TURNING THE PAGE

AVAC
Global Advocacy for HIV Prevention

Report 2010

Acknowledgements

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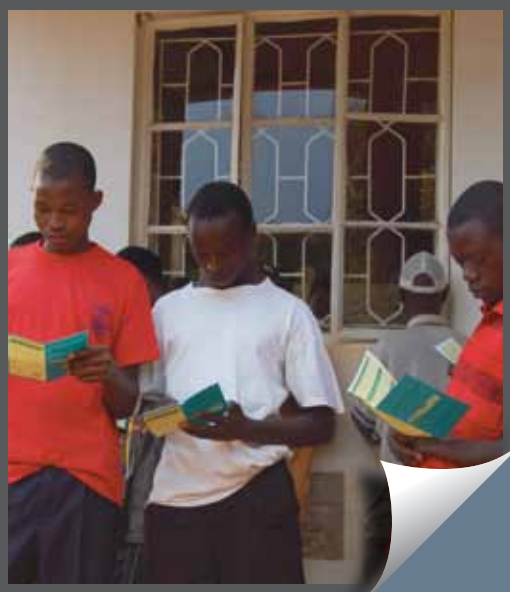
What belongs in the next chapter . . .

A letter from the Executive Director

AVAC Report 2010: Turning the Page, marks 15 years of AVAC's advocating and agitating, watching and waiting, for the end of AIDS.

Are we there yet? No, but the AIDS vaccine field can at last say that it is closer. The Thai Prime-Boost trial known as RV144 provided the first evidence in humans that a vaccine can protect against HIV. As we discuss in the pages that follow, there is a vast array of caveats, questions and next steps that the field has to tackle.

But before you turn this page, we want to reiterate some of the top-line messages about RV144 that must be shared outside the small world of AIDS vaccine research:



Many media, many messages From left to right : A community discussion of the Thai Prime-Boost trial in Rayong City, Thailand; global news coverage of the Thai trial result; young men learning about medical male circumcision for HIV prevention in Uganda. *[Thai photos courtesy of Tom Paulson, Ugandan photo courtesy of US Military HIV Research Program]*

- **Prevention of HIV via a vaccine is possible.**
- **An AIDS vaccine is as urgently needed as it has ever been.**
- **A partially protective vaccine would be a powerful tool for controlling the epidemic. RV144 data suggest that the vaccine reduced HIV risk by around 30 percent. This is lower than the threshold the trial team set with the Thai government for pursuing vaccine licensure. But this doesn't mean—as some observers have suggested—that *any* vaccine providing moderate protection would be useless.**
- **The results obtained to date by the AIDS vaccine field are evidence of what enthusiastic community support for a study can achieve—and are the reason why communities should continue to partner in trials.**
- **Pre-exposure prophylaxis (PrEP), microbicides, treatment as prevention and proven strategies like male and female condoms and male circumcision are part of the "big picture" of AIDS vaccine research. Stakeholders working within the AIDS vaccine field know that combination prevention is key. There will be no silver bullet for HIV prevention.**

continued on next page >

The Thai Prime-Boost trial announced its results in September and October of last year. Now that the dust has settled, it's clear that the messages listed on the previous page have barely taken hold for much of the general public. In conversations with advocates, frontline HIV treatment providers and even staff at other clinical trial sites, we have encountered confusion about the trial and its results. Some people believe that the vaccine succeeded and now exists in Thailand. Others think it failed completely.

The truth, of course, is somewhere in between. There is a glimmer of hope that has to be followed. Sometimes a glimmer is enough; sometimes it is the only sign of the bright day to come. At AVAC, we're not convinced that RV144 is going to lead the AIDS vaccine field to a preventive vaccine—but we are convinced that the result is a substantive lead. How the field communicates about and acts on this result is absolutely critical to future work on AIDS vaccines.

With its data on efficacy, RV144 generated momentum that never existed before. There is no telling what will come from aggressive pursuit of the result—but that is the nature of science. This is the bottom line message that should be communicated loudly and clearly to the general public and key stakeholders, including policy makers, political and community leaders, civil society advocates and activists and others.

The effort to follow up on the Thai trial result must be a priority. There should be a clear, coordinated and well-funded plan jointly developed and executed in the collaborative spirit that animated the Global HIV Vaccine Enterprise at its inception.

At the same time, the field has to pursue other options. Whether the RV144 clues lead to an effective candidate or not, there will be a need for further improvements and/or wholly novel approaches.

In other words, the AIDS vaccine field needs to further explore the RV144 result *and* pursue unique approaches. And it needs to do this in the context of constrained resources.

Today, there are yawning gaps in funding for proven prevention and treatment and a crisis in political will supporting AIDS programs. Those of us working on the AIDS epidemic face skepticism about whether disease-specific funding for AIDS is cost effective. Those of us working on AIDS vaccines face skepticism about whether limited funds for AIDS should include funding for AIDS prevention research.

We hope that the next chapter of AIDS vaccine research shows the field to be capable of triaging current projects—jettisoning some, streamlining others, scaling up still others—and developing a clear strategy for collaborative action on key goals. The field must be able to define how it will function in the absence of new funding and how additional resources would be spent, if they became available.

It's easy to call for all of these things and much, much harder to achieve them. The pages that follow contain our best suggestions for how to do so.

In **Chapter One: "Proof of Concept" and its Consequences**, we propose some guiding principles for the post-RV144 scientific agenda.

In prevention research, scientific breakthroughs cannot be achieved without the participation of trial participants and their immediate and national communities. To take the full measure of community engagement undertaken for the Thai Prime-Boost trial, AVAC commissioned award-winning reporter Tom Paulson to travel to Thailand and interview many of the trial staff and advocates who were closest to the process. The result is **Chapter Two: The Thai Way Forward**, a thought-provoking look at what worked and what didn't work in the world's largest AIDS vaccine trial to date.

In any budget crunch, it's critical to do more with what is already available. For the AIDS vaccine field and for HIV prevention research in general,

this means doing as much as possible with the information gleaned from trials. In **Chapter Three: Data and Materials—A "to do" list for the future**, we look at some of the essential steps to optimize the value of samples and data from clinical trials.

While the first three chapters in the Report have a specific vaccine focus, the reality is that the next big results are going to come from trials of ARV-based prevention—both topical microbicide gels and oral PrEP. Whether these results are positive, flat or indeterminate, they'll be big in the sense that they'll raise tricky and important questions about what to do with the results and what trials are needed next. **Chapter Four: Trials and Trial Design—Where does prevention research go from here?** zeroes in on some of the key issues emerging in discussions of next-generation trials.

The report's conclusion, Speak with one voice, work towards one goal, weighs the impact of developments in ARV-based prevention, debates around "test-and-treat", and treatment shortages on the global AIDS response.

This year's report is titled *Turning the Page* because we see the Thai trial result as starting a new chapter for AIDS vaccine and prevention research. These are some of the things we hope will be part of the next chapter:

- A balance between focused investigation to better understand the Thai trial result and its implications for further vaccine development, and ongoing basic scientific work exploring other potential directions for vaccine design and development.

- Clinical trials that are innovative in how they collect, analyze and act upon data. This might include adaptive trial designs that allow analysis and adjustments while the study is still ongoing.

- More extensive and better-funded community engagement than ever before. This is essential as the field seeks support for and participation in trials with increasingly complicated designs.

- Approaches to gathering and sharing data that are cutting-edge, collaborative and that cut across disciplines. These are needed to optimize the information gleaned from trials of AIDS vaccines and of other prevention strategies.

- An AIDS vaccine field that adapts to emerging results from other biomedical prevention trials, like pre-exposure prophylaxis (PrEP) and microbicides, by preparing for positive data with new ideas for trial design and combination prevention.

- Better answers about if, when, how and to whom a partially effective product would be introduced. This goes for AIDS vaccines, PrEP, microbicides *and* male circumcision.

- A biomedical prevention research field that invests as much in socio-behavioral research and community partnership to understand and define participants' risk before, during and after a trial, as it does in scientific evaluation of prospective candidates.

The African American poet and author Maya Angelou writes, "History, despite its wrenching pain, cannot be unlived, but if faced with courage, need not be lived again." As we've spent the past

We Are All Advocates

One of the founding principles of AVAC is that scientists and civil society members need to work together to set, and implement, a single agenda. Scientists can be "community". Civil society can be technical experts. And we all belong at the table together, facing the challenges of the epidemic head on. Simply put, we are all advocates. What does this mean? What, exactly, does advocacy look like? Throughout the pages of this year's Report, you'll find exciting perspectives from a range of individuals who hail from different parts of the world and work in a variety of professions—all working toward the goal of ending AIDS.

several months preparing this year's Report and contemplating the next chapter of AIDS vaccine research, we've also looked back.

It's not possible to unlive the tumultuous decision-making, budget-cutting and protocol-editing that went into launching the Thai Prime-Boost trial, but it is possible to ensure that trials going forward have sufficient budgets and data management systems to be in the best position possible to answer questions about what the results mean—whatever they show.

It's not possible to unlive the miscommunications, missteps and occasional lack of commitment to authentic community engagement that have complicated several HIV prevention clinical trials. It is possible to expend the resources to do better, using the Good Participatory Practice Guidelines as a backbone for this work and recognizing that "success" may sometimes mean shelving the plans for a study because potential trial-site communities do not want to see it done.

And it's not possible to unlive the sometimes-divisive skepticism about whether an AIDS vaccine was possible or whether money should continue to go to AIDS prevention research in the face of yawning gaps in funding for proven prevention and treatment. But it is possible to communicate how momentous the RV144 result was, how it is a strong signal that we must hold fast in the search for an AIDS vaccine and how, because this search will continue for many years, we cannot afford to cut corners on treatment and prevention that can save lives today.

Turn the page. Together, we will write the future.

Mitchell Warren, *Executive Director*
July 2010

AVAC Report 2010: Dedicated to gay men and their allies

The fight to end the AIDS epidemic is, ultimately, a fight for the rights of every human being to live with respect, dignity and health. This year, the struggle of many gay men and other men who have sex with men to secure these rights has come into stark focus. From a proposed Ugandan law seeking to punish homosexuality with the death penalty, to the criminal persecution of a gay male couple in Malawi, to large groups of anti-gay Kenyans intimidating and shutting down prevention projects working with gay men—the obstacles for gay men living freely and openly have rarely been so clear.

These repressive tactics cannot and will not staunch individual and collective efforts to raise the visibility of homosexuals living in developing and developed nations alike. Around the world, there are vibrant leaders with bold visions of a more just and open society. This year's Report is dedicated to all of the individuals and organizations engaged in the brave and necessary work of saying, "We are here. We exist. We demand our rights." We are inspired by your work, committed to your cause and proud to be your colleagues, comrades and friends.

AVAC's Top Recommendations for 2010 and Beyond

We hope you'll turn all the pages of this Report—but here's a quick look at some of the critical messages we hope will guide the next chapter of HIV prevention research.

- **The biomedical HIV prevention field needs to respond to the contraction of global resources for HIV with clear messages, stringent priority setting and well-articulated plans for pursuing leads suggested by trials like RV144 as well as wholly novel lines of inquiry.**

- **Global stakeholders—donors, governments, research sponsors and civil society—need to develop and fully fund an ambitious agenda aimed at sustaining and expanding ARV treatment for HIV-positive people, exploring treatment as prevention strategies *and* preparing for delivery of ARV-based prevention in HIV-negative people.**

- **Build systems for sharing data and consensus on a core set of assays to be used to evaluate candidates to ensure that the AIDS vaccine field optimizes the data gleaned from every trial.**

- **Complex trial designs require complex, long-term, multi-layered community engagement strategies. Investment in this work has to be upfront, not an afterthought, as ambitious plans for adaptive designs and other novel concepts are discussed by the scientific community.**

To stay up-to-date with developments in these recommendations and many other issues, subscribe to AVAC's Advocates' Network ***www.avac.org/advocatesnetwork***.

Status Report: An update on last year's recommendations

The AIDS vaccine field needs more predictive measurements to guide development of substantially improved next-generation candidates.

The game changed with the RV144 result—and the search is now on for answers about what that result means, how to improve on it and what wholly novel approaches should be explored. See Chapters One and Three for discussion of these issues.

Biomedical prevention researchers and sponsors, along with WHO and UNAIDS, must plan for the steps that would be needed if PrEP or any other emerging strategy shows benefit.

Expanded discussions facilitated by Georgetown University, Imperial College, WHO, UNAIDS and AVAC, all with financial support from the Bill & Melinda Gates Foundation, have started to map out what next steps for the PrEP agenda might be. See Chapter Four for more.

The Global HIV Vaccine Enterprise needs to demonstrate its value through timely publication of an updated Scientific Strategic Plan by early 2010.

At press time, the Scientific Strategic Plan was scheduled for publication in September 2010. See page 18 for more analysis of the Enterprise.

The HIV Vaccine Trials Network needs to develop a suite of easy-to-understand materials regarding HVTN 505.

While HVTN 505 has fact sheets and a range of promotional materials, it still lacks the additional materials AVAC called for last year to provide "depth and detail" on the study for advocates and potential participants. This complex trial is facing recruitment challenges, and it is possible that confusion over its purpose could be contributing. With proposals for more complex trial designs in the works (see Chapters One and Four), it is critical to support and learn from the HVTN 505 community engagement process.

Stakeholders exploring PrEP and treatment as prevention need to add specificity around financial, health care infrastructure and human rights implications.

"Test and treat" and other approaches to treatment as prevention seized global attention this year with a range of publications, mathematical models and intriguing findings. Unfortunately, this vigorous engagement is coming at the same time as a looming crisis in meeting the needs of people already on or waiting for ARV treatment.

Prevention research stakeholders need to embrace an agenda focused on HIV testing and counseling as the cornerstone for implementing male circumcision and any new ARV-based prevention strategy.

Prevention programming is getting more attention, but there still isn't a broad-based, developing country-focused advocacy agenda aimed at delivering improved, comprehensive prevention including expanded testing services.

Governments around the world need to respond to the HIV prevention needs and priorities of gay men and other men who have sex with men.

It has been a deeply troubling year on this front, with anti-gay legislation introduced in Uganda and the persecution of a gay couple in Malawi. Legal and social environments that uphold the human rights and dignity of all individuals are the cornerstone of effective HIV prevention. This year's *AVAC Report* is dedicated to those on the front line of this struggle (see p. 6).

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In this Chapter:

- Draw a clear distinction between a trial that would seek to replicate the RV144 result, versus one that would probe the finding, without aiming to reproduce it
- Craft a coherent scientific rationale for next steps—in the absence of a correlate
- Mobilize new resources with a well-prioritized plan
- Explore HIV risk as closely as product development
- Maintain research efforts in all the populations hardest hit by HIV
- Consider more complex trials and more thorough community engagement
- Emphasize the positive potential of this next chapter of AIDS vaccine research

"Proof of concept" and its consequences

Making sense of the post-RV144 world

The AIDS vaccine field has never been a place for people who craved certainty. For more than two decades, clinical research to find a vaccine has yielded a plethora of disappointing, and sometimes perplexing, results. Paradoxically, these same results have produced meaningful scientific insights, among them details about HIV's cunning ability to evade immune responses. Still, the specific responses that might effectively prevent HIV infection remain undefined. As a result, many vaccine scientists and related stakeholders have, in large part, been propelled by faith, with ardent hope that the science will reveal fundamental clues as to how a vaccine must perform to provide protection against HIV infection.

The result from the Thai Prime-Boost efficacy trial changed the field dramatically. For the first time, a human clinical trial demonstrated that a vaccine regimen can reduce risk of HIV infection (see p. 11 and 12 for trial details). As exciting as this news is, it's raised many important questions. Yes, the field has "proved" a concept, but how strong is the proof? What are the best ways to test its mettle? And what actually is the concept—in terms of the immunological mechanisms of the observed effect and the relative contribution of the prime versus the boost?

Over the past 10 months, AVAC has participated in a range of formal and informal conversations about what life in the post-RV144 world could or should look like. Here are some observations about where the field is now and what lies ahead, particularly in the areas of research and development, communications and community engagement.

Draw a clear distinction between a trial that would seek to replicate the RV144 result, versus one that would probe the finding, without aiming to reproduce it

The results of RV144 can be used to justify trials that aim to replicate and possibly improve on the finding. They could also be used to justify an expanded scientific agenda. Trying to replicate the finding is a different undertaking from using the result as the launching pad for a range of related inquiries. This distinction could be lost on many audiences, leading to confusion about the goals and expectations of follow-up studies. Clarity in trial design and communication are therefore of the utmost importance.

Conventional scientific wisdom says that to validate the result of a trial, another trial should be run using a protocol that changes as few variables

as possible. In RV144 the observed protection waned over time and was highest in the first year post vaccination. Conducting a second trial that resembled RV144 could provide a relatively clear path to improving on the duration of protection. Proponents of such a trial say that it could also provide insights into a correlate of protection.

But another trial in a general population cohort in Thailand with an incidence of less than one percent would be a large and costly undertaking. In addition, vaccine supplies of both ALVAC and AIDSVAX are too limited for another large trial, which means that new products would need to be manufactured in any case. Committing resources to a new study that sought to replicate the Thai result could also potentially limit the opportunity to concomitantly test newer vaccine concepts. However, these considerations don't rule out a trial that controls for most of the variables of the original trial. Such a trial could take place in Southeast Asia in high-incidence populations such as gay men.

An alternative approach would center on trials that were, in effect, inspired by RV144. These trials would change so many variables that they couldn't fairly be called attempts to replicate the finding. A strong case for this approach has come from the US HIV Vaccine Trials Network. The proposal is to use the RV144 results as the springboard for a series of trials using adaptive designs (see figure on p. 14).

