



AIDS VACCINES AT THE CROSSROADS



AVAC AIDS VACCINE ADVOCACY COALITION 2005

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When AVAC was formed on World AIDS Day in 1995, we were optimistic that with more resources, more cooperation and more scientific knowledge, an AIDS vaccine could be found in time to stem the growing epidemic. A decade later the field has more resources, more cooperation and more depth of scientific knowledge—but still no AIDS vaccine.

While the field has learned much in the past decade and made great strides in scientific, policy and ethical arenas, the road ahead is still a long one.

We travel this road with thousands of others—researchers, policy makers, advocates, trial volunteers and their communities. Thousands more will need to join us before we reach our goal.

In this 2005 AVAC Report, we lay out what we see as some of the major challenge areas we all will face and offer recommendations for navigating them.

We are also increasingly aware that the global terrain on which trials will be conducted and a vaccine will eventually be provided is rapidly changing. The overall global response to the AIDS epidemic is also at a crossroads.

- + The raging global pandemic increases both the need for, and the complexities of, bringing vaccine prevention to the world.
- + Provision of existing prevention options and trials of new prevention technologies present the world with difficult research design and ethical issues.
- + Though treatment programs are receiving needed priority and attention, access to treatment is still far short of need.

We realize that future AIDS vaccine trials and eventual rollout will be done in the context of other prevention trials, changing required baseline standards of prevention and care, and evolving knowledge, expectations and involvement of the communities where trials will be conducted.

AVAC is committed to continuing to be a voice in the ongoing discussions about these issues. For example, this 2005 AVAC Report includes an article to follow up on our report on the trials of tenofovir as pre-exposure prophylaxis (PREP), published earlier this year. (See page 42.)

As we work to accelerate the development of a safe and effective AIDS vaccine, many of the thousands of new volunteers will come forward in the face of fear, uncertainty or stigma, and at a time when there is increasing public concern about medical research. There is a growing need to ensure adequate scientific and research literacy among trial volunteers and communities so that individuals can make informed decisions about participation. And there is also a need for researchers to increase their community literacy—to understand the needs, motivations and expectations of the communities from which volunteers will be drawn.

All of us in the global community of researchers, policy makers and advocates must work together to ensure that trial participants can have the understanding and confidence they need in order to be a part of the global enterprise of AIDS vaccine development.

In this report, we offer recommendations for the field in general, the Global HIV/AIDS Vaccine Enterprise, policy makers, researchers and communities. Some of these recommendations will be familiar because

we've made them before, and we reiterate them because we believe they are still needed and useful. (See our timeline of ten years of AVAC recommendations on page 17.)

And some analysis and recommendations are new. For example, we take an in-depth look at intellectual property issues and offer some "small step" recommendations that we believe will help move the field forward. (See page 33.)

To help you get the most from the report, on the next page you'll find a list of our major recommendations with the pages where you'll find the detailed analysis and thinking that leads us to make them.

So, we stand here at a crossroads. We know that our roadmap is ever-evolving and by definition cannot be straightforward.

Sincerely,



Mike Powell
AVAC Board President

We at AVAC are committed always to finding and nurturing a diverse cadre of new AIDS vaccine advocates all over the world. We are committed to strengthening the worldwide coalition of humans who understand and support the road to a vaccine. And we are enthusiastic about our role and the work ahead of us in the next years.

We hope you will find this report useful and re-energizing, and we look forward to your feedback and guidance on how the AIDS Vaccine Advocacy Coalition might best help to pave the road forward.



Mitchell Warren
AVAC Executive Director

WHAT AVAC RECOMMENDS IN THIS REPORT

In this report, AVAC documents what we see as the needed tasks in the search for an AIDS vaccine during a time of redirection. In brief, our list of resulting recommendations includes:

FOR AIDS VACCINE SCIENTISTS:

- + Carry out a smart, evidence-based science agenda, even when that means giving up once favored products, combinations or trials that lack incrementally superior data. (Page 09)
- + Tell everyone the basis for those decisions and explain them in ways all stakeholders can understand. (Page 23)
- + Do prompt work on important areas of new constructs such as mucosal or innate immunity. (Page 12)



FOR THE GLOBAL HIV/AIDS VACCINE ENTERPRISE AND OTHER COLLABORATIONS:

- + Set technical and legal procedures to facilitate knowledge sharing. (Page 23)

- + Be forthright and public about overcoming intellectual property obstacles that might inhibit private sector involvement. (Page 36)
- + Overcome those obstacles with model and public sharing arrangements, harmonization, and reasonable reward distribution. (Page 36)

FOR FUNDERS:

- + Supplement existing mentoring and investigator grant programs that expand the number of young scientists, especially international scientists, who make this work their career. (Page 24)
- + Rich country governments that have not yet invested adequately in AIDS care, prevention and research need to step up their efforts. (Page 28)

FOR CLINICAL TRIAL LEADERS:

- + Listen carefully to civil society and communicate openly and often with the communities on whom, for whom, and with whom research is performed. (Page 14)
- + More fully integrate prevention, testing and treatment with clinical trials. (Page 14)
- + Researchers testing tenofovir as pre-exposure prophylaxis need to better coordinate their studies and determine whether additional trials are needed. Collaborative efforts among trial sponsors and communities are urgently needed to address ethical and other concerns. (Page 45)



FOR THE BLUEPRINT AND ROADMAP MAKERS:

- + On the many different organizational blueprints and agendas, you've said what you mean. Now is the time to mean what you say. The science agendas are great ones. Now implement them with due speed and enthusiasm! (Page 08)
- + Examine past experiences of setting milestones and learn about common pitfalls made in establishing processes and making projections, then use that information as a reality check for the future. (Page 49)

FOR GOVERNMENT POLICY MAKERS AND INFLUENCERS:

- + Support some of the current Bioshield II legislation in the US for infectious disease but amend it to correct problems with both its liability and its intellectual property incentives features. (Page 31)
- + Organize advance purchase incentives as soon as possible and create additional incentives for vaccine developers. (Page 28)

- + Provide open public access to research results including peer-reviewed articles of work funded by taxpayer dollars. (Page 41)
- + Support the research collaborations, and keep them continually accountable. But don't underestimate the power of independent research. (Page 23)

FOR ALL AIDS VACCINE STAKEHOLDERS AND ADVOCATES:

- + Press forward with both existing prevention methods and expanded access to treatment that are responsive to local needs and demands today. (Page 14)

01



THE PAST YEAR: UPDATE, ANALYSIS & RECOMMENDATIONS



THE PAST YEAR: UPDATE, ANALYSIS & RECOMMENDATIONS

AVAC sees 2005 as a crossroads year. Our fundamental focus remains the same—doing what we can to help accelerate AIDS vaccine development. And our list of core needs for the field has not changed: more money, greater collaboration, novel approaches explored, more and better vaccine candidates, ethical clinical trials, improved capacity and innovation.

We know that an AIDS vaccine is *not* around the corner and that making time-bound predictions only serves to raise unrealistic expectations. At the same time, we see changes and early indications that the field is positioning to move in new directions and with clarity of purpose. In this chapter, we review the events of the past year, give our interpretations of what they may indicate, and make recommendations on how we, and the field as a whole, can make progress along these promising trajectories.

THE GLOBAL HIV/AIDS VACCINE ENTERPRISE

First proposed in *Science* magazine in June 2003¹, the Global HIV/AIDS Vaccine Enterprise is beginning to command the attention of both scientists and donors as it moves beyond the planning stage. There's probably no better way to understand the state of HIV vaccine science than to read the Enterprise Scientific Strategic Plan published in February 2005². More than one hundred scientists from fourteen industrialized and developing countries contributed their best estimates and appraisals to identify the work to be done, the time frame and the cost. The Bill & Melinda Gates Foundation, the US National Institutes of Health (NIH), the International AIDS Vaccine Initiative (IAVI), The Wellcome Trust, the French Government, the European Union and all the other institutions that have contributed are to be commended for taking this idea and voluntarily moving it forward.

The Enterprise has already helped focus the field-at-large by identifying work to be done, and there are

now both significant funding commitments to implement aspects of the plan and renewed political commitment to AIDS vaccine development.

It will now be up to the public and the scientific community to hold them to their plan and to help continue to get it funded. For more AVAC analysis and recommendations on the Enterprise, see our open letter to the soon-to-be-appointed executive director. (See page 23.)

In the next year, AVAC will be looking for the Enterprise to move forward rapidly and prove its worth.

COLLABORATION

The Enterprise concept is grounded in a call for improving collaboration. The basic question then must be, "How do we ensure that the collaboration streamlines rather than adds another level of complication and politics?"

There are these important signs of collaboration:

CHAVI: In July, NIH chose a group led by Barton Haynes of Duke University to form the new Center for HIV/AIDS Vaccine Immunology (CHAVI). This consortium includes researchers from several academic institutions, and from developed and developing countries, who will be working together with a shared plan and goals.

OCTAVE: A partnership initiated by EuroVacc (the European Vaccine Effort against HIV/AIDS) and the HIV Vaccine Trials Network (HVTN) supported by NIH's Office of AIDS Research in collaboration with IAVI, CANVAC, WHO, ECRIN (European Clinical Research Infrastructures Network) and Institute Pasteur called OCTAVE, the On-line Collaborative Training for AIDS Vaccine Evaluation project/EFGCP, the European Forum for GCP will provide training for clinical site staff and students worldwide on how to perform trials using Good



COUNTRIES CONDUCTING AIDS VACCINE TRIALS (AUGUST 2005)



Clinical Laboratory Methodology and Good Clinical Practice. HIV pathogenesis and vaccinology training programs are also under development.

