sequencing scenarios should PrEP, PRO 2000, or an ARV-based microbicide compound show efficacy.

10. Reconsider how clinical trials infrastructure is sustained and clinical research agendas are developed—in discussions led by developing country voices.
Throughout the first section of the *Report*, there are first-hand accounts of innovative activities taking place at vaccine trial sites throughout sub-Saharan Africa. But there's more work to be done to capture best practices and, where warranted, harness capacity of under-used sites.



Puzzling Out Progress

As we take stock of the scientific landscape of AIDS vaccine research in mid-2009, there's much to be positive about. Data from individual scientists and from "big science" consortia have added nuance to our understanding of HIV-specific cellular, humoral, and innate immunity. Vaccine-related goals are being refined, and we're continuing to learn from the Step trial of Merck's MRK-Ad5 candidate that failed to show any benefit in late 2007. This section considers what it may take to ensure that this progress sets us on the right course for success.

Balance

Pursuing Prevention: Are there missing pieces?
What might help the field balance research on virologic control with the pursuit of complete protection (see page 12)?

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Fitting AIDS Vaccine Science into the Bigger Picture
What happens if there's evidence of benefit from trials of strategies like pre-exposure prophylaxis (PrEP) or microbicides? There will be opportunities and challenges for future trials (see page 22).

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Solving the Enterprise Equation: When is a whole greater than the sum of its parts? It's been five years since the field joined together in the collective venture of the Global HIV Vaccine Enterprise, and one year since Alan Bernstein became its inaugural executive director. How well is the vision being realized (see page 24)?

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Pursuing Prevention

Are there missing pieces?

Over the past year, the AIDS vaccine field has intensified its focus on discovery and basic research. More scientific questions are being generated than answered, and it's not possible to put these sometimes disparate pieces of knowledge together to "solve" the AIDS vaccine field. Just as with a real puzzle, the number of pieces gives us some idea of how big the "big picture" really is.

How do we handle this pile of pieces, which keeps growing? First of all, by not discarding any piece prematurely. We learn as children that even if it doesn't look like it fits, it might later on, once more has been filled in. In the adult world, this means that the field must continue to balance funding decisions and scientific portfolios so that no single assumption—however cherished—gets a disproportionate investment of time, money or human resources. For example, in the arena of T cell–mediated immunity, where there's ongoing work to define the qualities of an effective HIV-specific response, this means striking a balance between research on epitope specificity and breadth, and research on functionality.

On a larger scale, this means that work on understanding the mechanisms of virologic control must be balanced with research aimed at vaccine-induced prevention of infection. And on an even broader scale, it means making connections between AIDS vaccine research and research on pre-exposure prophylaxis (PrEP) and other proven and emerging strategies. This article looks at some of the areas requiring balance and attention to *all* the pieces.

Piecing together the puzzle of control

Vaccines are among the most powerful public health tools in the world. With a single or a few immunizations, they simply and effectively prevent illness from pathogens such as poliovirus, smallpox, measles, and yellow fever, all of which claimed many lives before effective vaccines were developed. These successes have led to the oft-voiced opinion that an AIDS vaccine that prevents infection would be the single most powerful tool for ending the epidemic. This is true, but it's also true that for some time now, the AIDS vaccine candidates that have reached clinical trials have aimed not at complete protection but at reducing viral load in people who get vaccinated and go on to become infected. The hope here is to delay time to treatment or HIV-related disease.

This goal has come about because recent candidates have primarily aimed at T-cell immunity, which is often assumed to be incapable of preventing infection on its own. This is suggested by animal model studies and the primary function of cytotoxic T lymphocytes—to kill already infected cells. (This doesn't mean that T cells aren't part of the suite of protective immune responses that an effective vaccine might induce. There are also intriguing hints of T cell–mediated protection, as we discuss later.)

Finding a T-cell vaccine that improves clinical outcomes would be a valuable step toward developing a more traditional vaccine. However, for laypeople and health professionals outside the AIDS vaccine field, it's a major leap from a traditional vaccine to the potential profile of a T-cell vaccine. Impact on viral load setpoint as a surrogate for improved clinical outcome is a very different endpoint than complete or near-complete protection. It's also a major contrast with other interventions, like PrEP or male circumcision or microbicides, where reducing the risk of infection is still the primary goal.

The past few years have seen T-cell vaccines move into efficacy trials. These include the Step test-of-concept vaccine trial, which evaluated Merck's MRK-Ad5 candidate. This study, which looked at the vaccine's impact on both viral load setpoint and HIV acquisition, ended in 2007 when a planned data analysis showed no evidence of benefit, and a potential for increased risk of infection in specific subgroups (for more on Step, see page 32).

The NIH Vaccine Research Center's (VRC) DNA prime/Ad5-vectored boost combination is next to be evaluated in

Clinical Research Continues

Throughout this section, you'll find quotes from AIDS vaccine trial sites in Africa describing some of the work they've undertaken in the past year.

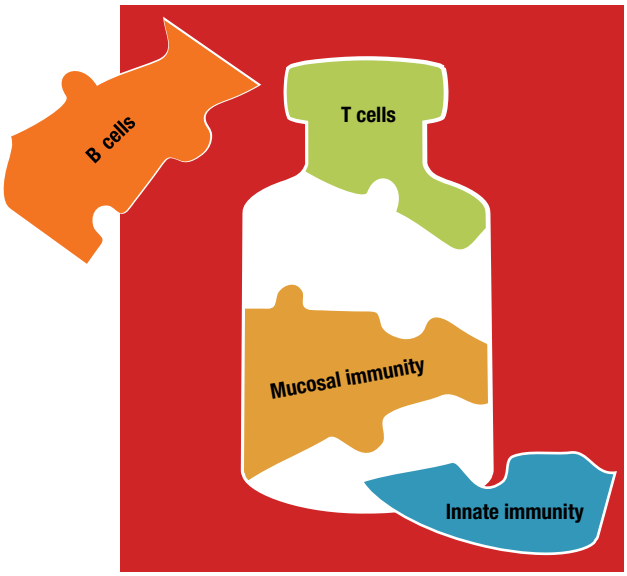
While the field is focused on a range of fundamental basic scientific questions, clinical trials continue to play an important role in vaccine discovery and development. At clinical trial sites, where plans for specific trials may have changed, there's a varied and vibrant range of activities contributing to the overall search for a vaccine.

As demonstrated in our annual table of *Ongoing Vaccine Trials* on pages 42-43, there remains a long list of products in different stages of clinical development.

Notably, results from the Thai prime-boost vaccine trial are expected in September. With over 16,400 participants, this is the largest AIDS vaccine trial ever undertaken. Despite its size, sponsors have pointed out that it is a "test-of-concept" meaning that if there's any sign of efficacy from the strategy—which consists of a canary pox–vectored candidate and the gp120-based AIDSVAX candidate—there will need to be follow-up studies to confirm and learn more.

If there is benefit, there will undoubtedly be questions about whether it is due to the combination of both vaccines or to a single component. (AIDSVAX alone showed no signs of efficacy in two prior Phase III trials.) AVAC will be providing an expanded discussion of the Thai trial as part of its "Anticipating Results" series which will be published prior to the data release.

Working on the Puzzle of Vaccine-Induced Protection



test-of-concept trial called HVTN 505 (see page 38). The strategy being tested in HVTN 505 isn't being considered for development as a licensed product. Instead, its exploratory goals are focused on how vaccine-induced cell-mediated immunity impacts viral load in people who receive the vaccine and later become HIV–infected. (The vaccine itself cannot cause HIV.) Of note, HVTN 505 will be the first AIDS vaccine test-of-concept trial conducted without an acquisition endpoint.

The focus, in these test-of-concept trials, on altering the course of disease is both complemented and informed by discovery research on mechanisms of control. For example, CHAVI collaborators David Goldstein and Jacques Fellay, both of Duke University, have worked with colleagues to identify variations in the major histocompatibility region of the human genome that help determine virologic control. These data came from genome-wide association studies of samples from the Euro-CHAVI consortium of cohorts. They reinforced the connection between specific alleles, like B57, and control (see box on page 17 for more on genomics research).

The International HIV Controllers Study, headed by Bruce Walker of the new Ragon Institute, has been another source of insight. The study has developed an innovative approach to researching elite controllers—who it defines as individuals who, without ARVs, have maintained less than 50 copies of HIV per cubic milliliter in their blood over at least a year. The study is also looking at individuals who control the virus at low, detectable levels. Researchers in the consortium are looking to learn from these rare individuals and are studying issues like innate immunity, B-cell and T-cell immunity (with a focus on the role of epitope specificity and breadth), host genomics, and patterns of viral evolution. These interconnected topics are often pursued in siloed agendas, and their integration in this project is commendable. So is the engagement of young scientists, several of whom have emerged as new leaders in the field based on their work with Walker and colleagues.

At the National Institutes of Health (NIH), Mark Connors and his lab have focused on other determinants of control including *in vitro* cytolytic capacity, which they're measuring with a single-cell killing assay. At the Keystone Symposium on HIV prevention this year, Connors compared the cytolytic function of elite controllers' T cells with T cells from HIV-positive people who were not controllers, and samples from individuals immunized with the MRK-Ad5 vaccine. The immune responses from the vaccinees had cell-killing abilities similar to those of HIV-positive people

who were not elite controllers. (This doesn't mean that their immune responses were linked to progression, just that they lacked some of the distinctive characteristics Connors and his team have identified in T cells isolated from elite controllers.) No cell-killing assay has yet to be scaled up or standardized for use as part of standard immunogenicity analyses, but as noted in last year's *Report*, it is an important measure that should be considered and adopted more widely when possible.

One of the subtexts for many of the papers and plenaries around these data has been the emergence of what often seem like distinct schools of thought about the underlying mechanisms of T cell–mediated viral control in elite controllers. Some researchers, like Walker and colleagues, are looking at the roleof epitope recognition. Others, like Connors, argue that aspects of functionality like cytotoxicity are more relevant and ultimately more predictive. Both lines of thought are fruitful to pursue, and donors and scientists must guard against funding decisions or research plans that stifle either approach.

The pursuit of prevention

The guiding principle behind all of the work described above is that identifying the elements of the immune profile that are associated with virologic control may yield specific targets for vaccine design. This is logical if one assumes that control mechanisms are the same as the mechanisms underlying prevention. But this assumption is uncertain.

We also don't know whether the immune mechanisms that operate in elite controllers are different from those that may be needed to prevent infection.

There is a narrow window when HIV is confined to the genital tract and could, in theory, be contained and even cleared by the right defenses.

So, in addition to keeping a balanced portfolio and a wide-open mind about cell-mediated mechanisms of viral control, it's also vital to maintain, assess, and strategically expand investments in vaccine strategies aimed at prevention.

When prevention does arise in the AIDS vaccine field, it is most frequently linked to potent, neutralizing antibodies—one of the holiest of "Holy Grails" that the field is seeking. The International AIDS Vaccine's (IAVI) Neutralizing Antibody Consortium, some of the consortia of the Bill & Melinda Gates Foundation–funded Collaboration for AIDS Vaccine Discovery (CAVD), and the National Institutes of Health's Center for HIV/AIDS Vaccine Immunology (CHAVI) and the VRC have all continued efforts to identify and isolate broadly neutralizing antibodies.

They've also worked on designing antigens that mimic transiently exposed targets on the virus. There's growing interest, too, in harnessing innate immune responses to help stop infection at the earliest points of entry into the body. However, the timeframes for developing candidates for clinical trials based on this work are long and the challenges are many.

One of the more interesting questions that we've heard this past year, which frequently emerges in discussions about all that's being learned about the multifaceted mechanisms of virologic control, is this:

Is the vaccine research agenda, which has focused in recent years on the immunobiology of viral control through T-cell vaccines and other work, in the best shape possible to fully explore the potential for preventing infection?

This question is easier to raise than to answer. The science of protection from HIV infection hasn't had as many advances as that of viral control; the latter being easier to study given appropriate resources for screening and identifying the right cohorts.

In addition, the borderline between the studies of prevention and control is fuzzy at best. Information about transmitted viruses and about the immune defenses that get mounted in the very early stages of established infection can provide critical clues for design of both preventive and disease-slowing vaccines. Likewise, studies of people with HIV have yielded rare but potent neutralizing antibodies. There's also more recent data from Scheid et al.[1] suggesting that several type- or strain-specific antibodies with limited neutralizing abilities individually can be combined to achieve effective *in vitro* viral control.

However, there are some novel ideas worth considering, such as the possibility of quelling a localized infection in the genital tract before it spreads and establishes systemic infection. To explain how this might work, Robin Shattock of St George's Hospital at the University of London uses the comparison of installing a sprinkler system to control a small fire, versus pulling up fire trucks to extinguish a roaring blaze. In this case, the small fire is the localized infection that HIV establishes in the cells of the genital tract in the very first hours of infection. HIV spreads very rapidly from the site of entry to the rest of the body. However, there is a narrow window when it is confined to the genital tract, where it could, in theory, be contained and even cleared by the right defenses present in the right quantities at the right time.

The fire-truck approach is how Shattock describes work on vaccines aimed at blunting early viral damage and viral load. A vaccine that induces defenses aimed at control is targeting HIV as it is establishing infection. The aim of this type of vaccine isn't to clear the virus but to control it. This encompasses possible effects including blunting peak viremia, lowering viral load setpoint, or helping to achieve durable control without treatment, all of which might lay the foundation for better outcomes by preserving immune responses.

But there's also been a surge of interest in T cell–mediated clearance of local infection, since data presented by Louis Picker et al.[2], which report complete protection observed in four out of 18 rhesus macaques immunized with a replication competent RhCMV-vectored vaccine. Picker and colleagues identify cell-mediated immunity—specifically effector memory cells in the mucosa—as the primary mechanism of protection. They suggest that the animals were infected with SIV and managed to clear the local infection before it spread. This argument is shored up by the fact that the protected animals had SIV-specific immune responses to antigens that were

[1] Scheid JF, et al. Broad diversity of neutralizing antibodies isolated from memory B cells in HIV-infected individuals. *Nature.* 2009 Apr 2;458(7238):636-40. Epub 2009 Mar 15.

[2] Hansen SG, et al. Effector memory T cell responses are associated with protection of rhesus monkeys from mucosal simian immunodeficiency virus challenge. *Nat Med.* 2009 Mar;15(3):293-9. Epub 2009 Feb 15.

not contained in the vaccine—an indication that they had "seen" the virus, even though they were not infected. This is a single, small animal study that has to be confirmed and further clarified, but it's intriguing nonetheless, both for its suggestion of protection and because it underscores the importance of looking at mucosal immune responses.

If a vaccine were to help control infection at the local site it would have to win what

Using Genomics to Generate New Hypotheses

Across the field, entities like CHAVI, Bruce Walker's group at the Ragon Institute, the French research agency ANRS, and others are using genome-wide association studies to look for regions of the human genome associated with viral control or disease progression. Participants at a January NIH-convened meeting on genomics and HIV underscored that these genes, while important, might be different from those associated with protection. One innovative approach to identifying protective alleles: a proposed CHAVI study of HIV-positive and HIV-negative hemophiliacs known to have been exposed before stringent blood bank controls were introduced.

At the NIH genomics consultation, there was great interest in whether ongoing HIV prevention research trials, such as PrEP studies—which will enroll over 17,000 individuals by mid-2009 (see article, page 46)—could aid this effort by contributing samples and helping to identify individuals in the earliest days of infection. "We are especially concerned that observational or prevention studies already underway be examined for their utility in informing genetic associations with transmission mechanisms," noted the meeting working group, on the host immune response and susceptibility to HIV chaired by Myron Cohen of the University of North Carolina.

What information can we glean from current studies, and what are the barriers? This is an area where immediate action could clarify opportunities swiftly and relatively easily. In some ongoing studies, participants give permission for samples to be used for genetic analyses; in others, no explicit permission is given. Different studies have different schedules for HIV testing and/or viral load monitoring in individuals who become infected. The field needs to review procedures in different trials and look across biomedical prevention research to determine what's possible to standardize in sample collection.

There's also a need to explore novel designs for studies in humans, where the timing of sampling is more frequent. The US Military HIV Research Program (MHRP) is working on a protocol in this regard that involves biweekly blood draws for rapid turnaround HIV nucleic acid testing to identify acute infections and to compare the host genetics of those who are at risk of infection and become infected versus those at risk who do not become infected.

Big Questions for 2009 and Beyond

AIDS vaccine research has many enduring questions: Does clade matter? What constitutes an effective immune response? How can we best use the non-human primate (NHP) animal model? In these pages, we look at some of the recent research on these topics, but our *Report* is far from exhaustive. Below are some important questions that we hope will be addressed in the coming year and beyond.

1. What are the roles of various characteristics like epitope specificity and functionality in CD8 T cell–mediated viral control?
2. How does HIV genetic diversity matter for vaccine research? What systematic attempts can be made to address the relevance of clade—and at what stage in the vaccine discovery process should these take place?
3. What future directions best guide improvements in animal modeling efforts? Are current NHP vaccines and challenge viruses sufficiently predictive given their limitations?
4. What are the next steps in learning about immune activation and its impact on susceptibility to HIV infection? What clues can be gleaned from studies of nonpathogenic non-human primate models, like African Green Monkeys? How can this be applied to vaccine design?
5. If combinations of many antibodies are necessary for protection, is there a definable set?
6. What needs to happen to optimize progress in the study of adjuvants, especially for DNA products or toll-like receptors (to harness innate immunity)?
7. How can studies of candidate vaccines best elucidate the contribution of more than one type of immune response to protection?
8. Will vaccine studies evaluating candidates for their impact on virologic control take sufficient account of the effects of viral persistence and latency?

University of Minnesota scientist Ashley Haase calls the "race between the virus and the host," which starts the instant HIV penetrates the mucosa and begins to infect or be engulfed by cells of the immune system. Within hours, HIV spreads from the local mucosal sites of exposure to the lymph nodes. There are cells present in the local mucosa that try to block HIV, but they're there in insufficient quantities—outnumbered by the viral particles. (This mechanism has limited relevance to exposure via injection drug use in which there's no mediating mucosal barrier.)

Haase has put forth an "enough, soon-enough hypothesis." This proposes that a vaccine might reduce risk of infection by inducing sufficient responses at the mucosal sites of sexual exposure to stop HIV from expanding to a systemic infection.

Haase doesn't limit his thinking to what vaccines can do alone. Microbicides could also play a role by blocking the receptors on the local mucosal cells that HIV targets early in infection, or perhaps, by delivering ARVs that block or slow viral replication, delaying the spread from local sites to the bloodstream. In this scenario, PrEP or a microbicide (both ARV- and non-ARV formulations) might buy time for vaccine-induced immune responses to expand and swing into action.

