WHAT'S (Y)OUR POSITION?

Where we stand in the post-STEP era

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It's now been nearly nine months since the public announcement of the failure of MRK-Ad5, the AIDS vaccine candidate that had generated the most consistent enthusiasm throughout the field in recent years. Overall, the candidate neither prevented infection nor lowered viral setpoint, and in some individuals, receiving the vaccine was associated with an increased risk of acquiring HIV.

In the weeks and months that have followed, the phrase "more questions than answers" has all but worn out its welcome. There are, for the moment, more questions than answers about the cause of the apparent increase in susceptibility to HIV in some volunteers. There have also been more questions than answers about the best way for the field to move forward scientifically in the wake of this setback.

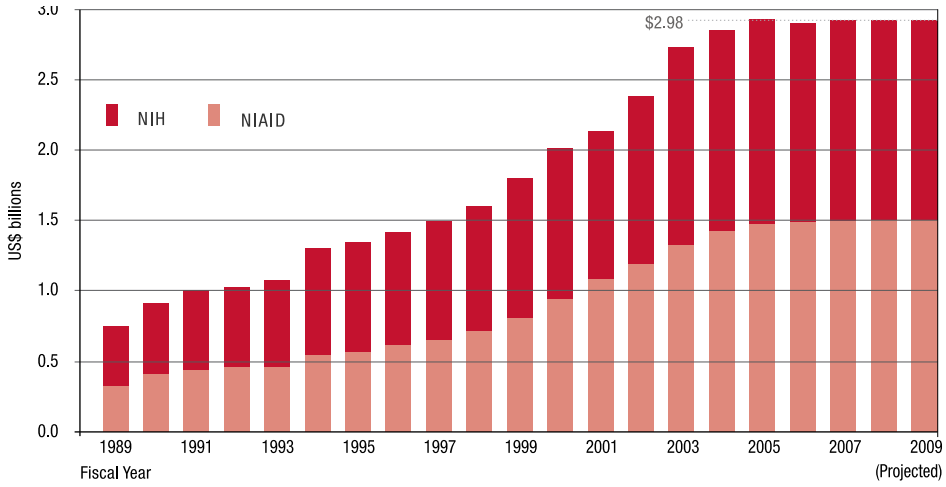
Some critics and provocateurs have used this opportunity to offer definitive answers to some tough questions, like "Is an AIDS vaccine even possible?" At the annual Conference on Retroviruses and Opportunistic Infections, Harvard's Ron Desrosiers raised many of the scientific issues hindering development of an AIDS vaccine. He also raised a few hackles when he flashed a slide that read "Has the NIH lost its way?" and then said that, in his opinion, the answer was "Yes." Everyone has—and is entitled to—an opinion. But the reality is that no one has the roadmap that will guarantee a vaccine; no one can say for certain that he or she knows the way. With that caveat, it's time to tackle some of the tough questions head on and to come up with workable answers to use as the basis for the next steps forward.

In this section, we present some of the questions and our answers. In doing so, we stress that as much as our view is informed by input from civil society around the world, we remain a US-based organization and neither claim nor want to be the only civil society voice weighing in on these critical issues. That's one reason for this article's title: we're also interested in hearing *your* position.

1) Is it time to step back from more clinical trials and instead focus on basic scientific challenges?

No. Both are essential and each informs the other. Clinical trials in humans can answer key scientific questions. These include "discovery" trials, which are not part of a product development pathway that's designed to get a candidate to licensure, and clinical trials of vaccine candidates that look safe and potentially effective based on pre-clinical studies. By choosing the best available candidates and testing them in well-designed and ethical clinical trials, we gain incremental but important insights. Discovery studies that do not test products can build out knowledge on areas like: What is the mechanism of protection of licensed vaccines? What are the characteristics of vector-specific immunity? What are the characteristics of mucosal versus systemic immune responses

Figure 3 THE ERA OF FLAT FUNDING: NIH AND NIAID AIDS RESEARCH FUNDING FY 1989-2009



Source: NIAID (http://www3.niaid.nih.gov/news/events/meetings/HIV_Vaccine_Summit.pdf)

induced by different candidates or vaccine components (vectors, immunogens, etc.)? What are the characteristics of different immunogens *in vivo*? What insert designs are best at eliciting broad responses?