As statistician Peter Gilbert of the Statistical Center for HIV/AIDS Research and Prevention explained at a recent meeting, "adaptive" means

I am an advocate because...

I advocate for policy change, informing the South African National AIDS Council and the National Strategic Plan on issues of women and prevention. As for other activists, I recommend that you do it from the heart. Then you don't have to be fearful because you're talking about what you know best.

Nomfundo Eland, AVAC HIV Prevention Research Advocacy Fellow, Treatment Action Campaign, South Africa

Basics of RV144

Trial: A Phase III randomized, double-blinded, placebo-controlled trial of Sanofi Pasteur live recombinant ALVAC-HIV (vCP1521) priming with VaxGen gp120 B/E (AIDSVAX B/E) boosting in HIV-negative Thai adults

Experimental Vaccine: PRIME: canarypox viral vector with *env* and *gag-pol* (ALVAC-HIV (vCP1521)) / BOOST: *env* protein/gp120 subunits (AIDSVAX B/E)

Study Question: Whether the prime-boost vaccine combination was safe and effective at reducing rates of HIV infection or reducing viral load in vaccine recipients who became HIV-infected over the course of the study. Trial participants' primary risk factor for HIV was sexual exposure.

Sponsor: US Army Surgeon General

Funders: Division of AIDS, National Institute of Allergy and Infectious Diseases, NIH; US Army Medical Research and IMateriel Command

Collaborators: US Military HIV Research Program (MHRP)/Walter Reed Army Institute of Research, the Thai Ministry of Public Health, Mahidol University, the Armed Forces Research Institute of Medical Sciences—US and Thai components, the National Institute of Allergy and Infectious Diseases, Sanofi Pasteur, Global Solutions for Infectious Diseases and the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.

Participants: 16,402 HIV-negative Thai men and women between the ages of 18 and 30

Location: Forty-seven health centers and eight clinical sites in Rayong and Chonburi provinces, Thailand

Results: Initial data showed that vaccine recipients were approximately 31 percent less likely than placebo recipients to become infected with HIV. However, the data suggest that the effect of the vaccine could have ranged from a 1.1 percent reduction in HIV acquisition to a 51.2 percent reduction in HIV acquisition for trial participants who received the active vaccine compared to those who received the placebo. It is important to consider the full statistical analyses to gain a more complete understanding of the results. (See box on next page for a more detailed analysis of the results.) There was no observed effect on viral load. Additional analysis is ongoing.

that one or more decision points are built into the trial design. Based on data reviewed at the decision point, the trial design could be modified in one or more pre-determined ways. In the RV144 context, an adaptive trial might compare several different variations on the prime-boost combination.

The first phase of such a study might gather information on efficacy; the second phase would look more closely at correlates of protection. The HVTN proposal focuses on conducting these trials in high-incidence southern African settings where results might come more quickly, as compared to the original six year Thai Prime-Boost study. Such studies would also provide information about whether the strategy works in one of the areas of the world in greatest need of new prevention tools.

The details of both classical and adaptive designs to follow up on RV144 are still being fleshed out, and it is difficult to draw sharp distinctions. But on a general level, a more classical trial might be more likely to confirm that the Thai RV144 result was "real" and could be improved upon. An adaptive trial might be more likely to identify the ways that an RV144-like regimen could be developed for high-incidence southern African populations where HIV subtype C predominates. There is merit and risk in both approaches. However the danger is that the two approaches could get hopelessly tangled in the public eye or the planning efforts of leaders of the field. It is critical that the subtle distinctions between these approaches, including the questions that each would answer, be explained clearly to the broad array of stakeholders following the AIDS vaccine field in the wake of the RV144 result.

Craft a coherent scientific rationale for next steps—in the absence of a correlate

The best-case scenario for RV144 follow-up would be identification of a correlate of protection from analysis of immunological samples from the

RV144 Results

On October 20, 2009, expanded data analyses by RV144 investigators were presented at the AIDS Vaccine 2009 conference and published in the *New England Journal of Medicine (http://content.nejm.org/cgi/content/full/NEJMoa0908492)*. These included a comparison of rates of infections in vaccine and placebo recipients, using three approaches: intent to treat (ITT), modified intent to treat (mITT) and per protocol (PP) analyses. Each of these analyses looked at a slightly different number of individuals and yielded slightly different results. One of the most important facets of the Thai trial results is that all three analyses—ITT, mITT and PP—show the same trend: in every case, fewer infections were observed in the vaccine arm compared to the placebo arm. However, the wide confidence intervals around the point estimates of vaccine efficacy in each of the analyses indicate a fair amount of uncertainty about how much the vaccine may have reduced the risk of HIV acquisition for participants who were given the active vaccine. This underscores the need to conduct further research and analyses to help gain a greater understanding of the findings. The results from each type of analysis are below.

THAI TRIAL DATA	Analysis		
	ITT	mITT	PP
Participants	16,402	16,395	12,542
Infections in vaccine group	56	51	36
Infections in placebo group	76	74	50
Point estimate of vaccine efficacy	26.4%	31.2%	26.2%
95% Confidence Interval	-4.0, 47.9	1.1, 51.2	-13.3, 51.9
P-value	0.08	0.04	0.16
Statistically significant?	No	Yes	No

For more on the different statistical analyses, please see AVAC's document on understanding the Thai trial results, available at *www.avac.org/thaitrial*.

Turning the Page: The need to diversify funding sources

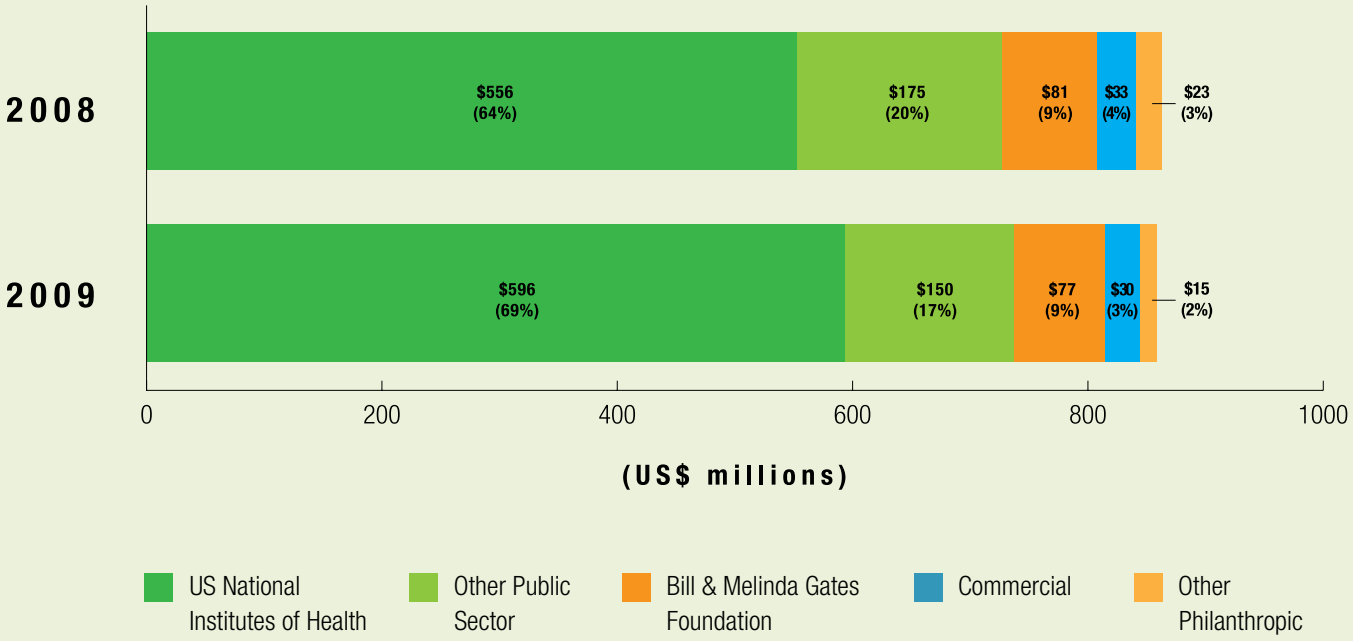
Despite the global economy's contraction in 2009, funding for HIV vaccine research and development (R&D) remained relatively steady, with funding for HIV vaccine R&D at US$868 million, the same level of investment documented in 2008. This is the good news from this year's report from the HIV Vaccines and Microbicides Resource Tracking Working Group *(www.hivresourcetracking.org)*.

More sobering is the lower level of investment by the commercial sector and donors in Europe. In total, contributions by all other public sector and philanthropic funders fell by roughly 20 percent from 2008 to 2009. The US National Institutes of Health and the Bill & Melinda Gates Foundation were the primary sources of funding in 2009, contributing roughly 78 percent of all public sector and philanthropic AIDS vaccine funding.

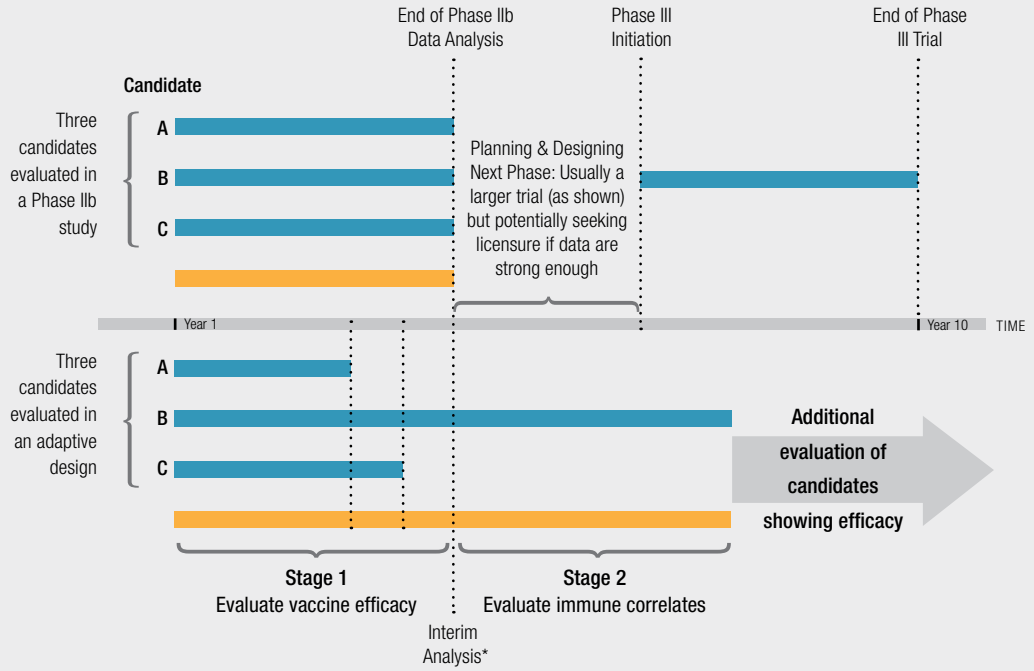
Now is the time to turn the page to an environment where funding for this critical work is more evenly distributed across a more diverse group of funders. It is time to engage new investors from government and industry and from developing and developed countries. Projects in the vaccine field can be calibrated to different capacities and budgets—there is more than enough work to do.

Equally important, it is time to do the difficult work of finding efficiencies and triaging projects so that the most critical work stays on track even if funding remains flat or declines. AVAC isn't in the position to identify specific projects or lines of inquiry that should be set aside or made a lower priority. However, across the field, funders and program administrators need to look closely at how such decisions are made and include some reckoning of what might be given up or postponed along with any set of new activities.

HIV Vaccine Funding



Adaptive Trials versus Classical Trials: One (simplified, optimistic) comparison



"Adaptive" simply means that one or more decision points are built into the trial design. Trial conduct following the decision point depends on the data observed to that point. There are many ways for trials to be adaptive. The graphic above compares one possible design for an adaptive AIDS vaccine trial with a more classical trial sequence. The goal in stage one of the adaptive design is to advance or eliminate candidates as soon as reliable data are available.

*The classical design might use one or two interim analyses, where the adaptive might use up to nine interim analyses. Fewer are shown here for sake of clarity.

trial. This may or may not happen. The prevailing wisdom, which AVAC believes is correct, is that the field should not count on finding a correlate to explain the RV144 results and should not wait for one to be identified before embarking on its next steps. Therefore, the next set of trials will have to advance candidates based on hypotheses about what might work again and hopefully, better.

Newer types of immunological assays can help inform these hypotheses and will also be used as high-tech tools in the search for a correlate. But lack of firm consensus about a core set of reproducible assays to be used across the field is a roadblock to a coherent process for selecting the next candidates to evaluate.

The range of assays being used as part of in-depth analysis of RV144 samples provides a window into the current state of the field. As *AVAC Report* went to press, more than 30 proposals for intensive laboratory studies of RV144 specimens had been approved (for more detail see p. 37). In addition to the well-characterized assays such as neutralizing antibody, binding antibody (ELISA), intracellular flow cytometry, ELISPOT and sequence analysis, many of the RV144 ancillary studies will utilize less well-characterized assays that employ less standardized methodology. It is critical that the most robust of these assays are standardized so that comparable evaluations can be carried out on samples from other trials.

Comparable data sets for different candidates will help substantiate decisions about which iterations of an RV144-like prime-boost combination to test next. We're hearing cases being made for virtually every poxvirus vector that was in development prior to the Thai result and even all the adeno vectors that were already under development before Step. The RV144 result has also invigorated the already energetic discussion of viral insert selection—i.e., which fragments of HIV genes to incorporate into candidate vaccines.

With finite resources, it isn't feasible to test every combination that has a strong argument behind it. Although there is a range of poxvirus

candidates other than ALVAC in development, particularly NYVAC and multiple MVAs, the field had largely moved away from using proteins like the AIDSVAX candidate after the flat result in the two VaxGen trials.

It's also not possible to tell from RV144 whether the protection came from one or both candidates—a critique voiced when the trial was launched. Hence, almost all of the follow-up regimens under discussion include some form of protein boost on the unproven assumption that ALVAC wouldn't have worked alone. DNA as a prime is also being considered. Given the paucity of these candidates—and the lack of AIDSVAX doses—the field will have to make a decision about manufacturing a new protein candidate for further testing. (Poxvirus manufacturing will also have to be scaled up, but those processes have been in development.)

Because a costly, time-consuming manufacturing decision will be difficult if not impossible to reverse, proponents of various strategies must provide clear public explanations about why a strategy was selected and how the trial will build on the data that are already available. Trial plans should also explain how assays will be selected to evaluate the candidate and ensure some degree of compatability with other trials.

Mobilize new resources with a well-prioritized plan

A research agenda that explores RV144 and continues pursuing other avenues is, by definition, expanded, as compared to what the field would be doing if RV144 had not produced intriguing results. At the moment, however, it's unclear as to how expanded the funding will be. Now is the time to identify projects that can be triaged, and to find ways to do more with the resources currently available to the field (see Chapter Three).

After many years of increases, funding for HIV vaccine research has leveled off just as there is exciting evidence to justify more support (see p. 13). The Bill & Melinda Gates Foundation can increase its stake or US National Institutes of Health can free up additional resources by finding efficiencies in its current programs, but new government and foundation funding as well as expanded industry involvement sorely need to be developed.

The troubled global economy, paired with growing arguments against disease-specific funding, make it more important than ever to soundly spend every dollar on HIV in general and on prevention research in particular. Despite the very real constraints, it seems very little is being reevaluated or abandoned in light of RV144. Rather, it sometimes seems that the trial result is being used to confirm the wisdom of everything that's already going on. Plans for what might happen next should also explain what may not happen. This necessary step will also build credibility in the public eye as the field enters this next critical chapter.

Selling the idea that the AIDS vaccine field is closer to a vaccine than ever before can raise more support. But the field also needs to develop a scientific agenda that addresses the question: *When and how will we go forward if RV144 isn't validated or if what we learn precludes building on its approach?* Such an agenda should include work on novel candidates including those that elicit neutralizing antibodies. There should be forward-thinking plans for how new approaches could be folded into clinical evaluation if an RV144-like prime-boost strategy makes progress.

Explore HIV risk as closely as product development

The Thai trial results hint that the vaccine combination may have been more effective in

I am an advocate because...

I work in a poorly resourced and disenfranchised community. We ask them what they think is the best way and what kinds of questions they would like answered in their own community. To me, that's the true engagement.

Janet Frohlich, Community Program Manager, CAPRISA, South Africa

I am an advocate because...

When I interact with different people and communities, I have the chance to understand their motivations for fighting the HIV epidemic and what their needs are. I try to provide all the information I have to help them protect themselves. This has been my motivation for the last 22 years, and I think it will continue to be until, hopefully, there is a cure.

Pedro Goicochea, Researcher, iPrEx study, Peru

people who identified themselves as low-risk than in those who reported higher-risk sexual activity. This observation is based on post-hoc analysis and so is hard to interpret. Since it appears that the vaccine efficacy wore off within a year, it could be that those who self-identified as "ever at high-risk" were more likely to have HIV exposures after the first year and, therefore, were out of the window of protection. That the categorizations are based on self-reporting also leaves a wide margin for error. Whether or not the effect is real, the discourse that it has generated is a reminder of how critical it is for the field to seriously try to improve both the measurement and categorization of risk in future trial designs. Excellent work on this front is being done by relevant groups, including the HVTN high-risk women's group, the University of Washington team that is working on finding higher-risk pairs within cohorts of serodiscordant couples and several groups working in microbicides and PrEP research. If follow-up vaccine research aims to address this high- versus low-risk question, it needs to be in the context of these and other multidisciplinary approaches to measuring risk behavior.