It's a concept that some are calling biological synergism: pursue prevention by combining different biomedical interventions with complementary mechanisms. One theory, which is yet to be tested, proposes that ARV-based prevention plus an effective vaccine strategy could provide even better protection than PrEP alone or could be a way to enhance and back up PrEP effectiveness for people who may not take PrEP dosing as scheduled or prescribed (see page 46 for more information about PrEP and ARV-based microbicides).

There's also the possibility of combination approaches that aim to prevent infection and also to provide improved control of the virus if infection does take place. There are animal data to suggest that PrEP might work this way, i.e., blunting viremia in people who get infected while taking the drug. And improved virologic control is one of the primary endpoints being measured in T-cell vaccine studies. (As discussed on page 34, there's also a faint glimmer that a small subset of vaccine recipients in the Step vaccine trial might have had some level of vaccine-induced virologic control.)

Innate immunity might also play a critical role in protection, both as a primary defense and mechanism through its modulation of adaptive immunity. This assertion has more specificity behind it thanks to work from Bali Pulendren and Rafi Ahmed of Emory University, and collaborators, who have used systems biology approaches to begin to decode the complex, integrated immune responses induced by the highly effective, licensed yellow fever vaccine.

When it comes to prioritizing prevention as a goal for AIDS vaccines there are some broad areas where additional work could be done. The Global HIV Vaccine Enterprise, which is currently revising its

"Science dictates that we change as the field changes. When the Step results were released, KAVI had to make some adjustments. With no HIV vaccine candidates immediately available for testing, we have focused increasingly on participating in a series of basic research and epidemiological protocols. The highlight of these is a multi-country study looking for the presence of neutralizing antibodies in HIV-positive individuals not on ART and not progressing to AIDS, which may inform vaccine design. We hope KAVI's contributions to these studies may help answer some of the fundamental questions in HIV vaccine development."

Prof. Walter Jaoko, Principal Investigator, Kenya AIDS Vaccine Initiative, Kenya

Scientific Strategic Plan (see page 24), is well-positioned to catalyze and monitor some of this work:

- **Validating and expanding on recent scientific developments**
  - Repeat, validate, and explore mechanisms underlying findings from non-human primate models, including the evidence found by Picker et al. of protection with an RhCMV-vectored vaccine and the work by David Watkins's group using heterologous challenge stocks with limited viral diversity.[3] (At the same time, there is a need to explore regulatory feasibility of moving replication-competent vectors like RhCMV into humans.)
  - Continue to follow directions suggested by immunogenicity data from human trials of licensed vaccines, such as those generated by Pulendren and Ahmed.
  - Follow up on the various hypotheses regarding mechanisms of control by elite controllers, including those advanced by Walker and David Heckerman regarding epitope recognition, and Mark Connors's work on cell killing.
  - Ensure that, where possible, mucosal samples are collected and analyzed to provide clues to immune responses in humans and non-human primates. One avenue for this could be the new HVTN/CHAVI initiative that aims to foster interaction between non-human primate researchers and clinical researchers.

- **Field-wide goal setting aimed at taking on prevention as a goal for the AIDS vaccine field**
  - What are the options for gathering samples that might help individuals who are protected from, or manage to clear, a localized infection? Can timing of sample collection (i.e., after sex or unplanned exposure) be used to reach these goals?
  - What are the resource needs in terms of funding and organizations to pursue these questions? Are there gaps based on current contributions from IAVI, NIH, the Gates Foundation, amfAR, and other donors?
  - How can the current CHAVI and CAVD groups contribute, and how should the next iterations of these ventures—if they come to pass—be organized in light of these questions? (For more on field-wide organization, see the article on the Global HIV Vaccine Enterprise, page 24.)

"With Phambili closed and PAVE 100 not started, we had to turn to other prevention-related issues, like involvement of adolescents and minors in prevention research, understanding the role of circumcision in HIV prevention, examining the impact of Phambili closure, examining our participatory practices and level of risk-reduction counseling services among other things. At our Emavundleni site, we've taken on *'poly prevention'* and have diversified our prevention research efforts in order to keep interest and activity."

Linda-Gail Bekker, Principal Investigator, Desmond Tutu HIV Foundation, South Africa

[3] Watkins DI. Vaccine-Induced Cellular Responses Control Acute SIV Replication After Heterologous Challenge. *Keystone Symposia Conference: Prevention of HIV/AIDS (X3). Keystone*, Colorado, 2009 March 22-27. Abstract #005.

All of the above are interconnected like, yes, puzzle pieces. For example, understanding the mechanism of vaccine-induced protection could strengthen the rationale for testing specific vaccines with PrEP.

The good news is that much work is underway, and the diversity of players is striking and encouraging. Haase, unlike Walker and Picker, isn't linked into any of the "big science" consortia like CAVD and CHAVI, but he does receive funding from NIH and IAVI. Louis Picker is part of IAVI's Live Attenuated Consortium, and IAVI is funding some of the follow-up studies, as is CAVD. CHAVI is following a cohort of exposed, seronegative individuals, and its work on acute infection and isolating transmitted viruses is also focused on very early events of transmission.

The CAVD portfolio includes several relevant projects including the work of Julie McElrath of the University of Washington and colleagues on adjuvants that might manipulate the innate immune system. amfAR has supported work out of St. George's University in London using *ex vivo* models to examine how candidate microbicides might enhance colorectal immune responses and/or block viral activity to HIV at six and 24 hours after exposure.

Understanding the mechanism of vaccine-induced protection could strengthen the rationale for testing specific vaccines with PrEP.

This is a fertile mix of big science and individual efforts, of product-oriented work and of slow and steady basic science. (It's also a reminder that seasoned veterans like Haase, Connors and Walker have as much to contribute as young investigators, and that both cadres are essential.) This is why we'd like to see a quick, strategic, scientific analysis of all the efforts underway, with a goal of identifying gaps and opportunities for synergy both within the AIDS vaccine field and across the vaccine, PrEP, and microbicide fields. ✱

Fitting AIDS Vaccine Science into the Bigger Picture

For the past year, we've been hearing variations of this sentence: "If PrEP works, AIDS vaccine trials will be impossible." Or, "If MDP 301 shows effectiveness of the microbicide PRO 2000, we won't ever be able to do an AIDS vaccine trial again." Or, "The window is closing for AIDS vaccine trials… once we get a positive result from another biomedical prevention strategy, we won't be able to test a vaccine again."

You can just as easily substitute "microbicide" for "vaccine" in the sentences above. The concerns stem from the simple—and positive—assumption that prevention strategies that show effectiveness in clinical trials will be introduced and used, so that eventually rates of new HIV infections will go down. When incidence goes down, trial size and/or length increases, as does cost. So if new, proven strategies get introduced into communities that are also being considered as partners and participants in trials of other new experimental strategies, these trials could be larger, longer, and more expensive.

But the conversation shouldn't be about whether any specific trial type will become impossible. Instead, the focus should be on the various options for research that might combine AIDS vaccines and other interventions as they emerge. One concern is when and how new interventions become the standard of prevention and get offered to all trial volunteers. Another is the opportunity for testing new strategies in combination with emerging ones, to ask questions like: could a vaccine plus another intervention (e.g., PrEP or microbicide) provide improved protection over that intervention alone?

These two lines of reasoning are obviously closely related, and each impacts the other. If an emerging strategy becomes the standard of prevention and is routinely offered to all participants, then that complicates the design of future trials of single strategies.

On the other hand, it raises the possibility of trials to compare combinations like vaccine plus PrEP or vaccine plus PrEP plus male circumcision versus PrEP alone. Such studies might be large and highly challenging, but they are being considered. Both IAVI and the HVTN are exploring scenarios for evaluating vaccine-PrEP interactions in various ways.

Combining vaccines with other strategies could achieve different goals depending on the vaccine's mechanism of action. A vaccine strategy that reduced viral load setpoint might be evaluated to learn about the level of virologic control offered to people who get infected in spite of PrEP. (PrEP itself might have an impact on post-infection viral load.) Another strategy might be aimed at inducing persistent

defenses at mucosal sites, with the goal of augmenting PrEP- or microbicide-mediated protection against infection.

Although it's critical to plan for new prevention options, we also need to recognize that change won't immediately follow a positive result from a single trial. Additional trials are usually needed to validate and expand on the results. And when they aren't, there's still a set of steps between the initial finding and actually getting programs and products on the ground. These need to happen swiftly and without unnecessary delay. In practice, there is a substantial gap between the announcement of a research result and the introduction of the intervention on a national scale. (For a discussion of the critical role that WHO and UNAIDS play in this process, see the article on page 54.)

Male circumcision provides one example of how prevention trial research teams have already thought through this issue. South African investigators in the Phambili vaccine trial decided that male volunteers should be offered circumcision, even though there was no national policy on the procedure. This decision came about in part because the research demonstrating the effectiveness of male circumcision for HIV prevention had been done in South Africa and so could be assumed to have relevance to the trial population. The teams at the Phambili trial sites ensured that trial participants had access to the service if they wanted it. This effort was supported in part by the HVTN Foundation. Trial sites in other countries have been less active in this regard, providing information and referrals for male circumcision but not necessarily establishing services.

The male circumcision scenario points to whether there should be a difference between what's done in a community and what's done in a trial setting. Are there certain cases when a research site is obligated to act in advance of national policy? What's the role of community in making these decisions? The emphasis needs to be on specific scenario-planning to identify solutions.

"With IAVI's support, we've done clinical trial preparations with men who have sex with men. We've also found out that HIV incidence in these men is much higher than in female sex workers. The other significant milestone is in regard to community engagement. While homosexuality is illegal in Kenya, coastal health authorities in partnership with KEMRI and IAVI are now engaging community groups and other district health stakeholders to prepare HIV prevention and behavior change interventions addressing anal sex."

Dr. Eduard Sanders, Principal Investigator, Centre for Geographical Medicine Research-Coast, Kenya Medical Research Institute-Kilifi, Kenya

Solving the Enterprise Equation

When is a whole greater than the sum of its parts?

Every year since the Global HIV Vaccine Enterprise was first proposed in 2003, the *AVAC Report* has devoted some of its pages to considering the role and responsibilities of that entity. We've done this as both the Enterprise and the field have changed—and this year is no exception. In this article, we report on how the Enterprise is regarded by a wide range of stakeholders and on how it might improve and expand its mandate. We heard both recognition of contributions and ambivalence and caution amongst many stakeholders. This divided sentiment represents something of a catch-22 for the organization: its added value is not yet completely convincing, therefore it can't draw full buy-in from the people and organizations it's meant to convene. As a member of the Enterprise, AVAC's hope is that this input—along with attention to some of the key issues we've raised in previous years (see box at right)—can help strengthen it for us all.

January 2009 marks the one-year anniversary of Alan Bernstein's leadership as executive director of the Global HIV Vaccine Enterprise secretariat. As we discuss in the previous pages, it's been a year of new insights from vaccine science, renewed emphasis on innovation and discovery research, and expanded appreciation of the scientific contributions from the Step study (see page 32). There have been interesting research findings from teams spanning the globe, including ones working through the NIH-funded CHAVI consortium, the Bill & Melinda Gates Foundation–funded CAVD, the HVTN, and IAVI, along with work funded by European entities like the French ANRS and the European Commission.

With the engines of research chugging along, what does the Enterprise look like in 2009? How relevant and/or responsive is it to the current times? For those looking for a take-home message, we'll say this: there's some good news but also many places where we find stasis—a sense of "here we are again"—in situations that have not changed since last year's *Report*. Most significant, we're concerned that it's still unclear whether the Enterprise in 2009 has the influence to accelerate and activate conversations between funders and scientists that will lead to swift action in critical directions.

Many of the 20-plus people interviewed for this piece* focused on the need for an entity that could influence spending, organization, and scientific priorities.

The key roles envisioned for the Enterprise can only be accomplished through collective work. AVAC remains committed to supporting the Enterprise through our participation in various Enterprise-related activities. Our goal with this article is to help catalyze conversation and contribute to setting the Enterprise on a sustainable course.

* We aimed for diversity and included scientists, donors, funders, policy makers, advocates, US-, Africa-, and Europe-based respondents, scientists working in "big science" consortia and those working in smaller laboratories, clinical trialists and basic scientists. We had one or two respondents, sometimes more, in each category—enough to get a qualitative sense of differing perspectives, though obviously in small numbers.

AVAC's Quick Take on the Enterprise

AVAC has been involved with the Enterprise from its beginning in 2003, and we have provided updates and recommendations in each of our annual reports since then. In 2005, we identified eight issues that needed to be addressed. Below we've reprinted those key recommendations and updated them. They're broad and ambitious, and many of them could not be accomplished in the single year that the Enterprise secretariat has had an executive director and staff. But they're still targets and there's both progress in some areas and indications of the Enterprise falling short in others.

1. **Communicate frequently and transparently.** More information, more opinions, more leadership. We'd like to see the Enterprise communicating with stakeholders about emerging issues on a more regular basis, and not just through periodic letters. On the other hand, the meeting reports and minutes posted on the website are useful resources and demonstrate a commitment to transparency.
2. **Set policies for sharing and coordination of data and technology.** Work here is ongoing; we're eager to hear reports in the coming year.
3. **Ensure the ability to take risks.** As we discuss in the main article, there's a time for caution and a time for provoking discussion, and we look forward to even more of the latter to balance the former in Enterprise activity.
4. **Bring new investigators into the search.** This has been a particular area of strength, evidenced by investments in the development of the New Minds, New Ideas initiative to address the need for young and early career investigators, and efforts to build bridges to systems biology. The key now is to set metrics for measuring progress and to update the field on what's working and what's falling short.
5. **Make the Enterprise truly global.** Commitment to African and Asian regional networks, and on the 2008 AIDS Vaccine Conference in South Africa has helped the Enterprise strengthen global ties. Now the challenge is to get more developing country scientists to the table for scientific deliberations in addition to discussions of geography-specific issues.
6. **Involve civil society in a meaningful way.** Much more needs to be done here, and the Enterprise needs to be clear about its goals. Is developing country civil society involvement a priority? Is input on scientific issues, such as the Strategic Plan, a priority as the secretariat has stated? If not, that's alright. If so, what's the plan for ensuring the scientific literacy that's needed for meaningful community involvement? Clear expectations and commitments are needed either way.
7. **Take on the politics and ethics of clinical trials.** This hasn't happened yet. From HVTN 505 to plans for what AIDS vaccine trials might look like if there's benefit from PrEP, there are many issues where the Enterprise can and should play a critical leadership role.
8. **Establish realistic milestones and a process for monitoring progress.** We look to these as an integral part of the Scientific Strategic Plan and will expect the Enterprise to provide status reports on an ongoing basis.

We posed the same four questions to all of our interviewees:

1. Describe your involvement with the Enterprise to date.
2. What are some of the places where Enterprise-related activities have added value to the field?
3. Are there specific areas where the Enterprise could either change what it's doing or add new areas of expertise to further fulfill its mission?
4. What are your expectations of how Enterprise leadership might or should cause both the overall field and your specific organization to look different a year from now?

When asked to describe their involvement, interviewees had a broad range of answers. Some had been involved with the Enterprise since day one; others, only recently. Some felt a strong affiliation with the entity in its first years when it was steered by an interim secretariat based at the Gates Foundation in Seattle. For other people, the strongest tie was a conversation or consultation with Dr. Bernstein.

But for everyone there was a sense of engagement and interest in the Enterprise. Whether tempered by optimism or frustration or a little of both, a sense of investment was conveyed by every interviewee.

The Enterprise was originally conceived as the whole of the field, united in a loose, additive structure that would speed the identification of an effective AIDS vaccine. In 2004, the Enterprise was all of us. In 2009, with the New York office, an expanding staff, and the leadership of Dr. Bernstein, it looks more like an independent entity.

As the interviews revealed, if the Enterprise that belongs to all of us is going to succeed, then the Enterprise secretariat must continue to nurture the whole—all of us working toward an AIDS vaccine—while maintaining a clear identity as one of its parts. This is a tall order, perhaps nearly impossible, as several of the interviewees pointed out. But this is, by definition, an ambitious field.

"We're now working to strengthen long-term capacity for phase II/III trials of HIV vaccine candidates in Uganda and Malawi through a collaboration among the UVRI, MRC/UVRI Uganda Research Unit on AIDS, IAVI, the Malawi-Liverpool-Wellcome Trust Clinical Research Program and World Fish. Screening and enrollment of a population cohort among four fishing communities is already underway in Masaka and Wakiso districts, Uganda. Also, we plan to continue with vaccine preparedness studies (funded by IAVI) that we've been doing since 2003, in addition to conducting a pilot study to evaluate the safety of daily and intermittent dosing of pre-exposure prophylaxis (PrEP)."

Dr. Anatoli Kamali, Principal Investigator, Medical Research Council/Uganda Virus Research Institute Research Unit on AIDS, Uganda

Contributions to date

Five years ago, the Enterprise was proposed to address frustrations of stakeholders and spectators of the AIDS vaccine effort about the lack of coordination across the major scientific players. There were nearly 50 vaccine candidates, many of which were highly similar, in various stages of clinical development. There was no mechanism for making field-wide "go/no-go" decisions. Assays being used to evaluate candidates were not standardized, making it impossible

Major Contributions of the Enterprise

- Historically, a galvanizing and catalytic force for funding decisions on major programs and for scientific agenda-setting based on a shared plan
- Increased coordination and communication among scientists
- Leadership on involvement of young and early career investigators
- A neutral voice representing "good science"

to compare some candidates. There were also major gaps, such as funding for manufacturing capacity, and concerns about clinical trial capacity being exhausted in the near future, as multiple vaccine, microbicide, and other prevention trials launched across the globe.

Today the world looks different, and many of our interviewees credited the Enterprise for some of these changes, particularly around resource allocation for specific areas identified in its Scientific Strategic Plan, the first version of which was published in January 2005. Both the CAVD initiative and CHAVI were created with the explicit goal of addressing areas identified in the plan. The Gates Foundation also initiated a collaboration with the Canadian HIV Vaccine Initiative on vaccine manufacturing capacity, in line with a gap identified in the plan. The European and Developing Countries Clinical Trials Partnership was seen as part of the solution to some of the clinical trial capacity issues identified in the plan.

This success is the result of a sense of the scientific community's endorsement of the plan and, by extension, of the Enterprise and a close alignment of donor decision-making with the plan. The very existence of the Enterprise made it possible for donors and scientists to develop and execute a joint vision.