The field must also continue conducting AIDS vaccine research in humans. This means developing an agenda for human discovery trials. It also means heeding calls for more stringent criteria for advancing candidates into and through human clinical trials. However, even with concerted efforts to standardize and expand the range of assays used to evaluate candidates, there's still no way of predicting with certainty what level of protection will be provided to humans. In the absence of a correlate of protection, this will always be the case. This is one reason why human clinical trials are essential.

It's also important to remember that the data looking at potential correlates of immune response and control of viral load in the STEP trial are just beginning to emerge. While it is clear that MRK-Ad5 was not an effective vaccine, data from the trial may provide clues about the types of immune responses associated with better control of viral setpoint.

Instead of debating whether clinical trials have a role in AIDS vaccine discovery, there should be an ongoing discussion geared towards the question "What's the suite of studies that's needed, at this time, to help guide development of better vaccine candidates?" There may not be one answer that fits the agendas of all the different players in the field—and that diversity of views is a good thing. But all trials, including the proposed PAVE 100 trial efficacy of a DNA-Ad5 combination (see page 28) must be considered in light of this question.

Some movement on this front is already underway. The HIV Vaccine Trials Network (HVTN) is developing a fleet of discovery trials that its leader, Larry Corey, described to AVAC as geared towards

"filling out [our understanding] of the immunological space" in which vaccines work. This means looking at vector-specific immunity and tissue-specific responses in the mucosa, and at which antigens are optimal for which types of immune responses.

Recent meetings, like the National Institute of Allergy and Infectious Disease vaccine summit in March 2008, have also zeroed in on the criteria for advancing candidates into human trials. In order to more clearly define these criteria, work must be done to standardize some of the newer assays, like the viral suppression assay (which measures the ability of vaccine-induced T cells to inhibit HIV replication by killing HIV-infected cells *in vitro*) that has been developed by Otto Yang (University of California, Los Angeles) and taken on by IAVI, HVTN and others. More also needs to be done to define and understand the significance of polyfunctionality. (As discussed on page 55, there are multiple ways to define polyfunctionality. Studies in HIV-positive elite and viremic controllers have found that these individuals have more T cells that produce multiple types of substances, such as IL-2, interferon gamma, TNF-alpha and others, compared with HIV-positive people with more traditional rates of disease progression.)

Recommendation: Develop institution-specific and field-wide agendas to address the question of which key discovery studies that should go forward in humans. NIH, Europrise, IAVI, the Bill & Melinda Gates Foundation, and others should all look at their portfolios in light of this question, and should develop and share plans in a process that could be convened by the Global HIV Vaccine Enterprise. Plans may change and ideas may vary. The need isn't for a homogenized approach but for one that is flexible, comprehensive, and supported by work from all stakeholders. This could also set in motion the process of standardizing some of the newer assays.

2) Is the National Institute of Allergy and Infectious Diseases (NIAID) spending its AIDS-vaccine related funds appropriately?

It's doing well enough—under the circumstances. A more important question: Is the United States spending its science-related funds well? Here, the answer is a resounding no. There are crises in US government research funding in many areas including physics, environmental science, and stem cell research. This context is critical. Likewise, the context for asking any question about NIAID-related funding is that the NIH has been flat-funded for the past five years (see Figure 3, page 22). When factoring in inflation, the budget has actually decreased by more than 12 percent, according to NIAID's own accounting (see Figure 4, page 25). This has a direct impact on the number of "R01" grants awarded to individual investigators.

NIAID awards applications in percentile or priority score order until a cutoff point, or payline, is reached. In the context of flat funding, the payline shifts to a smaller percentile. A healthy payline is at about the 20th percentile. Today the overall payline for scientists submitting R01s to NIAID is at the 12th percentile.

Under these circumstances, every resource allocation question receives scrutiny that is as political as it is scientific.

US investment is critical because at the moment, the US government is the source of roughly 80 percent of all funds directed towards AIDS vaccine research worldwide. Other governments and funding agencies should commit funds to increase the overall resource pool, as well. In 2006, for example, donations from Europe constituted just 10.6 percent (US $82 million) of all public, philanthropic and commercial spending on AIDS vaccines (see www.hivresourcetracking.org). This is proportionally low compared to US funding and should be remedied through EU and individual government support to Europrise and other initiatives. The Canadian government has committed CA $111 million over five years to support its Canadian HIV Vaccine Initiative (CHVI). Should the Government of Canada increase its support for the initiative, the Bill & Melinda Gates Foundation has pledged to contribute up to US $40 million towards this effort. CHVI has a strong focus on manufacturing issues and could cover costs of manufacturing high-quality GMP lots of critical reagents for small studies of promising ideas. It will be important to monitor both this gap and the CHVI program in the coming years.