Maintain research efforts in all of the populations hardest hit by HIV

Where to go next? This is one of the key questions raised by the RV144 results. Factors to weigh include the interests of the host country and communities in laying out a follow-up agenda (see Chapter Two), scientific expedience and the best fit between trial design and site location. The proposed discovery-style adaptive trials would take place in a limited number of high-incidence, high-prevalence settings. However, breadth is as important as focus. It's as important as ever to conduct the search for a vaccine in all of the populations hardest hit by HIV. Trial sites and cohorts take time and expertise to identify, develop, nurture and maintain. Global networks exist under different management and maintenance systems. Although limited in capacity, they are well-varied by populations, risks and community needs. Moreover, they are in regions that are home to many viral subtypes. These resources must be sustained in case scientific requirements change suddenly, based on the future findings—and because the field will ultimately need to be able to test and probably vary vaccines for use under these many circumstances.

The epidemic is driven by biology as much as it is divergent circumstances. We need a vaccine for MSM, IDU, adolescents and maybe infants, for discordant couples and for particularly vulnerable women and men. Not all candidates need to be tested in all populations at the same time, but the most forward-looking agenda needs to ensure that capacity is built, not lost, in these populations and that there's a plan for sequential evaluation of emerging data in various populations. Executing such a plan is risky but critical.

Consider more complex trials and more thorough community engagement

Well before the RV144 result, human discovery trials that would explore and test key immunologic concepts outside the traditional path to licensure marked by Phase I, Phase II and Phase III trials were being discussed.

HVTN 505 is the first such trial to be launched in the post-Step era. It is the first vaccine efficacy trial that does not have prevention of infection as a primary endpoint. Its primary efficacy endpoint is the vaccine strategy's impact on post-infection viral load. It is facing ongoing challenges with recruitment which may be some indication of challenges that will surround other such discovery trials.

Other factors, including trial site funding for and preparedness to work with target groups,

may also be affecting HVTN 505 recruitment. But the fact remains that more complex trials require more complex, sustained strategies for community engagement. The onus is on those proposing these ideas to invest now in materials, consultations and collaborative protocol development as outlined in the *Good Participatory Practice Guidelines for Biomedical HIV Prevention Research Trials* for stakeholder engagement to explain the new direction to regulators, policy makers, media, community advocates, activists and potential participants in countries where the trials might take place. Just as a truly informed consent process results in some individuals' deciding not to enroll or to opt out early, one measure of successful communication around novel trials would be how many of these audiences weighed the information and decided that such trials weren't right for their needs.

Even before new trials can be initiated, data may emerge about new prevention methods, including PrEP, possibly antiretroviral-based microbicides, and community-wide treatment programs designed to reduce community risk.

Community consultations need to incorporate discussions of how data on other interventions would be incorporated into plans for future AIDS vaccine trials. A positive finding from a single trial of PrEP or any other strategy won't result in immediate widespread introduction. But there will still be questions from civil society, policy makers, regulators and others about if and when such a strategy should be included in an investigational arm of a trial or as part of the standard of prevention offered to all participants.

Emphasize the positive potential of this next chapter of AIDS vaccine research

There are many challenges that must be addressed as the field moves forward. But for a global endeavor, the AIDS vaccine field often feels like a small village that speaks in its own language and has its own small-town feuds and factions. All AIDS vaccine stakeholders must work together to emphasize the bottom line from the RV144 result to a broader audience: it is the first proof in humans that an AIDS vaccine can provide protection against infection. It is a cause for hope. Funding for AIDS vaccines is funding to resolve a profound public health problem. This tangible evidence should inform and motivate funding and research expansion. The field now has a place to look for a correlate and a lower bound to which future products can be compared. Carefully and thoughtfully, let us turn this page together and start writing the next one.

AVAC's Web-based Resources

In past *AVAC Reports,* we have published tables and timelines of ongoing AIDS vaccine and HIV prevention trials. This year, in an effort to provide the most current information, we're inviting readers to view up-to-date versions of these resources on our website, *www.avac.org*. Below are quick links to these and other documents that enrich the issues discussed in this Report.

- Good Participatory Practice Guidelines for stakeholder engagement in biomedical prevention research at ***www.avac.org/gpp.*** These guidelines are being revised and public comment is highly encouraged!
- Timeline of expected HIV prevention research efficacy trial results at ***www.avac.org/timeline***
- Global map of ongoing biomedical HIV prevention research trials at ***www.avac.org/globalmap***
- AIDS vaccine, PrEP and microbicides trials tables at ***www.avac.org/trials***
- Funding for HIV prevention research at ***www.avac.org/resourcetracking***

Moment of Truth: Action and accountability from the Global HIV Vaccine Enterprise

In each of the past five years, AVAC has assessed and made recommendations for the Global HIV Vaccine Enterprise. We are both a member and a watchdog of the Enterprise, and we'd like to think that all of its members have similar, dual roles. Being part of a collective includes the responsibility to make sure it fulfills its mission.

In that spirit, we've made observations every year about what we'll be looking for in one year's time and in the medium and long term. We've placed benchmarks for the Enterprise as a whole and for the secretariat, recognizing that it needed time to establish itself and staff up.

One of the major milestones we have been tracking is the revision of the Scientific Strategic Plan, which was first published in 2005. The purpose of the Plan is to provide a field-wide agenda that guides funders, minimizes duplication and ensures that the field's myriad stakeholders work in synch.

As *AVAC Report 2010* went to press, a summary of the Plan was in production for release at the upcoming International AIDS Conference in Vienna. A full version of the Plan was slated to be published in September 2010. The big question for all of the Enterprise stakeholders will be whether the drafting process will yield a Plan that is worth the considerable cost and effort that went into it. The metric for evaluating this is whether the updated Plan stimulates substantive action in the funding priorities and research goals of Enterprise stakeholders.

The paper document alone cannot effect this change. The secretariat, under the direction of Alan Bernstein, must drive execution of the Plan. It should hold accountable the full range of stakeholders, including donors, scientists and organizations, for matching their work to the Plan's priorities with urgency.

Whether this will happen is, to be frank, an open question—and one that we'll be tracking closely in the coming months, since it cuts to the heart of whether the Enterprise secretariat and its stakeholders are meeting expectations.

The good news is that a range of activities, large and small, is being animated by the spirit of collaboration envisioned by the authors of the original Science article calling for the Enterprise. Stakeholders are working together more efficiently and with greater transparency, and funding has been directed to some of the specific priorities identified in the original Plan of 2005.

The collective field has made important progress towards achieving many of the original Enterprise scientific goals, like broadening exploration and understanding of early events in infection and creating systems for broader collaboration and communication. This has happened because of the good will and strenuous efforts of its members and because donors aligned their funding with areas that Enterprise members identified as priorities.

Even with these advances, the field still requires a Plan that emphasizes activities and initiatives beyond those that are already ongoing or planned. It needs an ambitious vision for how the field should seek to build upon the RV144 result and, at the same time, pursue a strategic set of future activities that take the field in new directions. The Plan doesn't need to provide the specifics of the scientific agenda, but it should suggest structures and provide the leadership needed to accomplish these aims.

It also needs to articulate how the AIDS vaccine field can continue strategic growth under constrained funding and backlash against AIDS exceptionalism. If the Enterprise cannot effectively champion judicious spending and tough decision-making, then who can?

But while the Plan itself, and the process to create it, are important, the process by which the Plan is implemented, monitored and updated will matter the most in moving the field forward. And, since responsibility is shared and individual partners choose which aspects of the Plan to address, mechanisms must be put in place to prevent important components of a complete program from being deferred or relegated again, as was the case with many of the recommendations from the 2005 Plan.

We recommend the following actions after the final Plan is released:

- The Enterprise secretariat take ownership for leading the field to implementation of specific aspects of the Plan and set formal timelines for achieving progress.
- The Enterprise, through the secretariat and its governing Council, develop a comprehensive and ambitious strategy for identifying new funding sources.
- The Enterprise secretariat, with guidance and input from the scientific working groups, identify three to five specific, time-sensitive issues that could be resolved or refined by small meetings, with recommendations and Enterprise-led follow-up on deliverables.
- Each Enterprise member articulate how their funding and/or scientific decisions are aligned with the Plan, or deliver a critique of the Plan to articulate why not.

We at AVAC will publish an end-of-year comment on the new Plan, with specific recommendations on how it could be operationalized and monitored.

The Enterprise remains an entity that belongs to all of us. Progress and success are a collective responsibility.

More will always need to be done, but there is some momentum to build upon. And it's time—if not past time—to rigorously evaluate if and how the Enterprise, as a collaboration and as a supportive organization, has the ability to do so.

In this Chapter:

- Science can, and should, surprise. Critics from many quarters argued against RV144—and had they prevailed, the field would not have the leads it has today.
- The Thai Prime-Boost study's approaches to solving shortcomings in community engagement need to be addressed as part of the trial's valuable legacy.
- The voices and perspectives of participants, policy makers, community advocates and other in-country stakeholders need to be front and center in trial planning and discussionsof trial results.
- "What's next?" is a question for Thailand as much as it is for the international scientific community—and the answers may be different in each case.

The Thai Way Forward

What comes after the largest AIDS vaccine trial in the world?

It's not only the scientists. The Thai people, the ones who made this happen, also want to know what to expect next from the RV144 results. What does 31.2 percent protection mean? Is the vaccine a success or failure? Both?

The surprising news last September that a vaccine, for the first time, had offered some protection against HIV was generated by a ground-breaking—and controversial—study done by hundreds of scientists, clinicians and health workers. But the study was also done by the thousands of farmers, fishers, factory workers, students and others here who volunteered their time, bodies and blood.

"Why did it take so long just to find out it didn't work?" said Boonchoke Kohkaew, repeating the question, and one he hears often.

Boonchoke, a government health worker known as "Lucky" who likes to tell jokes and clearly knows how to educate people by keeping them laughing, was fielding questions at a local community health forum. It was an open forum about many health issues, including the recently completed AIDS vaccine trial conducted here and throughout many communities in the southeastern provinces of Rayong and Chonburi, Thailand.

The vaccine did work, Boonchoke explained, just not well enough to use without more research and refinement.

"Would you participate in another trial?" he asked the crowd. Some said they would; a few said it involved "too many injections." The discussion then moved to further describing the nature of clinical trials, statistics, why some had to get placebo rather than the vaccine and the inherent uncertainty of research.

"A lot of people are still getting infected," said one man. He asked if Thailand's commitment to make this trial happen will guarantee the nation's access to an effective AIDS vaccine if it is discovered elsewhere. At the outset of the trial, Thai officials had said that one benefit of public participation was to secure the nation's access to the vaccine.

"People still have many questions," Boonchoke said.

A SCIENTIFIC STUNNER

A vaccine that can prevent HIV. It seems possible again, thanks to the Thai government and scientists agreeing to test a two-vaccine combination many experts had given up on. One top American scientist had even complained at the outset of the trial that this combo vaccine was as likely to protect against HIV as "maple syrup."

The trial took six years to complete, including a recruitment period that stretched over two years (one year longer than anticipated). Technically known as RV144 but more generally referred to

as the "Thai Prime-Boost" trial, it was the largest and most expensive AIDS vaccine study ever conducted. Some 26,000 young Thais were screened as potential trial participants. Of these, over 16,000 were enrolled to be vaccinated and followed up for years afterward.

I am an Advocate because...

When I first worked on an HIV prevention program about 15 years ago I saw how HIV ruined people's lives. Many children were growing up with no parents and many of them didn't even have a decent childhood. I thought that if we let HIV run its course, life would be too depressing and not worth living. So we had to do something to stop this.

Udom Likhitwonnawut, Community Advocate, Thailand

The strategy featured immunizations with a "prime" vaccine, Sanofi Pasteur's ALVAC-HIV (vCP1521), and a follow-up "boost" vaccine, VaxGen's AIDSVAX B/E. Multiple versions of ALVAC-HIV had been through numerous safety studies but none had ever been tested for efficacy in humans. AIDSVAX B/E had been tested in Thai injecting drug users, and AIDSVAX B/B had been tested in men who have sex with men in the US and Europe, but both failed to show efficacy.

The combination approach tested in RV144 had more than its share of high-profile critics, such as HIV co-discoverer Dr. Robert Gallo (who made the maple syrup comparison), Harvard University's Dr. Ronald Desrosiers, renowned HIV virologist Dr. Beatrice Hahn from the University of Alabama Birmingham and former director of the National Institutes of Health (NIH) Office of AIDS Research Dr. Neal Nathanson.

"People said we were wasting time and money on a lousy prime along with an even lousier boost," said Dr. Jerome Kim, one of the scientists leading the trial and deputy director of science for the US Military HIV Research Program at the Walter Reed Army Institute of Research. But, Kim said, "We had empirical data that indicated it might work, and really no one knew then (or now) just what immune response was needed to protect against infection."

In September 2009, Thai officials and scientists, along with Kim and other US researchers, stunned the world when they announced that this much-derided experimental vaccine had shown "modest" efficacy at preventing HIV infection. It's still not clear why, or how, but participants who received the prime-boost vaccine regimen had approximately 30 percent fewer HIV infections than did those who received the placebo (see box on p. 12).

"Nobody had ever shown efficacy in humans with any other HIV vaccine," said Dr. Jose Esparza, a longtime AIDS vaccine expert who worked with the Thais on their National AIDS Vaccine Plan while at the World Health Organization and who is now a senior advisor to the Bill & Melinda Gates Foundation. "This just reinvigorated, energized the field."

With this, Thailand moved the search for an AIDS vaccine into an encouraging new chapter in a long, frustrating story. But this was not easily accomplished, and even after its completion the trial continues to raise as many questions as it is answering.

Activists, scientists, health officials and others here are concerned that the trial's overall success may serve to mask some of its limitations and challenges—including ones that could have been avoided. It is important to explore any structural flaws before the approaches to large-scale clinical trials used in RV144 are adapted in Thailand or elsewhere. And equally important is determining whether members of Thai civil society, including AIDS non-governmental organizations (NGOs), citizens of Rayong and Chonburi, activists and advocates, are truly invested in AIDS vaccine research, discouraged or, worse, alienated.

COMMUNITY ENGAGEMENT CHALLENGES

Vaccine development depends on a successful partnership between researchers and the community. It takes people, lots of people, to find out whether a vaccine works. Unlike many areas of health research where people participate because they are sick and may benefit from the experimental treatment, people in prevention trials are healthy. AIDS vaccine development, in part because of the

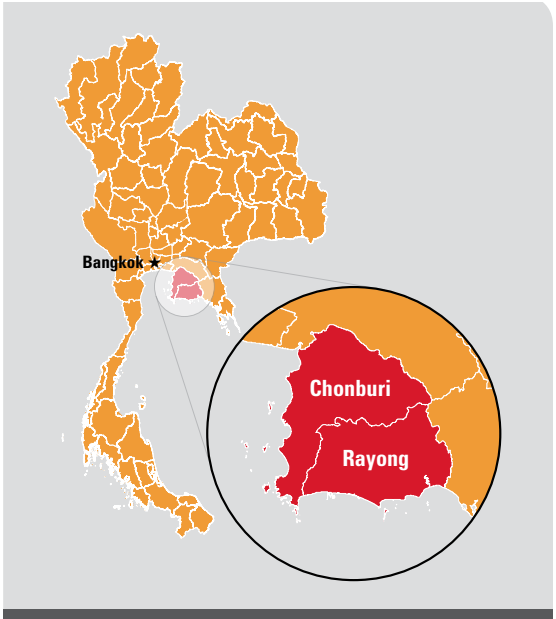
social stigma and fear surrounding the disease, depends upon an especially attuned collaboration.

Having helped to conduct two of the five AIDS vaccine efficacy trials completed to date, Thailand has had unique success in pairing science and society in the search for an effective AIDS vaccine. But behind the scenes, the marriage still appears a bit rough at times.

The Thai Ministry of Public Health (MOPH) was the official lead partner in the RV144 trial, working with the teams from the US Armed Forces Research Institute of Medical Sciences (AFRIMS), Mahidol University and other collaborators (see box on p. 11).

"In the beginning, the government's [MOPH] plan for community engagement was just public relations, radio ads and banners calling for people to volunteer," said Nimit Tienudom, director of the AIDS Access Foundation. It wasn't about listening or fostering true engagement with the community, Nimit said, but more about telling them of the need and lecturing them on their public obligation to participate.

The trial's community advisory board (CAB), he said, wasn't established until recruitment had already started—and was never truly encouraged to act as a means for the community to question or inform the researchers. It was hamstrung from the start, Nimit said, and often ignored by the Thai researchers and officials.



Thai provinces where RV144 took place

"We were never clear about what our role was supposed to be," said Rasikha Phongsri, a volunteer health worker in Ban Khai, Rayong who was asked to join the CAB. "They never told us. We had many questions, but few of us felt we could question the researchers. We mostly talked about it outside the meetings."

The local health care workers in her district felt so alienated by the entire project, Rasikha said, they refused to even get involved in recruitment. A research team from Bangkok had to come down to carry out the recruitment, she said.

"I agree that the CAB did not work as intended," acknowledged Dr. Supachai Rerks-Ngarm, senior disease control expert with the MOPH and the principal investigator for the trial. But it was not for lack of trying, he said.

Some of the problems identified in carrying out this study were attributed, perhaps justifiably, to the difficulty of marrying East and West: two cultures, codes of ethics and sets of social norms.

"We were basically using a recipe based on western researchers' concept of community oversight," Supachai said. Amid all the other demands at the launch of this massive study, he acknowledged that this one slipped through the cracks. But he added that many communities, especially in rural areas, actually recoil at the idea of a CAB because they trust and expect government to best serve their interests.

"We have our own ways of doing things, our own set of beliefs and traditions," Supachai said. "We just couldn't find a way to effectively merge the western concepts with the Thai way of doing things."

Ah, the Thai way. This came up a lot when discussing the trial.