PAVE: In addition to its work on assay standardization and the estimation of the state of readiness for international trials, the US government's Partnership for AIDS Vaccine Evaluation (PAVE) has designed, and is now waiting approval for, a series of trials of vaccine candidates developed by the NIH's Vaccine Research Center (VRC). The trials will be conducted in multiple sites sponsored by different organizations—HVTN, the US Department of Defense and IAVI.

Gates Foundation: The Bill & Melinda Gates Foundation issued requests for proposals to support research priorities identified in the Scientific Strategic Plan of the Enterprise, focusing on vaccine discovery and laboratory standardization. Decisions will be announced early in 2006 and, depending on the content and quality of the applications received, the Gates Foundation may commit up to \$360 million over the next five years to support these projects, which will be organized as a network of collaborating centers and consortia.

Partnership is hard to argue with. It sounds great, but it is the operationalized agenda—experiments carried out with increased speed, transparency, efficiency, and effectiveness—that matters and gives teams credibility.

In the next year, we look forward to seeing how these collaborations translate intention into action.

PROVING THE CONCEPT OF PROOF OF CONCEPT TRIALS

Merck & Co. and the HVTN this year initiated a critical proof of concept trial of Merck's Adeno5-vectored trivalent vaccine candidate. Because most of the current vaccine candidates in the pipeline are, like this trivalent Adeno5 vaccine, aimed at stimulating similar measures of cellular immunity, this will be an extremely important study for the entire field. This trial aims to test the hypothesis that a vaccine based on three portions of HIV genetic material from a single clade (B) can stimulate cellular immunity to prevent HIV disease, and perhaps infection. Proof of concept trials are only large enough to give

an indication if an approach has merit, so they are faster and smaller than the trials needed to measure efficacy accurately enough to make licensing decisions. They are designed to weed out poor candidates and identify very strong candidates, but mid-range results are not precise enough to be definitive. (More information about proof of concept trials is available in AVAC's *AIDS Vaccine Handbook*.)

The multi-centered, international trial is being conducted in both Merck- and HVTN-sponsored trial sites in the US, Australia, the Caribbean and Latin America and is the first of potentially many proof of concept trials that could give the field better direction.

Adeno5 is a common cold virus to which many people have a pre-existing immunity, which could potentially make the vaccine less effective in those people. But the vector may be good at shuttling HIV immunogen material into cells. In earlier studies, approximately 65 percent of vaccinees showed a positive response on ELISpot assays, which are used to measure cell-mediated immunity quantitatively, the best showing of any cellular-based product so far. The trial was initially set to enroll 1,500 people who had low titers of Adeno5 antibodies, but as the trial was enrolling, new data indicated that pre-existing immunity may not matter as much as first thought, so the trial is now being doubled in size to test the vaccine candidate in two strata: people with high and low levels of previous exposure to Adeno5. This is certainly encouraging news, but Merck and many others in the field are still exploring the issue of pre-existing immunity and different Adeno virus types.

Should this trial not give statistically significant results, Merck and others will need to rethink to what degree stimulating cellular immune responses is a scientifically sound approach to an AIDS vaccine, and how best to do it. While that would be a serious setback, it would also contribute data that could help point efforts in another direction, avoiding the waste of time and money on comparable

products. If the trial does meet its endpoints, it paves the way for a much larger efficacy trial to test the effectiveness of this product among people living in non-clade B countries, which are the areas hardest hit by the pandemic. Results from the current proof of concept trial are only anticipated in 2007 at the earliest, but it is not too soon to plan for both scenarios.

At the same time, the VRC is moving ahead with its DNA-Adeno5 prime boost vaccine candidate. This Adeno5 includes multiple genes from multiple clades, and it is anticipated that this trial will happen internationally, in sites with multiple clades present.

With Merck, the VRC, IAVI and other product developers already exploring a number of strategies to expand or make adjustments to vaccine candidates based on the current proof of concept trial, the next three years will bring important decisions for the AIDS vaccine pipeline.

MAKING GO/NO-GO DECISIONS MORE QUICKLY AND ACCURATELY

Progress is often judged by how many products are in the pipeline, but it is increasingly important to weed out products when they look no better than others that are more advanced. This year the end of an IAVI DNA/MVA trial gave indications of how this weeding process can work to clear the way for more promising candidates.

IAVI and its Oxford University and University of Nairobi partners conducted Phase I/II trials of this DNA/MVA based product in studies conducted among 205 volunteers in the UK, Kenya, South Africa, Switzerland and Uganda. Often, after that much safety and immunogenicity data are collected, there is an institutional reluctance to drop an approach. But after looking at the data on the immunogenicity of the vaccine, IAVI announced that it would drop the candidate from its portfolio and focus on other approaches, even though there were no major safety problems with the vaccine.

PREVENTATIVE AIDS VACCINES IN CLINICAL TRIALS (AUGUST 2005)				
SPONSOR	DEVELOPER	TRIAL SITE(S)	VACCINE(S)	CLADE
PHASE III				
US Military HIV Research Program (USMHRP), Ministry of Public Health, Thailand	Aventis, Vaxgen	Thailand	Prime: canarypox viral vector with <i>env</i> and <i>gag-pol</i> Boost: Env protein (gp120 subunits)	B, A/E
PHASE IIB				
NIH Division of AIDS (DAIDS)/HIV Vaccine Trials Network (HVTN)	Merck	US, Dominican Republic, Haiti, Peru, Canada, Australia	Adenovirus vector with <i>gag, pol, nef</i>	B
PHASE II				
Agence Nationale de Recherche sur le SIDA (ANRS)	Aventis	France	5 lipopeptides with CTL epitopes from <i>gag, nef, pol</i>	B
PHASE I/II				
International AIDS Vaccine Initiative (IAVI), UK Medical Research Council (MRC)	U. Oxford, Kenya AIDS Vaccine Initiative (KAVI)	Kenya, Uganda, UK	Prime: DNA vaccine with <i>gag</i> + CTL epitopes from <i>gag, pol, nef, env</i> Boost: MVA with <i>gag</i> + same CTL epitopes	A
FIT Biotech	FIT Biotech	Finland	<i>nef, rev, tat, gag, pol, env</i> , CTL epitopes	B
DAIDS/HVTN, ANRS	Aventis	USA	Prime: canarypox vector with <i>env, gag, pro, RT, nef</i> Boost: 5 lipopeptides with CTL epitopes from <i>gag, pol, nef</i>	B
DAIDS	Australian/Thai HIV Vaccine Consortium	Australia, Thailand	Prime: DNA vaccine with <i>gag, RT, rev, tat, vpu, env</i> Boost: foXPox viral vector with same genes as prime	B
PHASE I				
DAIDS	US NIH Vaccine Research Center (VRC), USMHRP, Makerere Univ.	Uganda, US	Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag-pol + env</i>	B +A, B, C
DAIDS/HVTN	Therion	US	Prime: MVA viral vector with <i>env, gag, pol, nef + env</i> Boost: foXPox viral vector with the same genes as prime	B
University of Massachusetts Medical School (UMMS), Advanced BioScience Laboratories (ABL)	UMMS, ABL	US	Prime: DNA vaccine with <i>gag</i> + 5 different <i>env</i> genes Boost: 5 Env proteins (gp 120) in adjuvant (QS21)	A, B, C, A/E
DAIDS/HVTN	Chiron	US	Prime: DNA vaccine with <i>gag, env</i> attached to microparticles Boost: Env protein (oligomeric gp 140) + adjuvant (MF 59)	B
DAIDS/HVTN	VRC	US	DNA vaccine with <i>gag, pol, nef + env</i> One trial testing vaccine with or without cytokine (IL-2)	B + A, B, C