It's also important to look at how NIAID is apportioning its AIDS vaccine related funds. In FY 2007, 47 percent of extramural funds (grants given to scientists working outside the NIH system) for AIDS-vaccine research went to discovery work, 11 percent to preclinical work, and 38 percent to clinical research. As this break-down illustrates, the majority of NIAID funds are already going to discovery and preclinical work. Post STEP, there have been a number of calls for NIAID to shift funding priorities away from clinical trials and toward basic science and discovery. But the balance is already tipped in that direction, both at NIAID and across the field. US $200 million of the $273 million

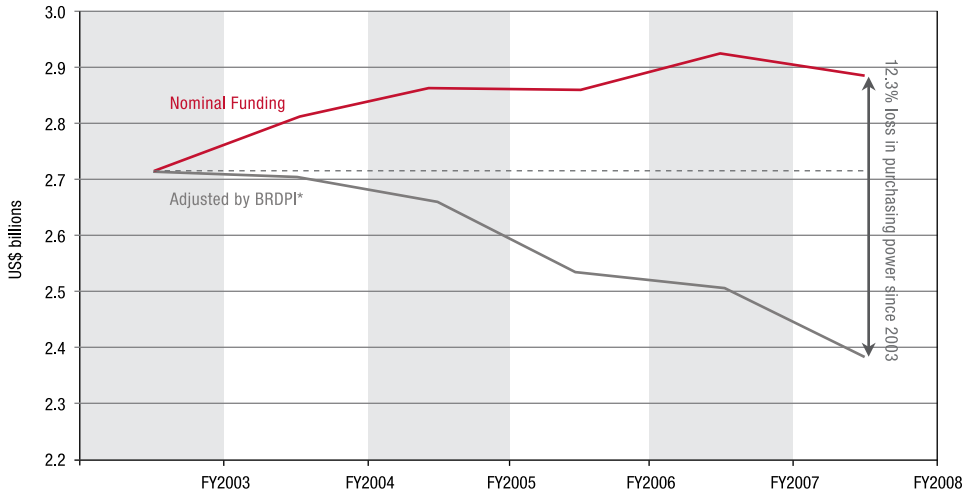
AVAC joins other AIDS organizations in supporting the legislation proposed by US Senators Charles Schumer and Hillary Clinton that would increase NIH funding to $3.4 billion in FY2009, a 15 percent increase. This is a first step towards redressing years of neglect.

Collaborative for AIDS Vaccine Development (CAVD) grants funded by the Bill & Melinda Gates Foundation has also gone to basic science and discovery work.

The issue is not whether there should be more basic science and fewer clinical trials, but what kind of clinical trials in humans are needed most at this time. Likewise, the question is not whether more basic science funding is needed, but whether there's an appropriate balance between consortia and individual laboratories.

The extramural funding includes a grant of up to US $300 million over seven years to support the Center for HIV/AIDS Vaccine Immunology (CHAVI). This is different from traditional NIH funding which goes to investigators who come up with their own proposals. CHAVI funds went to a consortium of investigators from Duke University, the Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, Oxford University, and the University of Alabama-Birmingham, led by Dr. Barton Haynes of Duke. This consortium, and a range of other collaborators including IAVI, have so far used the funds to explore characteristics of transmitted viruses and early events in infection. Under CHAVI grants, teams of investigators from different institutions work together, pool samples, share data and address questions at a scale that's not possible when individual laboratories go it alone. The CAVD grants also work on a consortia-style model.

Figure 4 LOSING POWER: THE IMPACT OF INFLATION ON THE FLAT NIH BUDGET



** The Biomedical Research and Development Prince Index calculates inflation for scientific research*
Source: NIAID (http://www3.niaid.nih.gov/news/events/meetings/HIV_Vaccine_Summit.pdf)

The shorthand for these consortia and collaborations is "big science." It's a model that aims to harness the muscle of collaborative work to take on some of the enduring challenges facing the AIDS vaccine field. But while a laboratory run by an established researcher who is tied into consortia-style projects may be an excellent proving and training ground for young scientists, it is not a clear stepping stone for an emerging talent to become independent and establish his or her own laboratory.