Activists countered that this is just as often a defense used by authorities to slough off outside critics, maintain control and stifle dissent.

"We heard from many volunteers they were told they 'should' volunteer by health workers under pressure to enroll people," said Boripat Donmon, president of the Thai Network of People Living with HIV/AIDS. It is also not the Thai way, he said with a grim smile, to refuse a strong suggestion from an authority figure.

This didn't happen everywhere, Boripat acknowledged, but it was claimed often enough

to raise concerns about whether the ministry was truly encouraging voluntary participation or just exploiting its significant authority in the community to speed up enrollment when participants began to drop out of the trial.

An external review of the study conducted by UNAIDS in 2006 didn't find any evidence of unethical recruitment, but, Kim acknowledged, "We did have trouble in the beginning with both recruitment and retention."

Recruitment took two years instead of one year as planned, Kim said, which may have been partly caused by the failure to ramp up community engagement in the beginning, back in 2003. But of equal concern to the sponsors was a huge loss of participants even as study enrollment was still underway.

"Based on previous experience, we expected to lose maybe five percent during vaccination and five percent every six months after that," he said. But in January 2005, Kim said, they discovered they were "hemorrhaging" participants and called an emergency meeting with the ministry and Thai scientific colleagues.

"We had to make it clear to the ministry that these rates of retention were not consistent with good clinical trials practice and could lead to the discontinuation of the study," Kim said. He said they all decided they needed to launch a new approach to community engagement, which would include creating an active CAB, to stop the exodus.

"The ministry had been reluctant to create any new kind of structure, like the community advisory board, feeling they already had an established presence and a good relationship with the village councils," said Nusara Thaitawat, a former journalist hired by the ministry to improve, reorient and implement its community engagement plan.

But the village councils deal largely with local economic issues, Nusara said, and many had since become defunct. Those that did exist, she said, were not interested in taking on the responsibility of overseeing a complex medical research project. Further, she said, the activists and NGOs were making a strong case that the ministry and many local health center staff simply did not understand community engagement.

What is Community Engagement?

Community engagement entails a meaningful and participatory process of involving stakeholders early and continuously in trial design, development, implementation and results dissemination. Stakeholders include people who may be asked to volunteer for clinical trials, local community members, NGOs, community-based organizations, local and national leaders and a wide range of other constituencies.

AIDS treatment activists helped define some of the key principles of community engagement during the first decades of the epidemic. One key principle is that community engagement is distinct from recruitment activities.

In 2007, AVAC and UNAIDS launched guidelines for Good Participatory Practice (GPP) to provide a road map on community engagement in the trials process for trial sponsors, implementers and advocates. To learn about GPP and the current process of revising the guidelines, go to *www.avac.org/gpp*.

Nusara, who is now working with AFRIMS in Bangkok, said true community engagement required a big conceptual shift for ministry and health officials used to achieving results by issuing top-down instructions.

"They [the MOPH] often did a terrible job at community engagement," said Supatra Nacapew, an attorney and director of the Foundation for AIDS Rights. Even when health workers did a good job engaging with the community and working with individual trial participants, Supatra said, this still posed a serious problem for study participants that may not have been obvious to non-Thai outsiders or even the ministry.

"In Thailand, people really do not think of individual rights in the same way as they do in the US," she said. She emphasized that Thais depend upon the health centers for routine medical care. It's hard to say "no" to the person who delivers your baby or determines what kind of care you get when you are ill.

"Because of the nature of the power dynamic, it just isn't possible to guarantee freedom of decision," Supatra said. This became an even bigger concern to the NGOs, she said, when they heard the ministry had given health staff financial rewards depending upon how many people they enrolled.

I am an advocate because...

I try to break down the silos of prevention science, to ask the questions that matter, and to mentor young investigators who will carry us into the future. I grew up with the AIDS epidemic and need to do this for all the people we all lost.

Susan Buchbinder, Director of the HIV Research Section, San Francisco Department of Health, USA

"There was a need to create something new," said Nusara, who began—with the ministry's approval—working with the activists and others to launch a more vibrant and independent community engagement plan.

TURNING A CORNER

No trial is seamless from beginning to end, and one of the most positive aspects of the Thai trial experience may have been its approach to problem solving. Faced with retention challenges and critiques of community engagement, the trial team adopted new approaches that, by many accounts, helped turn the tide for the study.

Community engagement eventually took place, to some extent, with the guidance of experienced AIDS advocates and NGOs. For example, one of the most popular strategies for engaging and informing the communities, Nusara said, was a "parlor game" of sorts thought up by a member of the AIDS Access Foundation called Game Laek Nam (a.k.a., the game of fluid exchange). In it, participants are given vials of fluid and, over the course of several hours, interact and exchange the fluids as a proxy for sexual behavior. In the end, a chemical is added to the vials to see whose vials turn pink, indicating the spread of HIV.

"It can get pretty wild and dirty," laughed Nusara. More importantly, she said, it educates people about HIV in an open and friendly way that builds lasting trust and a dialogue, fostering long-term commitment to projects like AIDS vaccine trials.

On the more practical side, Kim's colleagues at AFRIMS responded to the initial loss of participants by creating new software programs for tracking and notifying enrollees of their vaccinations and next appointments.

The lead Thai clinical researcher on the project, Prof. Punnee Pitisuttithum, chief of the Tropical Medicine Research Unit at Mahidol University in Bangkok, also mobilized her research team to contact participants individually to improve retention. Punnee and her team knew what to do, having had experience with previous AIDS vaccine trials.

"We were responsible for all the clinical research, starting with the initial enrollment, informed consent, vaccinations and follow-ups," Punnee said. As she explained her role, it was clear that most of the actual logistical and clinical duties for this trial were carried out by her academic colleagues working in close collaboration with AFRIMS scientists. The Thai Ministry of Public Health was still the formal leader of the study—an important and unprecedented structure for an HIV prevention trial in the country.

THAI LEADERSHIP

The decision to name an MOPH staff person as the Thai principal investigator for the study was a departure from previous studies in Thailand.

For example, Punnee, an academic researcher, had been a senior investigator on several earlier AIDS vaccine trials, including the Thai AIDSVAX efficacy trial in injecting drug users. In the recent past, most vaccine trials here had been conducted by outside researchers working in collaboration with academicians like Punnee.

The structure that placed the MOPH at the helm was one way of ensuring full Thai government ownership of the project.

In the more distant and troubled past, research was imported to Thailand in a way that didn't always adequately involve or credit the Thai scientific community or health officials, or ensure that Thailand benefited from the research findings. More recently, unresolved community concerns continue around an ongoing trial of pre-exposure prophylaxis, or PrEP, in injecting drug users in Thailand (see box on p. 26). Several people interviewed for this article cited a trial of a successful hepatitis A vaccine conducted by Thai and international investigators in northern Thailand. There was a widely held feeling that Thai collaborators hadn't had joint ownership, leadership or credit for that study. In addition, when the

hepatitis A vaccine was manufactured, Thailand still had to pay the full commercial price. The people who had tested the vaccine were in effect denied access due to cost.

The Thai government was not going to let that happen again.

For the Thai Prime-Boost trial, an access agreement was negotiated up front with the vaccine's developers guaranteeing—if the vaccine proved effective—that Thailand would get it at discount or even be able to manufacture it locally.

Giving the MOPH primary authority for the trial was not just to ensure public access to the vaccine. Given the size of the trial, officials thought the research could be best done through Thailand's decentralized but fairly well organized and extensive system of community health care delivery. Rayong and Chonburi Provinces were selected because of a somewhat higher HIV incidence (nearly 0.4% at the start of the trial, which appears to have dropped to about 0.2% by the time it was completed) than in other parts of the kingdom.

Supachai was appointed principal investigator. This may have addressed the Thai government's concern about protecting the public interest and the balance of power between Thai investigators and international collaborators. But for Supachai and for the MOPH overall, leading the world's largest AIDS vaccine trial was an enormous new responsibility.

"I had done some epidemiological research in the past, but I had a lot to learn," Supachai said. He agreed that they failed to adequately engage the community early on, but said he had approached Nimit, Supatra, Boripat and others in the NGO community to seek their assistance and guidance at the outset.

Nimit has a different recollection. "We actually approached him when we heard about this trial after it had already started." And even after meeting with ministry officials to figure out how to collaborate on community engagement and education, Nimit said, they consistently had trouble getting basic information—such as the study protocol, the access agreement or just answers to routine questions as they arose.

There are multiple perspectives on almost every aspect of a major trial like the Thai study. By most accounts, the arrangement of having

RV144: A Brief History

Selected key dates for the RV144 trial and its candidate vaccines

1992-2003	Approximately 20 studies evaluate safety, immunogenicity and dosing strategies of ALVAC HIV vaccine candidates in humans
1998	Two Phase III trials of AIDSVAX launch following safety testing
2001-2002	Thai and US collaborators develop and seek approval for RV144 protocol
2003	The two AIDSVAX Phase III trials show no evidence of benefit
	September: RV144 protocol approved by Thai and US regulatory bodies; volunteer screening begins
	September: Three AIDS NGOs receive a grant from Thai Ministry of Public Health for community engagement in study provinces
	October: First vaccination
2004	**January:** 18 AIDS researchers sign letter in *Science* magazine expressing concerns about scientific rationale for RV144
	July: Additional letters from scientists and advocates about RV144 published in *Science*
2005	Viral load added to protocol as a co-primary endpoint
	February: Low retention rates trigger US and Thai trial team overhaul of community engagement, recruitment and retention strategies
	December: Participant enrollment complete
2006	**May:** First Community Advisory Board meeting
	June: WHO-UNAIDS HIV Vaccine Advisory Committee external review of ethical and community-related aspects of the trial
	July: Vaccinations complete
2008-2009	Development and presentation of "road map" for potential trial outcomes
2009	**June:** Final protocol-specified study visit for participants
	September: Trial team announces initial findings that vaccine recipients had lower risk of HIV compared to placebo recipients
	October: Full data analysis published in *New England Journal of Medicine* and presented at AIDS Vaccine 2009 Conference in Paris
	October: Scientific working groups formed by trial team to develop follow-up research agenda
2010	**March:** Multi-stakeholder meeting in Bangkok to discuss ethical, regulatory, scientific and access issues of RV144 results for Thailand
	(*Planned/anticipated*): Announcement of next steps based on RV144 result

the ministry run this large-scale clinical research project had some real problems. Some had to do with the challenge of doing something new, and big. But some difficulties may have been structural, with observers suggesting the need for a serious reassessment of whether this is a role the ministry can play.

"It is too much for the ministry to try to do large-scale clinical research, of any kind," contended Boripat. They have their hands full doing health care delivery, he said, and can't be expected to also shoulder major research projects. It puts a strain on the health system, he added, and also poses ethical concerns.

What's needed, Boripat said, is for Thailand to strengthen and expand its biomedical research network through the universities—with input from the affected communities, of course.

Nimit and Supatra, however, think the ministry has to have a leadership role in any major clinical research project. The government, through the ministry, is accountable to the Thai people and it is important that it play a leadership role to protect Thailand's interests. At the same time, nobody else has anything close to the MOPH's extensive health infrastructure. Across the two provinces involved in this trial, there were eight clinical sites and 47 health centers involved in screening, enrolling and tracking participants. This is an extraordinary task by any estimation, they said, and a trial of this magnitude could not be done without the infrastructure provided by the Ministry.

OVERCOMING SKEPTICISM

The RV144 result was a surprise to virtually everyone in and outside the vaccine field—and all the more remarkable given the skepticism and uncertainty this trial faced before it even began.

"I don't think it's overstating things to say this was revolutionary," said Dr. Donald Francis. Francis led the development of VaxGen's AIDSVAX and then took it with him when he left the company (which had "moved on" from AIDS vaccines) to form a non-profit corporation, Global Solutions for Infectious Disease.

In addition to the scientific skepticism RV144 faced in the beginning, Francis noted that the dedicated US Army research team that pushed this forward also had the rug pulled out from underneath them by the Department of Defense. In 2003, just as the Thai trial was to start, the Army lost funding for its vaccine research program and it was

Learning our Lessons on Community Engagement: Another trial, another lesson?

The ongoing trial of pre-exposure prophylaxis (PrEP) in Thai injection drug users provides another example of challenges and evolving community engagement.

Results are expected in early 2011 from the trial, the first to evaluate PrEP in IDUs.

Civil society groups, led by the Thai Drug Users' Network (TDN) and the Thai AIDS Treatment Action Group (TTAG), have raised concerns about various issues including potential coercion since the same methadone clinic staff who were providing services to injection drug-using clients were also charged with recruitment. Another concern centered on the fact that the prevention package provided to participants on site did not include clean syringes.

Before the trial began in 2005, the trial sponsors (US Centers for Disease Control and Prevention, the Thai Ministry of Public Health and the Bangkok Metropolitan Administration) sought input from Thai advocates and community representatives. However while the research team has included IDU representatives on the community relations committee and there has been dialogue between different stakeholders over the past five years, not all of the concerns were fully addressed from some community stakeholders' perspectives.

As important as the effectiveness results from this clinical trial might be, the lessons of community engagement and working with the IDU community and stakeholders may be an even more important contribution to biomedical prevention research going forward.

Turning the Page: Applying lessons from recent trials

Clinical trials are complicated to design and conduct—and even harder to explain. Their results frequently defy simple explanations. But grappling with the complexity pays off. No one's captured this better than Susan Buchbinder, director of the HIV Research Section at the San Francisco Department of Public Health, who developed this list of "top 10" lessons and presented it at the 2010 Microbicides Conference. We've reprinted and annotated the list here.

Good science often yields surprising results

No one would have predicted the RV144 results—and many critics predicted failure. Every trial has the potential to surprise.

Results take time to process

Advocates need to work together to map out next steps and manage expectations regardless of whether news is good, disappointing or just plain confusing. This principle was recently illustrated with RV144 and trials of the microbicide PRO 2000, and will be put to the test again when the ARV-based prevention effectiveness data are available from CAPRISA 004 and iPrEx later this year.

It takes many villages to implement a trial

When it comes to trials, it's not just the participants or the scientists who make it happen. Every HIV prevention research trial takes "villages" of allies in civil society, government, treatment and care delivery and many other fields. As we say throughout the Report, "We are all advocates."

Statistics are confusing—to almost all of us

The past year of work on the vaccine and microbicide trial results illustrates the pitfalls of focusing on a single aspect of a trial finding—e.g., the percent reduction in risk of infections—without looking at the full statistical analysis. Without the complete picture, the implications of a result can be easily distorted, whether by the media, advocates or scientists.

Behavior change is difficult

Funders, governments, program implementers, civil society and many other groups must keep doing more—much more—to deliver proven prevention aimed at individual and structural drivers of HIV risk. HIV prevention trials offer a wealth of information on how to improve delivery of proven prevention and overcome related challenges.

Mucosal responses are important and difficult to measure

Blocking sexual transmission means getting the right defenses in the right place at the right time. In the future, the most effective strategy might involve a combination of approaches such as PrEP, a microbicide, circumcision and a vaccine. But to figure this out, improvements are needed in approaches to measuring these defenses and evaluating potential combinations.

Human clinical trials are an important part of the discovery process

Nearly three years out from the initial (and disappointing) result of the Step vaccine trial, the field is still learning valuable lessons from the study data. The Partners in Prevention trial of HSV-2 treatment for HIV prevention in serodiscordant couples continues to provide fascinating data long after the release of initial results. These are just two examples of the ways that a single trial can provoke and expand the field for years after its initial finding.

Transparency yields many rewards

Time and again, clinical trials have proven the fundamental value of telling it like it is. Talking about the trial and its potential outcomes well before the results are released and sharing data with community stakeholders as soon as they become available are key elements of good participatory practice. Be honest about what conclusions can be drawn and what remains unclear or uncertain.

There will be no silver bullet for HIV prevention

Expanding, not replacing, the range of options is the overall goal for HIV prevention. No single approach will work for everyone, and explaining and repeating this goal should be on the top of every HIV prevention research advocate's to-do list.

Discovery is a multi-step process and all partners must work together

Discovery means more than just finding out trial results. It means finding out what these trial results mean to communities; discovering what the priorities and next steps are for the host country; applying results to the next trial design; and exploring what implications data in one population may have for another.

temporarily transferred to the National Institutes of Health. "I don't think most people realize how unlikely it is that this thing [the RV144 trial] even happened," said Francis.

"I think everyone now views this as a great success, despite all the problems and the initial skepticism," said Dr. Nelson Michael, director of retrovirology at Walter Reed and one of the Army scientists who was a key player in keeping the study alive. Michael emphasized that the Army's 2003 "de-funding" of the program was restored later and that the entire episode has worked out well by encouraging greater collaboration between NIH and Army researchers.

At the February 2010 Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco, Michael said he gave a half-hour talk on the results of RV144. It covered many of the questions, the efforts aimed at finding correlates of protection and where to go from here. He said he only got one, mostly *pro forma*, question from the moderator.

"That compares to the CROI meeting two years ago, when I felt more like I was the target of a series of drive-by shootings by those who thought this trial was a huge mistake," Michael said. "That's the way science works. We debate."

LOOKING FOR ANSWERS

In addition to lessons about community engagement, approaches to international collaboration and the importance of human trials, the Thai Prime-Boost trial is a reminder of how critical every aspect of the protocol is when it comes to data analysis.

For a variety of reasons—cost, a scaled-back budget, logistics and the government's sense that larger sample volumes would have been unpopular—only a minimal amount of blood was collected from each participant: 8 milliliters, or less than 2 teaspoons, two weeks after the final vaccination and 16 milliliters, or about 1 tablespoon, six months later. This will make even more difficult the task of identifying the correlates of protection—normally antibodies but for HIV a mystery.