PREVENTATIVE AIDS VACCINES IN CLINICAL TRIALS (AUGUST 2005) *Continued*

SPONSOR	DEVELOPER	TRIAL SITE(S)	VACCINE(S)	CLADE
IAVI	Aaron Diamond AIDS Vaccine Research Center (ADARC)	US	DNA vaccine with <i>gag, env, pol, nef, tat</i>	C
Istituto Superiore di Sanità (ISS)	ISS	Italy	DNA vaccine with <i>tat</i>	
DAIDS/HVTN	Epimmune	US, Botswana	DNA vaccine with 21 conserved CTL epitopes from <i>gag, pol, env, nef, rev, vpr</i> and T-helper epitope	
DAIDS/HVTN	Merck	US, Puerto Rico, Brazil, Haiti, Malawi, South Africa, Peru, Thailand	Adenovirus vector with <i>gag</i>	B
DAIDS/HVTN	VRC	US	Adenovirus vector with <i>gag-pol</i> or <i>gag, pol, nef + env</i>	B +A, B, C
DAIDS, HVTN, South Africa AIDS Vaccine Initiative	AlphaVax	US, South Africa, Botswana	VEE (Venezuelan equine encephalitis) vector with <i>gag</i>	C
IAVI, Indian Council of Medical Research, National AIDS Control Organization (India)	Targeted Genetics	Belgium, Germany, India	AAV (adeno-associated virus) vector with <i>gag, pro, RT</i>	C
EU, Imperial College, London, UK MRC Clinical Trials Unit	EuroVacc	UK, Switzerland	NYVAC-HIV-C (vaccinia vector) with <i>gag, pol, nef, env</i>	C
IAVI	ADARC	US	MVA vector with <i>gag, pol, nef, tat</i>	C
IAVI, MRC, SAAVI	U. Oxford. KAVI	UK, Switzerland, Kenya, South Africa	MVA vector with <i>gag + CTL</i> epitopes from <i>gag, pol, nef, env</i>	C
DAIDS/HIV Prevention Trials Network (HPTN)	Aventis	Uganda (in infants)	Canarypox viral vector with <i>env</i> and <i>gag/pol</i>	A/E
DAIDS/HVTN	Wyeth	US	Conserved CTL epitopes from <i>gag, nef</i> and helper T epitopes from <i>env, gag</i> in adjuvant (RC329-SE), with or without cytokine (GM-CSF)	B
ANRS	Aventis	France	5 lipopeptides with CTL epitopes from <i>gag, pol, nef + helper</i> epitope from a mom-HIV protein (tetanus toxoid)	B
ANRS	Biovector SA	France	4 lipopeptides with CTL epitopes from <i>gag, pol-RT, pol, nef</i> and helper epitope from a non-HIV protein (tetanus toxoid)	B
USMHRP	AVANT, Harvard University	US	Portion of Gag protein (p24) fused to anthrax derived protein (minus toxin)	
ANRS	Aventis	France	Env proteins <i>gp 120</i> and <i>gp41</i> given mucosally (nasally or vaginally) with or without adjuvant (DC-chol)	B
Changchun BCHT	Changchun BCHT, Jilin University	China	Prime: DNA vaccine Boost: recombinant adenovirus vector	C

For more information:

The IAVI clinical trials database is online at <http://www.iavireport.org/trialsdb>

A database of trials sponsored by the US NIH is online at <http://clinicaltrials.gov>

A table of trials conducted by the US HVTN is online at <http://chi.ucsf.edu/vaccines/vaccines?page=vc-03-00>

But the bottomline take-home message is that the immunogenicity of the product was considered to be poor by current standards.

Neither IAVI nor the field-at-large is giving up on DNA/MVA or MVA as a platform with other constructs that may perform better and with other inserts.

In the next year, we hope the field will be able to achieve some consensus on how to determine when there will be enough data to make decisions on DNA and poxviruses.

PROMISING ANTIBODY AND MUCOSAL IMMUNITY RESEARCH

Anyone who has been tenacious enough to follow AIDS vaccine research over the past two decades knows that the ability to make a vaccine that could induce effective antibodies against circulating strains of HIV remains one of the great unsolved mysteries. A handful of promising constructs in the lab have turned out not to induce even minimal neutralizing antibodies in human trials, and the only design tested for efficacy, VaxGen's recombinant gp120, was not efficacious.

Using findings in structural biology, though, some scientists report that they have identified new, theoretically workable antibody approaches. Teams from NIH, Merck, the biotech firm Maxygen, The Scripps Research Institute, and Rutgers University's Center for Advanced Biotechnology and Medicine, working with the biotech company ViroLogic, have all announced potential solutions to the search for neutralizing antibodies in the last year. None of these approaches has reached the clinic, but they

may breathe life into the quest for a much-needed antibody-based vaccine.

Another relatively untapped area for increased research is mucosal immunity. A big unknown, which the field may very well need to answer and factor into product development, is whether protection against HIV requires different or stronger immune responses early at the several ports of entry for HIV during mucosal surface transmission. Immune responses that stop HIV in these mucosal tissues, where many types of immune cells and chemicals are found, could very well contribute substantially to protection.

There are only a few vaccine research projects specifically targeting mucosal immunity. One of the few is a new Gates Foundation Grand Challenges grant to a UK-South Africa partnership working to find a vaccine to stimulate immunity in the lining of the vagina. (See a list of Grand Challenges grants related to AIDS vaccines on page 13.) The Canadian Network for Vaccines and Immunotherapeutics (CANVAC) has a Mucosal Vaccine Development Group that has also been looking at possible vaccine constructs to stimulate mucosal immunity, but the recent withdrawal of Canadian government funding from CANVAC may jeopardize this research program.

In the next year, we look for more new research on antibodies and mucosal immunity to accelerate the development of new vaccine candidates into the pipeline.

DEVELOPING WORLD RESEARCH COLLABORATIONS

Vaccine research and development (R&D) efforts have become more global every year, and 2005 was



AIDS VACCINE-RELATED GRAND CHALLENGE GRANTS

In June, the Bill & Melinda Gates Foundation, working with the Foundation of the National Institutes of Health, along with The Wellcome Trust and the Canadian Institutes of Health Research, committed over \$480 million to 43 projects aimed at answering the Grand Challenges in Global Health. Several of the grants are for projects directly related to AIDS vaccine development, and others will help with development and delivery of AIDS vaccines. Grants include the following:

A Mouse Model to Evaluate Live-Attenuated Vaccine Candidates

Lead investigator: Richard A. Flavell, Yale University and Howard Hughes Medical Institute, US, \$17 million

Novel Mouse Models for Testing HIV and HCV Vaccines

Lead investigator: Rudi Balling, German Research Center for Biotechnology, Germany, \$9 million

Development of Novel Mouse Models for HIV and HCV Infection

Lead investigator: Hongkui Deng, Peking University, China, \$1.9 million

Enhancing the Immunogenicity and Efficacy of Vectored Vaccines

Lead investigator: Adrian Vivian Hill, University of Oxford, UK, \$10 million

Improved Vaccine Efficacy via Dendritic Cells and Flavivirus Vectors

Lead investigator: Ralph Marvin Steinman, Rockefeller University, US, \$14 million

Novel Antigen Design and Delivery for Mucosal Protection Against HIV-1 Infection

Lead investigator: Robin John Shattock, St. George's, University of London, UK, \$19.7 million

Increasing Vaccine Stability Through Novel Technology

Lead investigator: Colin R. Gardner, TransForm Pharmaceuticals, Inc., US, \$8.8 million

Comprehensive Studies of Mechanisms of HIV Resistance in Highly Exposed Uninfected Women

Lead investigator: Francis Allen Plummer, University of Manitoba, Canada, \$8.3 million

Molecular Analysis and Modeling of HIV-1 Transmission, Containment, and Escape

Lead investigator: George M. Shaw, Howard Hughes Medical Institute at the University of Alabama at Birmingham, US, \$16.3 million

Engineering Immunity Against HIV and Other Dangerous Pathogens

Lead investigator: David Baltimore, California Institute of Technology, US, \$13.9 million

Thermostable Vaccines With Improved Stability at Non-Refrigerated Temperatures

Lead investigator: Marazban Sarkari, RxKinetix, Inc., US, \$789,000

Development of a Targeted Mucosal Vaccine Delivery Technology

Lead investigator: David D. Lo, Neurome, Inc., US, \$3.9 million

Nanoemulsions as Adjuvants for Nasal-Spray Vaccines

Lead investigator: James R. Baker, University of Michigan, US, \$6.3 million

no exception. Vaccine trials were initiated in India and China, and feasibility and preparedness trials were initiated in additional countries. (See the map of countries where vaccine research is underway or planned on page 08 and a list of current trials on page 10-11.) “These trial sites in communities of high HIV incidence and prevalence offer opportunities in terms of further studies of protective immunity and for future efficacy trials, but we still need to develop capacity and infrastructure in the coming years,” said Pontiano Kaleebu of the Uganda Virus Research Institute. “And scientists and researchers from these communities can be active partners in basic science and product development as well as in implementing clinical trials.”

For those focused on research aimed at developing new prevention technologies or interventions, though, the past year also provided a startling wake-up call for how research can and cannot be done in the developing world. Controversies surrounding the conduct of trials to test whether tenofovir, a drug now widely used in treatment of HIV/AIDS, could also be used as pre-exposure prophylaxis—a product HIV-negative people could take regularly to reduce their risk of HIV infection—lend urgency to our call made in last year’s report:

Instead of doing research *on* communities, scientists need to do research *with* communities. Instead of narrowly focusing on trial outcomes only, scientists need to care about the overall health of individuals and their communities.

AVAC published a thorough report in March (*Will a Pill a Day Prevent HIV? Anticipating the Results of the Tenofovir “PREP” Trials*), and we provide an update elsewhere in this year’s report. (See page 42.)

Many of the issues AVAC has always been committed to—accelerated research and product development,

meaningful community involvement and education, commitment to research ethics, global access, and policy analysis—are as relevant to PREP (and other biomedical prevention technologies) as they are to AIDS vaccines. All interested parties—researchers, community advocates, policy makers in developed and developing countries and others—must work together to solve the problems and controversies surrounding the PREP trials. Answering these questions will help pave the way for multiple AIDS vaccine efficacy trials and eventual access to an AIDS vaccine and other biomedical prevention methods.

Training partnerships such as OCTAVE should include community literacy for researchers as part of their curricula and should consider developing adequate training programs for Good Community Practice that could be made readily available to leaders of communities where trials will be held.