The issue is not whether there should be more basic science and fewer clinical trials, but what kind of clinical trials in humans are needed most at this time.

The desires to work with greater autonomy and to head one's own laboratory are natural and necessary—ambition and competition have fueled science throughout the years. At the NIAID vaccine "summit" in March, many audience members and presenters voiced concern about the lack of opportunities for young scientists who may look elsewhere if the future in AIDS vaccine research appears too constrained or, frankly, doomed. In the context of current peer review systems and constrained funding, young scientists cannot afford failure. Preliminary promising results are often the *bona fide* for securing a grant. They may also be dettered by the fact that a single failed trial prompted a slew of doomsday editorials about the entire field, not to mention a scientific summit at NIAID. There need to be mechanisms which support young scientists interested in entering a field that is high risk and undoubtedly requires persistence. These could include longer-term awards (seven years as opposed to the standard five-year NIH

Table 2 ONGOING TRIALS OF PREVENTIVE HIV/AIDS VACCINES WORLDWIDE (APRIL 2008)

Protocol #	Start Date	Sponsor, Funder, Developer	Trial Site(s)	# of Participants	Vaccine(s)	Clade
PHASE III						
RV 144	Oct-03	USMHRP, MoPH Thailand, Aventis, Vaxgen	Thailand	16,402	Prime: canarypox viral vector with *env* and *gag-pol* Boost: Env protein (gp120 subunits)	B A/E
TEST-OF-CONCEPT						
The two trials that follow, HVTN 503 and 502, stopped enrollment and immunizations, September 2007. Follow-up and data collection continue. For more information visit: http://avac.org/vax_update.htm.						
HVTN 503 (Phambili)	Feb-07	SAAVI, HVTN	South Africa	801	Adenovirus vector with *gag, pol, nef*	B
HVTN 502/ Merck 023 (Step study)	Dec-04	DAIDS, HVTN, Merck	US, Canada, Peru, Dominican Republic, Haiti, Puerto Rico, Australia, Brazil, Jamaica	3,000	Adenovirus vector with *gag, pol, nef*	B
PHASE II						
IAVI A002	Nov-05	Children's Hospital of Pennsylvania, Columbus Children's Research Center, Indian Council of Medical Research, National AIDS Control Organization, Targeted Genetics Corp.	South Africa, Uganda, Zambia	91	AAV2 (adeno-associated virus type 2) vector with *gag, pol*, ΔRT	C
HVTN 204	Sep-05	DAIDS, HVTN, VRC, Vical, GenVec	US, Brazil, South Africa, Haiti, Jamaica	480	Prime: DNA vaccine with *gag, pol, nef* + *env* Boost: Adenovirus vector with *gag, pol* + *env*	A, B, C
ANRS VAC 18	Sep-04	ANRS, Aventis	France	132	5 lipopeptides with CTL epitopes from *gag, nef, pol*	B
PHASE I / II						
EV 03/ANRS Vac20	June-07	European Commission, ANRS	UK, Germany, Switzerland, France	140	Prime: DNA vaccine with *env* plus *gag, pol, nef* Boost: NYVAC-C	C
HIVIS 03	Dec-06	MUCHS, Karolinska Institute, SMI, Vecura, USMHRP	Tanzania	60	Prime: HIVIS DNA with *env, gag, rev*, RT Boost: MVA-CMDR with *env, gag, pol*	A, B, C A, E
RV 172	May-06	NIH, USMHRP, VRC	Kenya, Uganda, Tanzania	324	Prime: DNA vaccine with *gag, pol, nef* + *env* Boost: Adenovirus vector with *gag, pol* + *env*	B A, B, C
PHASE I						
N/A	Apr-08	IPCAVD, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Crucell	US	48	Recombinant adenovirus serotype 26 (rAd26) vaccine	A
HVTN 070	Oct-07	NIAID, HVTN, UPenn/Wyeth	US	120	PENNVAX-B alone, in combination with IL-12, or with 2 different doses of IL-15	B
HVTN 072	Aug-07	NIAID, HVTN, VRC	US	17	DNA and Adenovirus 5 or 35 vectors, all with *env* in varying prime-boost combinations	A
HVTN 071 [As of Sept 07 enrollment and vaccinations have been discontinued]	Jul-07	NIAID, HVTN, Merck	US	35	Adenovirus 5 vector with *gag, pol, nef*	B
DVP-1	May-07	St. Jude's Children's Research Hospital	US	20	Prime-boost regimen with *PolyEnv, EnvPro, EnvDNA*	A, B, C, D, E
VRC 012	May-07	NIAID, VRC	US	35	HIV-1 adenovirus vector vaccine VRC-HIVADV027-00VP: dose escalation and prime-boost with an HIV-1 adenovirus vector vaccine, VRC-HIVADV038-00-VP	A
HVTN 067	Apr-07	NIAID, HVTN, Pharmexa-Epimmune, Bavarian Nordic	US	108	DNA Vaccine EP-1233 and recombinant MVA-HIV polytope vaccine MVA-mBN32, separately and in a combined prime-boost regimen	B A, B, C, D, E, G