"That is the most important next step," said Punnee. The prime-boost approach, she said, was used because it was hoped it could stimulate both the cellular and humoral arms of the immune system. Given that the vaccine seemed to work, yet apparently prompted neither neutralizing antibodies nor a strong cellular response, the correlate is something that the field hasn't yet identified as a marker of vaccine-induced protection.

It's entirely possible that a correlate won't ever be identified, and many scientists in the field are talking about what next steps might be without one. But there's also strong interest in Thailand—and globally—in searching for an answer.

In early March, Punnee, Supachai and others at the ministry met to consider the idea (advocated by Kim, Francis and others) of asking some of the participants to receive additional vaccinations to see if immunogenicity can be improved. In additional analysis of the study results, the vaccine's efficacy appears to have waned over time.

Punnee said a new trial protocol would aim to collect a larger volume of blood along with mucosal samples.

Scientifically, there's a lot left to do—figuring out how best to search for the correlates of protection, looking for further evidence supporting the assumption that protection was due to the combination of vaccines (and not just one or the other), deciding whether to further boost participants—the list goes on.

The question of what to do next with the prime-boost regimen is of major significance in Thailand and around the world. But beyond the scientific issues are questions for Thailand about how best to conduct such large clinical trials, protect the public interest and engage the community. Clearly, it's a learning process.

For Thailand, there is much to celebrate but also some serious concerns that need to be addressed openly: Should the Ministry of Public Health run large-scale clinical trials or is some new structure needed? What needs to happen to improve community engagement and avoid some of the problems experienced during RV144?

Wherever the next steps are, this extraordinary scientific achievement—made possible by the Thai government and people, working in collaboration with the international community—has transformed AIDS vaccine research and given new hope.

3

In this Chapter:

- Broaden, and increase flexibility of, materials transfer agreements
- Increase global exchange of samples and reagents
- Develop clear, coordinated plans for data collection and analysis
- Develop mechanisms to engage and facilitate “smaller science”
- Ensure engagement of early-career investigators and explore a consortium specifically for this group

Data and Materials

A "to do" list for the future

Data shape the vaccine science agenda and vice versa. The agenda is framed around hypotheses that guide the samples that are collected and the assays that are conducted. The interpretations assigned to the data that are generated shape the agenda. It's an intricate cycle that's influenced by a range of factors—politics, prevailing wisdom, funding, technology and, at almost every turn, the legal and intellectual property frameworks that govern the institutions, trial networks and consortia conducting the research.

It's been five years since the *AVAC Report* that last analyzed intellectual property (IP) and data and materials management as they relate to AIDS vaccine research. A lot has happened since. For this year's Report, we have returned to the issue, with a focus on data and materials. Data and materials are the bricks and mortar of research. (For definitions of these terms see p. 38.) With a licensed AIDS vaccine still many years away by almost all estimates, questions about how data are generated, compared, stored and interpreted are of the utmost importance. Based on conversations with a range of stakeholders, review of documents and presentations or discussions at recent conferences and public forums, AVAC believes the field is at a critical juncture, with existing systems that need to be expanded for the field to achieve its next set of goals.

The good news is that there are strong structures to build upon. We heard that access to data is widely regarded as far easier than it had been in the past. There is more collaboration on many levels, facilitated by various consortia that can be used as models going forward.

The Center for HIV/AIDS Vaccine Immunology (CHAVI), Collaboration for AIDS Vaccine Discovery (CAVD), the International AIDS Vaccine Initiative's (IAVI) Neutralizing Antibody Consortium (NAC), and other entities have made great strides in creating collaborative, big science-oriented approaches to tackle some of the field's major scientific questions. Researchers at different institutions are sharing information and ideas in unprecedented ways. Larger quantities of samples than ever before are being collected and mined for clues to guide AIDS vaccine development. On the clinical trials front, first Step and then the Thai Prime-Boost trial yielded surprising, valuable results that underscore the irreplaceable value of human studies in advancing the field.

The fact that progress has been made is no reason for complacency. As important as these advances are, today's systems for collecting, storing and sharing data are insufficient for some of the goals of upcoming AIDS vaccine research. More can be done to ensure that data from various trials are comparable and to broaden access to data and materials even further.

These steps are critical as the field moves in the direction of an expanded and iterative array of exploratory trials in humans. These trials propose to look at specific scientific questions using particular candidates, without presuming that the candidate would advance for further development. Such trials are often, though not necessarily, small. And the only way for a suite of these trials to be truly useful is if the results across studies are, to some degree, comparable.

As Ron Germain of the US National Institute of Allergy and Infectious Diseases said at an open forum on the Global HIV Vaccine Enterprise Scientific Strategic Plan at the Paris AIDS Vaccine Conference in 2009, "You can have many small trials but unless you know each trial will collect comparable and comprehensive data sets, they will not be comparable and you will not be able to use them as a basis for going forward." These systems are perhaps even more problematic for larger experimental Phase IIb or proof-of-concept trials.

Improving the current systems for managing data and materials will require some substantial up-front investments in infrastructure and operations management. But over the medium and long term, systems that make data more consistent and widely available will also help the field optimize its resources. "I think at the moment everyone collects and stores data in different ways. It makes it almost impossible for one trial to be compared to another," said Robin Shattock of St. George's, University of London, at the same Paris forum. Shattock suggested that one easy way for the field to "do less with more" is to ensure that data are even more comparable and accessible than they have been to date.

Many people we spoke to echoed Shattock and expressed the need for more centralized repositories of data and more transparent and coordinated approaches to data collection and analysis.

We also heard a strong call to address issues of assay selection and comparability and to strive for more globally accessible systems for data storage. A new combined initiative of CHAVI and the CAVD to establish an "HIV vaccine relational dataspace" could help address this. The initiative will allow many databases that contain different types of information (e.g., data on genomics, antibody and cellular responses) to be relationally queried.

Many of these opinions have been voiced in discussions about what belongs in the updated version of the Global HIV Vaccine Enterprise Scientific Strategic Plan (see p. 18). Indeed, the ability of the Enterprise to shape the way the field collects, stores and shares data and materials may be its most important impact in the next few years. At the Paris meeting, HVTN head Larry Corey said, "The original Enterprise article was all about reorganizing what we do. I think we've not done such a great job in that." Many of the priorities identified below have been noted before and may appear in the next Enterprise plan. This time next year, all Enterprise members—including AVAC—will be responsible to show that we've moved from words to action.

Broaden, and increase the flexibility of, materials transfer agreements

When we last explored these topics five years ago, CHAVI, CAVD, IAVI's NAC and its consortia for vectors and live-attenuated vaccines were just emerging. Today it's possible to measure how they have moved the field. Although each has a different structure, they share the goal of facilitating collaboration among researchers working in different institutions and disciplines. These consortia have aimed to reduce duplication and harness the power of their membership to gather and analyze data from large numbers of samples. They have prioritized approaches for enhanced comparability. They have resulted in new institutional linkages, such as IAVI's partnership with the Scripps Research Institute.

Each consortium has Materials Transfer Agreements (MTAs), centralized repositories of specimens and reagents and information-sharing systems that allow rapid dissemination of results to other consortia members. This increases the efficiency with which other scientists can make course corrections or conduct independent analyses. These innovations have slashed through much red tape and legal roadblocks that have stymied inter-institution collaboration in the past.

The discoveries that have emerged from these consortia include CHAVI collaborators' work on identifying genetic signatures associated with improved control of HIV in acute infection, understanding infection by founder virus and its difference from chronic replicating virus, breakthroughs in identifying novel neutralizing antibodies from IAVI's NAC collaborators, and CAVD's work on teasing out critical aspects of humoral and cellular immunity to target in vaccine design.

We looked at the MTAs being used by different consortia. Material requestors must promise to:

- Conduct only non-commercial pure research or research solely focused on HIV and not other diseases (NIH transfers are an exception).
- If commercial use is permitted, prices for products sold in the developing world or where research was conducted must be set at "reasonable", at cost or cost-plus terms. Given the uncertainty around cost and pricing for hypothetical products, it is difficult to estimate what these would be or whether this condition is useful in guiding decisions about whether a project will be feasible over the long term.
- Abide by consortia restrictions regarding material use and transfer to others.
- If products can be made and sold, negotiate future revenue-sharing with research and trial consortia. This may involve determining a fixed share of revenue payment.
- Transfer technical knowledge or manufacturing skills to countries that participate in trials, so that products can be locally produced for their populations.

The existing agreements seem to work well enough for scientists within the consortia, but we heard that the process for engagement by outside collaborators is still time-consuming and somewhat "creaky". Approaches to engaging innovative thinkers outside consortia—and outside the AIDS vaccine field—need to be streamlined through revised, flexible MTAs and other related agreements. There are other models that could be explored, such as California's

Intellectual Property and Access: Revisiting our 2005 recommendations

AVAC Report 2005 *contained a number of recommendations regarding intellectual property (IP) and access agreements.* These are reviewed and updated below.*

- Develop consortium agreements that appeal to all capable stakeholders including the private sector. The consortia must address: how participants will value, protect or be proportionately rewarded for their existing IP provided to and used by the consortium; and how participants will be allocated rewards for the new IP the consortium creates from its work.

  The private sector is largely missing from consortia efforts including CHAVI, CAVD and IAVI's initiatives. There is still little in existing IP agreements regarding valuation and allocation of future rewards.

- Adopt a "Covenant Not to Sue" as a mechanism to reduce preclinical and early-stage research risks from IP uncertainty, while preserving potential economic rewards should the research prove to be successful later. The covenant can also apply to research tools.

  Features of current MTAs used by AIDS vaccine consortia help to serve a similar function as the model covenant that AVAC proposed in 2005, even though that specific model has not been adopted.

- The US Government should extend its "authorization and consent" language to reduce IP research risks for projects funded by government grants.

  No modifications to government language have been made.

- Include plans for eventual product access in clinical trials for the participants in AIDS vaccine and other prevention trials.

  Access commitments continue to be determined on a trial-by-trial basis, with differing levels of clarity, ranging from the relatively detailed "road map" generated by the RV144 team in advance of their data analysis, to much more open-ended questions about post-trial access for the microbicide candidate PRO 2000 (see Chapter Four). Much more can be done to ensure that every trial has a clear plan for next steps regarding access for placebo recipients, expanded manufacturing, launch of confirmatory trials, introductory studies and other issues.

- Set up secure, encrypted, licensed database systems to allow authorized users to share trade secret data under carefully controlled circumstances.

  CHAVI and CAVD have online lists of completed studies and available data. An expanded "bibliography" of similar information should be created. Access could be by application or password-protected.

* To read the full article visit *www.avac.org/download/reportarchive*

[1] Article XXXV, California Constitution; Section 125290.40(j), Health and Safety Code. Available at URL: *http://www.cirm.ca.gov/Files/Regulations/100604.pdf*

state government-funded stem cell research program, through which biomedical materials are shared without the requisite of consortia membership.[1]

The current MTAs tightly restrict ownership and use of data and materials. Restrictions on non-commercial use specify that the sample and any progeny or derived materials are owned or controlled by the consortium in question and cannot be used for commercial purposes unless specifically negotiated. This restriction may serve to keep the resulting research in line with a public benefit agenda and avoid diversion to non-AIDS-vaccine-related priorities. However, this provision needs to be considered as a potential disincentive to industry and some academic involvement since it leaves great uncertainty as to whether the costs of research could be recouped by selling unrelated products or producing funds for a university transfer office at any later date through multiple use of transfers.

Here are some ways in which MTA conditions of sharing should be more flexible.

- Permit non-AIDS-vaccine-related commercial uses of derived materials, providing that users are first able to meet the consortia's AIDS vaccine-related research directions and that these other uses do not delay or take away any resources from meeting that obligation.

- Produce GMP (Good Manufacturing Practices) lots to share vaccines and reagents more widely.

- For entities that must recoup costs, establish up-front arrangements for revenue-sharing for any of their income related to the materials. Because all of this work is still considered early-stage research and future revenues are speculative, we also believe—as we said back in *AVAC Report 2005*—that valuation of the shares must not be overinflated and could adjust only as milestones of success are achieved.

- Specify that a portion of any revenue generated by using a material or sample would be returned to the consortia as a reinvestment in the AIDS vaccine research agenda.

I am an advocate because...

How am I an advocate? After 20 years you think the answer would be simple. I don't speak the "I" any more. After creating an organization, the work is done through a constellation of people. We teach about the cross section of HIV and human rights, engage in prevention research and its implications for women and work with women living with HIV to become part of the leadership.

Dazon Dixon Diallo, Founder of Sister Love, USA

Stakeholders and entities that control data can reserve control over its release to outsiders. CHAVI, for example, has collaborators sign an internal confidentiality agreement that ensures non-disclosure of results discussed within the consortia for up to three years.[2] "That policy was essential for building trust in CHAVI so that we could get out of the traditional mode of not talking to our colleagues and revealing data until the data are published. Now large numbers of scientists working together are being completely open and telling what happened that day in the lab," says CHAVI head Barton Haynes of Duke University. Ways to structure such policies so that trust gets built and data are released more quickly for legitimate public use should be identified.

The MTA agreements we reviewed set principles that allow commercial use of materials in a future AIDS vaccine in exchange for reasonable but undetermined cost pricing. This is probably as specific as the language needs to be, given the long timeframes for development of products. Specific efficacy trials, like RV144, have gone ahead with more detailed access agreements in place

[2] Quay J. *Intellectual Property and Legal Issues.* CHAVI Annual Meeting 2007. Available at: *https://chavi.org/wysiwyg/downloads/CHAVI_Annual_Meeting_2007_legal_and_IP_update.pdf*

I am an advocate because...

I engage communities in Kisumu, Nyanza province, where the male circumcision clinical trials research went on. They still lack information, but I bring them into the fold through photo documentaries passing on correct knowledge and information on where to seek medical male circumcision services.

Simon K'Ondiek, Coordinator, HIV/AIDS Research and Advocacy Programme, Kisumu, Kenya

(see Chapter Two). AVAC maintains its strong endorsement of lowest-cost pricing for any vaccine in a low-income country.

Increase global exchange of samples and reagents

The results from both the Step and RV144 AIDS vaccine trials have reaffirmed the utility of evaluating vaccine candidates in humans. These trial results were not fully predicted by preclinical challenge trials in animals or by Elispot assays measuring interferon-gamma production by vaccine-induced T cells. The unexpected finding, in RV144, of an impact on HIV acquisition by a vaccine that did not induce traditional neutralizing antibodies underscores the need to measure a range of innate, mucosal and non-traditional antibody effects. Some of the assays to measure these parameters exist, others will need to be developed, and still others will need to be standardized and validated. All of this needs to happen at the same time as the clinical trial agenda advances.

While there's scientific merit in an expanded array of exploratory clinical trials, including small Phase I, Phase IIb or trials with adaptive designs, there's also a real risk that these trials won't achieve their own goals if they are conducted in the field's current context. A proliferation of small trials will be greater than the sum of their parts only if the data these trials gather are comparable and, to some extent, accessible to researchers not directly involved in the study or who are working in other, related fields. Confusion surrounding interpretations of data from non-human primate studies is an object lesson in this problem.

We have heard positive reviews of the sample sharing arrangements established by Step sponsors (see box, p. 37), which have been adapted for samples owned by the Thai government for RV144 analysis.

To further facilitate exchange of data and samples, centralized "curators" of both samples and data could be established, either as new entities or by giving resources to existing entities such as SCHARP (the Statistical Center for HIV/AIDS Research and Prevention). These entities would serve as single points of contact and would have the resources to manage and honor requests for sophisticated data sets or analyses. Based on our interviews, there can be a bottleneck in obtaining this type of information, even when raw data are more readily available.

Different types of data raise different issues. As discussed at the 2010 Conference on Retroviruses and Opportunistic Infections (CROI), there is no central clearinghouse to share the increasingly large volumes of data from HIV genomics and microarray expression, which examines gene activity. This can impede data analysis. In a discussion of genomics research and HIV at CROI 2010, John Ioannidis of Tufts University, described a recent effort requested by the journal *Nature Genetics* and carried out by various researchers to replicate the results of selected gene-expression studies it had published.[3] More than half the repeated studies yielded results different from the original. In addition, other studies had discrepancies because of differences in the software used to mine the data.

The challenges with genetic data illustrate the complex interplay of technical, institutional, legal and ethical factors affecting many types of information. Compatible computer frameworks are needed to store the data. Institutional agreements are needed to facilitate sharing and comparison. Technical fine-tuning is needed to generate reproducible results. And ethical and legal issues need to be addressed. For example, in the US, a

[3] Ioannidis JPA, et al. Repeatability of published microarray gene expression analyses. *Nat Genet.* 2009 Feb;41(2):149-55. Epub 2008 Jan 28.

Turning the Page: Engaging new talent in the search for an AIDS vaccine

New minds and new ideas are critical for the future of the AIDS vaccine field. Researchers in the early stages of their careers—e.g., post-doctoral students and clinical instructors—need support and resources to help them establish and advance careers as AIDS vaccine scientists. One recent initiative that aims to provide this support is the Early Stage Investigator Scholar Award (ESI), which is funded by the National Institute of Allergy and Infectious Diseases (NIAID).

The program offers three to eight awards, which include up to US$450,000 over two years plus mentorship from established researchers working in clinical trials and primate research. Participating organizations include the Center for HIV/AIDS Vaccine Immunology, the HIV Vaccine Trials Network, the National Center for Research Resources, the Global HIV Vaccine Enterprise and NIAID.

The award program's twin aims are to attract and retain promising early-stage investigators and to foster increased collaboration between clinical and non-human primate scientists working on AIDS vaccine discovery. Integrating the non-human primate and clinical agenda is one of the field's top priorities. The program's strategy of targeting funds to early-stage investigators to engage them in this work should be evaluated over the long term by tracking the career paths of grant recipients. Because evaluating such a program can take time, in the near term its funding should remain in the NIAID AIDS vaccine budget. The model should also be investigated for other key areas.