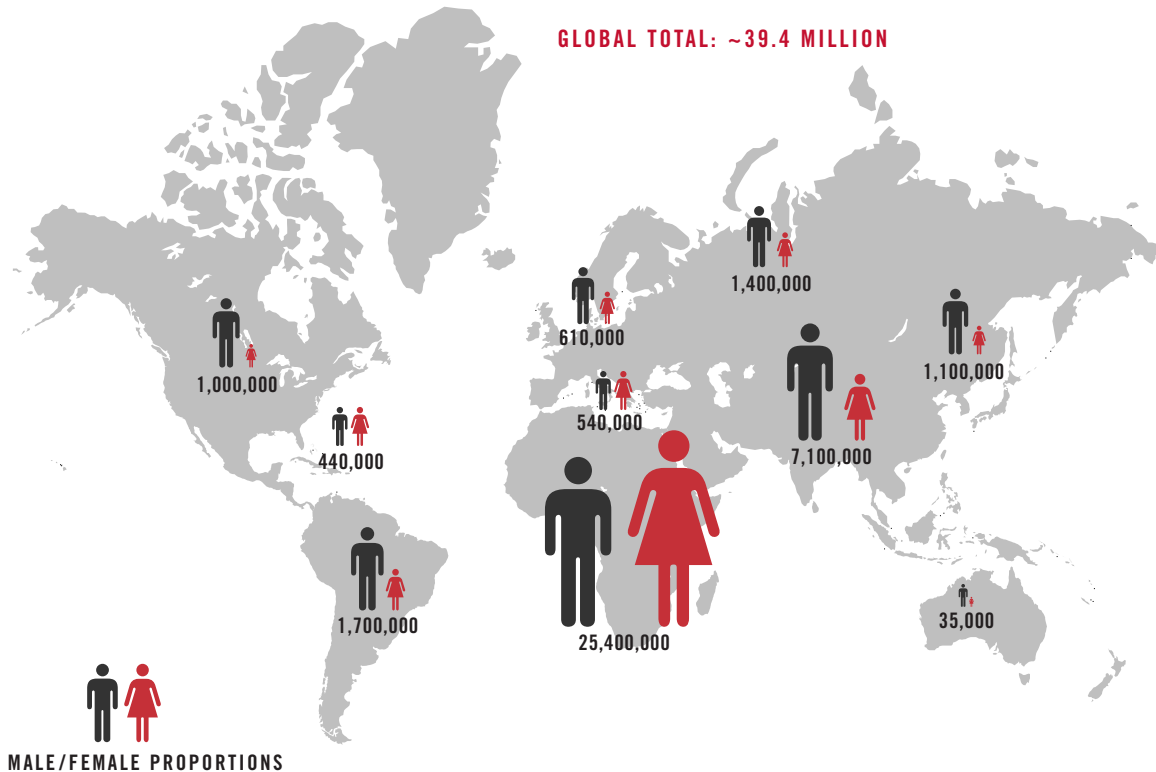
AVAC also reiterates its commitment to a truly comprehensive response to the epidemic. We would like to think that this is obvious, but there still seems to be a desire to pit methods against one another: prevention or treatment, vaccines or microbicides.^o

The world needs combination HIV therapy and combination HIV prevention. In the current lexicon of the “ABCs” of HIV prevention, we argue for a much more robust alphabet. In addition to ABC, (Abstinence, Be Faithful, Condoms) we need to add Clean Needles, HIV Testing, and Expanded Access to HIV Treatment now, as well as Microbicides, PREP Regimens and Vaccines when they are proven effective.

In the next year, we look forward to working with others to help ensure that prevention research continues and improves in the context of demands for better collaborations.



ESTIMATED NUMBER OF PERSONS LIVING WITH HIV/AIDS (DECEMBER 2004)



Source: UNAIDS, December 2004

TAKING NEW ROADS MEANS ENTERING UNCHARTED TERRITORY

So what makes this crossroads different from previous junctions in the road to an AIDS vaccine? How do we build momentum to keep moving forward? As the Global Enterprise, CHAVI, the Gates Foundation, and other partnerships bring welcome cooperation and funding, we need to adjust the way we work.

- + We need new ways of thinking about research and research partnerships and new ways of ensuring data sharing and coordination of technology.
- + We need coordination of assays and study designs to find the best candidate in each category and also planning of combinations of products based on data, not convenience of ownership.
- + We need new ways of thinking about partnerships and communications among researchers and communities.
- + We need intellectual property arrangements that will not only enable but spur cooperative research and participation of all stakeholders.

- + We need researchers willing to venture out onto the precipice of innovation and funders willing to fund those chances.
- + We need new policies and legislation in developed and developing countries that help foster the global work of AIDS vaccine development.
- + We need data-driven, just-in-time decision making.
- + We need to be strategic in planning now for various scenarios as we move forward.

A decade ago when AVAC started out, we hoped that by now we would at least have the end of the road in sight. In 1998, a year after President

Clinton's call for a vaccine within a decade, we published *Nine Years and Counting*. Though we stopped counting time last year, we continue to believe that progress (or lack of it) can be measured rigorously as part of this new way of working. We believe AVAC's role in watching, analyzing, assessing and recommending for the field as a whole will continue to be useful.

CHAPTER FOOTNOTES

¹ Klausner, R. et al. "The Need for a Global HIV Vaccine Enterprise," *Science* 2003 300: 2036-2039

² Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise (2005) "The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan," *PLoS Med* 2(2): e25


FOR MORE INFORMATION

- + AVAC's tenofovir report, *Will a Pill a Day Prevent HIV?* is online at <http://www.avac.org/pdf/tenofovir.pdf>
- + "The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan" is online at http://medicine.plosjournals.org/archive/1549-1676/2/2/pdf/10.1371_journal.pmed.0020025-L.pdf
- + "The Need for a Global HIV Vaccine Enterprise" is online at <http://www.sciencemag.org/cgi/reprint/300/5628/2036.pdf>
- + AVAC's *AIDS Vaccine Handbook* is online at <http://www.avac.org/handbook>

TEN YEARS AND COUNTING...

AVAC Looks Back at a Decade of Recommendations

Since its founding on World AIDS Day 1995, AVAC has been monitoring the state of AIDS vaccine research and making recommendations to researchers, policy makers, communities, funders, and others to help ensure that the field stays on target to find a safe and effective AIDS vaccine as quickly and as ethically as possible. In this decade, we have seen increased commitments to AIDS vaccine research from governments, communities and researchers. We have seen new players: IAVI, the Gates Foundation, and industry and biotech companies have joined the search. We have seen extremes of optimism and doubt. Over the years, some of our recommendations were heeded, some were not—and many kept coming back again and again. This timeline offers a glimpse of the road behind us.

YEAR	RECOMMENDATIONS	OUTCOMES AND EVENTS
<p>1996</p> <p>Industry Investment in HIV Vaccine Research</p> 	<p>To fully engage private sector resources in the effort to develop an HIV vaccine:</p> <ul style="list-style-type: none"> + Increase government funding for HIV vaccine research. + Target scientific research to stimulate industry investment. + Expand commitment by large pharmaceutical companies. + Increase commitment by affected communities. + Expand public leadership. <p>The US President should make development of a safe, effective and inexpensive vaccine by 2007 a national priority.</p>	<p>UNAIDS and IAVI are formed.</p> <p>Early-phase AIDS vaccine trials have already been conducted in US by NIH through its AIDS Vaccine Evaluation Group, by Walter Reed Army Institute with Thai government, and by US and European pharmaceutical and biotech companies in US, Europe, Thailand, Brazil and China.</p> <p>NIH AIDS review (Levine Report) identifies vaccine-related research as a highest priority and recommends formation of an external HIV vaccine oversight board.</p> <p>AVAC interviews 23 companies with active or once-active HIV vaccine programs and makes five key recommendations shown here.</p>
<p>1997</p>	<p>President Clinton calls for a commitment to develop an AIDS vaccine within the next decade (on May 18, which becomes HIV Vaccine Awareness Day in subsequent years). G8 summit leaders call for an AIDS vaccine.</p> <p>New vaccine research awards by IAVI and amFAR.</p> <p>NIH forms AIDS Vaccine Research Committee, chaired by David Baltimore. Innovation Grants for HIV vaccine development program is initiated at its request. (Some years later, this committee is redefined as a working group.)</p> <p>AVAC holds National AIDS Vaccine Advocates Forum in San Diego.</p>	