Protocol #	Start Date	Sponsor, Funder, Developer	Trial Site(s)	# of Participants	Vaccine(s)	Clade
PHASE I						
DHO-0586	Oct-06	ADARC, IAVI	US	8	ADMVA with *env/gag-pol, nef-tat*	C
HPTN 027	Oct-06	Makerere University, Johns Hopkins University	Uganda	50	Canarypox viral vector with *env* and *gag-pol*	B
C86P1	Sep-06	SGUL, Richmond Pharmacology, Novartis Vaccines	UK	31	Prime: HIV gp140 with LTK63 Boost: HIV gp140 with MF59	B
VRC 011	Apr-06	NIAID, VRC	US	60	DNA vaccine with *gag, pol, nef + env* or Adenovirus vector with *gag, pol + env*	A, B, C
HVTN 065	Apr-06	NIAID, HVTN, GeoVax	US	120	Prime: DNA plasmid with *gag, pro, RT, env, tat, rev, vpu* Boost: MVA vector with *gag, pol, env*	B
HVRF-380-131004	Mar-06	Moscow Institute of Immunology, Russian Federation Ministry of Education and Science	Russian Federation	15	VICHREPOL with polyoxidonium adjuvant	B
IAVI D001	Feb-06	IAVI, Therion	India	32	Modified vaccinia Ankara (MVA) viral vector with *env, gag, tat-rev, nef-RT*	C
HIVIS 02	Jan-06	Karolinska Institute, Swedish Institute for Infectious Disease Control, USMHRP	Sweden	38	Modified vaccinia Ankara (MVA) viral vector with *env, gag*, and *pol* to volunteers from HIVIS 01	A, E
RV 158	Nov-05	USMHRP, NIH	US, Thailand	48	Modified vaccinia Ankara (MVA) viral vector with gp160, *gag* and *pol*	A, E
HVTN 063	Sep-05	DAIDS, HVTN, Wyeth	US, Brazil	120	Prime: Genevax Gag-2692 +/- IL-15 DNA Boost: Genevax Gag-2692 + IL-12 DNA or IL-15 DNA	B
HVTN 060	Aug-05	DAIDS, HVTN, Wyeth	US, Thailand	144	Prime: Genevax Gag-2692 +/- IL-12 DNA adjuvant Boost: DNA plasmids with *gag* or RC529-SE and GM-CSF with *env, gag, nef*	B
*Env*DNA	May-05	St. Jude's Children's Research Hospital	US	6	Recombinant HIV-1 multi-envelope DNA plasmid vaccine with *env*	A, B, C, D, E
VRC 008	Apr-05	NIAID, VRC	US	40	Prime: DNA vaccine with *gag, pol, nef + env* Boost: Adenovirus vector with *gag, pol + env*	B A, B, C
N/A	Mar-05	Changchun BCHT, Guangxi CDC	China	49	Prime: DNA vaccine Boost: recombinant adenovirus vector	C
HIVIS 01	Feb-05	Karolinska Institute, Swedish Institute for Infectious Disease Control, Vecura	Sweden	40	Intramuscular or intradermal injections of plasmid DNA with HIV genes *env, rev, gag,* and *RT*.	A, B, C
EuroVacc 02	Feb-05	EU, Imperial College London, UK MRC Clinical Trials Unit, EuroVacc	UK, Switzerland	40	Vaccinia vector with *gag, pol, nef, env*	C
RV 156 A	Nov-04	NIAID, HVTN, VRC, USMHRP, Makerere U.	Uganda	30	VRC-HIVADV014-00-VP alone or as a boost to VRC-HIVDNA009-00-VP	A, B, C
IAVI C002	Jan-05	IAVI, ADARC, University of Rochester	US	48	Modified vaccinia Ankara (MVA) viral vector with *env/gag-pol, nef-tat*	C
HVTN 050/ Merck 018	Jan-04	NIAID, HVTN, Merck	Thailand, Brazil, Haiti, Puerto Rico, South Africa, US, Malawi, Peru	435	Adenovirus vector with *gag*	B
EnvPro	Jun-03	St. Jude's Children's Research Hospital	US	9	Recombinant Purified HIV-1 Envelope Protein Vaccine	D