For more information, visit *http://www.hvtn.org/science/esi.html*.

tribe of Native Americans in Arizona recently won a lawsuit brought against the University of Arizona after genetic samples from the community were mined for information that was beyond the scope of the research project the community had originally agreed to participate in.[4] Questions and controversies like this one are sure to arise again as new technologies or new questions are brought to bear on samples that may have been given for more narrowly specified research projects.

On the data-sharing front, there are emerging approaches in other arenas that could be considered by the AIDS vaccine field. For example, the National Academy of Science and others have started to design a "microbial research commons".[5] Its features include standardization of data and software, developments in "cloud computing" (internet-based computing that provides a platform for sharing software and other resources on demand) and governance of clearinghouses that facilitate wide sharing. A similar approach could be used to positive effect in the burgeoning field of HIV genomics as well as for the large sets of other immune function information being generated.

Develop clear, coordinated plans for data collection and analysis

The data from RV144, though tantalizing, did not establish a correlate of protection or a clear set of criteria for advancing candidates. No one knows which assays will measure the parameters that could turn out to be predictive of benefits. Assays specified at the outset of a protocol may be outmoded by the time the trial is over. Even with all of these caveats, the field can and must do better at developing clear, coordinated plans for sample collection and measurement and data analysis associated with clinical trials.

[4] Designing the Microbial Research Commons: An International Symposium. 2009 Oct 8-9. Available at URL: *http://sites.nationalacademies.org/PGA/brdi/PGA_050859*

[5] Harmon A. Indian Tribe Wins Fight to Limit Research of its DNA. *New York Times*. 2010 Apr 21. Available at URL: *http://www.nytimes.com/2010/04/22/us/22dna.html*

These could include newer assays for mucosal immunity, signatures of innate protection, cell-killing ability, avidity and other parameters of immune function. The most robust of these assays should be standardized across trial networks, in the way that Elispot for *gag* responses and neutralization assays were several years ago. As one investigator said, "If you don't believe in [the predictions of a competitor's] assay you won't say it's valid."

As the field works towards consensus, it should expand the conversation about the strengths and weaknesses of any given assay. Published studies typically have limited discussions of the variability of their assay methods even though they often acknowledge when their scope is limited by alternative biological models or assumptions.

The range of assays that can be conducted is limited by the quantity of samples collected from trial participants. Sample quantity is, in turn, limited by a range of factors including cost, consideration for participants and site collection capabilities.

There will always be limitations, but some of these can be avoided. RV144 is hampered by the small number of biological samples collected during the trial. The initial plans for blood draws were scaled back during the debate over whether the trial should happen at all. The consequences are still felt seven years after the trial started. Trials need to be sufficiently funded to collect the samples needed to optimize scientific discovery. Participants give time, energy, blood and tissue to studies, with the understanding that each trial will be able to answer the questions it has laid out—and to engage unexpected questions that may emerge when the trial is over. The next generation of trials must honor this expectation.

Maintain and expand mechanisms to engage and facilitate "smaller science"

IP and MTA agreements like the ones outlined above may fail to entice innovative participation from smaller entities that need revenue today—not 30 years from now. Private-sector involvement in AIDS vaccine development is still minimal—within and outside the main consortia—and the existing agreements may not be optimal for engaging smaller biotechs or scientists who are outside the mainstream of AIDS vaccine research. There need to be additional structures in place to nurture and facilitate such "smaller" science. These could include innovation grants and approaches to intellectual property that balance public and private benefit with expanded access to data and materials.

Ensure engagement of early-career investigators and explore a consortium specifically for this group

Access to data determines, and drives, careers. The consortia-based approach to data management and sharing assists young and early-career investigators who need to publish on experiments they have designed and led. Working within a consortium like CHAVI allows young investigators the opportunity to collaborate with more senior scientists outside of their primary institution and to access reagents and materials that might be difficult to obtain otherwise. However, the experiments conducted with these samples may be constrained by the goals of the consortium and/or the scope of the MTAs. Young investigators need access to the samples, reagents, and materials to advance their training, gain recognition and explore their ideas. (Mature investigators do too, but there's a particular urgency around this when it comes to fostering the next generation of scientists.) Since an effective vaccine is still decades away, the field needs to provide incentives for young scientists to make this their life's work.

KEEP THE BIG PICTURE IN FOCUS

If the Global HIV Vaccine Enterprise secretariat, or any other entity, takes on key tasks like developing a set of guidelines for sharing data and material, such guidelines are meaningful only if they are followed.

Big-science management and the work of hundreds of investigators and of thousands of participants have advanced our understanding of this virus in ways that could not have been predicted in 1981, when AIDS was first reported. The field requires adjusted ways to produce, control and disseminate the data and materials to finish the work finding an AIDS vaccine.

Sharing the Search for Clues: Step and RV144 post-trial analysis

A collaborative effort is swiftly being launched to understand the result of RV144. This effort is modeled directly on the approach taken to understanding the Step result. The Step trial team set up a committee of leading scientists who evaluated requests for samples and also made recommendations about which assays to carry out. After approval and completion of a materials transfer agreement, researchers who hadn't worked on the study had access to data and samples. Each researcher agreed not to share specimens or data, and publication and presentation of data were permitted subject to review by HVTN and Merck, the trial sponsors.

The consensus is that this committee-based approach granted data access to scientists affiliated with big-science consortia and those who were working more independently. With Step, 27 proposals were submitted, of which 19 were approved.

As *AVAC Report* went to press, more than 30 proposals for studies of RV144 samples had been approved. More than 20 institutions and 35 investigators will work on these studies, which were selected in a review process involving topic-specific working groups (humoral and innate immunity, T-cell immunity, host genetics and animal models) and a scientific steering committee, chaired by Barton Haynes of Duke University. To put these proposals into action, 26 MTAs had to be negotiated. These had to be fully compliant with pre-existing agreements between the Thai and US governments. While this process was complex and time consuming, more than 80 percent of the agreements were fully executed within two months. The MTAs were facilitated by the Walter Reed Army Institute for Research and the Henry M. Jackson Foundation for the Advancement of Military Medicine, a non-profit organization that supports the US Military HIV Research Program.

Both the Step and RV144 processes for post-trial analyses appear to be strong models for sharing trial samples and data with researchers not involved in the original trial. It will be important to evaluate these processes in more detail and look for areas that could be improved, such as the scope of researchers engaged in follow-up (in terms of institutional affiliation and area of expertise) and the degree to which sample availability was a limiting factor in approving proposals.

In conversations about Step data analyses, we were told that although scarcity of samples was not a factor in rejecting any proposals, it was a factor in modifying some of the proposals that were approved. However, there were additional samples from participants in other trials of MRK-Ad5, the vaccine tested in Step. There are no other trials of the ALVAC-AIDSVAX combination tested in RV144 so far, so the only available samples are those obtained during the trial—and any potential follow-up studies. When plans for RV144 developed, sample-collection plans were dramatically scaled back so that fewer blood draws were done on participants over the course of the study.

Scaling back sample collection can be a cost-saving measure in the near term. But initial savings can take a long-term toll on efforts to understand a trial result. This isn't an area where future trials should cut corners.

Data and Materials: Defining the terms

What are data and materials?

Two important US agencies (the National Institutes of Health and the Office of Management and Budget) define "data" as recorded information, regardless of the form or media on which it may be recorded, or as the recorded factual material commonly accepted in the scientific community as necessary to validate research findings.[6,7] Research data consist of a set of numbers or information resulting from measurements or analyses, or of materials such as chemical and biochemical molecules, cells or genetically modified organisms. In the case of genomics, data consist of trillions of bytes located on multiple computer servers that often are not connected to each other. Materials can refer to biological samples, usually blood and blood products or tissue, reagents or standard biological materials against which viruses or vaccines are tested and "progeny" materials that are derived, grown or made from source materials.

Who Owns or Controls Data and Materials?

Ownership of biomedical data and materials is like having title to a house or a car—if you own them legally, you alone control them, which includes having the right to share them with someone else freely, with conditions, or for payment. In biomedical research, responsibility and stewardship for the data and materials also settles on a number of other stakeholders who could be called "co-owners" in the sense that they have control over the data even if they do not hold the title for them. The difference between the legal possessors of data and the individuals or entities who have control over its management is not always clear. Legal distinctions regarding these different types of owners vary from country to country and may be negotiated by agreements specific to a trial or product. Possible "owners" with power to control, either fully (by permission or assignment) or because they assert ownership rights that others dispute, include:

- The funded grantee to conduct a trial, usually an institution, university, agency or group
- The party that creates or generates data, such as a principal investigator, a team, an individual or a company
- The study sponsor, joint parties such as two governments in RV144 or a sole sponsorship as with Merck in Step
- The supplier of test vaccines, such as Sanofi or VaxGen/Global Solutions for Infectious Diseases
- Funders who pay for all the work or make in-kind contributions such as the NIH, the Thai government, the military or philanthropic foundations
- Participants in a trial who give their samples to be used. Trial coordinators might recoil at the idea that participants may own their samples, the data or rights derived from them, but almost every trial requires an individual's release of those rights in consent forms. In some countries, such as Brazil, those rights are not transferred.

Why might access to data and materials be restricted?

Access to data and materials may be restricted, withheld or negotiated due to many considerations: best use of resources for science, commercial rewards from future patents, consequences of first publication and analysis of data, effects on individual careers, equity concerns between developed and developing countries or long-term benefits to affected populations. As one person we spoke to said, "People who hold data have an edge in competition."

[6] U.S. Department of Health & Human Services. NIH Grants Policy Statement. 2003 Dec 1. p. 114. Available at URL: *http://grants1.nih.gov/grants/policy/nihgps_2003/*
[7] Office of Management and Budget. Circular A-110. 19 Nov 1993. Further Amended 1999 Sep 30. Available at URL: *http://www.whitehouse.gov/omb/rewrite/circulars/a110/a110.html*

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In this Chapter:

- Explore adaptive trial design with curiosity and caution
- Make strategic choices about trial sequence, phase and size
- Create clear road maps for decisions and processes triggered by different levels of observed effect
- Follow the epidemic and select trial locations carefully

Trials and Trial Design

Where does prevention research go from here?

The question a trial asks affects the answer it provides. This simple statement has many ramifications when the questions being raised are hypotheses about new HIV prevention strategies.

Ask a relatively open-ended question—such as whether there is preliminary evidence of benefit—and the answer may be vague to the point of being indeterminate. That happened with the HPTN 035 microbicide trial that evaluated BufferGel and PRO 2000 and found a non-statistically significant trend towards effectiveness in the PRO 2000 arm. There was statistical significance in the Thai Prime-Boost trial (see p. 12)—but only in one analysis, and its wide confidence intervals have fueled an ongoing debate about whether the finding was "real" or what it may mean.

Ask whether an experimental candidate provides a relatively low level of protection, and you may get questions about whether the observed effect is "good enough" to warrant continued development. Both the Thai Prime-Boost vaccine trial and the MDP 301 microbicide trial of PRO 2000 were designed to detect as little as a 30 percent reduction in risk of HIV infection. Prior to announcement of either trial's results, there were discussions about what the next steps would be if this moderate level of protection were detected. These discussions were largely independent of each other and had different frames of reference derived from the inherent differences in the products, from historic differences between the AIDS vaccine and microbicide fields and from differences in planning around the specific trials.

Setting out to answer a question, and then discovering that you can't raises still other issues, particularly for the stakeholders who have supported your inquiry. That's what happened with the BOTUSA PrEP trial, which was designed as an effectiveness study but, after four years, announced at the end of 2009 that incidence and retention rates were too low for the trial to ever generate an answer about effectiveness in HIV prevention. It is now an expanded safety, acceptability and behavior study.

As these and other examples from HIV prevention research make clear, there are very few simple questions and no simple answers. And the questions are likely to get more complicated (and more interesting), whether they concern designing studies to probe initial findings from PrEP trials, exploring adaptive trial designs for evaluating vaccines and microbicides or developing combination prevention trials that look at multiple emerging strategies alongside the proven tool box.

One thing is clear: large clinical trials continue to be vital to guiding HIV prevention research.

For this article, we spoke with several key researchers about the ongoing and recently completed HIV prevention trials including iPrEx, FEM-PrEP, CAPRISA 004, VOICE and others (see table on p. 46 for more on these trials)—and about what the next set might look like. All were generous with their time and were frank, cautioning that in this rapidly evolving area, few perspectives, positions or plans are concrete.

Based on these interviews, ongoing discussions around trial design and other developments in the field, some of AVAC's key observations and recommendations are:

- Bring a range of trial design concepts, such as adaptive trial design, to the table—but be sure to weigh the risks and benefits in terms of feasibility, community buy-in, clarity of results, regulatory challenges and industry engagement.

- Continue taking risks in trial sequencing. There's proven value in launching trials that would confirm or elaborate on initial findings before those initial findings become available.
- Go into trials with a clear road map for what decisions and processes would be triggered by different levels of observed effect. This road map should be based on consensus discussions with key stakeholders in the international public health community and in the countries and communities where the trial is taking place.
- Build—and manage—clinical-trial capacity strategically, so that resources can be used optimally across the increasing range of research questions and designs.
- Be realistic about projections for recruitment, retention, incidence rates after enrollment, compliance with an intervention, and develop contingency plans for responding to shifts.

Explore adaptive trial design with curiosity and caution

In the wake of the RV144 trial results, there is an emerging call to consider adaptive trial designs to advance the HIV vaccine agenda (see Chapter One). This proposal is receiving a great deal of thought and attention from the HIV Vaccine Trials Network (HVTN).

Adaptive trial designs have advantages and potential for the vaccine field but also require a clinical research effort quite different from what the field has done to date (see p. 14 for an illustration of adaptive versus classical design).

Each of the many types of adaptive trial design allows for modifications in trial conduct during the course of the trial. These modifications are clearly specified in the trial protocol; as such, they are integral to the trial's design and do not compromise its scientific integrity. This approach allows researchers to respond to data collected in the trial as the trial is underway, such as by stopping arms that are not showing any benefit, enrolling more participants in arms that do show efficacy or increasing the size of the trial overall to strengthen confidence in a result.

Examples in the context of HIV vaccine trials might include designs that allow for shifts in vaccine regimen (such as adding an additional boost or dropping an arm) or decisions to expand a trial arm or move from Phase I to Phase II based on an early efficacy signal or validated correlate of protection (once available).

These adaptations would be based on data reviews at predetermined times. Similar to those conducted by a data safety and monitoring board (DSMB), these reviews would generally be much more frequent, consider a wider range of data and allow for more options than simply whether to stop or continue the trial (the only option typically available to a DSMB in reviewing trials with more traditional designs).

Even when automatically triggered by pre-determined criteria, these frequent data reviews may compromise some of the trial's statistical power. In a design that involves dropping trial arms, there always will be the risk of eliminating a product that would have demonstrated efficacy given sufficient time. Also, these trials can be complicated and difficult to design and implement, products need to be ready for testing at approximately the same time (although some approaches may allow for adding new arms to a trial already underway) and agreements among different product sponsors to allow products to be tested in the same trial are potentially complicated and difficult to negotiate.

Although the specifics of each adaptive trial would vary, in general more analyses of data could be required at each interim analysis. This means that clinical data need to be accessible in one place throughout the trial and analyzed in more depth much more frequently than for DSMB reviews. The research team needs to be able to take an accurate snapshot of the data to quickly inform interim decisions.

I am an advocate because...

When I share information about HIV prevention with people, they can evaluate with their own values what is the best option in their lives and how they can deal with HIV in their lives and relationships.

Gabriela Calazans, Community Educator, Unidade de Pesquisa de Vacinas Anti-HIV, Brazil

HVTN head Larry Corey has laid out the Network's vision for an approach to adaptive designs, including those that could follow up on the RV144 results. In this proposal, the trials would be designed in such a way that they would not provide sufficient data for licensure of a vaccine or vaccine regimen. Instead, such studies would more likely test variations on the prime-boost strategy, with the goal of identifying immunogenic combinations with initial signs of efficacy. Early data on immunogenicity and efficacy could be used to adapt the trial to provide even more information about how to optimize different aspects of the regimen. More specific details of the proposed trials are being worked out.

Although it's not clear whether the vaccine field will or should ultimately pursue this approach to following up on the RV144 findings, the approach warrants open examination and debate among a wide range of vaccine stakeholders (see Chapter One).

In theory, adaptive trial designs could also be used to test PrEP regimens and microbicide candidates. Such designs could provide an opportunity to test different products or formulations simultaneously. We have not spoken to any group that is actively considering an adaptive design for testing PrEP or microbicides. As one PrEP researcher noted, one type of adaptive design assumes that the trial will generate a clear signal of effectiveness among many different arms so that the research team feels confident about which arm or arms can be dropped. In his view, though, experience suggests that it may be difficult to obtain such clear early signals about effectiveness.

As proposals for adaptive trials move forward, it will be essential to clearly identify and explain their rationale, likely outcomes and next steps. Policy makers, funders and communities may be reluctant to support human trials that are unlikely to lead to a licensed product or clear benefit for participating countries and trial participants. Some long-time industry partners express real skepticism about these designs. These concerns, and their potential impact on industry engagement with AIDS vaccine research, must be taken extremely seriously.

Finally, new approaches to clinical trials will need to be justified to regulatory authorities, policy makers, communities and participants, not only on scientific grounds but in terms of what benefits they will and will not offer for trial communities and participants.

Make strategic choices about trial sequence, phase and size

Effectiveness, efficacy, proof-of-concept, Phase II, Phase IIb and Phase III. Over the past few years, HIV prevention research advocates have grappled on a daily basis with defining these terms and understanding how each type of trial can contribute to determining whether an intervention or technology is effective in reducing the risk of HIV acquisition.