Looking specifically at contributions made since Dr. Bernstein assumed leadership, interviewees repeatedly mentioned the sense of being listened to and commended Dr. Bernstein's commitment to understanding the priorities and concerns of stakeholders throughout the field. This was often coupled with a sense that, as a cancer researcher, Dr. Bernstein has brought a fresh perspective. One interviewee said, "Alan is trying to make the point that we can't fall into the trap of specific dichotomies: big versus small science; primate versus bench versus human trials. He's advocating for a harmonious development of ideas and cross-fertilization. It is reassuring that there is an entity that is a voice for 'good science.'"

"The Enterprise has become the spokesperson for the whole field," said another interviewee. "It has a much higher profile than it has had in the past. I think he [Dr. Bernstein] is a thought leader. In the year that he's been there, he's made contact with pretty much everybody at all continents and all levels. He's been promoting the young investigator angle. I think it's been a very positive thing … time will tell what [the] impact will be."

Several others mentioned the "New Minds, New Ideas" initiative, which has convened a committee of young and early career investigators to craft and execute an advocacy strategy aimed at addressing

Areas for Improvement and Expansion

- Timely publication of the updated Scientific Strategic Plan in early 2010
- Expand scientific leadership on strategically selected issues
- Demonstration of the ability to facilitate donor-scientist communication that impacts the course of the field

some of the needs and priorities of the next generation of scientists. The committee members have brought high energy to this nascent initiative, to which the Enterprise has given a platform and legitimacy. It's a strong example of how the Enterprise can use its convening function to catalyze activity on a specific issue that has long-term relevance and consequences for the field.

The Enterprise has also had some success in expanding participation of scientists outside the US and Europe. Under Dr. Bernstein's leadership, the Enterprise has worked with the African AIDS Vaccine Programme and with Asian stakeholders to increase coordination and capacity. Such regional efforts can have an impact, particularly if they're well-structured and focused on strategic goals. Looking forward, the Enterprise should ensure that its scientific convening work reflects this commitment to diversity, by bringing African, Asian, and Latin American researchers to forums where they remain underrepresented.

Areas for change or expansion at the Enterprise

Interviewees who cited the Scientific Strategic Plan as a success of the Enterprise also identified it as an area for change and expansion. How is this possible? In large part because an updated version of the entire plan hasn't been published since 2005. However, in this interval, reports on Enterprise-convened meetings on humoral, innate, and mucosal immunity have been published. Also in 2008, IAVI published its biennial *AIDS Vaccine Blueprint* "as a founding partner of the Global HIV Vaccine Enterprise." This valuable report hoped "to stimulate discussion among all stakeholders…" We hope that IAVI will continue to produce strategic plans detailing its singular approach to dovetail with an Enterprise-initiated field-wide drafting process.

In *AVAC Report* 2008 and 2007, we called for an updated plan to help organize and orient the field and to reaffirm the role of the Enterprise. Dr. Bernstein and his team have launched a process of updating the plan that highlights some of the strengths and challenges of the organization. The sense among our interviewees is that the plan update is overdue, in part because the field has shifted so much since 2005.

On the plus side, we've heard praise for how topics of interest are being parsed and assigned to specific working groups. We have also heard a sense of impatience with the pace of this work. Deliberation is important, but so is decisiveness.

Stakeholders will need to support the Enterprise secretariat in moving as quickly as possible to produce a hard-hitting

quality Scientific Strategic Plan. We hope that the goal of publication by early 2010 will be met, so that the updated plan might guide the possible NIH re-funding of CHAVI and the next steps for CAVD.

The ability, or lack thereof, of today's Enterprise to catalyze conversations among scientists, funders and donors was raised by several people we spoke with. These interviewees said that the response to the revised Scientific Strategic Plan would help them gauge whether the Enterprise in 2009 had the influence to accelerate and activate conversations between funders and scientists necessary to turn the plan's recommendations into reality.

Major funding initiatives were closely tied to the last Scientific Strategic Plan. Some interviewees characterized CAVD and CHAVI as the "carrots" that brought stakeholders together under the Enterprise umbrella. They questioned whether coordination would continue without these incentives. "I think it's going to be very challenging for Alan to make sure that the Enterprise is recognized as the entity that is going to propose new directions that all the other people in the field are going to support," said one interviewee.

Another interviewee said, "Decisions were made at the Gates Foundation to create the secretariat and to have distance from it, and at that point the air came out of the balloon."

For their part, the funders we interviewed stressed the importance of the first Scientific Strategic Plan in validating their decisions and looked to the updated plan to provide similar guidance. This is another reason why the updated plan must be as strong as possible, with every effort taken to guard against the dilution—and pork barrel proposals—that can creep into a document that's written by consensus.

The plan is a key component of Enterprise leadership, but it's not the only vehicle for guiding the field. Although the Enterprise has convened expert working groups on key scientific issues; there was a sense that the Enterprise could wield its scientific leadership and convening role in additional, useful ways. Several respondents would like to see the Enterprise take on specific, time-sensitive issues that could be resolved or refined by small meetings, with recommendations and Enterprise-led follow-up on deliverables.

"While we wait for the draft of the scientific plan, are we willing to say that there are no issues that have come up in the last year and a half that you wouldn't want to have discussion on?" said one interviewee. Some also mentioned that a senior staff member or advisory group with expertise in the AIDS vaccine field could help to catalyze and convene these discussions.

Donor-scientist dialogues that have measurable outcomes would help affirm and solidify that the Enterprise under Dr. Bernstein's leadership can serve as a bridge-builder between donors and scientists. "One thing the Enterprise could try to do is try to convince donors and investigators that they may not have the solution on their own," said one interviewee. "If you want to get a good strategy—a heterologous prime-boost for example—you need to get groups that have different [components] working together."

This type of action might bring clarity to the Enterprise's overall identity. Many stakeholders sounded as unsure of what the Enterprise is going to do next as about what its perceived influence will allow it to do. We heard statements like, "The Enterprise is whatever Alan wants it to be," "I view the impact of the Enterprise as ahead of us," and "It [the Enterprise] hasn't done much of anything yet." Some raised questions about its relevance today as opposed to five years ago and said that perhaps the field had built a structure that it wasn't actually willing to use.

If the Enterprise does its job, what's changed a year from now?

The fourth and final question in our interview imposed an artificial time frame on the Enterprise. Many of the things that Dr. Bernstein and his team are working on won't show dramatic changes in 12 or even 24 months. It will take time to see if the New Minds, New Ideas initiative leads to lasting change via programs and initiatives that improve the outlook for new investigators and whether young and early career investigators enter AIDS vaccine research from other fields and/or commit to it as a long-term career path. A year from now may be too early to evaluate the influence of the Scientific Strategic Plan in full because major funders like NIH and the Gates Foundation may not have indicated their specific plans for funding beyond CHAVI and CAVD, respectively.

Still, we decided to ask about measures of progress, if not success, and will use the answers to guide our analyses this time next year.

For many interviewees, the greatest portion of the worth of the Enterprise will be measured by the degree to which the Scientific Strategic Plan:

- Reflects clear, bold thinking for the field—as opposed to watered-down consensus, which some interviewees feared might come from the drafting-by-committee process; and
- Guides subsequent funding decisions by donors. (One interviewee proposed measuring added value by the answer to the question: "Do the funders and donors fundamentally embrace this as the way of doing business?")

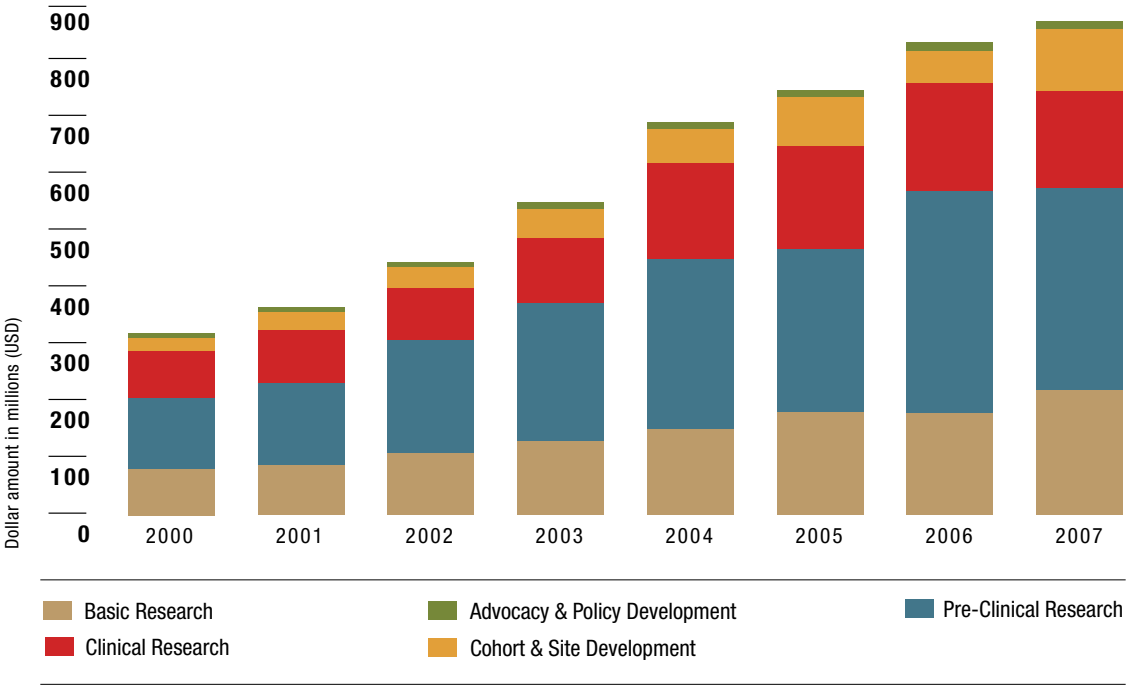
Expanded scientific leadership on specific gaps would be another metric of success. This work would complement the ongoing work on "enabling environment"–related issues like young investigators and systems biology. A year from now we'll ask: are there one or two scientific issues that the Enterprise has taken on with strategic consultations between funders and scientists that led to actionable recommendations—with funding suggestions, milestones, metrics of progress, and success?

We heard varying opinions on whether the work described above necessitates filling the Director of Science position that's been posted and vacant for nearly a year. It's a hard position to fill. Scientists with

"Our planned work on microarray analysis of responses to yellow fever vaccine is very exciting to the staff. There's a lot of interest in using systems biology to understand how the immune system works in response to vaccines. With yellow fever vaccine, we know it works but we don't know how it works, so we're going to look at how the immune genes switched on when people get the vaccines. This was done in North Americans and we're repeating it here in Uganda."

Dr. Pontiano Kaleebu, Principal Investigator, Uganda Virus Research Institute-International AIDS Vaccine Initiative Vaccine Program, Uganda

Figure 2 Annual Public and Philanthropic Investments in Preventive HIV Vaccine R&D from 2000 to 2007*



* Based upon a subset of total expenditures for which allocations could be calculated.

Source: HIV Vaccines and Microbicides Resources Tracking Working Group. Sustaining the HIV Prevention Research Agenda: Funding for Research and Development of HIV Vaccines, Microbicides and other New Prevention Options, 2000-2007. 2008. Available at: *www.hivresourcetracking.org*.

the depth of experience in the AIDS vaccine field that would serve the job well might not want to leave the lab. But there are other options for building the senior scientific leadership at the Enterprise: make the position a rotating seat to attract working scientists for a sabbatical year or develop a small core team of advisors, each monitoring a different topic.

Overall, a year from now, progress would be an Enterprise that's operating on two tracks: the all-of-us Enterprise that captures the big picture in the Scientific Strategic Plan and then works to execute its goals; and the secretariat-level leadership track, in which Dr. Bernstein and the New York office offer problem-solving resources and more rapid responses to emerging issues. With all of this, we'll be looking for as much clarity on roles, responsibilities, and measurable outcomes as possible.

We end with the reminder—that we take to heart as well—that the Enterprise isn't solely the responsibility of the people working in the secretariat office in New York. It continues to belong to all of us. Progress and success are collective responsibilities.

As one interviewee said, "The community as a whole should decide the top five things that need to get done by the end of 2010 and agree on how to measure success. What do we want from *our* Enterprise?"

Steps to Success

The Step vaccine study's scientific contributions to the field

For the past 18 months, we at AVAC have joined many other stakeholders in stressing that Step wasn't a "failed trial" but a successful trial of a candidate that failed to provide any level of protection. In the first few months after the result was released, we heard from critics who said that this distinction was a forced attempt to be positive about a massive disappointment. To these observers, the trial had failed, and the candidate had not only failed but might also have increased susceptibility to infection in specific subgroups of volunteers. It was easy to counter that the trial had succeeded in getting an answer quickly, recruiting and retaining volunteers, and, with a few snags, communicating the complex results as they emerged. Additionally, the Step and Phambili studies have made strong scientific contributions to the field. We now have far more valuable information to guide the search for an AIDS vaccine in 2009 than we did in 2007—all as a result of a candidate that failed. Below, we've summarized some of the suggested hypotheses or findings. These results are more hypothesis-generating than conclusive. Step has pointed towards questions that we otherwise would not have known to ask. The findings listed below point out clear paths for future work—no small feat for a trial that was used as evidence that the field had lost its way.

SHIV challenge experiment data may not predict the outcome of human trials of disease-modulating vaccines

Different strains of disease-causing simian-immunodeficiency virus (SIV) have been used in challenge experiments to evaluate vaccines and other biomedical prevention strategies in the non-human primate (NHP) model. In general, SHIV strains that are SIV-HIV hybrids are less virulent than disease-causing, lab-adapted SIV strains. Prior to the initiation of the Step trial, there had been debate about the relative merits of SHIV versus SIV. (The SHIV 89.6p virus came into favor because it caused a more consistent CD4 decline than SIVs.)

The best pre-clinical data supporting MRK-Ad5 (the vaccine tested in Step) came from an NHP challenge experiment in which immunized animals infected with SHIV 89.6p had significantly reduced viral loads out to 900 days after infection. The data from SIV experiments were less promising—mixed at best. Given that there was no overall protection or benefit from MRK-Ad5 in humans, it seems that the more stringent SIV challenge may have more predictive value for non-human primate evaluations of AIDS vaccines. (There may be settings in which SHIV or other challenges are also appropriate.)

Understanding how to use the non-human primate model and how to manipulate its many variables is critical. Although there is no single ideal model for non-human primate evaluations of AIDS vaccine concepts, data like those from Step can be used to refine and focus thinking about future experiments.

Step Data Have Led the Field To:

- Refine expectations of the animal model
- Delve into vector-specific immunity in unprecedented ways
- Reevaluate the qualities of an effective T-cell response
- Refocus on mucosal immunity

The field has a clearer sense of the inadequacy of a specific type of vaccine-induced immunity

There are at least three levels of uncertainty regarding vaccine-induced immune responses:

1. Scientists don't yet know what types of vaccine-induced immune responses are needed to either give durable protection against infection or reduce viral load after infection. Because of this, we also don't know exactly what measurable characteristics of T cells to track in order to predict whether a vaccine-induced immune response will provide a benefit. Potential traits include: how well T cells divide and reproduce (proliferative capacity), maturation state (memory versus effector phenotype), and functional activity (determined by looking at cell surface markers signaling molecules, and cytolytic activity).
2. What we want to measure is limited by what we *can* measure. By definition, the level of any given response is determined by the way it is measured. The assays for evaluating cell function evolve and often change from the time a candidate is moved into human trials, to when the trial is completed. Hence the definitions of what's measurable change over time.
3. The specific parts of the virus that are targeted by the immune responses are probably just as important as the types and levels of immune responses stimulated by a vaccine. The HIV genes or parts of genes delivered by a vaccine induce immune responses to specific parts of the virus. It is unknown which parts should be delivered or in what quantity. Animal models are of limited use in answering these questions because of differences between the challenge viruses used in animal models and the tremendous diversity of possible viruses that the human immune system might encounter.

Although it's not the result anyone would hope for, the flat result in Step does show us what immune responses, as measured, were insufficient for protection. This could be because of their qualities or perhaps because of the parts of the virus they were directed against. As the authors of the *Lancet* publication of Step immune analyses noted, the "MRKAd5 HIV-1 gag/pol/nef vaccine elicited a higher CD8+ T-cell response rate and magnitude than did that reported for any of the candidate immunisation regimens tested over the past 15 years, although immunological assays have changed greatly during this time."[4]

[4] McElrath MJ, et al. HIV-1 vaccine-induced immunity in the test-of-concept Step Study: a case-cohort analysis. *Lancet.* 2008 Nov 29;372(9653):1894-905. Epub 2008 Nov 13.

What are the improvements specifically suggested by these negative findings? There are several possible directions, including screening future vaccine candidates with a wider array of assays. Did Step measure the wrong immune response (i.e., T cells) or the wrong *aspect* of the immune response? Location is also important. Step samples came from the blood as opposed to mucosal surfaces.

Other directions include:

- Developing vaccines that induce both CD4 and CD8 responses (and different subsets of these responses), since only one-third of Step vaccinees developed both CD4 and CD8 T-cell responses.
- Getting a better sense of what's happening at the mucosal sites of exposure—the T-cell responses were measured mainly in the blood, which may or may not be indicative of the quality and magnitude of responses at the mucosal sites of sexual exposure.
- Using expanded and updated assays to evaluate vaccine-induced immune responses.
- Refining goals for breadth and specificity of HIV epitopes recognized by vaccine-induced T cells. The T cells induced by MRK-Ad5 recognized an average of three HIV epitopes.
- Investigating antigen selection. The MRK-Ad5 inserts didn't contain *env*. What are the right inserts and the right insert-vector combinations?

A possible hint of virologic control

The major histocompatibility complex, or MHC region of our genome, contains the instructions for, among other things, the set of proteins called human leukocyte antigens, or HLA. Previous researchers have shown that HIV-positive people with specific HLA types (and the corresponding MHC alleles) have better control of HIV viral load than people without these traits. This finding has reinforced the importance of host genetics in responses to the virus.

Although no overall benefit from the vaccine was seen in the Step study, there were intriguing differences among subgroups of volunteers. Researchers zeroed in on individuals with (1) MHC alleles associated with better HIV outcomes; (2) MHC alleles with no effect on HIV outcomes; and (3) MHC alleles with negative effects—faster disease progression or higher viral load. They found that among the very small number of individuals in group (1) who acquired HIV in the Step trial, those who had protective alleles and got the vaccine had significantly lower viral loads than those with protective alleles who received the placebo. Simply put: good genes + vaccine appeared to be better than good genes + placebo. The study wasn't set up for such analyses, so this is nothing more than a hint, perhaps a glimmer, of a suggestion of a positive benefit from the vaccine. But it warrants additional study, both of host genetics (see page 17) and of the mechanism of the possible vaccine-induced benefit.