ABL: Advanced BioScience Laboratories

ADARC: Aaron Diamond AIDS Research Center

ANRS: Agence Nationale de Recherches sur le Sida (France)

DAIDS: Division of AIDS

HVTN: HIV Vaccine Trials Network

IAVI: International AIDS Vaccine Initiative

IPCAVD: Integrated Preclinical/Clinical AIDS Vaccine Development

MoPH: Ministry of Public Health

MUCHS: Muhimbili University College of Health Sciences

NIAID: National Institute of Allergy and Infectious Diseases

NIH: National Institutes of Health

SAAVI: South African AIDS Vaccine Initiative

SGUL: St. George's, University of London

SMI: Swedish Institute for Infectious Disease Control

UK MRC: United Kingdom Medical Research Council

USMHRP: United States Military HIV Research Program

VRC: Vaccine Research Center

ZEHRP: Zambia Emory HIV Research Project

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

grant, or a grant along the lines of Howard Hughes Foundation awards that give six years of funding for scientists establishing independent laboratories). Europe should implement similar strategies through Europrise, and the Bill & Melinda Gates Foundation could explore a parallel process of extending grants to young scientists in the developing world.

NIAID and other funders should look at its funding allocations in light of the need to provide avenues for young scientists and scientists from outside the AIDS vaccine field to be involved. The goals of these programs should be specific. Young scientists are important—provided they're working in a context where the key questions are articulated, where risk-taking is rewarded, and where there's both coordination and openness to non-traditional thinking.

3) Should a revised version of PAVE 100 go forward?

News about the STEP study generated a lot of discussion about whether human clinical trials of AIDS vaccines should continue. No study received more attention than the PAVE 100 trial, a planned efficacy study of a combination strategy developed by the NIH Vaccine Research Center (VRC). One of the components of the VRC strategy uses an adenovirus serotype 5 (Ad5) vector that is similar, though not identical, to the Ad5 vector used in the Merck trials. PAVE 100 was scheduled to start in the Americas just days after the announcement that the Merck studies would halt immunizations and there has been considerable discussion about whether, and in what form, the trial might take place in the new "post STEP" era.

Current discussions about a revised PAVE 100 protocol are focusing on a test-of-concept trial that proposes to enroll only Ad5 seronegative men who have been circumcised. (Vaccine recipients in this group were at not at increased risk of HIV infection in the STEP study.)

A vaccine which showed benefit in such a restricted population wouldn't be appropriate for widespread use. If PAVE 100 shows efficacy, this precise regimen most likely won't move forward to pivotal licensure trials. A positive finding would be used to help design vaccine candidates that don't have the potential safety issues that appear to have been associated with the Ad5 vector in certain subpopulations. (We don't know whether the VRC strategy would have the same safety profile as the 3-dose MRK-Ad5 strategy, and the redesigned PAVE 100 trial will not tell us about this because of its restricted enrollment criteria.)

An initial proposed approach to PAVE 100 entailed two separate but closely-integrated trials known as PAVE 100A and PAVE 100B. "A" would have enrolled men who have sex with men in the Americas. "B" would have enrolled heterosexual populations in sub-Saharan Africa. Because of the high rates of Ad5-seropositivity in the potential participating African countries, many otherwise-eligible volunteers would have been screened out.

In March, IAVI, one of the original PAVE collaborators decided not to participate, stating, "From a practical standpoint, the new exclusion criteria for PAVE 100B […] limit the number of participants and speed with which IAVI could enroll from our existing cohorts in Africa, and to generate additional cohorts from which to recruit would require a huge increase in resources."

COMMUNITY INPUT ON PAVE 100: WHAT DOES "GPP" SAY?

"GPP" is short for *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials* (www.avac.org/gpp.htm). Developed in a collaborative process convened by AVAC and UNAIDS, this document identifies minimum elements of good practice for community engagement in HIV prevention trials.