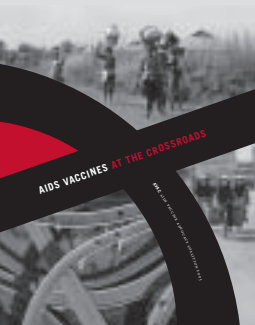
TEN YEARS AND COUNTING... *Continued*

YEAR	RECOMMENDATIONS	OUTCOMES AND EVENTS
<p>1998</p> <p>Will We Have an HIV Vaccine by 2007?</p> 	<p>At the current level of effort, we will not have an HIV vaccine in nine years. Unless more is done, the President's challenge will not be met:</p> <ul style="list-style-type: none"> + Agencies funded to conduct HIV vaccine research and development must establish clearer plans and goals to expand the HIV vaccine pipeline. + The US government must be clear about who should take responsibility and accountability to achieve these goals. + Increased commitment, funding and courage is required from all sectors. 	<p>IAVI initiates its first development partnerships, obtaining IP rights for international access.</p> <p>There are 9 products in Phase I testing, 5 in Phase II. VaxGen, with private financing, opens first Phase III efficacy trial in US, Canada, and the Netherlands, that is followed by a 2nd trial in Thailand; these trials ultimately enroll nearly 8000 volunteers.</p> <p>NIH revamps and expands initiatives in the areas between basic research and preclinical development.</p> <p>Existing NIH vaccine evaluation (Phase I-II) and efficacy trials/preparedness programs are reconfigured into Vaccine Trials Network and Prevention Trials Network.</p> <p>AVAC countdown begins.</p>
<p>1999</p> <p>What Will Speed Development of an AIDS Vaccine?</p> 	<p>US Government must request adequate funding increases, coordinate efforts, and set and adhere to interim goals.</p> <p>Expand the UNAIDS effort.</p> <p>Private industry must invest in a big way and leverage its private investment.</p> <p>Not-for-profits and community organizations must mobilize support for research and industry involvement, unite and organize, institutionalize CAB and community involvement and work for access.</p>	<p>South African AIDS Vaccine Initiative (SAVI) is formed. First African AIDS vaccine trial begins in Uganda.</p> <p>All major vaccine companies appear to be working on HIV vaccines.</p> <p>Rep. Pelosi and Sen. Kerry introduce Lifesaving Vaccine Technology Act, first legislation to propose incentives for vaccines for AIDS, TB, and malaria, but Congress takes no action.</p> <p>1st <i>HIV Vaccine Handbook</i> published by AVAC.</p> <p>AVAC formally requests that NIH set milestones for vaccine development, suggesting six areas for tracking.</p>

YEAR	RECOMMENDATIONS	OUTCOMES AND EVENTS
<p>2000</p> <p>How Can We Overcome Obstacles to an AIDS Vaccine?</p> 	<p>Expand government programs as rapidly as they can effectively handle expansion.</p> <p>Pass legislation that provides incentives for private sector involvement in HIV vaccine research-both “pushes” and “pulls” are needed because purposeful company activity is crucial.</p> <p>Fund public outreach, education and communication programs.</p>	<p>AIDS is finally understood to be a social, economic and security threat.</p> <p>UNAIDS publishes its guidance on ethical considerations in HIV preventive vaccine research.</p> <p>WHO/UNAIDS African AIDS Vaccine Program (AAVP) is formed.</p> <p>EU pledges new funds for HIV vaccines. Bill & Melinda Gates Foundation grants \$100 million to IAVI.</p> <p>The public-private partnership, Canadian network for Vaccines and Immunotherapeutics (CANVAC) is formed.</p> <p>Growing importance of international research, with active clinical trials and trials planned in 13 countries by 7 groups.</p> <p>The Dale and Betty Bumpers Vaccine Research Center (VRC) is opened and Gary Nabel is named Director.</p> <p>NIAID agrees to set annual milestones for products it supports and for funding initiatives.</p>
<p>2001</p> <p>Can a Shifting Landscape Accelerate an AIDS Vaccine?</p> 	<p>AVAC proposes a new vision for vaccine development:</p> <ul style="list-style-type: none"> + Gaps in research are filled. + The public is engaged. + Enlightened self-interest reigns. + Every avenue is pursued. + Leadership is ongoing. + Lives in the developing world matter. + Taking risk is rewarded. 	<p>About 15 new products are poised to begin clinical trials. IAVI DNA+MVA enters trials in Kenya. Merck and NIAID agree to collaborate on DNA and Ad5 vaccine trials.</p> <p>HVTN drop plans for Phase III study of ALVAC +gp120. Thai/Walter Reed trial goes forward.</p> <p>AVAC identifies FDA and patent issues as critical to vaccine development and has first meetings with FDA.</p> <p>Two books on HIV vaccines are published, <i>Big Shot</i> (P. Thomas) and <i>Shots in the Dark</i> (J. Cohen).</p>

TEN YEARS AND COUNTING... *Continued*

YEAR	RECOMMENDATIONS	OUTCOMES AND EVENTS
<p>2002</p> <p>Science, Urgency, and Courage</p> 	<p>AVAC issues a community call to action, asking individuals, communities and organizations to incorporate advocacy for AIDS vaccines into your work and your life:</p> <ul style="list-style-type: none"> + Protecting trial participants. + Accelerating ethical research. + Involving and educating communities. + Ensuring global vaccine access. 	<p>US Congress passes legislation to stimulate research and investment, accelerate regulatory processes, accept liability, and create adequate purchase capacity for bioterror vaccines.</p> <p>Department of Defense HIV research program transferred to NIH.</p> <p>The European Union and member states create EuroVacc, the European Vaccine Effort against HIV/AIDS.</p> <p>EuroVacc and CANVAC develop collaborative networks.</p> <p>AVAC's legal advisors identify over 1000 issued patents in 13 selected HIV vaccine component categories.</p>
<p>2003</p> <p>How Do You Fight a Disease of Mass Destruction</p> 	<p>A more systematic, integrated AIDS vaccine effort is needed to:</p> <ul style="list-style-type: none"> + Ensure products are not unnecessarily delayed en route to human trials. + Fully utilize advances in standardization of assays and validation procedures while retaining flexibility to develop and use new assays. + Serve the multiple needs common among vaccine producers: access to non-human primates, development of isolates and reagents and prepared clinical sites. + Meet international standards for multi-site trials, provision of treatment and community involvement. 	<p><i>Science</i> magazine publishes call for Global HIV Vaccine Enterprise.</p> <p>VaxGen results show Phase III trials are feasible, though reporting of results and results themselves are disappointments.</p> <p>First HIV vaccine trials in South Africa begin after long delays.</p> <p>AVAC analyzes NIH, IAVI, and WRAIR milestones. Altogether only 10 products entered Phase I and only 3 entered Phase II in 3 years since 2000. In analysis of “me-too” products in clinical trials, 52% are DNA and/or MVA, 29% are ALVAC variations, and only 19% test other approaches.</p>

YEAR	RECOMMENDATIONS	OUTCOMES AND EVENTS
<p>2004</p> <p>AIDS Vaccine Trials—Getting the Global House in Order</p> 	<p>Well-designed clinical trials are a necessity:</p> <ul style="list-style-type: none"> + Clinical trials cannot be confined to the industrialized world. + Trial infrastructure must be created. + Efficacy trials cannot be done overnight. + Clinical trials are just one element of the vaccine development process. 	<p>G8 endorses the Enterprise, and over 100 scientists collaborate on its mission and initial scientific plan in six critical areas.</p> <p>12 new products enter Phase I clinical trials. VaxGen Thai trial shows no efficacy.</p> <p>IAVI is developing six international trial sites.</p> <p>PAVE partnership of US government agencies plus IAVI is announced.</p> <p>AVAC defines 14 correlates of readiness for international vaccine trials, identifies adolescents as “the missing cohort,” and describes 8 ways vaccine trials can leave communities better off.</p>
<p>2005</p> <p>AIDS Vaccines at the Crossroads</p> 	<p>Scientists must follow an evidence-based agenda and work to achieve antibody, mucosal and innate immune responses.</p> <p>The Enterprise and other collaborators must address knowledge sharing, intellectual property, regulatory and access issues.</p> <p>Funders must improve incentives and support to bring talented young scientists into the field.</p> <p>Trial hosts and sponsors must engage civil society more fully and integrate local prevention, testing and treatment with trials.</p> <p>Leaders must implement strategies speedily with foresight and accountability.</p>	<p>Enterprise publishes its scientific plan in Public Library of Science and convenes its first stakeholders’ and funders’ fora.</p> <p>NIH and Gates Foundation commit up to \$900 million of new money for Enterprise-related initiatives. CANVAC loses its government funding.</p> <p>First proof of concept efficacy trial begins Ad5 vaccine in Western Hemisphere and Australia, by Merck and HVTN. IAVI opens first HIV vaccine trial in India. Large canary-pox/gp120 efficacy trial in Thailand nears full enrollment.</p> <p>Peer review of multipurpose international and domestic clinical trial sites and networks by NIH.</p> <p>AVAC publishes 2nd <i>AIDS Vaccine Handbook</i>, focused on global perspectives.</p>

02



GET ENTERPRISING



GET ENTERPRISING

It has been just over two years since the publication of an article in *Science* magazine calling for a new Global HIV Vaccine Enterprise to foster coordination in the search for an AIDS vaccine.¹ Since that time, many meetings have been held and working groups formed. With the publication of a strategic

scientific plan in early 2005 in *PLoS Medicine*, the Enterprise moved a step closer to becoming reality.² We hope to see two year's of organization lead to real action when its first executive director is appointed later this year. We offer here an open letter to the director with our thoughts on the eight issues that should be addressed.



MEMO

To: The new Executive Director of the Global HIV/AIDS Vaccine Enterprise
From: The AIDS Vaccine Advocacy Coalition (AVAC)
Subject: Get enterprising—quickly
Date: September 2005

Welcome to the first day of your new job!

The Scientific Strategic Plan of the Enterprise, published in February of this year, identifies scientific priorities in AIDS vaccine development and begins to look at ways of addressing those priorities. A number of committees—from the International Coordinating Committee, to working groups, to technical expert groups—have been meeting and discussing ways to move this initiative forward.

There are many issues that need to be quickly addressed as the Enterprise shifts from planning to action. AVAC believes that the following eight concrete tasks should be the focus of your work from the first day.