Vector-specific immunity can neither be ignored as a complex factor in vaccine design; nor be blamed for the Step findings

The surprising and disappointing Step finding raised questions about what was known about the immune responses to the

Ad5 vector by itself—without the synthetic HIV genes that were used as the insert in the vaccine construct. The answer was: not much. There wasn't much information on immune responses either to the empty vector or to naturally occurring Ad5. (Ad5 is a cold-causing virus; the vector was altered so that it wouldn't cause any illness.)

In the aftermath of the Step results, scientists looked closely at vector-specific immunity and Ad5-specific immunity. They also examined the differences between vaccine-induced immune responses in people who had pre-existing immunity and in those who did not, and, within these groups, between those who became HIV-positive and those who did not.

Overall, Ad5 seropositivity alone did not affect risk of infection. Instead, the vaccine-related effect is only seen in men who were Ad5-seropositive and uncircumcised.

Beyond this "headline" finding, there are additional findings worth noting:

- The presence of pre-existing Ad5 antibodies (also known as Ad5 seropositivity) wasn't linked to increased CD4 cell activation after vaccination or susceptibility to HIV infection.
- The antibody- and cell-based immune responses to Ad5 don't work in lock step: whether someone is Ad5-seropositive doesn't predict Ad5-specific cellular immune responses, or how these expand when the body "sees" Ad5 in the vaccine.
- Cell-based immune responses to Ad5 are cross-reactive with other Ad viruses, including Ad1 and Ad6. This means someone could be Ad5-seronegative and still have cellular responses to Ad1 and Ad6, which might be stimulated by and/or respond to Ad5 vector.

Scientists looked for evidence that pre-existing immunity to Ad5 increased susceptibility to infection in vaccine recipients, but they couldn't find a direct link. There's no evidence that Ad5 seropositivity correlates with T-cell activation following vaccination, and strong suggestions that seropositivity—which is a measure of antibody levels—doesn't predict what will happen to Ad5 cellular responses following Ad5-vectored immunization.

The critical, though sometimes mysterious, role of mucosal immunity

Although there is "cross-talk" between immune responses in the blood and mucosal tissues of the body, including the genital tract, gut, and lungs, there are also distinctions. Measuring immune responses in the blood does not give a complete picture of what may be present in or absent from mucosal tissues, such as the rectum, the vagina, and the foreskin,

"Since the Step results were announced, we've been diversifying our research portfolio. We're now actively involved in vibrant clinical research activities in HIV therapeutics, viral hemorrhagic fever vaccines, and surveillance programs for avian influenza. Although we had some of this work already planned, or in progress before the Step announcement, the Step results made it more timely, and more relevant."

Dr. Hannah Kibuuka, Principal Investigator, Makerere University Walter Reed Program, Uganda

"It's amazing that we retained so many participants in the trials despite the permanent halting of enrollment and vaccination of the Phambili study, and the negative outcome of the Step study. Getting regulatory approval to conduct the HVTN 073 study, which investigates the SAAVI DNA-C and MVA-C vaccines, was another huge boon for us, post Step/Phambili. Its execution is very exciting to us, as it is a subtype C vaccine and is the first time that an African vaccine is tested both in the Northern and Southern Hemisphere."

Glenda Gray, Principal Investigator, Perinatal HIV Research Unit, South Africa

in the case of sexual transmission. Obtaining mucosal samples can be invasive, and these tissues vary greatly, which complicates analysis. Despite these obstacles, AIDS vaccine researchers have been paying increased attention to the potential role of vaccine-induced mucosal immune responses as front-line defenses.

The Step study results underscore the need to pay attention to what's happening in mucosal tissues. In the analysis of all the data to date, increased risk of HIV infection is seen among uncircumcised men and is highest in Ad5-seropositive, uncircumcised men. Looking at individual risk from the time of enrollment in the study, the difference in infection risk between vaccine and placebo recipients is most pronounced during the first 18 months and then wanes. The mechanism behind this is still unknown; one hypothesis might be that vaccine-induced responses in the mucosal tissue of the foreskin provide additional target cells for infection during the first months post infection. Might the waning risk be linked to waning of vaccine-activated target cells in the mucosal tissue? It's not possible to answer this question with the available Step data—and it may never be. However, it's clear that future trials need to address how vaccine-induced immune responses affect protection from and susceptibility to HIV in the mucosal tissue.

These are just some of the findings that have emerged from Step to date. It's critical to continue learning from the Step trial and to recognize the wealth of information that can be gleaned from well-designed human trials.

Figure 3 PAVE 100 to HVTN 505: Key events and communications about testing the VRC strategy*

2007

September 19
Step and Phambili vaccine trials stopped immunizations

September 21
NIAID trials of vaccines that used adenovirus vectors, including PAVE 100, were put on hold until Step data could be further reviewed

November 7
Step data presented at HVTN Full Group Meeting

November 15
NHVREI first annual briefing of leaders of National AIDS Non-Governmental Organizations

December 12
AVRS meeting on Step and PAVE 100

2008

May 30
AVRS meeting to discuss PAVE 100A—committee recommended that the study move forward

July 17
NIAID announces it will not move forward with PAVE 100A but will consider a smaller trial of the vaccine regimen that had been proposed to be tested in PAVE 100A

September 11
NIAID began NGO consultations on HVTN 505

November 6
HVTN fact sheet describing HVTN 505 trial distributed

November 10
NHVREI annual briefing of leaders of National AIDS Non-Governmental Organizations, where HVTN 505 overview was presented and discussed

November 13
NIAID-sponsored HVTN 505 trial telebriefing for community

November 24
Black Gay Men's Consultation on HIV Prevention Research where HVTN 505 was discussed

December 5
NIAID-sponsored HVTN 505 trial telebriefing for community

2009

March 2
HVTN 505 protocol submitted for FDA review

March 9-10
NHVREI Partners Training and Update, where HVTN 505 protocol was discussed

March 12
Community town hall meeting in Philadelphia where HVTN 505 was discussed

April 2
Notification from FDA that the HVTN 505 protocol may proceed

May 6
Community forum for HIV Vaccine Awareness Day, Rochester, NY

May / June
Anticipated start of enrollment for HVTN 505

Many presentations on Step, PAVE 100 and next steps were done by HVTN and NIAID at national conferences.

* Throughout this period, sites have been engaged with their CBO partners to discuss the upcoming trial, and their CABs have been similarly engaged. NIAID and HVTN, through the NHVREI program *(http://bethegeneration.nih.gov)*, have been in ongoing dialog with both the local and the national partners to keep them informed and to answer questions and concerns that they have had.

A Trial by Any Other Name: HVTN 505 and the VRC candidate

As *AVAC Report* went to press, the US Food and Drug Administration (FDA) had recently approved the protocol for HVTN 505, the test-of-concept study of the National Institutes of Health's Vaccine Research Center's (VRC) strategy that consists of three DNA "prime" immunizations and a single adenovirus 5–vectored "boost." (See timeline on page 37, and for more detailed information on the history of this candidate, please visit *www.avac.org/vax_update.htm*.)

At roughly the same time, some members of the scientific community were discussing newer animal data that had some relevance to HVTN 505. Much of the talk centered on the results of a study by Harvard's Dan Barouch and colleagues, in which animals received one of two variations on a DNA plus chimeric Ad (Ad5 plus an Ad48 hexon protein), or one of two variations on the chimeric Ad alone.[5] In that experiment, presented at this year's Keystone conference on HIV prevention, the animals that got the DNA plus chimeric Ad had survival rates and clinical outcomes comparable to the placebo group, while the chimeric Ad-alone animals had improved survival outcomes and, in an exploratory combined analysis, significantly lower viral loads. Barouch noted that his findings should be viewed as hypothesis-generating rather than conclusive.

Monkey studies are, by definition, small and inconclusive. Monkeys aren't humans; the numbers are too small to draw firm conclusions; and in the absence of a correlate of protection, it's difficult to know whether we're measuring the right things. What's more, the data concern a different vector; thus the strategy cannot be directly compared with the VRC strategy.

So why were Barouch's data of interest in the context of HVTN 505?

Primarily because monkey data considered relevant to the VRC vaccine strategy to be tested in HVTN 505 have been part of the scientific rationale for moving the trial forward.[6,7,8] Monkey data were cited extensively at the December 2007 meeting of the AIDS Vaccine Research Subcommittee (AVRS) of the NIH and mentioned in the fact sheet that the HVTN produced on 505 one year later. Over the past year, AVAC has voiced concern about the lack of clear materials to help lay audiences understand HVTN 505. These include the lack of clarity in explanations of both the scientific rationale and the ways that the trial

[5] DH Barouch. Novel Adenovirus Vector-based Vaccines for HIV-1 *Keystone Symposia Conference: Prevention of HIV/AIDS (X3).* Keystone, Colorado, 2009 March 22-27. Abstract #017.

[6] Shiver JW, et al. Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. *Nature.* 2002 Jan 17;415(6869):331-5.

[7] Bolton DL, et al. Aerosol Adenovirus Immunization Controls Early Viremia.*Keystone Symposia Conference: HIV Immunobiology: From Infection to Immune Control (X4)*, Keystone, Colorado, 2009 March 22-27. Abstract #125.

[8] Casimiro DR, et al. Attenuation of simian immunodeficiency virus SIVmac239 infection by prophylactic immunization with DNA and recombinant adenoviral vaccine vectors expressing Gag. *J Virol.* 2005 Dec;79(24):15547-55.

was addressing the safety of participants—this in light of its use of an Ad5-vectored candidate that was similar to, though not identical to the candidate used in the Step trial.

Even though they're not directly related, the data presented by Barouch are still relevant to potential trial participants and communities as part of the broader body of knowledge around the proposed HVTN 505 trial, and they point to the unmet need for clear, simple statements of the rationale for the trial and how the varied body of non-human primate and human data have been analyzed to date.

These concerns aren't about whether HVTN 505 adequately addresses participants' safety in light of Step—we believe that this was addressed by the exclusion of Ad5-seropositive, uncircumcised men. The concerns are about the communication around these criteria and how the scientific rationale for the study is being explained to participants and engaged communities.

AVAC has followed and sometimes participated in many discussions about this candidate and whether it should be tested further. We feel that human trials are an invaluable part of the AIDS vaccine discovery process. The Step trial has provided a wealth of information that would never have been obtained otherwise. A trial of the VRC strategy could theoretically do the same. But, is such a trial possible? And have the NIH and the HIV Vaccine Trials Network (HVTN) taken the steps that would lead to such a trial? Here, the answers are more mixed.

The Step results brought an unprecedented dialogue involving NIAID, its Vaccine Research Program, and the broader community of HIV prevention advocates like AVAC who are not part of trial site communities. In the aftermath of the Step finding, there was a high level of information and materials sharing and constructive dialogue about how to craft messages that were accurate and moved the field ahead. This held true around PAVE 100 as well. But with the advent of 505, the gap has increased between the broader community (advocacy groups working on and impacted by HIV prevention research) and the trial sponsors, which has impeded community stakeholders from getting involved. The publicly available materials and consultations have fallen short in explaining such a complex undertaking. Specific concerns include:

- A series of calls held by the NIH allowed community members to hear a description of the trial and to pose questions to investigators in real time. Such forums are important and should be continued. But it's unrealistic to expect anyone to absorb the information for such a complex trial in a single conference call and to formulate the right questions. NIAID and HVTN representatives have made themselves available on an ongoing basis to answer questions. However, there's still a shortfall in terms of community-oriented materials that provide critical information in an easy-to-digest written format, such as a protocol summary, or a more detailed fact sheet addressing questions raised on the calls or

other topics. Such written materials are key to helping communities navigate the complexities of this proposed trial.

- Confusion and concerns about whether the proposed strategy is safe to test—and how HIV prevention advocates could responsibly represent the trial to their friends, colleagues, and allies—have not been adequately addressed in the forums where AVAC has heard them raised. These are difficult questions to be sure. And the investigators and staff involved have the best intentions. The current fact sheet outlines the safety issues but does not provide a detailed, coherent explanation that can be used as the basis for community-led discussions.

- The public information sheet distributed by HVTN instructed individuals who were interested in learning more about the trial protocol to join community advisory boards (CABs). However, because no details were listed regarding sites or cities where the trials would take place, individuals couldn't easily decide whether the effort was worthwhile. Moreover, the link to the HVTN site led to a map of HVTN sites' own home pages. Some of the links on the individual sites' websites were to staff people who no longer worked there; on others it was difficult to figure out how to join. A far better approach would be to create a link to a page that includes (1) the list of trial sites (or likely trial sites, with a proviso that the protocol is in formation); (2) a list of contacts for these sites; and (3) some explanatory text about what CABs do and what membership entails. As it is, individuals who may have wished to be involved in protocol review had slim chances of accomplishing that.

- Discussions of the scientific rationale for the trial have focused on the data from monkey studies that show a different quality of immune responses in animals that receive the DNA plus Ad5 combination versus Ad5 alone. Several of those studies show no difference in clinical outcomes of viral load or survival in animals that received DNA plus an adenovirus-vectored candidate versus the adenovirus-vectored candidate alone. There are numerous variables in each of these studies as well as others that preclude drawing one over-arching conclusion. This complexity doesn't mean communities can't hear a more detailed explanation of the scientific rationale than they have to date, including the following statement:

There are data suggesting a possible benefit from a DNA + adenovirus-vectored prime-boost strategy, and there are also data suggesting that this is not an optimal strategy to evaluate.

On the positive side, in March 2009 in Philadelphia, HVTN started a series of town hall meetings for community discussion about HVTN 505 and vaccine research in general. These are not recruitment events but discussion sessions that will happen in each city that's home to a site. This is an excellent initiative, and we look forward to learning from these discussions and hope that the questions generated will be documented and shared in broader forums. Principal investigators Scott Hammer and Magda Sobieszczyk have been unfailingly open to conversations, requests for information, and presentations, as have other staff members at the NIAID and the HVTN.

A social science, psychosocial, and behavioral research working group has been convened to look at additional questions that could be posed and possibly answered through HVTN 505. Some of these questions concern data gathering to support trial data analysis. Others are aimed at some of the gaps that have been articulated in the Black Gay Men's Research Agenda, the research agenda articulated at the Gay Men's Health Summit, and similar documents. This approach adds value to the communities involved in the study. Whether there's a direct clinical benefit from the VRC vaccine strategy, there could be useful information gleaned to help communities advocate and implement different types of programs and research.

With FDA approval in place, we're one step closer to posing the question about what the VRC strategy does in humans. Whether that question gets answered depends on how the trial happens. We at AVAC have long argued that this will likely be one of the most complex trials to explain and in which to enroll participants, making the collaborative work that should be in place for any trial all the more important.

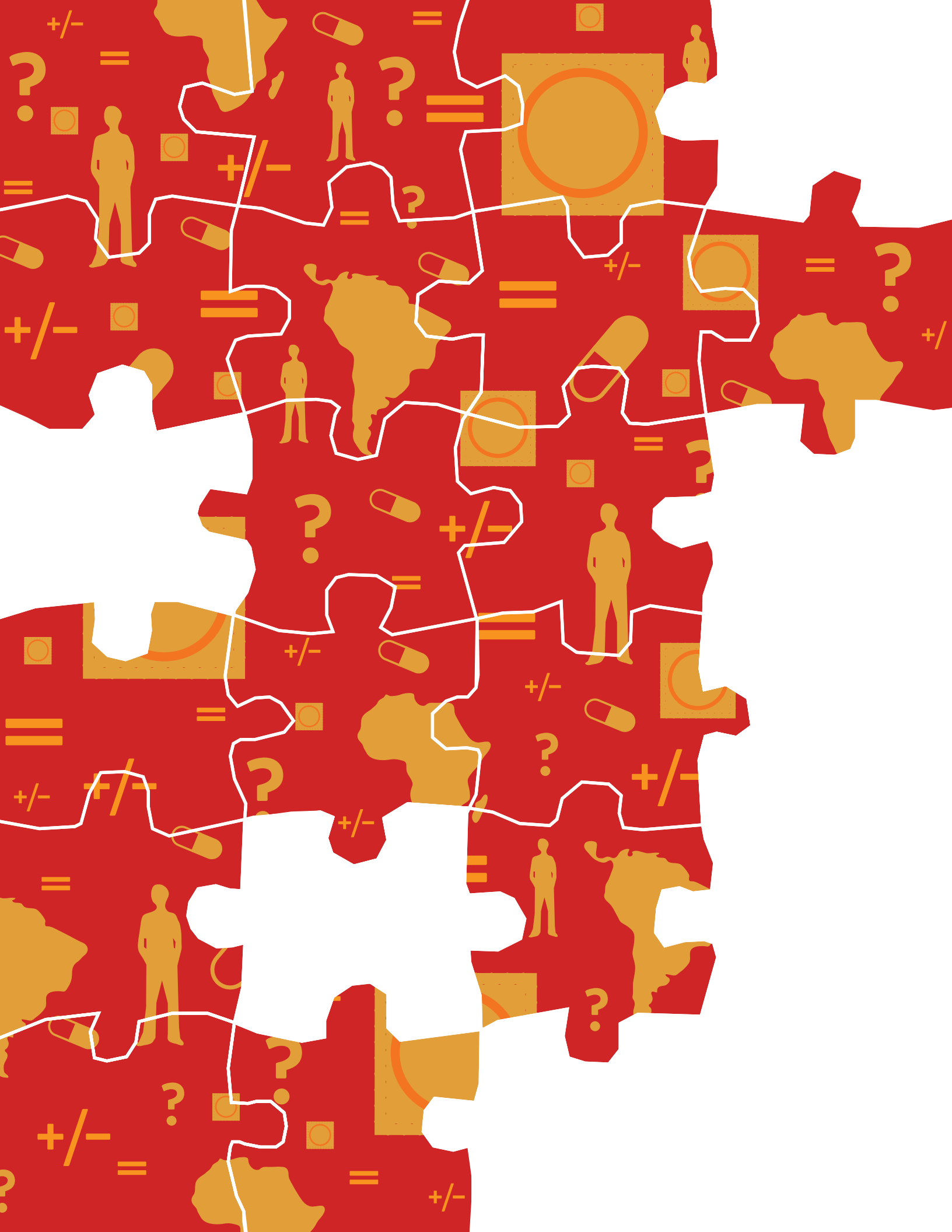
Table 1 Ongoing Trials of Preventive HIV/AIDS Vaccines Worldwide (May 2009)