Even basic statements like the assertion that Phase IIbs are smaller and provide faster answers than Phase IIIs don't hold up to close scrutiny. RV144 enrolled more than 16,000 participants and yet was designated a Phase IIb trial. Looking at trials currently in the field today, some that are designated Phase IIbs have more statistical power to generate a precise answer to the study question than some Phase IIIs. This runs counter to the common view that Phase IIbs generate early indications of benefit, which are confirmed in more precise Phase IIIs.

"One needs to not judge trials on their labels, i.e., Phase IIb or Phase III, as those are too vague," says Benoit Masse of the Statistical Center for HIV/AIDS Research and Prevention. "Rather one needs to look at the operational characteristics of the trial design and sample size of each trial."

Adaptive designs that seek to provide information on several products or regimens, allowing decisions about which ones to advance or abandon, need to be distinguished from other types of multi-arm trials. The Microbicide Trials Network's multi-arm VOICE study has been designed so that if one of the products being evaluated shows 58 percent or more effectiveness, that evidence could be used as the basis for pursuing licensure or a label change in the case of the oral PrEP agents. The first stage of a multi-arm adaptive trial wouldn't be designed to have the statistical power to support licensure or label change but could still yield valuable information to guide product development.

There is also ongoing discussion about the strength and type of evidence needed to advance a candidate from early to late-stage clinical trials. A related concern is when, if ever, it is appropriate to jump from small- or moderate-sized safety trials (Phase I) to a large efficacy trial.

These aren't easy questions, and most decisions will need to be based on the particular candidate.

Turning the Page: Innovation in prevention packages

While research into new prevention options continues, it is also critical to figure out how to better use existing and emerging new tools to meet the prevention needs of diverse communities. There's also still a great need for well designed studies of new "packages" of these strategies that seek to improve on current approaches.

One initiative on this front is the US National Institutes of Health's grants program called Methods for Prevention Packages Program (MP3). Launched in 2008, MP3 seeks to encourage collaborations between behavioral and biomedical scientists, epidemiologists, mathematical modelers and clinical trial designers. The multidisciplinary MP3 research programs are meant to:

- Develop optimal HIV prevention packages using combination interventions for specific populations;
- Conduct pilot studies to determine whether the new intervention could be evaluated in a clinical trial comparing it to a standard prevention package; and
- Design clinical protocols to rigorously examine the safety and efficacy of these packages

The initial pilot projects, and locations, awarded grants in 2008 are:

- *Prevention Umbrella for MSM in the Americas (PUMA) (Brazil, Peru, US)* is being developed for high-risk HIV-negative MSM in both North and South America, the population at greatest risk in both regions. In the approach, participants will be able to choose from a "menu" of options and services to tailor a prevention strategy to their individual needs.
- *HIV Prevention Packages for Injection Drug Users (Estonia)* is preparing a combination of individual interventions to reduce HIV infection among injection drug users (IDUs) in Tallinn, Estonia and to build community and policy support for HIV prevention in this population.
- *An HIV Prevention Package for Mochudi (Botswana)* will evaluate a combination of biomedical and behavioral interventions to reduce HIV incidence across an entire village.
- *Acute HIV Infection in Heterosexuals (Malawi)* will build on the technical capacity of CHAVI to identify acute infection and explore reducing HIV incidence through developing a prevention strategy combining behavior change counseling and treatment of acute infection.
- *Enhance Prevention in Couples (EPIC) (Lesotho)* will focus on couples who will be recruited through women at antenatal clinics.
- *PreventionRx (Uganda)* will use home-based voluntary counseling and testing and provide a prevention package in the home setting.

Availability and awarding of funding for clinical trials, which would compare the enhanced packages (piloted in the initial phase) to standard prevention services, will be determined based on the first phase. In addition, a second round of grants (MP3 II) is being reviewed in 2010, and they must emphasize new populations and new settings.

Several people interviewed underscored that debating which trial sequence is best is less important than the specific trial design, the number of endpoints and the corresponding statistical power to demonstrate an effect.

This makes it more important than ever that stakeholders work to establish a common language for describing trials of vaccines, microbicides and PrEP—and for explaining how each impacts the other.

Trial sponsors and product developers must also continue taking risks in trial sequencing. There's proven value in launching trials that would confirm or elaborate on initial findings from proof-of-concept *before* those initial findings become available.

HPTN 035 was designed as a Phase IIb proof-of-concept trial to determine whether BufferGel or PRO 2000 showed promise as a vaginal microbicide. For licensure, any finding would need to be replicated in a larger, more definitive trial, or possibly even two additional trials to meet the US FDA's requirement. The MDP trial of PRO 2000

I am an advocate because...

I help people see why the issue is an issue for them. I get them to believe in and share the cause, making it "our" issue. The difficulty is getting people to trust that you speak compassionately for them in a way that is transferrable and accountable. But they can see and feel it when it's there.

Morenike Ukpong, Coordinator, New HIV Vaccine and Microbicide Society, Nigeria

had greater statistical power and provided a more definitive, if disappointing, result.

On many levels, the sequence of HPTN 035 and MDP 301 worked beautifully. The first trial provided an initial finding, which, more than anything, raised the question of whether there was actual benefit. (Importantly, HPTN 035 also provided evidence that another candidate, BufferGel, was not effective in preventing acquisition of HIV or other STIs. A clear result about what doesn't work is also valuable.) MDP 301, which was already in progress, had greater statistical power to estimate the effectiveness of PRO 2000. Within nine months of the initial announcement of the HPTN 035 results, the MDP 301 data had provided a definitive answer.

In July, researchers will announce the results of CAPRISA 004, the Phase IIb trial of vaginal use of tenofovir gel. After that, the next example of data from a Phase IIb study will likely come from MTN 003, known as VOICE. This trial has been designed so that when 217 infections have occurred across the trial arms, it will have more than 90 percent power to detect a product that is at least 50 percent-effective. As with any efficacy or effectiveness trial, the point estimate of product effectiveness in VOICE will only be part of the story. When RV144 released its estimate of 31.2 percent efficacy among vaccine recipients (see box on p. 12) the resulting discussions about the wide confidence intervals surrounding this result led to confusion about whether the finding was or wasn't "real". These same conversations will continue to occur around any trial.

For the HIV prevention research field to continue and build on supportive alliances with civil society, policy makers and other non-scientists, everyone (including AVAC) will have to do an even better job of communicating these concepts and what they mean.

In the PrEP field, there currently seem to be few alternatives to conducting relatively large trials that consume much research capacity, time and financial resources. One researcher noted that the field is all too aware of the demands and risks of large trials, and somewhat defensive about what it means to launch a big efficacy trial, especially in the wake of prevention trials that have stopped early or not shown an effect. Everyone in the field is looking to conserve resources, move quickly and tie up as little of the available research capacity as possible. But to date, the field has not found a better way.

Create clear road maps for decisions and processes triggered by different levels of observed effect

When the RV144 team announced its results—a point estimate of roughly 30 percent efficacy with wide confidence intervals—they also stated that the vaccine regimen would not be further developed for widespread introduction and use. The trial team had agreed in advance what level of effectiveness would warrant further product development to move toward licensure. This clarity laid a foundation for subsequent discussions about next steps.

In contrast, the microbicide field was caught somewhat off guard in anticipating what to do and what to say if MDP 301 had shown PRO 2000 to be modestly effective. (The HPTN 035 data suggested a 30 percent reduction in risk.) Going into MDP 301, no clear effectiveness threshold had been set for taking the product forward. Key stakeholders held a range of views about whether a product with a relatively low level of effectiveness should be developed further, how to determine that, what the opportunity costs might be and who would decide. Some felt strongly that any safe and effective product—even one with a modest level of effectiveness—should be made available to women at risk. Others felt that introducing a 30 percent-effective product, given the difficulty of conveying partial efficacy to users and the potential for risk compensation, might be unethical or irresponsible.

The additional time and investment required, opportunity costs and uncertainty about delivery systems posed other challenges. There was agreement that advocates, community groups and potential users should be involved in decisions about next steps if MDP 301 did show evidence of protection, but there was little clarity around how these different constituencies should be engaged. All of this uncertainty was exacerbated by the fact that the company that developed PRO 2000 had recently been bought, leaving the product without a clear industry champion to drive it forward. Although all this became moot when the MDP trial showed a flat result, it did underscore the importance of establishing clear and transparent decision points and processes for determining what steps may follow trials.

Each trial needs to have some form of a road map that defines the next steps based on different levels of efficacy or effectiveness. Given the long time frame to plan and implement clinical trials, these plans and scenarios will need the flexibility to respond to changes in the epidemic; emergence of other HIV prevention technologies; shifts in funding for HIV prevention, treatment and research; and other developments. However, mapping out and publicizing scenarios and contingency plans can still provide some degree of clarity about options for next steps.

Sticking to It: Keeping up with the challenges of adherence

HIV prevention trials continue to face ongoing challenges with maximizing and measuring adherence to product use (whether the trial participant uses the test product such as a vaginal gel or an oral tablet as directed). This is a critical dimension of measuring product effectiveness and interpreting trial results. Because a trial team can know for certain whether a man has been circumcised, or whether all doses of a vaccine regimen have been administered, adherence challenges have generally been associated with user-controlled technologies like microbicides and PrEP.

Adherence is usually associated with trial participants' forgetting or choosing not to follow protocol. Trials continue to experiment with approaches to maximizing, managing and measuring adherence. Relatively simple steps can help prospective participants understand what the study intervention entails in a concrete rather than hypothetical way. These include having potential participants insert a ring or gel (for microbicide trials) or swallow a vitamin tablet (for a PrEP trial) prior to enrollment. This can help ensure that those who do agree to participate in the trial have some sense of what will be required.

The CAPRISA 004 trial of tenofovir gel requires participants to practice using the microbicide in the clinic as part of the screening procedures. The trial is also employing a tailored approach to counseling and support to remind and help individual participants to use the gel consistently and correctly and to report their gel use accurately. The International Partnership for Microbicides is experimenting with "directly observed application", a variation on directly observed therapy used in treatment. This approach uses a variety of techniques, including text messages, to help participants track and report their product use in real time rather than using often unreliable recall methods. Designing different technologies or delivery systems is another way to improve adherence. Vaginal rings, which can be inserted and remain in the vagina for a month without needing replacement, may also mitigate some of the challenges of product use and adherence, as may longer lasting or time-release drugs.

In some trials, these adherence issues may relate less to participant behavior—not remembering to use the product or finding it difficult to use or negotiate at the time of sex—than to the actual requirements of the trial protocol. For example, researchers in the iPrEx PrEP trial report that one of the main barriers to adherence is the monthly follow-up visits required by the protocol. Resupply of the study drug or placebo requires a negative HIV test, and study participants who cannot get to the clinic at the same time monthly may run out of the study drug.

Looking forward, it will be critical to use lessons from iPrEx and other studies to continue and expand efforts to measure and address adherence in trials and the implications for eventual product introduction.

Ongoing ARV-based Prevention Trials *(as of June 2010)*

Study Study phase	Location	Sponsor Funder	Population (*mode of exposure*)	Intervention arm(s)	Status / Results expected
US Extended Safety Trial (CDC 4323) Phase II, safety	US	CDC	400 gay men and other men who have sex with men (*penile/rectal*)	Daily oral TDF	Completed / Q3 2010
iPrEx Phase III, safety & effectiveness	Brazil, Ecuador, Peru, South Africa, Thailand, US	NIH, BMGF	2,499 gay men and other men who have sex with men (*penile/rectal)*	Daily oral TDF/FTC	Fully enrolled / Q1 2011
Bangkok Tenofovir Study (CDC 4370) Phase II/III, safety and effectiveness	Thailand	CDC	2,400 injecting drug users (*parenteral*)	Daily oral TDF	Enrolling / Q1 2011
TDF2 (CDC 4940) Phase II, safety & adherence	Botswana	CDC	1,200 heterosexual men and women *(penile and vaginal)*	Daily oral TDF/FTC; *switched from TDF Q1 2007*	Fully enrolled / Q4 2010
Partners PrEP Phase III, safety & effectiveness	Kenya, Uganda	BMGF	4,700 serodiscordant heterosexual couples (*penile and vaginal*)	Daily oral TDF; daily oral TDF/FTC	Enrolling / 2012
FEM-PrEP Phase III, safety & effectiveness	Kenya, Malawi, South Africa, Tanzania	FHI, USAID, BMGF	3,900 heterosexual women *(vaginal)*	Daily oral TDF/FTC	Enrolling / 2013
VOICE (MTN 003) Phase IIb, safety & effectiveness	Malawi, South Africa, Uganda, Zimbabwe	MTN, NIH	5,000 heterosexual women (*vaginal)*	Daily oral TDF; daily oral TDF/FTC; daily topical tenofovir gel	Enrolling / 2013
IAVI E001 & E002 Phase I/II, safety, acceptability, adherence	Kenya, Uganda	IAVI	150 serodiscordant couples and men and women *(vaginal and penile/rectal)*	Daily oral TDF/FTC; intermittent oral TDF/FTC (twice weekly + coital dosing)	Fully enrolled / Q4 2010
PrEP in YMSM (ATN 082) Phase II, safety, acceptability, feasibility	US	ATN, NICHD	99 young men who have sex with men *(penile/rectal)*	Daily oral TDF/FTC	Enrolling / 2011
CAPRISA 004 Phase II, safety & effectiveness	South Africa	CAPRISA, FHI, CONRAD, USAID, LIFElab	900 heterosexual women *(vaginal)*	Coitally dependent topical tenofovir gel	Completed / Q3 2010
PrEP Using TMC278LA Phase I/II, safety & pharmacokinetics	United Kingdom	St. Stephens AIDS Trust	100 men and women (*vaginal and penile/rectal*)	TMC278LA injected intramuscularly	Enrolling / 2011
IPM 015 Phase I/II, safety & acceptability	South Africa; additional African sites to be added	IPM	280 heterosexual women *(vaginal)*	Vaginal silicone ring releasing dapivirine over 28 days	Enrolling / 2011

ATN – Adolescent Trial Network; BMGF – Bill & Melinda Gates Foundation; CAPRISA – Centre for the AIDS Programme of Research in South Africa; CDC – US Centers for Disease Control and Prevention; FTC – emtricitabine; IAVI – International AIDS Vaccine Initiative; IPM – International Partnership for Microbicides; MTN – Microbicide Trials Network; NICHD – National Institute of Child Health and Human Development; NIH – US National Institutes of Health; Q1-4 – quarters 1-4; TDF – tenofovir disoproxil fumarate; US – United States; USAID – United States Agency for International Development

Follow the epidemic and select trial locations carefully

In the face of a rapidly changing epidemic, including treatment programs that may reduce infectiousness, incidence is continually shifting. As seen in the Botswana PrEP trial (TDF2) and a number of other trials, lower-than-anticipated incidence in a trial population can mean that a trial may not have enough endpoints to adequately assess effectiveness. In today's economic climate, the field can ill afford to repeat the TDF2 scenario, in which the trial ran for several years before determining that it would not be able to answer its original question. Ongoing monitoring of endpoints and adjustment must be built into every trial, along with the opportunity to stop a trial early for futility.

Several people mentioned that planning for clinical research needs to continue to follow the epidemic and that it is important to closely track emerging epidemics in Eastern Europe and other settings for potential trial sites.

As described in Chapter One, the vaccine field will need to make carefully considered choices about where follow up studies building on the RV144 result should take place.

WHAT'S NEXT?

In the coming months, the HIV prevention field will find out the results from the first two completed effectiveness trials of ARV-based products for HIV prevention. The CAPRISA team expects to release results of the CAPRISA 004 microbicide trial of tenofovir gel at the International AIDS Conference in Vienna in July 2010. Results from the iPrEx trial of daily use of oral TDF/FTC to reduce the risk of HIV infection among MSM should be available in early 2011.

What will happen after CAPRISA 004 and iPrEx results are released? The prevention field will need to respond rapidly and thoughtfully. A different dosing schedule of tenofovir gel is being tested in VOICE (daily gel use in VOICE vs. before and after sex in the CAPRISA trial). The results of the CAPRISA 004 study will need to be carefully studied to determine any implications for the VOICE trial and/or further research on tenofir gel, as well as research directions suggested for other ARV-based topical microbicides or oral PrEP.

The iPrEx study is one of a suite of PrEP trials underway among different populations, with different drugs and protocols, that are expected to release results over the next several years. One researcher described the PrEP field as akin to planes stacked up waiting to land in an airport. If the evidence all points in one direction, the field will look "like geniuses," as the researcher stated. However, if the results differ among populations, it will be much more difficult, perhaps impossible, to tease out the factors responsible—the trial population, the trial itself, the route of exposure, the drug or dosing schedule, some combination of these, or other unknown or unpredicted factors. And many questions remain—for example, whether PrEP is safe and effective during pregnancy, which populations to prioritize in initial introduction and how PrEP could be provided in clinical settings that do not have all the resources of a trial. Many of these questions will require additional focused human trials or operations research, whereas others will be best answered using a combination of animal and human data. Mapping out next steps and priority setting is ongoing within the PrEP field and will need to accelerate with the trial results.

HIV prevention trials have always presented challenges in design and implementation. Despite these challenges and much skepticism about whether people would enroll and remain in trials, the HIV prevention field has conducted more than 40 randomized controlled effectiveness or efficacy studies with tens of thousands of participants in more than 20 countries. There have been real victories, particularly of prevention of vertical transmission and medical male circumcision for prevention. As the epidemic, science and products continue to evolve, the field needs to critically examine and experiment with new approaches to clinical testing, build on its successes, and identify and prioritize the next questions to make any promising products available as rapidly and responsibly as possible.