GPP was published in 2007, and its true value will only be determined by testing it in the field. AVAC is using GPP principles to guide our analysis of consultative processes regarding the proposed PAVE 100 trial. As we went to press, the process had not yet included sufficient community input based on these guidelines. Plans were underway to expand community consultations. AVAC welcomes these developments and offers these suggestions for specific principles or activities identified in GPP that should be put into place by PAVE collaborators.

- The core GPP principle of "more transparency" states, "The principal investigator should strive to provide clear, comprehensible and timely access to trial-related information for communities affected by research."

A proposed PAVE protocol was presented at a public meeting in December 2007 and has been the basis for ongoing discussions. While the protocol hasn't been finalized, key elements could be used in community consultations in many settings.

- The section on Protocol Development identifies the following as "essential steps in all circumstances:
  - "Clear transparent communication about the kinds of input that the community can and cannot have incorporated into a protocol based on the circumstances of the trial…
  - "Opportunities created—and facilitated—for community advisory groups and/or mechanisms to provide input into study design mechanisms such as selection criteria, recruitment…."

So far, it has been unclear when and how community would be able to provide input into the critical conversation about whether PAVE 100 should go forward. A plan for gathering these viewpoints should be put forward and implemented.

The other PAVE collaborators with potential sites in Africa have also taken these issues into serious consideration. At press time, the primary focus was on a PAVE 100 study in the Americas. (For additional resources and updates visit www.avac.org)

And so the question remains: should PAVE 100 go forward in any form?

AVAC's answer is a conditional yes. A trial could be designed and conducted to provide a relatively quick and clear answer about whether the VRC candidate has any benefit in protecting against infection or reducing viral load setpoint. Information about whether the vaccine does provide any kind of protection could in turn help guide future vaccine design efforts.

At this moment, our answer is conditional because some of the critical issues related to community acceptability of this trial have not been addressed. As noted at the beginning of this chapter, AVAC is a small civil society organization that cannot and should not speak for the wide array of communities that may be asked to participate in this trial.

Is a trial that tests a candidate that almost certainly would not advance to licensure studies acceptable to communities? STEP and Phambili were also test-of-concept in that they were designed to provide an initial idea of vaccine efficacy. If there had been a clear benefit, additional larger trials would have been launched to learn more. If PAVE 100 shows efficacy, the strategy most likely won't move forward to pivotal efficacy trials. Communities need to be engaged and have input on what this means to them.

This boils down to questions like: What are community attitudes towards and questions about a test-of-concept trial of a candidate that will not move forward to further large-scale studies? What are community attitudes about a trial whose exclusion criteria (Ad5-seropositive people and, possibly, uncircumcised men) mean that the results will be hard to generalize? How do communities which were asked to participate in STEP feel about potentially being recruited for PAVE 100?

Right now, there's scant information to help answer these questions. And yet, the systems exist. For example, the NIH HIV Vaccine Research Education Initiative program has a robust network of experienced partners connected to an array of communities who were asked to participate in STEP and who may participate in PAVE. Every one of these partners could hold a consultation using a standardized discussion tool and feed these results into the decision-making process. The NIH HIV/AIDS Network Coordination office "Community Partners" program is another potentially valuable mechanism for gathering input. These conversations can and, in our reading of the GPP document (see page 29), must happen before a firm decision is made about proceeding with the trial.

NIH representatives have said that the proposed PAVE trial will answer important scientific questions even though it is not part of a product-development pathway for the current VRC strategy. Still, there needs to be a set of next steps that flow from whatever the data are. We'd call that a research pathway—and would like to see one before a final decision is made on whether PAVE 100 goes forward.

4) Is it possible to preserve clinical trial site capacity even when clinical trials are postponed?

Yes—but it may mean that AIDS vaccine trial sites have to work on other important areas like male circumcision, pre-exposure prophylaxis, other vaccine research, microbicides, epidemiological studies, or act as training sites or centers of excellence to build research capacity of other sites. It may also mean that funding structures need to reexamine how allocations are made for outreach and education, since these critical activities—which are often tied to specific trials—must continue and be expanded to address the questions and issues arising at a community level as a result of postponed or cancelled trials and disappointments like STEP, Phambili, Carraguard and others.