Protocol #	Start Date	Sponsor, Funder, Developer	Trial Site(s)	# of Participants	Vaccine(s)	Clade
PHASE III						
RV 144	Oct-03	MHRP, MoPH Thailand, Aventis, Vaxgen	Thailand	16,402	Prime: canarypox viral vector with *env* and *gag-pol* Boost: *Env* protein (gp120 subunits)	B A/E
TEST-OF-CONCEPT						
The two trials that follow, HVTN 503 and 502, stopped enrollment and immunizations, September 2007. Follow-up and data collection continue. For more information visit: http://avac.org/vax_update.htm.						
HVTN 503 (Phambili)	Feb-07	SAAVI, HVTN	South Africa	801	Adenovirus vector with *gag, pol, nef*	B
HVTN 502/ Merck 023 (Step study)	Dec-04	NIAID, HVTN, Merck	US, Canada, Peru, Dominican Republic, Haiti, Puerto Rico, Australia, Brazil, Jamaica	3,000	Adenovirus vector with *gag, pol, nef*	B
PHASE II						
HVTN 205	Jan-09	GeoVax, HVTN	US, Peru	225	Prime: DNA vaccine containing *gag, pol, env, rat, rev, vpu* Boost: MVA vaccine containing *gag, pol, env*	B
PHASE I / II						
EV 03/ANRS Vac20	June-07	European Commission, ANRS	UK, Germany, Switzerland, France	140	Prime: DNA vaccine with *env* plus *gag, pol, nef* Boost: NYVAC-C	C
HIVIS 03	Dec-06	MUCHS, Karolinska Institute, SMI, Vecura, MHRP	Tanzania	60	Prime: HIVIS DNA with *env, gag, rev*, RT Boost: MVA-CMDR with *env, gag, pol*	A, B, C A, E
RV 172	May-06	NIH, MHRP, VRC	Kenya, Uganda, Tanzania	324	Prime: DNA vaccine with *gag, pol, nef + env* Boost: Adenovirus vector with *gag, pol + env*	B A, B, C
PHASE I						
B001	Mar-09	IAVI, University of Rochester Medical Center	US	42	Adenovirus serotype 35 vector. Ad35-GRIN/ENV consists of two vectors: Ad35-GRIN vector with gag, reverse transcriptase, integrase, and nef Ad35-ENV vector with gp140 *env*	A
P001	Mar-09	IAVI, Indian Council of Medical Research	India	32	Prime: ADVAX (DNA vaccine containing *env, gag, pol, nef and tat*) Boost: TBC-M4 (MVA vector with *env, gag, RT, rev, tat and nef*)	C
P002	Dec-08	IAVI, St. Stephen's AIDS trust, Chelsea and Westminster Hospital	UK	32	Prime: ADVAX (DNA vaccine containing *env, gag, pol, nef and tat*) Boost: TBC-M4 (MVA vector with *env, gag, RT, rev, tat and nef*)	C
HVTN 073	Dec-08	HVTN, SAAVI	US, South Africa	48	Prime: SAAVI DNA-C2 Boost: SAAVI MVA-C; DNA plasmid vaccine with *gag, RT, tat, nef, env*	C
Ad26.ENVA.01	Apr-08	IPCAVD, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Crucell	US	48	Recombinant adenovirus serotype 26 (rAd26) vaccine	A
IAVI C004/ DHO-614	Oct- 07	ADARC, Rockefeller University, Gates Foundation, IAVI, Ichor Medical Systems Incorporated	US	40	Serial administration of ADVAX, ADVAX e/g + ADVAX p/n-t, by Ichor TriGrid™ in vivo electroporation. The ADVAX vaccine contains *two* vectors: ADVAX e/g, with *env* and *gag*, and ADVAXp/n-t with *pol* and *nef-tat.*	C
HVTN 070	Oct-07	NIAID, HVTN, UPenn/Wyeth	US	120	PENNVAX-B alone, in combination with IL-12, or with 2 different doses of IL-15	B
HVTN 072	Aug-07	NIAID, HVTN, VRC	US	17	DNA and Adenovirus 5 or 35 vectors, all with *env* in varying prime-boost combinations	A

Protocol #	Start Date	Sponsor, Funder, Developer	Trial Site(s)	# of Participants	Vaccine(s)	Clade
PHASE I						
HVTN 071 [As of Sept 07 enrollment and vaccinations have been discontinued]	Jul-07	NIAID, HVTN, Merck	US	35	Adenovirus 5 vector with *gag, pol, nef*	B
DVP-1	May-07	St. Jude's Children's Research Hospital	US	20	Prime-boost regimen with *PolyEnv, EnvPro, EnvDNA*	A, B, C, D, E
VRC 012	May-07	NIAID, VRC	US	35	HIV-1 adenovirus vector vaccine VRC-HIVADV027-00VP: dose escalation and prime-boost with an HIV-1 adenovirus vector vaccine, VRC-HIVADV038-00-VP	A
HVTN 067	Apr-07	NIAID, HVTN, Pharmexa-Epimmune, Bavarian Nordic	US	108	DNA Vaccine EP-1233 and recombinant MVA-HIV polytope vaccine MVA-mBN32, separately and in a combined prime-boost regimen	B A, B, C, D, E, G
HVTN 069	Nov-06	NIAID, HVTN, VRC, NY Blood Center, IMPACTA	US, Peru	90	Prime: DNA vaccine with *gag, pol, nef + env* Boost: Adenovirus 5 vector with *gag, pol + env* (intramuscularly, intradermally, subcutaneously)	A,B,C
DHO-0586	Oct-06	ADARC, IAVI	US	8	ADMVA with *env/gag-pol, nef-tat*	C
HPTN 027	Oct-06	Makerere University, Johns Hopkins University	Uganda	60	Canarypox viral vector with *env* and *gag-pol*	B
C86P1	Sep-06	SGUL, Richmond Pharmacology, Novartis Vaccines	UK	31	Prime: HIV gp140 with LTK63 Boost: HIV gp140 with MF59	B
VRC 011	Apr-06	NIAID, VRC	US	60	DNA vaccine with *gag, pol, nef + env* or Adenovirus vector with *gag, pol + env*	A, B, C
HVTN 065	Apr-06	NIAID, HVTN, GeoVax	US	120	Prime: DNA plasmid with *gag, pro, RT, env, tat, rev, vpu* Boost: MVA vector with *gag, pol, env*	B
HVRF-380-131004	Mar-06	Moscow Institute of Immunology, Russian Federation Ministry of Education and Science	Russian Federation	15	VICHREPOL with polyoxidonium adjuvant	B
HVTN 068	Feb-06	NIAID, HVTN, VRC	US	66	DNAprime/AD boost vs. Ad prime/Ad boost	A, B, C
HIVIS 02	Jan-06	Karolinska Institute, Swedish Institute for Infectious Disease Control, MHRP	Sweden	38	Modified vaccinia Ankara (MVA) viral vector with *env, gag*, and *pol* to volunteers from HIVIS 01	A, E
RV 158	Nov-05	MHRP, NIH	US, Thailand	48	Modified vaccinia Ankara (MVA) viral vector with gp160, *gag* and *pol*	A, E
*Env*DNA	May-05	St. Jude's Children's Research Hospital	US	6	Recombinant HIV-1 multi-envelope DNA plasmid vaccine with *env*	A, B, C, D, E
RV 156 A	Nov-04	NIAID, HVTN, VRC, MHRP, Makerere U.	Uganda	30	VRC-HIVADV014-00-VP alone or as a boost to VRC-HIVDNA009-00-VP	A, B, C
EnvPro	Jun-03	St. Jude's Children's Research Hospital	US	9	Recombinant Purified HIV-1 Envelope Protein Vaccine	D

ADARC: Aaron Diamond AIDS Research Center
ANRS: Agence Nationale de Recherches sur le Sida (France)
HVTN: HIV Vaccine Trials Network
IAVI: International AIDS Vaccine Initiative
IPCAVD: Integrated Preclinical/Clinical AIDS Vaccine Development
MHRP: United States Military HIV Research Program
MoPH: Ministry of Public Health
MUCHS: Muhimbili University College of Health Sciences
NIAID: National Institute of Allergy and Infectious Diseases
NIH: National Institutes of Health
SAAVI: South African AIDS Vaccine Initiative
SGUL: St. George's, University of London
SMI: Swedish Institute for Infectious Disease Control
VRC: Vaccine Research Center

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



Puzzling Out Success

As complex as clinical trials are, they sometimes seem simple compared to the puzzle of implementation: getting the right product, in the right program, to the right people, at the right time. If we wait until there's an actual research finding to start preparing for positive results then, in many instances, we will lose valuable time in delivering potentially lifesaving innovations. In this section, we review some of the issues that need to be considered now, before results from PrEP trials, the Thai prime-boost AIDS vaccine trial, and microbicide studies begin to come in over the next year.

Context

The PrEP Implementation Puzzle: Many missing pieces

No new prevention option will be a simple solution. Although enthusiasm is mounting about ARVs as prevention, it's essential to consider how PrEP or treatment-as-prevention of HIV-positive people to reduce infectiousness would impact health systems, human rights and current programming (see page 46).

Leadership

Part of the Solution: Setting expectations for WHO and UNAIDS

The World Health Organization and UNAIDS play essential roles offering guidance and technical and advocacy support to developing countries. What has recent experience with male circumcision taught about these agencies' strengths? What roles can they play in preparing for PrEP or other trial results (see page 54).

Community Involvement

Te queremos—but are we ready? Taking the next step with HIV prevention research and gay men in the developing world

Research projects can provide valuable information to guide implementation. Gay men and other men who have sex with men in the developing world have participated in a range of HIV prevention studies, and the first results from a PrEP trial may come from the iPrEx study involving gay men. What have these studies taught us, and what are the next steps (see page 64).

The PrEP Implementation Puzzle

Many missing pieces

What happens if pre-exposure prophylaxis or, PrEP, works?

Although we love illustrations like the one that shows PrEP, or any other new intervention, fitting into the big picture of existing programs and strategies (see opposite page), the reality is nebulous. Different PrEP trials could have different results. Even if one or more of the ongoing PrEP trials shows protective benefit—and this is by no means guaranteed—there isn't a neat, PrEP-sized slot sitting vacant in the vast puzzle of the AIDS response. Instead, plans for PrEP introduction must address many of the missing or incomplete pieces of the AIDS response to date.

A strategy like PrEP or a topical ARV-based microbicide involves issues that set it apart from a non-ARV microbicide like PRO 2000 or from a vaccine. An HIV test is not needed for counseling about using a male or female condom. If a person becomes infected with HIV after male circumcision or, hypothetically, after using a microbicide like PRO 2000, these previous prevention strategies won't have any bearing on treatment options. PrEP is a different story altogether. This article considers some of the reasons why.*

PrEP and other forms of ARV prevention, like topical ARV-based microbicides, would require HIV testing and counseling for the HIV-negative individual using them. The details of program design are impossible to forecast, but we assume that providing ARVs to someone HIV-negative would happen in the context of regular HIV testing to minimize the risks of developing drug-resistant virus should the person acquire HIV while using an ARV-based prevention method. (HIV-positive people using one or two ARVs for prevention would in effect be receiving suboptimal HIV treatment and run the risk of developing drug resistance.)

Using ARVs for prevention in HIV-negative people will require substantial investments and innovative programming around HIV testing, delivery of integrated services, and community education.

The same goes for use of ARVs to reduce HIV-positive individuals' risk of transmitting the virus. This "treatment-as-prevention" approach posits that reducing viral load will reduce infectiousness and therefore slow rates of transmission. With ARV-based prevention in HIV-positive people or PrEP in HIV-negative people, the potential prevention benefits won't come without serious attention to a range of cross-cutting issues.

For both PrEP (should it work) and treatment-as-prevention for HIV-positive people, specific work is needed in the areas of:

- Human rights
- HIV testing
- Health care infrastructure
- Financing
- Comprehensive programming

* This article is adapted from "Life in the ARV Generation," a forthcoming AVAC publication that looks in-depth at the benefits and pitfalls that could come with using ARVs as prevention tools for HIV-positive and/or HIV-negative people. Look for the publication at *www.avac.org*.

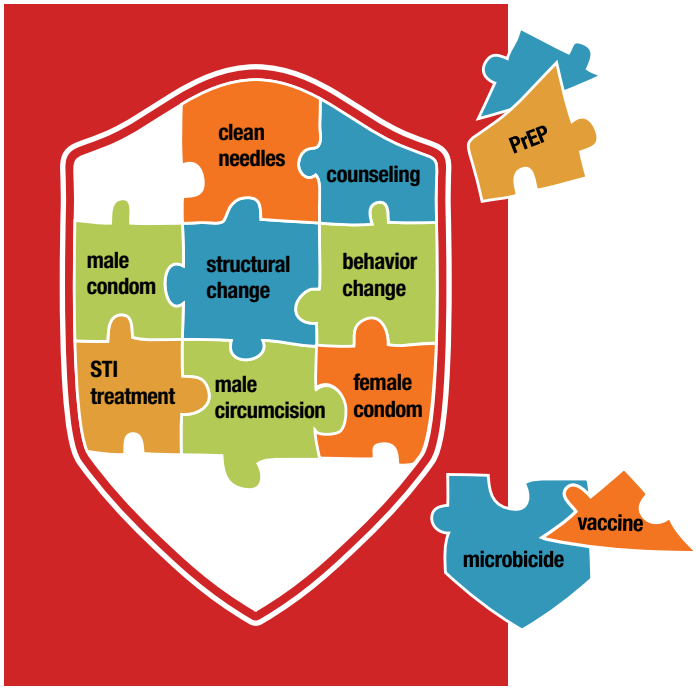
Human rights

ARV use by both HIV-positive and HIV-negative people may prove valuable in HIV prevention (see table on page 50 for more explanation of these different approaches), but it will not solve the fundamental individual, social, logistic, or political challenges that complicate prevention programming. We have to guard against letting the power of a drug seduce us into ignoring the personal and social complexities of vulnerability to HIV. Personal choice is of central importance in health care, and it is imperative to provide interventions that first and foremost serve the patient.

There is growing recognition that HIV prevention efforts have focused too much on individual decision-making and not enough on the social and environmental context of vulnerability to infection. HIV prevention approaches often assume that given accurate information and tools like male and female condoms, people rationally choose to protect themselves. Yet the reality is much more complex for many people, for example, for women who do not feel they have equal power in their relationships, or gay men and other men who have sex with men (MSM) whose sexual behavior is illegal and are constrained to have furtive sexual contacts.

If PrEP has a high level of efficacy in trials, then ARV-based prevention programs might be aimed at high-risk groups, potentially emphasizing individual choice and behavior change at the expense of social context and structural factors that contribute to HIV risk. Even if delivery is not targeted, people taking ARV prophylaxis may be assumed to be in a high-risk group, subjecting them to stigma and discrimination.

The Proven and Possible Puzzle Pieces of Prevention



PrEP—which involves ARV use in HIV-negative people—will have one set of testing considerations. The treatment-as-prevention approach, which suggests early ARVs for HIV-positive people to reduce viral load and therefore infectiousness, will have another. There's an ongoing trial in serodiscordant couples that is looking at the impact of early treatment of the HIV-positive partner on transmission risk, which could provide evidence in addition to the observational data that already support this strategy. If there is a sea change, and treatment-as-prevention gains traction among programmers and policy makers, it could lead to intense pressure on individuals to accept HIV testing so that public health authorities can identify as many people living with HIV/AIDS (PLWHA) as possible. PLWHA may come under pressure to treat early, whether or not they want to start ARVs. While

"Surveys in sub-Saharan Africa have shown that a median of just **12%** of men and **10%** of women had been tested for HIV and received the results."[1]

Sub-Saharan Africa

expanded treatment delivery is a good thing, coercion in health care undermines autonomy, a pillar of medical ethics, and threatens to drive people away from health services.

HIV testing

Any discussion of expanded use of ARVs for prevention has to start with a clear-eyed reckoning of the state of HIV testing worldwide. In the era of ARV-based prevention, an HIV test would be the gateway both to treatment and to comprehensive prevention services. Individuals using PrEP or ARV-based microbicides would also need regular HIV testing to determine whether they had become infected. The frequency of this testing is already being debated in the scientific literature. We feel strongly that community perspectives on testing and other aspects of service delivery for PrEP should help shape context-specific programs if they are warranted by clinical trial data. It's premature to make recommendations about introduction of widespread genotyping and resistance testing should PrEP show any benefit. It will be essential to gather information on the emergence (and waning) of detectable drug-resistant virus in people using PrEP who become HIV-positive. These data can help guide long-term strategies.

Expanding access to HIV testing is clearly a good thing. The challenge is to surmount the many logistical, human-resource, and financing hurdles involved, while minimizing potential negative outcomes of testing like stigma, discrimination, violence, and breaches of confidentiality. In 2008, the World Health Organization (WHO) reported that although HIV testing coverage rates had increased over the previous two years, they remain very low in many areas with serious HIV epidemics. How low? The statistics and facts on this page and throughout the section are glimpses of the shortfall in different contexts.

Unless access to and utilization of HIV testing expands, the impact of PrEP and early treatment in HIV-positive people will be greatly limited. There are numerous approaches to reaching more people with HIV testing, and ideally HIV testing will increasingly be included in scaled-up systems of comprehensive primary care. Since 2007, WHO has recommended that HIV testing and counseling be offered on a routine basis to everyone who uses health facilities in countries with generalized HIV epidemics (i.e., epidemics that have spread beyond subgroups to at least one percent of the general population). The agency says that provider-initiated testing and counseling has met with generally high acceptance, but it acknowledges challenges with protecting confidentiality of test results and with potential negative consequences of disclosure of results, including violence and stigma. Several other models for broadening access to HIV testing have demonstrated success in increasing testing rates, yet human rights concerns about expanded testing remain.[2,3]

[1] UN, World Health Organization. Guidance on Provider-Initiated HIV Testing and Counselling in Health Facilities. 2007 May. Online. UNHCR Refworld. Available at URL: *http://www.unhcr.org/refworld/docid/467f952f2.html*

Health care infrastructure

ARVs might not do for prevention what they have done for treatment, given the many stumbling blocks in delivery of ARV treatment. Scale-up of AIDS treatment access has in many ways been a success, reaching over three million people with lifesaving drugs in low- and middle-income countries. Yet, five years after the WHO set an ambitious goal to greatly increase access to AIDS treatment, these drugs remain out of reach for an estimated 69% of people in need.[4] This includes millions of people in rural areas with limited or no access to health care facilities, marginalized populations who fear coming forward for treatment, and children who need tailored treatment approaches. There are also major infrastructure challenges in health care human resources, sustainable procurement mechanisms, laboratory capacity, and other areas.