01 COMMUNICATE FREQUENTLY AND TRANSPARENTLY

There are many people anxiously waiting to see how the Enterprise will work. There are many others who know little or nothing about it, but whose help you will need if the Enterprise is to succeed. To lead the field, you must commit to transparency and clear communication. This will not be easy, but it is critical to the success of the Enterprise. Communicate frequently to as large an audience as possible about the

work of the Enterprise and its partners. Your communications plan must be international in scope and should reach beyond the parochial borders of AIDS vaccine researchers and advocates.

02 SET POLICIES FOR SHARING AND COORDINATING OF DATA AND TECHNOLOGY

Arguably the most important component of the Enterprise's scientific plan is the goal of creating a common pool of data, reagents, assays and technologies that cooperating researchers can draw upon. This will address one of the major roadblocks in AIDS vaccine development to date. AVAC believes that publicly available incentives, policies and procedures need to be put into place by the Enterprise Secretariat to ensure full and fair sharing of data and technology. Researchers from academia to government to big industry have that obstacle as a high priority to solve. It is up to you to build a technical and legal framework that will make this possible.

03 ENSURE THE ABILITY TO TAKE RISKS

As the Enterprise works to coordinate vaccine development efforts, bringing together the best minds (many of whom have been searching for a vaccine for decades), it is important that valuable ideas are not left behind. Seek out and foster innovation in basic research, vaccine development, community advocacy, and regulatory and intellectual property issues—and all areas that have the potential to contribute to the faster development and ultimate distribution of a safe and effective AIDS vaccine.

04 BRING NEW INVESTIGATORS INTO THE SEARCH

To ensure that the momentum continues apace, it is critical to bring young investigators into the search now. Scientific research fields are growing and changing rapidly, making the competition for the best and the brightest scientific minds fierce. But AIDS vaccine research still offers exciting opportunities to young researchers, and the chance to contribute to solving the greatest public health threat of our lifetime. Ensure that there are adequate incentives for young researchers (from developed and developing countries) to enter the field and work with current researchers.



05 MAKE THE ENTERPRISE TRULY GLOBAL

The Enterprise has been seen by many—fairly or not—as a US organization. In part, this is because the majority of funders and scientists working on basic research and AIDS vaccine development are based in the US (or Europe), and that will likely continue to be the case. But there are scientists outside of Europe and the US who have valuable contributions to make, and vaccine development does not stop at the doors of a laboratory. Clinical trials need to be carried out in countries around the world, and we need to always prepare communities where the vaccine is most needed. Brazil, China,

India, South Africa, Thailand and an increasing number of other countries have growing pharmaceutical R&D and manufacturing capacities. There are many people and organizations around the world with significant contributions to make to the enterprise of developing an AIDS vaccine. Seize the opportunity to be a truly global leader by reaching out to all of them.

06 INVOLVE CIVIL SOCIETY IN A MEANINGFUL WAY

Civil society in both developed and developing countries has a critical role to play in helping the Enterprise achieve its goals. AVAC has been involved from the beginning—Chris Collins, then executive director, was a co-author of the 2003 *Science* article, and AVAC staff and board members have attended meetings and served on working groups and committees as the Enterprise has developed. A wider group of civil society leaders came together in London in May 2005 to hear about the Enterprise and to offer suggestions. For many who attended, it was their first opportunity to hear plans for the Enterprise and offer input. This dialogue should be expanded, and you should specifically ask members of civil society how best to establish the mechanisms for their input, then work to incorporate their valuable insights into the framework of the Enterprise. It is not enough to listen to suggestions; we must find meaningful ways to engage civil society in this effort.

07 TAKE ON THE POLITICS AND ETHICS OF CLINICAL TRIALS

The tenofovir prevention trials in Asia and Africa have shown us that there are still many unresolved issues surrounding the politics and ethics of clinical trials of new prevention technologies. The Enterprise cannot focus only on scientific bottlenecks and leave the political and ethical bottlenecks to resolve themselves. The HVTN, IAVI, NIH and UNAIDS have all made strides in responding to community concerns and addressing issues around provision of treatment and care to trial participants. You should build

strong relations with the Global Fund, WHO and the President's Emergency Plan for AIDS Relief (PEPFAR) program that encourage them to work in close collaboration with vaccine research efforts so that expanded access to prevention and treatment today are linked to the development of new technologies for tomorrow.

08 ESTABLISH REALISTIC MILESTONES AND A PROCESS FOR MONITORING PROGRESS

Dozens of individuals—researchers, funders, policy makers and community advocates—have worked together on a voluntary basis to get the Enterprise to this point. The strategic plan lays out the major issues and begins to articulate the way forward. Now, a much more concrete plan is needed as the true work begins. AVAC believes that within the first six months on the job, you should articulate a set of milestones for the Enterprise to achieve over the

next two years. Moreover, this plan should identify a process to monitor progress, achieve accountability, and modify plans accordingly.

The world will be watching as you and the Enterprise Secretariat begin to turn a plan into a structure. We know that what we have suggested will not be easily achieved, but we believe that it can and must be done—and done quickly—if the Enterprise is to succeed.

CHAPTER FOOTNOTES

- ¹ Klausner, R. et al. "The Need for a Global HIV Vaccine Enterprise," *Science* 2003 300: 2036-2039
- ² Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise (2005) "The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan," *PLoS Med* 2(2): e25

FOR MORE INFORMATION

- + "The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan" is online at http://medicine.plosjournals.org/archive/1549-1676/2/2/pdf/10.1371_journal.pmed.0020025-L.pdf
- + "The Need for a Global HIV Vaccine Enterprise" is online at <http://www.sciencemag.org/cgi/reprint/300/5628/2036.pdf>

03

FOLLOW THE MONEY: MONEY, DEVELOPMENT & RESEARCH



**FOLLOW THE MONEY: MONEY,
DEVELOPMENT & RESEARCH**

This was the year everyone was talking about “development” (of economies, if not AIDS vaccines). Big financial promises were made and creative financing tricks were created. World leaders are finally beginning to come to grips with the fact that the paltry sums spent on global health delivery and health R&D are not sufficient to accomplish the closely related goals of taming major epidemics and making sustained economic progress in poor countries. But how to pay for what we know is needed?

The price tag was updated in several categories this year. UNAIDS said US\$15 billion will be needed in 2006 to fund HIV prevention, treatment, orphan care and human resource costs. That is over \$6 billion more than what is currently pledged.

A study from AVAC, IAVI, the Alliance for Microbicide Development and UNAIDS estimated total spending on AIDS vaccine research in 2004 at just under US\$700 million.¹ It noted significant overall increases in spending on this research in recent years and higher funding levels expected in 2005 given current commitments. But it found an actual *decrease* in investment by the private sector (not good news

since much of the expertise to make vaccines resides there). The report called for substantial new funding to accelerate the hunt for an AIDS vaccine.

At this year’s G8 Summit, there was no paucity of ideas about how to come up with more resources. When they met in Scotland in July, leaders of the richest countries considered a range of proposals:

- + *Promise:* The G8 pledged to double aid to Africa by 2010 but balked at living up to commitments to spend 0.7% of GDP on development.

- + *Forgive:* An agreement on 100% debt relief was a major Summit accomplishment.

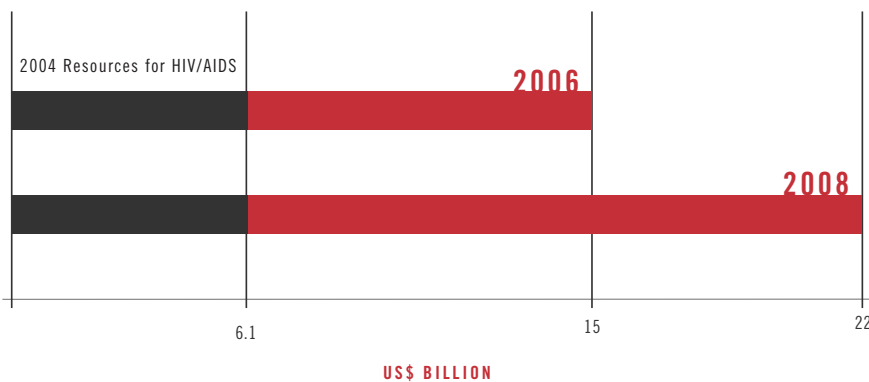
G8 leaders made the cryptic promise to “take forward” a range of other proposals:

- + *Tax:* The “air-ticket solidarity levy” proposed by the French.

- + *Borrow:* Loans on future development monies through an “International Financing Facility” proposed by the English and others.