There are some signs that this is happening. At press time, IAVI was working with the clinical research teams that are its partners to consider various alternative projects. Some of the teams that were planning to conduct PAVE 100 are now considering conducting TB vaccine trials, making

Communities that may be targeted for PAVE 100 must have the chance to consider whether the trial is a priority and what the questions are in the wake of the STEP study, and to ask for and consider additional information that might help inform their thinking. AVAC can help support consultations on this topic. NIH and the PAVE collaborators should work through multiple mechanisms including NHVREI, Community Partners, and other structures to solicit this critical feedback.

plans for Phase I studies, and looking for ways to use site capacity to help train newer research teams. HVTN leader Larry Corey told AVAC that it was focusing on additional Phase I studies (see page 22) and would collaborate with the HPTN on work to determine whether cohorts of high-risk women could be enrolled for future vaccine or prevention trials in the US and the Caribbean.

These are promising steps, but they are also incomplete. Phase I trials require types of infrastructure and staffing levels that are different from what is needed for efficacy trials. If there is no efficacy trial for two or three years, then some of that infrastructure, including experienced staff and prepared communities, may be lost. Yes, some sites may end up conducting other studies—the new NIH funding structure for trial networks allows for sites to explore and apply to participate in a range of research studies. But is this sufficient? Probably not, especially when it comes to maintaining community education and outreach programs, which have been shown to thrive with consistent staff and sustained relationships with communities. As the human clinical trials agenda is revamped and reconsidered, priority needs to be placed on maintaining community outreach and education staff and capacity.

As we discuss in the first chapter, the broader HIV prevention research arena is dealing with a range of opportunities including how to introduce male circumcision and how to manage disappointments such as lack of efficacy in recent microbicide, diaphragm, and HSV-2 trials. Trial sites and the structures that fund them must be prepared, logistically and financially, to find new and innovative ways to adapt to unforeseen circumstances. They need research agendas that can be flexible enough to respond to the evolving HIV prevention landscape. Financing should go where it can do the most good in the short-term and also aim to ensure that trial capacity that exists today is maintained for the long term.

5) Are T-cell vaccines dead?

No, not by a long shot. As we discuss at greater length in our "Science Snapshot" (page 52), the failure of a single candidate, Merck's MRK-Ad5, in no way spells the end to the notion that a vaccine can be developed to generate cell-mediated immunity that blunts viral replication and slows disease progression. The arguments that supported T-cell vaccine development in the past remain relevant. The MRK-Ad5 vaccine stimulated a subset of the many types of T-cell responses that can be induced by a vaccine. There is still a whole range of open questions that are relevant, and a whole body of data suggesting that potent T cells can play a role in controlling infection. This is the basis for the ongoing T-cell work funded by CAVD, CHAVI, IAVI, and Europrise. The recent NIAID AIDS vaccine summit identified additional key research areas

around T cell vaccines, as did this year's Keystone AIDS vaccine meeting. AVAC will be looking in greater detail at the scientific agenda for both T-cell and antibody-based vaccine strategies and discovery work in the coming months, and we will issue a separate report on this topic.

6) Is an AIDS vaccine possible?

Yes, an AIDS vaccine is possible. We have no secret insights, no crystal ball, no scientific breakthrough waiting in the wings to put behind this statement. But the world must continue to operate as though the answer is yes because the indicators are still there, and still good (see Figure 5). We just don't understand them well enough as yet.

The AIDS vaccine we believe is possible is not necessarily one that provides sterilizing immunity—the holy grail of complete protection. It could be a vaccine that reduces viral load or protects against some modes of exposure but not others. Moreover, when we look at elite controllers—those who are infected and maintain low or undetectable viral loads for many years—we see evidence that the immune system can control the virus. We belive it is possible that a vaccine can create this immune profile, even if it may be a long way off.

Will an AIDS vaccine be possible in the next ten, twenty, thirty years? In the lifetime of a physician who saw the first AIDS cases on the wards in the 1980s? Maybe not. Or in the lifetime of an infant being born today, perhaps one who is being protected from HIV infection through the use of antiretrovirals for prevention of parent-to-child transmission? We hope so. We wish the time horizons were shorter and hope we will figure out how to abbreviate them in the future. In the meantime, we must be as clear about the long haul of this endeavor as we are about its merit. Looking across the world at rates of new infections and at the human costs and dismal coverage of proven prevention strategies, we still say: We need an AIDS vaccine, no matter how long it takes.

Figure 5 WHY AN AIDS VACCINE IS POSSIBLE