Financing

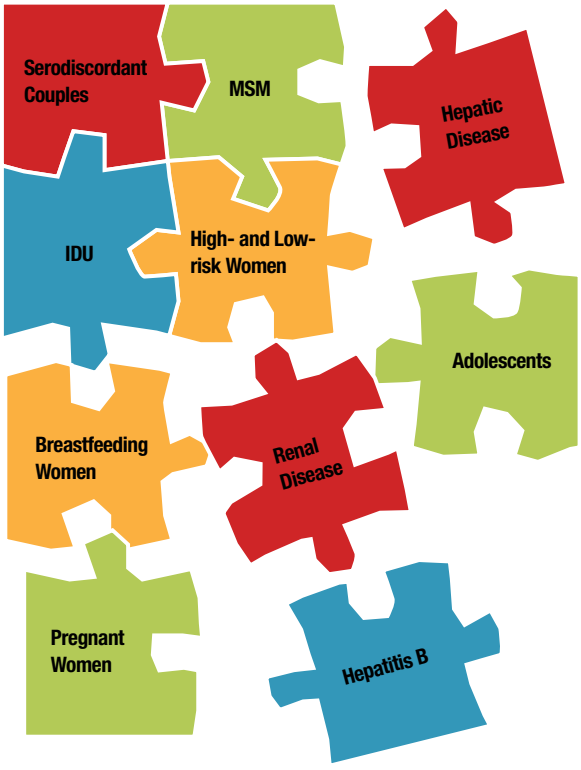
ARVs used in prevention may remove some barriers between prevention and treatment, but additional costs for drug purchasing (both PrEP drugs and ARVs for treatment that could be used by PrEP users who become HIV-infected and acquire resistance) and delivery will put new strains on overburdened health budgets, health systems, and human resources.

Comprehensive programming

A comprehensive package of HIV prevention interventions will be needed alongside ARV-based approaches. Behavioral HIV prevention programs will need to be infused with new messages and approaches appropriate for the new context. There also needs to be an informed decision-making process to determine where ARV-based prevention approaches should be used for greatest public health impact.

Many stakeholders have argued that if PrEP shows a benefit that warrants its introduction, delivery will need to be carefully targeted to maximize its impact and make it cost-effective. But personal choice will be a central factor in use of PrEP as well. Helping individuals assess

Studies to Complete the PrEP Puzzle



[2] AIDS & Rights Alliance for Southern Africa (ARASA) and Human Rights Watch. A Testing Challenge: the Experience of Lesotho's Universal HIV Counseling and Testing Campaign. 2008 Nov. Available from URL: *http://www.hrw.org/en/reports/2008/11/18/testing-challenge*

[3] Abdool Karim Q, et al. The influence of AIDS stigma and discrimination and social cohesion on HIV testing and willingness to disclose HIV in rural KwaZulu-Natal. *South Africa Global Public Health.* 2008; 3(4):351-365.

[4] WHO, UNAIDS, UNICEF. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: Progress Report. 2008. Available at URL: *http://www.who.int/hiv/pub/towards_universal_access_report_2008.pdf*

Table 2 ARVs Now and in the Future

Intervention	Description	Status	Key Issues
Current uses of ARVs in HIV-positive and -negative people			
HIV treatment	ARVs used in combination inhibit HIV entry into cells or replication within cells, reducing viral load	As of 2007, 31% of the nearly 13 million people needing HIV treatment were receiving it.	• Challenges in reaching rural and marginalized populations • Need for adherence and other supports
Prevention of vertical transmission	ARVs given to a pregnant woman during pregnancy and to the infant at birth greatly reduce the likelihood the newborn will become infected with HIV	As of 2007, 34% of HIV-positive pregnant women were receiving ARVs to prevent mother-to-child transmission.	• Challenges with access and uptake due to stigma and limited access to healthcare system • Need to ensure pregnant, postpartum and breastfeeding women receive appropriate care and other services • Need clarity about use of ARVs with breastfeeding
Post-Exposure Prophylaxis (PEP)	ARVs given soon after high-risk potential exposure to HIV are thought to significantly reduce the likelihood of infection	PEP is used mainly in the case of health care worker exposure, though is available more broadly in some industrialized countries.	• Inability to do randomized clinical trials • Need to begin month-long regimen soon after exposure
Strategies being researched			
Oral Pre-Exposure Prophylaxis (PrEP)	ARVs taken regularly or before and after exposure might reduce the likelihood of infection	Seven current or planned clinical trials of PrEP. The first efficacy trials may report data as early as the first quarter of 2010.	• Need for additional research on: intermittent (vs. daily) use; long-term toxicity and drug resistance; adherence; use by pregnant women and adolescents • Need to plan for targeted rollout • Will require expanded and frequent HIV testing • Need to develop new agents for potential use in PrEP
ARV-based microbicides	ARVs used in gels, films, vaginal rings or other products that would be inserted in the vagina or rectum to reduce the likelihood that the user becomes HIV infected during sex	The first efficacy trials may report data as early as 2010.	*All issues with oral PrEP above, and:* • Need to optimize vaginal and rectal delivery methods to maximize acceptability • Need for more research on potential rectal use
Emerging uses of ARVs as prevention in HIV-positive people			
Treatment as prevention and earlier initiation of treatment	ARV treatment of people living with HIV may reduce their infectiousness	• Growing body of evidence suggests earlier ARV treatment initiation benefits the patient, but effects of immediate treatment in those who don't need it are unknown. • Swiss Commission on AIDS-Related Issues released statement in 2008 arguing that PLWHA on treatment and with no STIs are sexually non-infectious. • NIH study, HPTN 052, on earlier initiation of treatment and infectiousness to report results in 2014.	• Concerns that assumptions about non-infectiousness will lead to increased risk taking, undermining prevention effect • Need to update global policy to initiate treatment earlier and measure prevention impact • Need to confirm lower HIV viral load (VL) in blood correlates with reduced infectiousness given that VL can be measured in seminal fluids of some men with undetectable VL in blood
Testing and immediate treatment	Theoretical model suggesting that widespread HIV testing and immediate treatment of all those identified as HIV-positive would greatly reduce HIV incidence	Article in *The Lancet* (Nov 2008) proposed model and said WHO will hold consultations in 2009.	• Enormous logistical challenges in scaling up HIV testing and immediate treatment • Need to determine whether immediate treatment is medically optimal for PLWHA

Even if multiple studies show that PrEP reduces HIV transmission, there will be much to be done before global implementation:

- Additional research on delivery, impact, safety, alternative dosing and other issues
- Increased counseling and testing
- Expansion of innovative, integrated HIV prevention and treatment programs
- Collaboration with communities to develop introduction strategies and identify groups to benefit most

their personal risk for HIV infection will likely be a critical element of successful PrEP programs because these assessments will help guide an individual's decision-making. Issues that might be weighed include the risks and benefits of taking an ARV for prevention; individual ability to take PrEP as prescribed; and the duration an individual might spend on PrEP.

Even if PrEP or other forms of ARV-based prevention are highly effective, they are unlikely to provide 100% protection from infection or transmission. Current HIV prevention approaches—including male and female condoms, clean needles, male circumcision, HIV education and behavioral interventions, and safe blood supplies—will remain essential to controlling HIV incidence and will need to be part of a package of prevention services. One worry is that policy makers, public health leaders, and donors, captivated by the availability of a drug to prevent infection, will invest in ARVs at the expense of other effective interventions. Community-based HIV educators will need training to play an active role alongside health care workers in dispensing ARV-based prevention.

To get prepared, we need to acknowledge the urgent actions needed by virtually every stakeholder group working in the field.

Recommendations

- **The research community needs to invest much more time in understanding how ARV-based prevention could best be used in real-world situations, in addition to testing whether particular drugs work in the context of a clinical trial.** This means an increased emphasis on the types of programs that might be used to deliver PrEP, drawing on the expertise and priorities of implementers and service providers. Some of this can happen before there are results from PrEP trials. If findings warrant introduction of PrEP, then systematic research, monitoring, and post-marketing must take place to learn more about safety, including renal and hepatic issues and drug resistance, and about delivery strategies.

- **Funders, researchers, and community stakeholders need to clarify and execute a research agenda to address questions that may not be answered by current trials.** What types of intermittent dosing strategies will offer protection for users

who are unwilling or unable to take PrEP every day? What will current trials tell us about this, through adherence and blood-level data? What else could be gathered from current effectiveness trials and/or small trials that might be launched while the large studies are ongoing? More research is also needed on rectal microbicides.

- **Public health leaders, funders, community advocates, and researchers need to develop a strategic plan of action for piloting delivery of PrEP in various settings.** What should initial programs look like? What's the best way to integrate PrEP into existing services and to provide clear messages to all audiences, while perhaps only delivering to targeted populations? What bridging and long-term safety research should be built into programs so that data are gathered during rollout?

- **Funders must explore ARV-based prevention as an opportunity to change the course of the epidemic,** an opportunity requiring early and substantial additional investments that will pay dividends down the road. Although there's no one-size-fits-all approach to PrEP implementation, it will require substantial investments in HIV testing and an emphasis on integration of prevention treatment and care. Harnessing the prevention potential of using ARVs to reduce infectiousness in people with HIV will also take vision, innovation and substantial resources.

- **Funders and policy makers (in donor and heavily affected countries) have to be prepared for strategic delivery of PrEP that maximizes public health impact.** Mathematical modeling and cost-effectiveness studies are needed to define best approaches for targeted delivery of PrEP and other interventions in different epidemic settings. An access plan is needed that anticipates purchase capacity, drug registration, and manufacturing and delivery of PrEP and treatment-as-prevention programs. Support is needed for public health research on issues such as how to minimize stigma when identifying and recruiting individuals most at risk for HIV infection. Systems need to be in place for tracking drug adherence, drug resistance, and incidence. The long-term success of ARV treatment programs depends on affordable, reliable access to first-, second-, third-line, and salvage therapy regimens. This would become more critical if ARVs were used for prevention, in order to ensure appropriate treatment options for people who used PrEP and went on to become infected. Normative agencies including UNAIDS and WHO should develop a work plan that includes consultation with multiple stakeholders, development of guidance documents, and assistance to help country governments determine whether and how to use PrEP (see page 54).

Each PrEP Trial is a Piece of the Puzzle

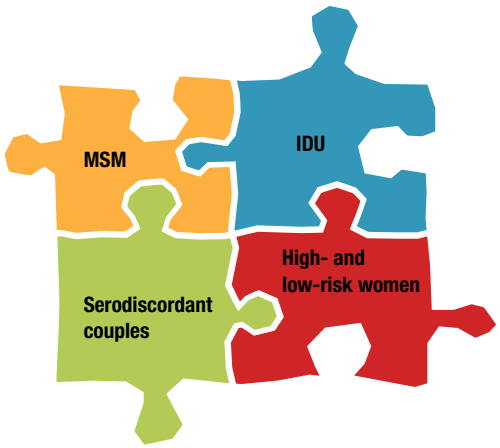
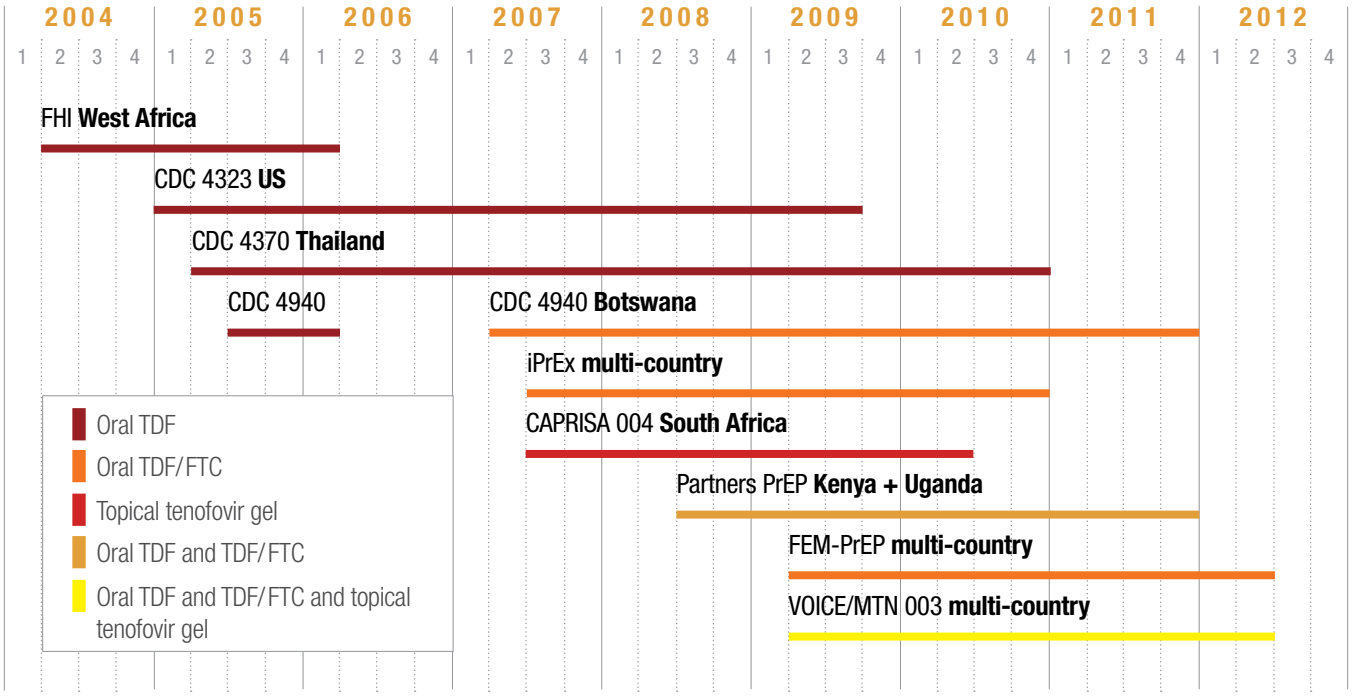


Figure 4 Timeline for Ongoing and Planned PrEP Trials* (May 2009)



* The trail end-dates listed in this table are estimates. Due to the nature of clinical trials the actual dates may change. AVAC will continue to monitor trial progress and will update the timeline accordingly. To view or download an updated timeline visit *www.prepwatch.org*.

- **The pharmaceutical industry should work with global agencies and governments to make sure PrEP will be accessible where needed.** This includes using voluntary licensing and tiered pricing to lower costs, anticipating manufacturing capacity needs, and working with partners to minimize delay in moving ARVs through the drug registration process in heavily affected countries. Pharmaceutical companies should also make new agents with potential use in PrEP or other ARV-based prevention available for testing if they themselves will not test these agents for such applications.

- **AIDS and health advocates must articulate an ambitious, balanced agenda for HIV testing, PrEP, and early initiation of treatment in HIV-positive people.** It is time to fully embrace HIV testing and prevention as we have embraced HIV treatment and to help identify how to widely deliver these services in a way that respects human rights and minimizes stigma and discrimination. This will require closer connections among advocates for AIDS treatment, human rights, maternal and child health, and health systems generally.

Part of the Solution

Setting expectations for WHO and UNAIDS

Over the past year, AVAC has underscored the importance of the World Health Organization (WHO) and UNAIDS getting involved in planning for the results from pre-exposure prophylaxis (PrEP) trials before data are available. A CDC-sponsored PrEP safety study in the US is slated for completion before the end of the year, and two efficacy studies—iPrEx and the CDC Thai study—may have interim data in the next 12 months (see page 53 for PrEP trials timeline). Given these timelines, the contributions of international entities like WHO and UNAIDS are key. WHO's authority and mandate to set norms and issue guidance on health interventions, including vaccines and medications, is nearly universally recognized in the international arena, as well as at the regional and country level. Countries look to WHO for guidance, and it is rare for developing countries—even those with relatively good capacity to conduct independent review—to implement policies, health innovations, or new drugs without guidance from WHO. Donors also look to WHO, and many will not consider providing funding support to efforts outside WHO guidance. UNAIDS is the joint venture of all UN agencies working on HIV/AIDS, and WHO is one of its members. With its global scope, UNAIDS can collect civil society and developing country input to shape influential initiatives and documents like the *Ethical Considerations in Biomedical HIV Prevention trials*.

In recent months, we've had conversations with a range of stakeholders* to help flesh out recommendations of what should be expected fromWHO and UNAIDS when it comes to preparing for results—good, bad, or hard-to-interpret—from ongoing PrEP trials.

We focused on four key areas:

- Anticipating and shaping the response to emerging innovations
- Setting international norms and standards
- Working with national-level actors
- International and national advocacy

Anticipating and shaping the response to emerging innovations

Timing is critical when it comes to these two agencies, both of which provide important support to many developing countries in shaping both regulatory and policy priorities. Waiting until extensive data are available for any given strategy is waiting too long. It can take many months, and often over a year, to develop technical guidance and to conduct regional dialogues that have characterized the WHO and UNAIDS approach with other interventions, including male circumcision.

WHO and UNAIDS swung into action after the results of the Orange Farm trial of male circumcision for HIV prevention showed efficacy in 2005. By the time the results from the Rakai, Uganda, and Kisumu, Kenya, studies were released in December 2006, WHO/UNAIDS had

* To inform this piece, we interviewed 16 individuals inside and outside WHO and UNAIDS, working at international and country levels, including advocates, scientists, and others.

already conducted regional consultations, held meetings on social science, drafted technical manuals, and completed other activities outlined in a male circumcision work plan that was supported by the Bill & Melinda Gates Foundation. All of this work fed into the March 2007 consultation in Montreux, Switzerland, where the guidance on the implications of male circumcision for HIV prevention was drafted. Without all of the preparatory work, it simply wouldn't have been possible to convene such a meeting three months after the data were released.

Several people noted that the collaboration on male circumcision has worked reasonably well even when the specific mandates, credit, or boundaries of responsibility were blurred between WHO and UNAIDS. Nearly everyone attributed this in large part to the professionalism, commitment, and focus of the high caliber individuals leading the effort for the two agencies: Kim Eva Dickson from WHO and Catherine Hankins from the UNAIDS secretariat.