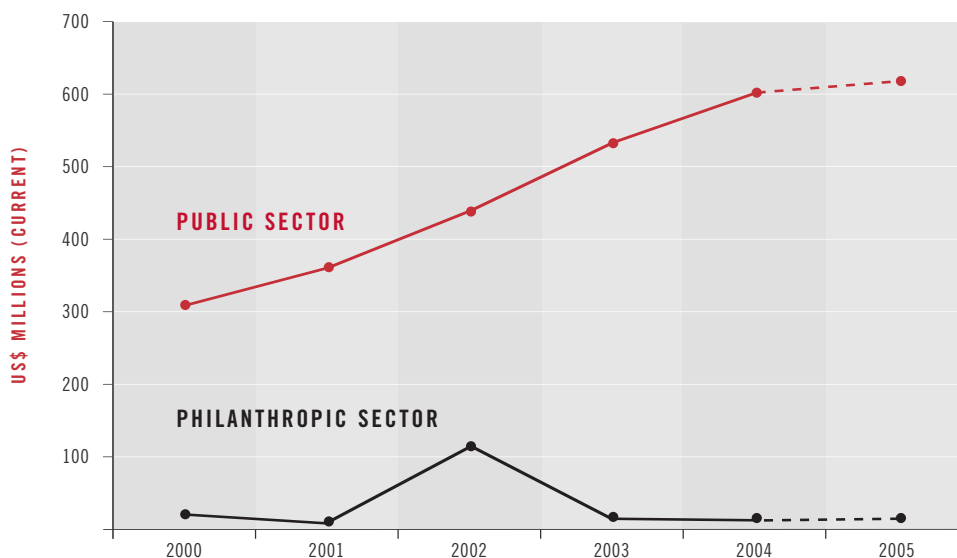
ESTIMATED FUNDS NEEDED TO RESPOND TO GLOBAL AIDS EPIDEMIC



Note: This estimate does not include funding for HIV/AIDS research.
Source: Kaiser Family Foundation and UNAIDS



FIGURE 1. ANNUAL INVESTMENTS IN PREVENTATIVE HIV VACCINE R&D BETWEEN 2000-2005



Source: HIV Vaccines and Microbicides Resource Tracking Working Group, *Tracking Funding for Preventive HIV Vaccine Research & Development*
2005 estimates are based on actual disbursements and firm commitments made as of April 5, 2005.

- + *Stimulate*: Public Private Partnerships and Advance Purchase Commitments, both of which got a nod in the G8 communiqué.

What does all this mean for financing the development of AIDS vaccines? The big public money in AIDS vaccines has come from the US, with notable contributions from Canada, the UK and Ireland. The Gates Foundation has also made substantial investments. Getting money into AIDS vaccines now requires the laggard but rich countries of Europe, as well as Japan, to make the decision to increase overall investment to fight AIDS, including vaccines—however they decide to pay for it.

The advance purchase commitment is a worthy proposal, valuable for pushing investment in many important vaccines of the future. We do not know how much an advance purchase commitment will

actually spur investment in AIDS vaccines (which are many years off, with large and unknowable investments required, and for which there is already a rich country market). Still, a legally binding commitment to buy large quantities of AIDS vaccines for poorer countries can only help when the time comes. Work should be performed to determine the needed threshold amount.

AIDS vaccine research is increasingly set in the context of other development issues. It's hard to think of another product that could do more to help accomplish long term development goals. But the link between AIDS vaccines and development needs to focus on the short term as well. We need to discuss how resources in AIDS vaccine clinical trials can help advance HIV prevention, testing, treatment, community engagement and infrastructure development in communities involved in research.

As we wait for better products to enter testing, everyone involved in AIDS research needs to ask: Are we using current clinical resources to maximum effect in the resource-limited countries hosting trials? Is AIDS vaccine research appropriately coordinated with treatment and prevention scale-up efforts on the ground? We need to understand AIDS vaccine research as part of the development equation, long-term and short-term.

As part of this, we urge the US Congress and other development agencies to link their support for

expanding prevention and treatment programs (such as the Global Fund, PEPFAR and WHO) to work in close collaboration with the vaccine research efforts so that primary prevention and expanded access to treatment today are linked.

CHAPTER FOOTNOTES

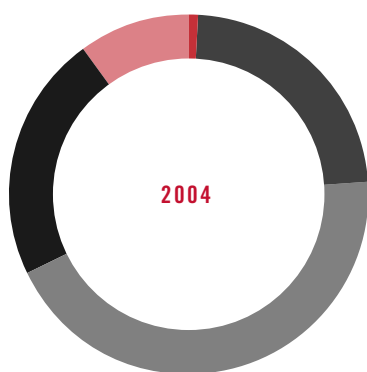
¹ HIV Vaccines and Microbicides Resource Tracking Working Group, *Tracking Funding for Preventive HIV Vaccine Research & Development: Estimates of Annual Investments and Expenditures 2000 to 2005*

FOR MORE INFORMATION

- + *Tracking Funding for Preventive HIV Vaccine Research & Development: Estimates of Annual Investments and Expenditures 2000 to 2005* is online at http://www.avac.org/pdf/vacc_inv_exp_june_05.pdf
- + The 2005 G8 Communique on Africa is online at http://www.fco.gov.uk/Files/kfile/PostG8_Gleneagles_Africa,0.pdf



TOTAL EXPENDITURES ON PREVENTIVE HIV VACCINE R&D BY CATEGORY

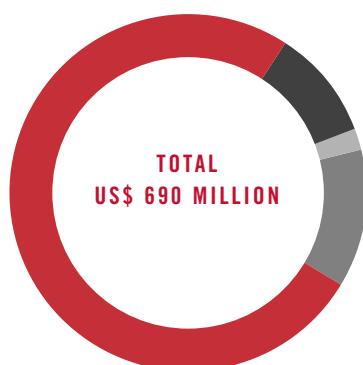


- Advocacy & Policy Development: 1%
- Cohort & Site Development: 10%
- Clinical Research: 22%
- Pre-Clinical Research: 44%
- Basic Research: 23%

Source: HIV Vaccines and Microbicides Resource Tracking Working Group, *Tracking Funding for Preventive HIV Vaccine Research & Development*



2004 AIDS VACCINE R&D FUNDING



■ Public-US Government: 76%

■ Commercial: 10%

■ Philanthropic: 2%

■ Public-Non-US: 12%

Source: HIV Vaccines and Microbicides Resource Tracking Working Group, *Tracking Funding for Preventive HIV Vaccine Research & Development*



ANNUAL INVESTMENTS IN PREVENTIVE HIV VACCINE R&D BETWEEN 2000 AND 2005

	2000	2001	2002	2003	2004	2005
PUBLIC						
US	272	314	376	463	516	568
Europe ¹	23	32	39	44	57	39
Other ²	10	12	21	24	28	8
Multilaterals	2	2	2	2	2	2
Total Public	307	360	436	533	603	617
PHILANTHROPIC						
Total Philanthropic	20	7	112	15	12	10
COMMERCIAL						
Pharmaceutical Companies	—	—	—	—	59 (47-71 range)	—
Biotechnology Companies	—	—	—	—	9 (7-11 range)	—
Total Commercial	—	—	—	—	68 (54-82 range)	—

¹ This figure includes funding from the European Commission

² Other includes all national public sector funding apart from funding from the US and Europe

Source: HIV Vaccines and Microbicides Resource Tracking Working Group, *Tracking Funding for Preventive HIV Vaccine Research & Development*



Decades of lonely lament by public health advocates about the state of the vaccine industry are now over. Suddenly (since the tragedy of September 11 and scary reports from chicken farms in Southeast Asia), Washington insiders are bemoaning the industry's tribulations as well. Republicans and Democrats alike seem to want pharmaceutical and biotech industries to use some of their expertise creating vaccines against anthrax, smallpox and AIDS, not to mention making sufficient quantity of usable flu shots.

THE BIOTERROR—INFECTIOUS DISEASE CONNECTION

Four years ago, the US government responded to newly perceived bioterror threats with impressive alacrity, ramping up spending at NIH, procuring quantities of vaccines and making it easier to cut around red tape to get the work done. Last year Congress passed Project Bioshield which authorized \$5.6 billion to buy bioterror “countermeasures” (including vaccines). A principal goal of the legislation was to demonstrate to industry that a paying market exists for bioterror products. But company representatives and others said it was not enough to overcome the considerable disincentives for private investment in countermeasures.

This year, US Senator Joe Lieberman from Connecticut and his staffer, Chuck Ludlam, set to work on second generation legislation—Bioshield II. The Lieberman office was wise to recognize that the real problem is not just about getting industry engaged in bioterror, it's about addressing longstanding market breakdown in the vaccine and other health technology fields and marshalling private sector know-how in the biggest public health battles of the day. AVAC and a large group of public health advocacy organizations were very happy that Bioshield II included an array of incentives for infectious disease products like AIDS vaccines, along with countermeasures against weapons of terror.

The term “kitchen sink” could have been invented for Bioshield II. This legislation incorporates most of the industry-stimulating ideas that have been floating around for several years. These include expanded procurement programs, a selection of five tax credits, extended patent rights and liability protections. Title IV of the bill, stunningly named “The Valley of Death” provision, would offer an array of benefits to engage small companies. The most controversial provision of the bill would grant a “patent-exchange” to companies who could swap a patent on an AIDS or anthrax vaccine for extension of their patent on a blockbuster drug like Viagra® or Lipitor®.

Bioshield II is a commendable effort and a very complex bill. (In fact, the bill summary from the Senator's office warns readers that to fully understand the bill, “one needs command of a broad range of disciplines: the science of evolving threats; zoonotic diseases and bioagriculture threats; biopharma industry economics; procurement, tax, patent, and liability law; ... regulatory policy; animal models, human clinical trials, adjuvants, and vaccine industry issues; ...antitrust, export license, and visa law; Nunn-Lugar programs...”)¹

Congress should act on Bioshield II but take the time to look at the complexities and clean up the loose ends. We have a few concerns.