ARV-based Prevention Update

While the implications, lessons, and next steps from the surprising results of the RV144 trial dominate *AVAC Report 2010*, we also follow closely the search for other biomedical HIV prevention approaches. The main approaches described here—pre-exposure prophylaxis, microbicides and treatment as prevention (also called "test and treat")—are all based on antiretroviral drugs (ARVs). Using ARVs for anything other than treatment for people with HIV for whom it is medically necessary raises new issues: How would programs to deliver ARVs to HIV-negative people be designed? How would programs that sought to treat everyone diagnosed with HIV, regardless of clinical disease stage, be structured and sustained—especially given the current funding crisis facing AIDS worldwide? How might these programs relate to and, ideally, strengthen other prevention services?

We have summarized the status of some of the key issues for each of these ARV-based prevention approaches under development.

Pre-Exposure Prophylaxis (PrEP)

PrEP clinical trials are moving forward among diverse populations in a range of settings (see table p. 46). Their results are anticipated over the next several years. The first trial to study effectiveness, the iPrEx study of daily use of the combination tenofovir and emtracitibine (FTC) (also known commercially as Truvada) among MSM in six countries, is expected to report its results early in 2011.

All the effectiveness trials currently underway are testing tenofovir alone or in combination with FTC, both nucleoside reverse transcriptase inhibitor (NRTI) drugs widely used in HIV treatment. As NRTIs, especially tenofovir, become more common as first-line therapy for HIV-positive people, there is growing concern about the implications of using these same medications for prevention. In consultations in Kenya and Uganda, civil society groups have raised concerns that financial resources might be diverted from treatment programs for HIV-positive people to those aimed at prevention in HIV-negative people. There are also concerns that drugs themselves would be redirected to PrEP programs and/or that drug-sharing between HIV-positive and HIV-negative people might increase. There are also concerns about the emergence of resistance, which could occur in settings where people continued taking PrEP after becoming HIV infected, effectively using suboptimal treatment for their virus. These issues have been raised in various national and global consultations and will need to be monitored as part of any piloting or roll out of PrEP should the strategy show a benefit.

The PrEP field is also beginning to explore other drugs and classes of drugs. AVAC and other groups have stepped up advocacy to accelerate the expansion of the pipeline, with discussions of what an ideal PrEP product profile would look like and conversations with industry partners about existing drugs that might be developed to meet some or all of these criteria. This work should be expanded to include a wider range of stakeholders and scientists from industry as well as members of the public-health community. AVAC is preparing a background report on this topic for release later in 2010.

Microbicides

All of the microbicide candidates currently in clinical development contain antiretrovirals. As with PrEP,

all of the candidates in human trials contain reverse transcriptase inhibitors. The first effectiveness results from an ARV-based microbicide candidate will come in July 2010 with the release of results from the CAPRISA 004 study of tenofovir gel. Another large-scale trial, known as the VOICE study, is evaluating tenofovir gel alongside oral PrEP (both TDF alone and TDF/FTC). Results from VOICE are expected in 2013.

Other compounds are also being examined. Furthest along are the non-nucleoside reverse transcriptase inhibitors (NNRTIs) dapivirine and UC781, which are in Phase I safety trials. Other antiretroviral-based microbicide candidates include maraviroc, a CCR5 inhibitor. Looking at the preclinical pipeline, there are a range of candidates with different mechanisms of action. These are well-described in the recent report *Microbicides: The Way Forward* (available at *www.avac.org*), which argues for accelerating the development and management of a more robust and diverse pipeline.

In addition, rectal microbicide research has begun to accelerate in recent years, leading to several laboratory and animal studies. While initial studies on clinical safety and dosing have also been completed, there are now finally discussions to expand rectal microbicide research into actual product development activities.

Treatment as Prevention

Treatment as prevention is a term describing the use of antiretroviral drugs that are used to reduce the risk of HIV-positive individuals transmitting HIV to others. The strategy would function as a secondary benefit of antiretroviral treatment after its primary purpose of improving an individual's health. One approach to treatment as prevention is "test and treat", which proposes a shift from current approaches to treatment initiation, combined with significantly expanded HIV testing programs. In the test and treat paradigm people would be started on ARVs when they were diagnosed, regardless of their clinical stage of HIV disease. This would lower an individual's infectiousness. If coverage of test and treat-type strategies were high enough, there might be a population-wide effect on rates of new infections. There are different models for how high levels of HIV testing would need to be to achieve such an effect—and one of the critical tasks for the immediate future is to move beyond models to real world evaluation of the strategy.

HPTN 052 is a Phase III randomized trial to study transmission with and without early treatment in serodiscordant couples in Africa, Asia and South America. HPTN 065, also called TLC+, is a new study that will assess the feasibility of a program of enhanced HIV testing and its linkages to care and treatment in two sites in New York and Washington. These trials and associated operations research will begin to provide scientific underpinnings to ongoing debates about whether such an approach is realistic and what its long-term impact as a prevention strategy might be.

For updates on the full range of prevention research, please visit ***www.avac.org/byoption***

Speak with one voice, work towards one goal

The global response to AIDS is in trouble. Today, there are various proposals to use antiretrovirals for HIV prevention. But while the world is debating possibilities like "test and treat", TLC+ (testing with linkage to care plus) and PrEP, there's a looming crisis in existing AIDS treatment programs. New prevention programs can't be built while current treatment programs are faltering.

The goal remains the same: universal access to health care, which includes comprehensive AIDS treatment and prevention. To get there, prevention and treatment advocates need a shared platform of demands and priorities. Rather than talking about PrEP in one forum and AIDS treatment waiting lists in another, we need to bring these threads into a single conversation and agenda for action, more than they ever have been before.

Frontlines of the fight for universal access. From left to right: A crowd waits at an AIDS clinic in Tanzania; a member of the iPrEx PrEP trial team conducts AIDS education with transsexuals in Peru; South African activists rally for access to care. *[Photos courtesy of US Military HIV Research Program, Asociacion Civil Selva Amazonica, Gideon Mendel]*

SUSTAIN AND EXPAND CURRENT TREATMENT AND CARE PROGRAMS

There has been slow but heartening progress in expanding access to antiretrovirals and other forms of treatment and care for people living with HIV in the developing world. These gains are now imperiled in ways that should cause alarm to even the most cynical observers of global health funding cycles. HIV-specific commitments are being questioned; PEPFAR programs are being instructed to cap the number of patients started on ARVs; and the Global Fund to Fight AIDS, Tuberculosis and Malaria is restricting its Round 10 grants to funds raised by the end of 2011. These developments are starting to take a damaging toll at the precise moment that data are emerging to show that ARV treatment prevents deaths, lowers health care costs and can reduce the risk of HIV transmission between sexual partners.

These are some of the critical steps needed to forestall additional damage: donors must fully fund the Global Fund; PEPFAR must honor its stated commitments to achieving universal access to treatment and care; developing country governments must make the health of their citizens a top priority; UNITAID must remain on track with the launch of the Medicines Patent Pool

continued on next page >

The Global AIDS Response: Five Current Myths Versus Current Realities*

MYTHS	REALITIES
Too much money is being spent on AIDS	Funding for AIDS is billions of dollars short of what is needed[1] • Needed in 2010: $25.1 billion • Invested in 2008: $13.7 billion • Funding gap for 2010: $11.4 billion—assuming the world maintains its pre-economic-crisis commitment to AIDS.
Money spent on AIDS is at the expense of other health needs or investment in health systems	The total amount of development assistance for health quadrupled from $5.6 billion in 1990 to $21.8 billion in 2007[2]—much of this catalyzed by the increased funding and commitments to HIV/AIDS. Although the Global Fund and PEPFAR are among the largest global AIDS funders, they are also some of the biggest investors in health systems, with 35%[3] and 32%[4] of their respective funding devoted specifically to health systems strengthening.
Strengthening health systems alone will help address health problems including AIDS	Strong health systems alone do not guarantee equitable and universal health care. Past public health approaches failed to reach the most marginalized—women, MSM, sex workers, IDUs, the very poor and those living in rural areas. Health systems need both breadth and focus.
Prevention is more important than treatment	Activists never pit prevention and treatment against each other—on the ground they work together. Treatment can enable more effective prevention by reducing transmission and encouraging testing and prevention makes treatment affordable.
AIDS has been addressed unlike maternal health or other diseases	The AIDS crisis is not over. AIDS activists have been the most effective advocates for health in history. The energy and passion of AIDS activists can be used to build stronger health systems and tackle maternal and child health—since all these issues are interlinked in the first place. Let's stop pitting disease against disease.

*Adapted from International Treatment Preparedness Coalition Missing the Target 8 (2010) *www.itpc.org*

[1] UNAIDS. What countries need: Investments needed for 2010 targets. February 2009. Available at URL: *data.unaids.org/pub/Report/2009/jc1681_what_countries_need_en.pdf*

[2] Ravishankar N, et al. Financing of global health: Tracking development assistance for health from 1990 to 2007. *Lancet*. 2009;373:2113–24.

[3] The Global Fund to Fight AIDS, Tuberculosis, and Malaria. Scaling up for impact results report. 2007;1–112. Available at URL: *www.theglobalfund.org/documents/publications/progressreports/ProgressReport2008_en.pdf*.

[4] Piot P, et al, AIDS: Lessons learnt and myths dispelled. *Lancet*. 2009;374:260–63.

Foundation; and the US Congress must pass The Global HEALTH Act of 2010 (H.R. 4933), which encompasses the wide range of global health issues—HIV and AIDS; maternal, newborn and child health; sexual and reproductive health; TB, malaria and neglected tropical diseases—and seeks to ensure access to a comprehensive package of primary health services.

ACTIVELY EXPLORE TREATMENT AS PREVENTION

There is compelling evidence that earlier initiation of antiretrovirals in HIV-positive people can reduce the risk that they will infect sexual partners with HIV. Additional data on this will come from an ongoing randomized clinical trial, but the world should not wait to begin exploring the practical approaches and implications of scaling up HIV treatment as prevention. WHO/UNAIDS should work with countries to assess the potential impact of test and treat and PrEP, developing context-specific cost-effectiveness and impact modeling projects, as well as pilot projects. Civil society groups, advocates and networks of groups representing people living with AIDS should undertake consensus building work on treatment as prevention to identify their positions, questions and concerns regarding these strategies. Research sites should develop and disseminate site- and trial-related work on best practices for couples counseling and care and treatment; services for gay men and other men who have sex with men; and adherence support; and other aspects of comprehensive care. They should also contribute to efforts to gather detailed information on local behavior to incorporate into models of HIV transmission. These can help guide policy makers' decision-making about potential introduction of treatment as prevention when the data become available.

PLAN FOR PREP

ARV-based prevention—through oral PrEP or topical microbicides—isn't proven to have benefit. But, if it does, it will need to be delivered strategically, in programs that provide clear, integrated messages about the risks and benefits of ARVs for prevention in HIV-negative people. The next 12 months will bring a range of announcements from ARV-based microbicide and oral PrEP trials, and the field needs to be prepared to address the many questions that will emerge from these results. PrEP stakeholders must continue to expand multi-stakeholder work to develop national agendas and road maps for decisions around low-, moderate- or no-effect findings from current effectiveness trials. Industry and academia need to support an expanded pipeline beyond the two drugs in current late-stage clinical trials. Funders need to ensure funding—and a clear decision-making process to maximize what's learned from ongoing trials and sufficiently fund the burgeoning and essential intermittent PrEP agenda.

BE READY TO BE SURPRISED

The greatest advances in the fight against AIDS have come about because people and institutions refused to accept conventional wisdom about what was possible. There was a time in the all-too-recent past when AIDS treatment programs were deemed unfeasible in developing countries. There have been many moments when an AIDS vaccine that prevented infection was deemed a scientific impossibility.

And yet, AIDS treatment programs and their clients have flourished in every possible context around the globe.

And yet, a trial that had been all but discounted by many critics provided evidence that a preventive AIDS vaccine is possible.

Today, as always, there are instances of actions against AIDS that seem impossible but are, in fact, essential. The moment when treatment programs are struggling to meet existing demand could be the precise instant when countries should begin actively seeking to evaluate the possibility and feasibility of treatment as prevention, alongside planning for possible PrEP rollout. At a time when research funding is slowing down, it may seem overly ambitious to develop a streamlined scientific agenda that chases the leads from vaccine and microbicide trials while simultaneously seeking novel strategies. But that is exactly what must happen.

The global community of advocates for HIV prevention, treatment, research and implementation must continue to expect and demand an extraordinary response to this unprecedented epidemic—it is our only hope of closing the book on AIDS.

Global Partners in Prevention Research Advocacy

AVAC was founded nearly 15 years ago as the AIDS Vaccine Advocacy Coalition. Over that time, our mission has broadened to work on the full range of biomedical prevention strategies under investigation—including vaccines, PrEP, microbicides, male circumcision and more. We now go by *AVAC: Global Advocacy for HIV Prevention*. One thing that hasn't changed is our commitment to working in partnership with other groups. We have long-standing relationships with the African Microbicide Advocacy Group, the African AIDS Vaccine Programme, the ATHENA

Good Participatory Practice Partners

In November 2007, UNAIDS and AVAC published "Good Participatory Practice (GPP) Guidelines for Biomedical HIV Prevention Trials", which were created to set global standards in stakeholder engagement for biomedical HIV prevention trials. The guidelines provide trial funders, sponsors and implementers with systematic guidance on how to effectively engage with all stakeholders in the design and conduct of biomedical HIV prevention trials. Since 2008, AVAC has supported specific stakeholder groups—our GPP Partners—in Africa, the Americas, Asia and Europe in a process of reviewing and providing critical feedback on the guidelines. A participatory approach was used to design the consultations, which included focus group discussions, interviews, surveys, workshops and consultative meetings.

HIV Prevention Research Advocacy Fellowship Program

The HIV Prevention Research Advocacy Fellowship Program provides support to emerging and mid-career advocates to implement projects related to biomedical HIV prevention research activities in their countries and communities. The program is designed to expand the capacity of civil society advocates and their host organizations to monitor, support and help shape biomedical HIV prevention research worldwide. The Advocacy Fellowship is guided by the belief that effective, sustainable advocacy grows out of work that reflects organizational and individual interests and priorities.

Prevention Research, Outreach, Advocacy and Representation (PxROAR)

The Prevention Research, Outreach, Advocacy and Representation (PxROAR) program is one of AVAC's United States-based programs. The program centers on a small group of advocates working in communities around the US that are hard-hit by HIV. The program is designed to educate its members about HIV prevention research science and advocacy strategies and provide a platform for specific prevention research advocacy campaigns.

Women's HIV Prevention Tracking Project (WHiPT)

WHiPT is a collaboration between AVAC and the ATHENA Network, which supports women's community-based efforts to monitor, evaluate and develop or expand advocacy around new and emerging HIV prevention strategies. WHiPT provides support for teams working on specific issues within a local or national context. There are currently five WHiPT teams in southern and eastern Africa receiving support for pilot projects to monitor the introduction of male circumcision for HIV prevention and its implications for women.

Network, the Global Campaign for Microbicides, UNAIDS, various product-development partnerships and research networks and other international and national groups.

Equally important, we are committed to context-specific work in the countries and communities where HIV prevention research is happening. The programs noted here represent some of the ways we strive to achieve this goal. For more information on AVAC's program and partners visit *www.avac.org/programs*.

AVAC: GLOBAL ADVOCACY FOR HIV PREVENTION

Founded in 1995 as the AIDS Vaccine Advocacy Coalition, AVAC is an international non-profit organization that uses education, policy analysis, advocacy and community mobilization to accelerate the ethical development and eventual global delivery of AIDS vaccines and other new HIV prevention options as part of a comprehensive response to the pandemic.

AVAC is dedicated to:

- Translating complex scientific ideas to communities and translating community needs and perceptions to the scientific community.
- Managing expectations about the process of product research and development, testing and delivery.
- Holding agencies accountable for accelerating ethical research, development and delivery of HIV prevention options.
- Expanding international partnerships to ensure local relevance and a global movement.
- Ensuring that policy and advocacy are based on evidence.
- Building coalitions, partnerships, working groups and think tanks for specific issues.
- Developing and widely disseminating high-quality, user-friendly materials.

AVAC focuses in four priority areas:

- Develop and advocate for policy options to facilitate the expeditious and ethical development, introduction and use of AIDS vaccines and other HIV prevention options.
- 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.
- Monitor the HIV prevention research and development and mobilize political, financial and community support for sustained research as part of a comprehensive response.
- 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 *AVAC Report*, which analyzes progress in the field and makes recommendations for actions in the coming year, AVAC publishes *Px Wire*, a quarterly update on HIV prevention research, as well as a series on anticipating and understanding research results. We also manage the Advocates' Network, an electronic network for organizations and individuals interested and involved in AIDS vaccine and HIV prevention research advocacy.

The AVAC website contains these publications as well as comprehensive coverage of the full range of biomedical HIV prevention interventions in an easy-to-use format that is searchable by intervention and by topic like policy, ethics and community involvement in research. The site is designed to be a central hub of information for the complex array of challenging and exciting issues facing HIV prevention research stakeholders today.

AVAC's continuous policy analysis, advocacy, education and outreach work are made possible by the dedicated labor of AVAC advocates and support from the Bill & Melinda Gates Foundation, the Blum-Kovler Foundation, Broadway Cares/Equity Fights AIDS, the Ford Foundation, the International AIDS Vaccine Initiative, the International Partnership for Microbicides, UNAIDS, the Until There's a Cure Foundation, WHO and many generous individuals who have become AVAC Members.

For more information on AVAC's work and how to support it, please visit *www.avac.org*.

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Advocacy to accelerate ethical research and global delivery of AIDS vaccines and other HIV prevention options

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