Male circumcision is an issue that incorporates the strengths and mandates of both agencies, requiring clear technical guidance and implementation in the health sector, as well as policy development and sensitivity to complex issues around advocacy, culture, and rights that are part of UNAIDS' mission. In the work around implementing male circumcision, WHO has been in the lead—providing technical guidance, manuals, training and so forth. UNAIDS has provided critical complementary work in advocacy and policy development, such as a modeling tool that can help policy makers work through implications and cost effectiveness based on different types of epidemics, different target groups, coverage, and so forth.

> "The large majority **(82%)** of HIV-positive women and men have never been tested for HIV. Only **11%** have been tested and know the results of the most recent test."[5]
>
> *Democratic Republic of the Congo*

At the same time, there were some limitations in the way that WHO and UNAIDS approached male circumcision for HIV prevention, including concerns that underscore some of the challenges around timing and representation that can emerge in global processes. For example, HIV-positive women and their allies, along with sexual and reproductive health advocates, voiced concerns about belated and insufficient inclusion of women's perspectives into the early consultative work. These concerns persisted even though in South Africa in 2006, UNAIDS convened a meeting for social scientists that included gender, sexual, and reproductive health advocates. A handful of civil society advocates were also included at the Montreux consultation to develop a document analyzing the implications of male circumcision for HIV prevention, and that document did include several guidance points that related to gender and to concerns about the implications for women.

Even so, when the Orange Farm data were confirmed and recommendations for rollout issued, there was a sense among many women's health and HIV prevention

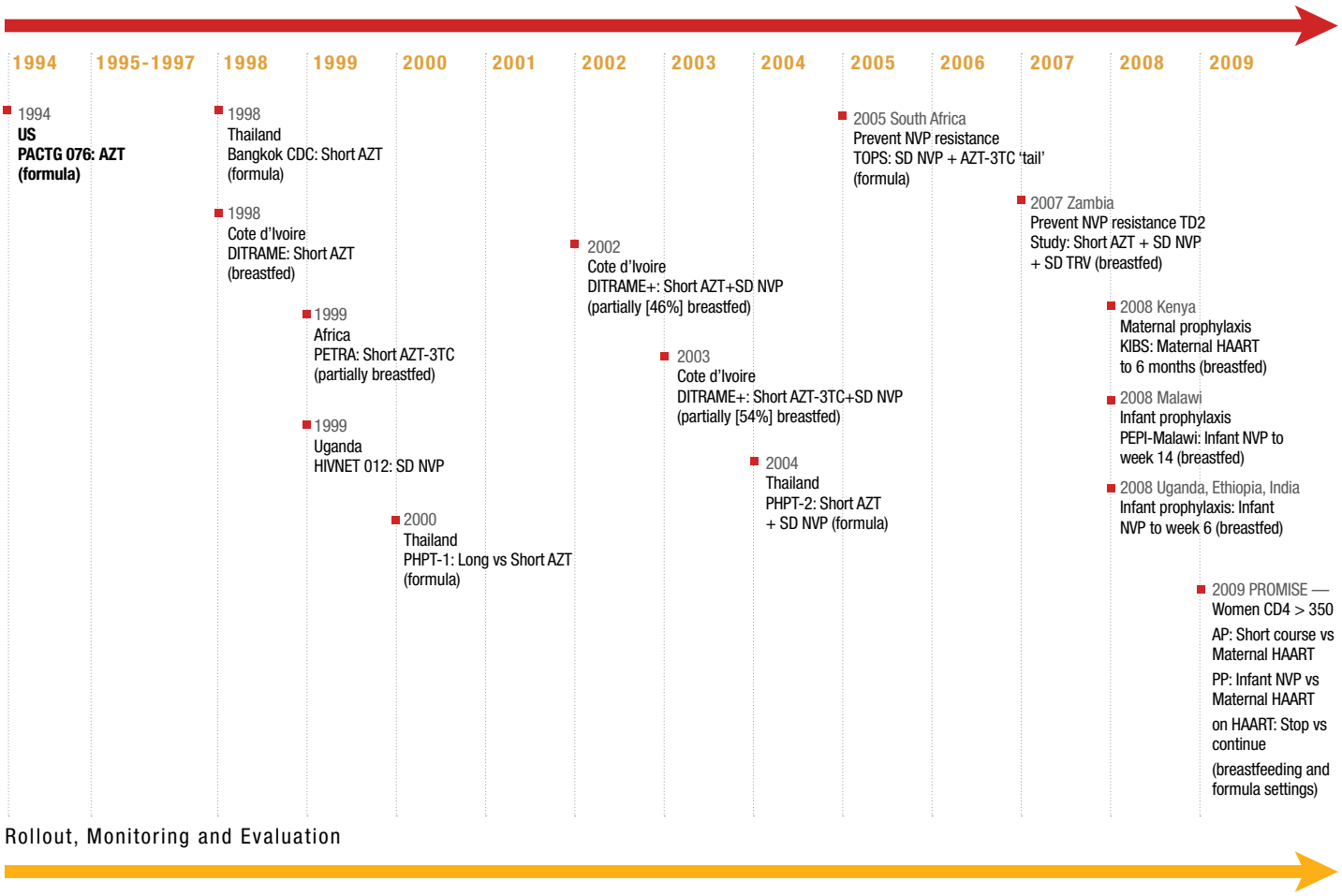
[5] The Ministry of Planning. Democratic Republic of the Congo. 2007. Available at URL: *http://www.measuredhs.com/pubs/pdf/HF25/HF25.pdf*

advocates that the issues for women had been ignored. This perception persisted even after AVAC and WHO collaborated on a pair of meetings focused on the implications of male circumcision for women—in part because women felt that the discussions in June 2008 were too little and too late to influence how services are designed and evaluated.

None of these preparatory activities would have been possible without external funding—provided by the US National Institutes of Health (NIH), the Gates Foundation, and the French ANRS. Despite their size and global influence, neither WHO nor UNAIDS have internal funding resources for preparatory activities for new technologies or innovations. The need to raise external funding and the consequent lack of flexibility can seriously limit the ability of WHO and UNAIDS to respond rapidly to new information and set preparatory work in motion.

Figure 5 Preventing Perinatal Transmission: 15 years of research and rollout

The first finding of efficacy in ARV-based prevention of perinatal transmission was in 1994. Since then, prevention of parent-to-child transmission programs have delivered ARVs to women, infants, and sometimes women's partners worldwide. There are continuing challenges in meeting global need, but there have also been strong successes in bringing down HIV infection rates in newborns. As this figure shows, research has continued alongside rollout. This will almost certainly be the scenario for any new biomedical prevention strategy.



Approximately 20,000 participants in trials completed, ongoing or planned

Adapted from: James McIntyre, Perinatal HIV Research Unit, Soweto, South Africa

Preparing for All of the Coming Year's Trial Results

Even though PrEP—which has yet to show efficacy—is in the spotlight, there are other trials of biomedical prevention options that will have results in the coming year. The Thai prime-boost vaccine trial will have data in the third quarter of 2009; MDP 301, the trial of the PRO 2000 microbicide, will have additional data in the fourth quarter of 2009. As the *Report* went to press, the results of the trial of HSV-2 treatment in HIV-positive people were announced.

No matter what the results, there will be questions about what happens next. Each of the trials has a slightly different set of considerations. The Thai prime-boost trial was designed as a test-of-concept study and not for licensure of the product, so a positive result would entail determining where and how to do follow-up research. This will be complicated by the fact that VaxGen, the developer of one of the components of the vaccine regimen, may have limited capacity to manufacture additional doses for expanded studies.

Positive data from the HSV-2 trial will likely raise questions about how to incorporate expanded HSV-2 treatment into prevention aimed at HIV-positive people. It might also stimulate discussion about early initiation of ARV treatment to reduce viral load and infectiousness—another example of using drugs as part of "positive prevention."

If data from MDP 301 show effectiveness for PRO 2000, this may be seen as the second such trial—although the trend toward protection observed in women who used PRO 2000 in a previous trial, HPTN 035, didn't reach statistical significance. Discussions need to consider whether one indeterminate and one confirmatory trial are sufficient for pursuing licensure, and how this candidate might be evaluated, contrasted, or perhaps combined with ARV-based compounds currently in clinical trials.

iPrEx is a Phase III PrEP effectiveness trial in gay men and other men who have sex with men. What would a positive result mean for introduction in other communities of gay men (see article on page 64)? How would findings of different levels of effectiveness (high, moderate, or low) affect the ongoing trials of PrEP in the context of injection drug use or heterosexual transmission?

For PrEP, HSV-2 and microbicide trials, there will be questions about how observed effectiveness relates to patterns of product use (adherence). A product that reduces the risk of HIV infection in volunteers who are highly consistent users might have substantially lower effectiveness in the "real world," where people don't have the trial-based reinforcement of correct use or the inclusion of other proven prevention strategies. It could also have higher effectiveness because unlike trial volunteers, real-world users would know the level of protection found in the trial and have an incentive to use the product correctly.

There are no simple or one-size-fits-all answers to any of these questions, and it's impossible to prepare fully without knowing the data. But it's critical to consider, anticipate, and begin conversations that encompass all experimental prevention strategies: vaccines, microbicides, PrEP, and others. If each of these fields meets its goals, then someday we will live in a world where people will be choosing from the full range of options currently in clinical trials. Even then, research will continue. As the timeline on page 56 reminds us, research on prevention of perinatal transmission has continued to help refine strategies long after the original data showing the efficacy of AZT were published in 1994. Preparing for this rich, complicated world is time well spent—no matter how long it takes.

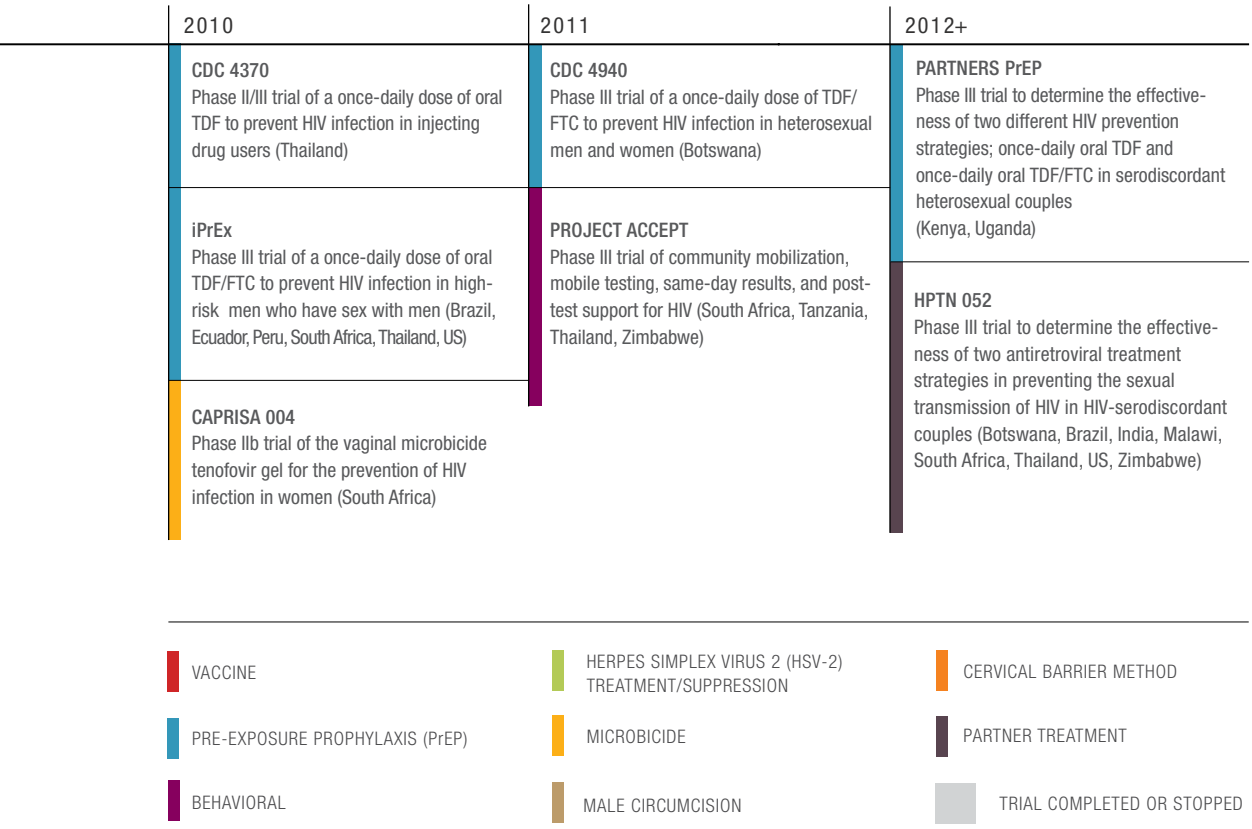
Every intervention is unique, and WHO/UNAIDS work on PrEP will be different from activities on male circumcision. Here are some considerations.

- As this article was being written, WHO's HIV department secured funding from NIH to convene an initial consultation on PrEP. A comprehensive PrEP work plan, similar to that executed for male circumcision, should be developed and funded based on the recommendations from this initial consultation, combining the expertise of WHO and UNAIDS.
- WHO needs to develop a clear internal plan for drawing on and coordinating the different parts of the organization to make PrEP available should it prove safe and effective. Accounting for the many dimensions of access and use, the project of planning for scale-up of PrEP will encompass drug regulation, essential

Figure 6 HIV Prevention Research: A Comprehensive Timeline of Efficacy Trial Results* (May 2009)

medicines, and several other of WHO's sections and departments in addition to its HIV department.

- Because the first PrEP results are expected from trials that are ongoing in gay men and other MSM, it's also essential that WHO/UNAIDS include MSM as researchers and civil society representatives in all consultations and drafting of guidance. Several people we spoke with—inside and outside the UN—acknowledged that it had not adequately addressed issues of MSM in the AIDS epidemic. The UN Development Programme (UNDP), one of the UN co-sponsors, is taking the lead on issues of gay, lesbian, and transgender communities. There's a forthcoming framework of action and a newly hired technical expert on gay, lesbian, and transgender issues. These are valuable resources for addressing implications of PrEP findings, if positive, in gay men (for more on this topic, see page 64).



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

To view this timeline online with trial details please visit *www.avac.org/timeline-website/*. If you have any questions or comments regarding the information presented here please email *avac@avac.org*.

"A South African national youth survey found **60%** of all 15- to 19-year-olds wanted to know their HIV status, but only **15%** of females and **9%** of males had been tested."[6]

South Africa

- There is a need to track plans for scale-up in manufacturing and distribution of TDF and TDF/FTC, the drugs currently being tested for PrEP. Gilead, the manufacturer of both drugs, has indicated in several forums that it will allow the drugs to be manufactured as generics for low-income countries and that plans are in place to facilitate rapid scale-up of manufacturing. But global and country-specific scenarios for access need to be made clearer and more transparent. This will make it easier to identify gaps and determine how to fill them. Even if WHO or UNAIDS does not assume this role directly, these agencies can help ensure that an appropriate partner does so.

Setting international norms and standards

Should positive data indicating that PrEP reduces risk of HIV infection emerge from any single trial, WHO and UNAIDS will play critical roles in framing the discussion around next steps. In all likelihood, there will be results from a single trial while other studies in different populations are ongoing. Given the precedent with male circumcision, and the statements WHO and UNAIDS have made at public forums in the past year, their initial response might be to indicate that they are following the research closely.

Given that PrEP involves products that are already available for treatment, there may be countries and communities where individuals make decisions about trying PrEP for prevention, whether it's been approved or introduced at a country level. This will depend in part on effectiveness data from the trials. For example, a high level of risk reduction might be more appealing and easier to understand than a 30 percent reduction.

This potential for people to "vote with their feet" and to use or potentially misuse PrEP before there's international or national guidance on the strategy means that at minimum, WHO and UNAIDS should be prepared with guidance on communications, messaging, and perhaps strategies for countries to monitor informal PrEP use. Many of the people we spoke to for this article stressed the importance and utility of WHO guidance. They also noted gaps: there is no WHO guidance on washing and reuse of the female condom, even though a normative agency intervention on this could potentially have a significant impact on national and international willingness to fund and program around the female condom. Given WHO's influence with donors and health ministries, any delay in guidance can result in an even longer delay for actual availability in programs. WHO guidance and recommendations are also prerequisite for developing bulk procurement approaches to many commodities, including vaccines. It's unclear how drugs for PrEP might be procured, given that they're already used for treatment, and this is another area where advance work is needed.

[6] Mathews C, et al. Quality of HIV Testing Services for Adolescents in Cape Town, South Africa. *J Adolesc Health.* 2009 Feb;44(2):188-90. Epub 2008 Sep 27.

One of the key issues in establishing technical norms for PrEP is what level of evidence will be needed on efficacy, safety, feasibility, and acceptability in different populations. WHO has guidelines on the levels and types of evidence that should drive decision-making. In practice, the application of these guidelines can be open to interpretation, especially if data come in over time. If, for example, WHO requires three separate efficacy trials for PrEP, all in the same direction and studied in the same population, it will be many years before there is formal guidance. Global leadership and communication about the implications of PrEP results will be essential even if formal guidance isn't issued on the basis of a single trial.

Working with national-level actors

The big question is what effect do UNAIDS and WHO have on the ground in terms of service or impact? So far the experience with male circumcision has been a success in terms of process: guidance has been developed, workshops held in key countries, manuals written, training conducted, and so forth. At the same time, there is still relatively little happening in terms of comprehensive programming "on the ground." (For detailed information on rollout in different settings visit *www.malecircumcision.org*, a collaborative project of WHO/UNAIDS, AVAC, Family Health International and other partners.) This is attributable in part to some countries' reluctance based on political or cultural concerns, and to the limited resources—including providers—in the health sector. It also underscores some of the limitations of these normative agencies: although they have a critical role in providing technical guidance, training and other assistance, they do not have a mandate or resources to implement programs or provide services. So making health innovation available needs to involve many other players: national ministries, training agencies, funding entities like the Global Fund to Fight AIDS, Tuberculosis and Malaria and PEPFAR, community-based groups, and health providers, among others.

Even without a direct role in implementation, leadership from these normative agencies can play a critical role at the country level. For example, when the former South African Minister of Health was obstructing consideration of male circumcision for HIV prevention, having a senior WHO representative from Geneva deliver a major address was critical to reinforcing it as a credible intervention that the government should make a priority.

Any real impact on transforming research into practice needs to include many entities at the national and international levels to conduct training, deliver services, ensure supply, and provide funding. WHO and UNAIDS are only two players. Looking specifically at their roles, here are some challenges:

- Neither WHO nor UNAIDS has the capacity or mandate to work on delivering new health innovations.
- WHO is governed by the World Health Assembly, which is comprised of ministers of health of member states. This means that WHO can sometimes be working to influence policies and practices of the same health ministries that govern it. This structure can limit WHO's willingness and ability to champion certain policies or approaches, or to monitor or report on countries with controversial policies or practices. In the case of PrEP, some

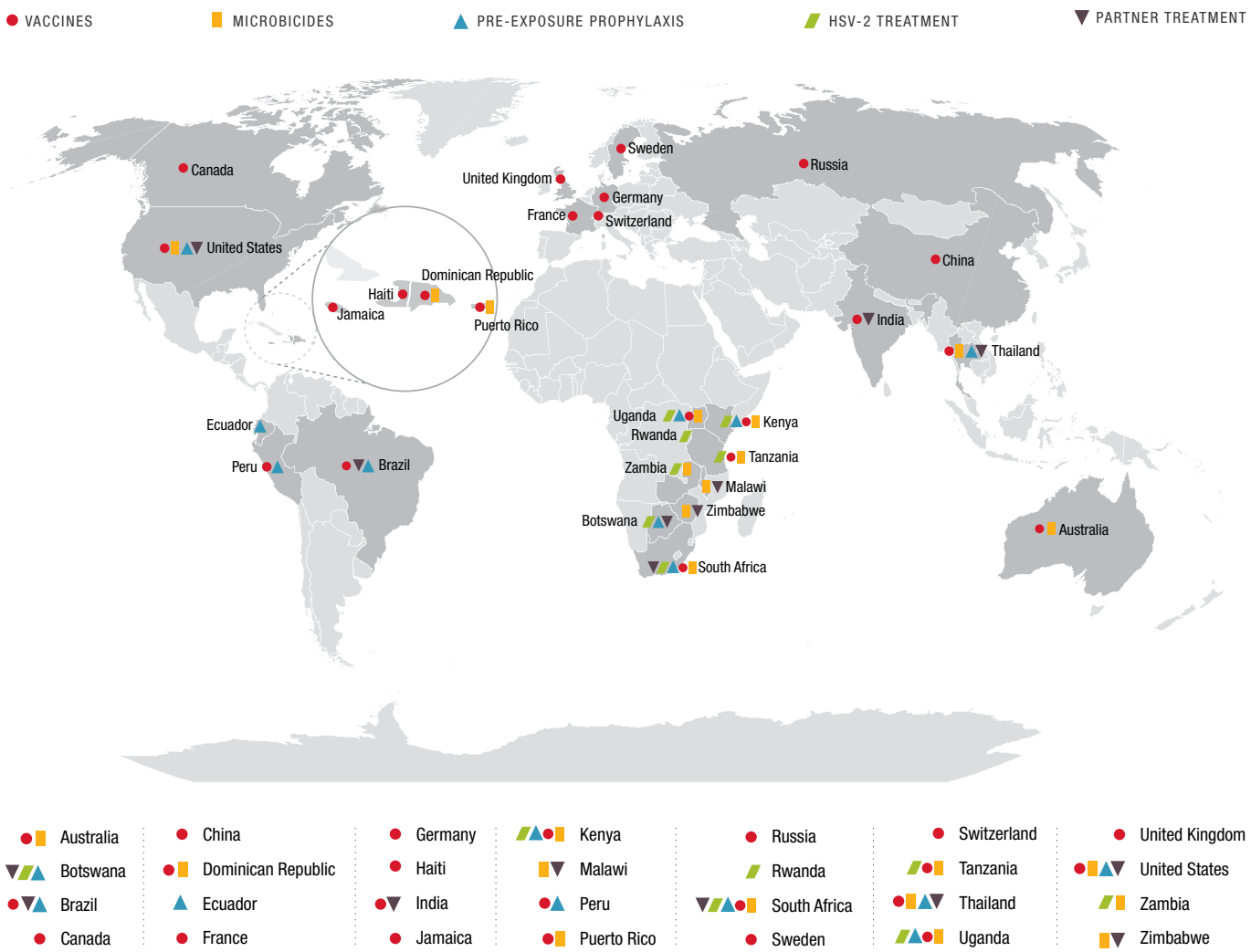
ministries may oppose it because countries have not yet reached their treatment goals or because of the stigma related to the high-risk groups, like MSM, to which PrEP may be targeted, among other reasons.

- WHO's management structure gives considerable autonomy to its regional and country offices. This decentralized structure can keep WHO aware of and responsive to regional and local needs, but it can also limit the organization's ability to move rapidly on new information.
- WHO works primarily with ministries of health and has a broad mandate across the health sector. It therefore may have limited technical capacity in its regional and country offices in a specific new area like PrEP.

International and national advocacy

UNAIDS is instrumental in advocacy, communication, resource mobilization, and coordination, as well as in highlighting important issues around rights and stigma, marginalized groups, and the inclusion of

Figure 7 Ongoing Trials of New HIV Prevention Options Worldwide (May 2009)



people living with AIDS. Its advocacy, or lack thereof, can mean that it is sometimes perceived—especially in-country—as biased or indifferent toward competing health priorities. UNAIDS and WHO both sometimes play important and underappreciated behind-the-scenes roles with respect to new technologies, for example, by supporting countries to incorporate new innovations into Global Fund applications or by helping design national programs and monitoring approaches.

Several people noted that the tool UNAIDS developed to model the impact and cost effectiveness of male circumcision in different epidemics was important to gaining attention and support among key policy makers and donors, and they suggested that its adaptation for PrEP or other new prevention approaches be made a priority.

Conclusion

If PrEP proves effective for HIV prevention, male circumcision and PrEP together have the potential to transform existing prevention paradigms. WHO and UNAIDS need to combine their strengths to provide leadership and coordination so that the world is ready to work with results from ongoing PrEP trials.

As next steps, these agencies should:

- Form a joint PrEP working group drawing on experiences with male circumcision. This group must provide a structure to respond to and synthesize new data and information as they emerge. There are some nascent efforts to form a PrEP working group within WHO and an ongoing need to ensure transparency and true collaboration with UNAIDS.
- Take leadership in identifying key implementation questions that will not be answered in the trials.
- Work to identify lead agencies, people, and resources—either within or outside the UN system—to start answering the outstanding questions.
- Articulate and build consensus around real community- and program-based plans for HIV testing in varied populations.
- Lead in scenario planning and consensus building among diverse constituencies.
- Adapt the UNAIDS "decision maker" tool developed for male circumcision to help policy makers consider the possible implications of PrEP.
- Coordinate interagency leadership—in the UN system and elsewhere—to develop and champion an integrated prevention program with a vision about prevention overall.
- Issue guidance on best practices for delivering integrated packages of prevention care and treatment tailored to different epidemiological scenarios. These should incorporate new prevention approaches like male circumcision or PrEP, rather than focusing on each new approach alone.

Te queremos—but are we ready?

Taking the next step with HIV prevention research and gay men in the developing world

The first efficacy data from pre-exposure prophylaxis (PrEP) trials are expected to come from studies involving gay men and other men who have sex with men (MSM), including the ongoing iPrEx study. These data will come at a moment of increasing attention to the global AIDS epidemic in gay men. In Africa, Asia, and Latin America, HIV prevalence rates of more than 10% are routinely found among men reporting sex with other men.[7] These rates are also found in some communities of color in the United States. In sub-Saharan Africa, even in countries with generalized heterosexual epidemics, at least one in 20 new HIV infections may be due to male-male sex, and MSM are nearly four times more likely to be HIV-positive than the general adult population.[8]

This context cannot be ignored in preparations for potential results from PrEP trials. The needs, priorities, and concerns of gay men and other MSM may get addressed by normative agencies (see page 59), but then again, that 20 years into this epidemic, we need to be reminded to pay attention to gay men suggests that nothing should be taken for granted. The question is:

Is the world ready to deliver* to *gay men if there's a result from a new biomedical prevention trial tested* in *gay men?

There is a need to think specifically about what success in the iPrEx PrEP trial could and should mean for gay men in the developing world. That's not to dismiss or minimize the issues, needs, and strengths of the communities of gay men and other MSM in the developed world—including the US, Australia, and Europe. Stigma, provider bias, and persistently high incidence exist in these settings, too. However, for this piece, we're focusing specifically on communities in the developing world.

The ongoing work to incorporate medical male circumcision, with its host of culture- and gender-specific issues, into HIV prevention services is a prime example of how good data are just the beginning of building good programs. Countries, communities, and normative agencies must act to ensure that the world is ready to deliver on a positive PrEP result if there is one in gay men—and to deliver on other prevention for gay men, whether the PrEP result is good, bad, or indifferent.

Where should this work begin? It helps to look at what has been achieved by trial sites in countries with homophobic policies and/or cultures. iPrEx builds on a rich and valuable history of collaborations involving gay male communities and research teams working on AIDS vaccines, behavioral prevention and other issues. These collaborations have shown that it is possible to recruit and retain gay men in countries

[7] Baral S, et al. Elevated Risk for HIV Infection among Men Who Have Sex with Men in Low-and Middle-Income Countries 2000–2006: A Systematic Review. *PLOS Medicine*, 2007

[8] Gouws E, et al. Short term estimates of adult HIV incidence by mode of transmission: Kenya and Thailand as examples. *Sex Transm Infect.* 2006;82 Suppl 3:iii51–iii55.

where homosexual identity and behavior is highly stigmatized and even criminalized.

One of the simplest, yet most radical acts of the research teams is creating safe and respectful spaces that validate gay men's rights to health and dignity. In turn, gay men, as advocates for new HIV prevention options, have validated the need for additional strategies and helped advance the research agenda.

"Te queremos" is the tagline for a video the iPrEx trial produced that shows lab personnel, recruiters, principal investigators, counselors, and outreach workers looking straight at the camera and pronouncing, "We care about you" to the trial's gay volunteers. It's a powerful statement that gay men's lives matter.

Reports from the field suggest that work like this is having ripple effects. In Ecuador, for example, gay staff at the community-based, non-profit Fundación Equidad say that the launch of PrEP studies marked a turning point in their efforts to draw attention to critical issues facing the community. Community groups are increasingly being considered "serious about public health issues and willing to actively contribute to stop the HIV pandemic,"[9] said one staff member. Others say that they think iPrEx has made it easier for sexual diversity and respect for homosexual lifestyles to be discussed in public meetings and reported in interviews with journalists. These are steps in the right direction—although there's still a long way to halt stigma, violence, and discrimination against sexual minorities.[10]

Research helps validate gay men's lives and create safe and respectful spaces for health care.

What's the next step?

Researchers often rightly point out that they can't change the entire human rights context in the countries they're working in. Nonetheless, research teams initiate dialogue with local government leaders and health programmers about results of research that can inform policy. Evidence from research studies can counter developing country views that programs for gay men and other MSM should not be a priority. It's also important, where possible, to partner with established and emerging groups representing gay men and other sexual minorities because these groups can provide additional support to volunteers, provide social context for clinical trial goals, and advocate implementation of research findings.

A finding of benefit from PrEP or any other prevention trial in gay men and other MSM will have implications for communities that participated and those that are farther afield. Research sites can help meet post-trial access commitments, if the results warrant this. It is also incumbent on normative agencies and governments in other countries to evaluate the relevance of this research. These processes should include gay male researchers and community leaders.

Research projects have also shown it is possible to provide platforms for emerging gay male leaders to advocate for and represent themselves. At the HIV

[9] Based on conversations with AIDS advocate Orlando Montoya, Fundación Equidad leader.

[10] Experiences with these issues were reported by community members and researchers in an AVAC-convened meeting on Latin American HIV prevention research and advocacy at the 2008 International AIDS Conference in Mexico City.

"Only **21%** of men have ever been tested for HIV and received the results, compared to almost half of women. This is most likely because half of women who gave birth in the **2** years before the survey were offered and accepted an HIV test during antenatal care."[11]

Ukraine

Prevention Research Stakeholders' meeting last December in Mombasa, convened by the Kenya Medical Research Institute with support from AVAC, a slender young man introduced himself as a local Community Advisory Board (CAB) member. He explained the importance of recognizing gay men's risk—a bold and, in its own way, seismic shift for a region of the world where homosexuality is criminalized.

That CAB member is one of the MSM participating in a research study that's been developed by IAVI and Kenyan collaborators. This innovative project is one of several taking place along the Kenyan coast, from Mombasa to Malindi. Researchers recruiting for potential HIV prevention studies have enrolled both men and women reporting receptive anal intercourse (RAI), characterized potential cohorts of MSM, and documented high HIV prevalence among more than 300 men, particularly among men reporting recent RAI or sex exclusively with other men.[12,13,14] These data have provided the basis for calls to expand HIV prevention research with these men, along with advocacy for improved sexual health screening, improved medical services, and targeted risk-reduction interventions.

Acknowledging that safety and confidentiality are of utmost importance, research projects should also follow the principles of the *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials* (downloadable at *www.avac.org/gpp.htm*) to make gay men partners in the research process. This means inclusion in community advisory mechanisms, protocol review efforts, and public forums. It also means listening to gay men's priorities and questions and addressing them, where possible, in the research process.

Gay men and other MSM have become active partners in prevention research by raising their voices and sharing their advocacy skills.

What's the next step?

In the partnerships that have emerged at research sites, gay men act as peer educators, CAB members, researchers, and experts on HIV prevention in their own communities. (In many settings this has to be balanced with site preparedness to deal with stigma and backlash that may endanger individuals or the project.) This same

[11] Ukraine Center for Social Reforms and the State Statistical Committee of Ukraine. The 2007 Ukraine Demographic and Health Survey (2007 UDHS). 2007. Available at URL: *http://www.measuredhs.com/pubs/pdf/HF26/HF26.pdf*

[12] Grijsen ML, Graham SM, Mwangome M, et al. Screening for genital and anorectal sexually transmitted infections in HIV prevention trials in Africa. *Sex Transm Infect.* 2008 Oct;84(5):364-70. Epub 2008 Mar 28.

[13] Stevens W, et al. Baseline morbidity in 2,990 adult African volunteers recruited to characterize laboratory reference intervals for future HIV vaccine clinical trials. *PLoS ONE.* 2008 Apr 30;3(4):e2043.

[14] Sanders EJ, et al. HIV-1 infection in high risk men who have sex with men in Mombasa, Kenya. *AIDS.* 2007 Nov 30;21(18):2513-20.

expertise needs to be incorporated into conversations about implementation, program design, and future research. This includes anticipating next steps if iPrEx has a positive result. And, critically, it means involving gay men in advocacy and planning for provision of comprehensive prevention services with appropriate information (about condom use for anal sex, for example) that is missing in many parts of the world. Involvement must go beyond tokenistic inclusion of one or two gay men in a 50- or 60-person meeting.

A PrEP result—no matter how positive—will not signal the end of research in gay men of the developing world.

What's the next step?

Positive results from iPrEx are by no means guaranteed. Even with a flat result, the biomedical prevention field has extensive work left to do on the gay men's health and rights agenda. That's particularly true in African contexts, where research work with gay men and other MSM is in its infancy compared to Latin America.

First and foremost, all stakeholders working with gay men and other MSM should prioritize improved access to existing prevention strategies, including behavior change, psychosocial support, male and female condoms (the latter can also be used for anal sex), lubricants, non-judgmental and affordable medical clinics, and so on. While providing what works now, it's also necessary to learn more and do better. Future biomedical HIV prevention research in Africa should build from emerging evidence of HIV exposure and distribution of new HIV infections among MSM. African MSM are clearly not benefitting from global efforts to address HIV sexual exposure or the underlying social and economic factors. Does this indicate that current HIV prevention strategies are ineffective for MSM populations? Or would current HIV prevention strategies be efficacious for MSM if they were effectively resourced, implemented, and promoted? And how do HIV prevention interventions more explicitly document and address the influence of social, legal, and economic environments (including issues of poverty, violence, arrest, and blackmail) on individual and social negotiation of sexual exposure to HIV? These research questions are profound, not only for combating current African HIV epidemics but for the future of behaviorally-mediated or medically-mediated prevention options that could be investigated for MSM, such as male circumcision (which has no proven risk reduction benefit for MSM) or rectal microbicides.

Table 3 HIV Prevalence Rates Among African MSM (2008)

Country	Sample Size	MSM Prevalence (95% Confidence Interval)	HIV Prevalence
Senegal	943	21.6 (19.0-24.3)	0.88%
South Africa	574	15.3 (12.4-18.3)	15.89%
Zambia	641	32.9 (29.3-36.6)	15.72%
Kenya	1125	15.6 (13.5-17.7)	7.49%
Tanzania	509	12.4 (9.5-15.2)	5.88%
Malawi	201	21.4 (15.7-27.1)	11.46%
Nigeria	1961	13.5 (12.0-15.0)	2.88%
Sudan	1119	8.8 (7.1-10.4)	1.26%
Egypt	340	5.3 (2.9-7.7)	0.02%
Total	6470	15.7 (14.9-16.5)	5.00%

Source: Baral, S. et al. A Systematic Review of HIV epidemiology and risk factors among MSM in Sub-Saharan Africa 2000-2008. *AIDS 2008 XVII International AIDS Conference.* Mexico City, 2008.

Future efficacy studies of HIV prevention options can and should be designed to include cohorts of African MSM, for whom the disproportionate failure of existing HIV prevention efforts implies a correspondingly urgent need for new HIV prevention options. ARV-based prevention strategies such as PrEP or ARV treatment-as-prevention to reduce viral load and infectiousness in HIV-positive people could offer new tools and new hope. This could also provide new impetus to support community-led mobilization for HIV prevention.

These steps aren't a complete solution. Change also depends on structural factors, social norms, human rights and legal frameworks. But they are pieces of the puzzle that the HIV prevention research field can address to ensure that there continues to be substance behind the statement, "We care."

WORKING TOWARDS A SOLUTION

We end this year's *Report* with a strong commitment to working as part of the global community of individuals and institutions dedicated to HIV prevention.

Every day, all around the world, people work toward solutions for their countries, communities, and families.

These nurses, counselors, activists, advocates, scientists, policy makers, politicians, men, women and children have more to do with solving the HIV prevention puzzle than any single technology ever can. Likewise, the potential of the strategies that do exist—and the ones that we are searching for—depends on the people who provide, explain, use, and advocate for them.

The solution will always be in our hands.

About AVAC

Founded in 1995, AVAC is a not-for-profit organization dedicated to creating a favorable policy and social environment for accelerated ethical research and eventual global delivery of AIDS vaccines and other HIV prevention options as part of a comprehensive response to the pandemic. This work is guided by the following principles:

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

AVAC focuses in four priority areas:

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

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

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

For more information about AVAC's programs and publications or to become a Member, please contact us at:

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