First, lawmakers need to review the legislation to make sure it would not inhibit rapid global delivery of the infectious disease products whose creation it seeks to stimulate. Provisions like the extended market exclusivity period may not have a negative impact on access to AIDS vaccines because, due to the technological complexity involved, these products are not likely to go generic soon after licensure. The story is different with urgently needed drugs to treat global infectious diseases. If applied to global markets, schemes like an extended market exclusivity period may keep prices high and delay widespread



access to the product unless other measures—such as voluntary licensing, price tiering, increased purchase capacity and access to approved generics—are in place.

Our understanding is that the liability protection provisions in Bioshield II would apply to claimed injuries during clinical trials. This is an important protection for AIDS vaccine makers, and it should stay in the bill. Some kind of administrative system is needed, similar to that now in place for marketed childhood vaccines, that reviews the liability claims of trial volunteers and provides compensation where justified. Still, we encourage lawmakers to make sure liability protection for industry is not overly broad. For example, we have been told that, under the bill, if vaccine makers are found “negligent,” victims would be compensated by the

government rather than the company. We are not sure that expansive level of corporate protection is justified.

Finally, the patent exchange provision is perhaps the bill’s most potent incentive for industry, but it’s a political nonstarter. It might have a place in a world in which seniors and others don’t have to empty their pocketbooks to buy expensive on-patent drugs. Removal of the provision will make the bill less of a political liability for would-be supporters.

SIDEBAR FOOTNOTES

¹ Office of Senator Joe Lieberman, Bioshield II, S.975; Section by Section

FOR MORE INFORMATION

- + Bioshield II, Senate Bill 975 can be found online at <http://thomas.loc.gov>
- + The section by section description of the bill is online at <http://lieberman.senate.gov/newsroom/reports/bioshieldsectionbysection.pdf>

04



INTELLECTUAL PROPERTY **AT THE CROSSROADS**



INTELLECTUAL PROPERTY AT THE CROSSROADS: UNIQUE CHALLENGES FOR AIDS VACCINES

The unique basic science, components and development steps for AIDS vaccines make them among the most difficult biomedical interventions to invent. As Barry Bloom of the Harvard School of Public Health has said, “The easy vaccines have already been made.”¹ Making AIDS vaccines is further complicated by intellectual property (IP) issues. One candidate AIDS vaccine may employ technology or biological materials requiring a dozen or more dispersely owned rights as well as needed access to data and samples the sponsor alone does not have; two in test combination multiplies the permissions needed. The field has great scientific minds to propose good vaccine candidates and combinations for development, but these researchers may be constrained to test what they are most easily allowed to use, rather than what is best from a scientific point of view. Until a way is found to resolve these issues, the field cannot move forward as nimbly as we would like.

Although IP consists of more than just patents—it includes trade secret data, manufacturing know-how, materials transfer and other rights—it has been tempting for some to view IP issues for AIDS vaccines through the lens of patent and license issues for AIDS treatments. But unlike vaccines, AIDS drugs require comparatively few patents covering a small size chemical matter composition and a relatively simple manufacturing process. The issues surrounding patents, pricing and licensing of AIDS drugs, while complicated, represent only a small part of the IP issues for both the near-term R&D for AIDS vaccines and the long-term licensure and use of an effective vaccine. Drugs can be copied generically (as allowed by law) with relatively less skill than is required to manufacture vaccines. Complex vaccines likely could not be made generically; in fact, agencies do not yet allow it. As a high molecular

weight biologic, rather than a small compound drug, a vaccine is made with living material and must be grown and made in a carefully controlled environment that requires private know-how companies will not share. The VRC—a government entity with sophisticated production power—may open up its process capabilities.

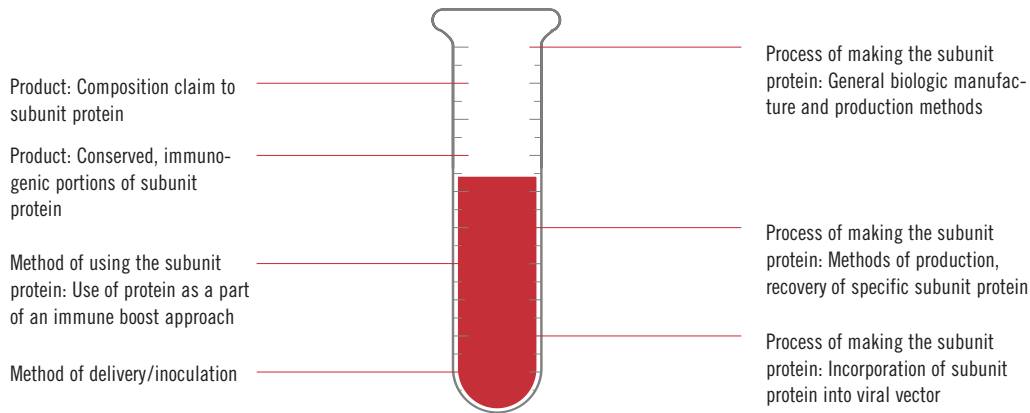
Making vaccines involves numerous overlapping thickets of patents and rights. For an AIDS vaccine, the correlates of protection and basic science are a mystery for now, which means that it is important to make it a priority to expand researchers’ freedom to use the IP they need to develop vaccine candidates and to help find ways to determine value for IP, so that those who own information or technology are adequately compensated. We saw recently, for example, that the government of Canada pulled program research funds because it was thought the work would not “pay.” The vaccine field needs early carrots, not late sticks.

One such expansion came from a June 13, 2005, US Supreme Court decision that broadened the ability of researchers to use compounds that are patented in the US in early preclinical studies without permissions from the patent assignees if the generated data will reasonably lead to submission to FDA for approval (actual submission is not required, though). The Court’s expansion included preclinical studies related to safety, efficacy, mechanism of action, pharmacokinetics or pharmacology. While this ruling is significant in broadening the freedom to operate in early drug development, we don’t know how this will impact vaccine development.

The court did not rule on the preclinical use of (or define) patented research tools used in vaccine discovery or how these research tools differ from patented compounds. Nor does the ruling apply outside the US. Owners of unique biological material,



MANY PATENTS FOR A SINGLE VACCINE CANDIDATE



Example: Candidate vaccine made from HIV-1 subunit protein

Note: HIV vaccine strategies are usually made up of a combination of multiple components. Each component may read on more than one patent and multiple components can read on many patents. Each patent may be owned by a different party, so a vaccine may infringe the patent rights of multiple parties. A trial combining two candidates would increase the number of required rights and the ability to combine the products.

including many private companies, may continue to reserve supplying it for others to use preclinically until long term agreements are hammered out.

Laws and regulations regarding IP differ from country to country, making global AIDS vaccine research, access to data and materials, and testing even more complicated. To further complicate matters, the legal rights of trial volunteers vary from country to country. In the US, trial volunteers specifically give up their rights to blood or other “biobanked” samples taken during a trial and all data derived from the samples as part of the informed consent process, but in other countries those rights are not so easily given up, and advocates in some communities have raised questions about the rights of trial volunteers to share in profits from a potentially effective intervention. These issues will become more important as larger vaccine trials in different countries get underway.

Pricing pressure is not the issue of immediate importance for AIDS vaccines administered a few times at most, nor is it an issue to be addressed within IP rules. For vaccines there is a huge demand but no certainty there will be a supply anytime soon. This means that the international treaties or laws invoked in discussion of AIDS drugs—TRIPS, Hatch-Waxman and generics, The DOHA Declaration—may have little or no effect on the current need to open up the creativity to experiment or bring in all stakeholder participants. It is important to learn the lessons of AIDS drugs and plan to ensure early access to those who most need vaccines, but if we focus only on the long-term goal of access, we lose key opportunities to invent them.

For this effort to succeed, stakeholders of different strengths and position must be encouraged to work cooperatively and share knowledge. The institutional

and economic drivers for government, academia, nonprofits, and large and small companies must be respected. And IP regulations across borders must be harmonized to foster the critical international partnerships that move vaccine development forward. These are not easy tasks.

AVAC RECOMMENDS SMALL-STEP SOLUTIONS

It is impossible to resolve all of the IP issues to speed research and development of AIDS vaccines and to reward innovators adequately to keep them interested. New laws and policies have the potential to help but are slow to take effect. So what can be done in the meantime?

AVAC recommends a few modest, smaller steps that can help foster workable IP arrangements among the many groups involved in this endeavor. Some of the steps discussed here were aired in discussions with other stakeholders in the Global Vaccine Enterprise IP Working Group and in a workshop conducted at the AIDS Vaccine 2003 Conference. We hope that further insights by all stakeholders are forthcoming and that other efforts to stimulate development will continue.

Consortia and Patent Pools

IAVI and the Vaccine Enterprise are to be commended for proposing consortia or collective shared efforts to develop immunogens that induce neutralizing antibodies or cell mediated immunity and useful standardized laboratory assays. To increase success, those efforts should be expanded to entice all capable stakeholders to join, including pharmaceutical and biotech companies that have held back. As the field evolves and advances, new and expanded consortia have the potential to speed development.

Consortium agreements face at least two significant IP obstacles:

- + Determining how participants will value, protect or be proportionately rewarded for their existing IP provided to and used by the consortium.
- + Determining how participants will be allocated rewards for the new IP the consortium creates from its work.

So far, private industry seems to be resistant to joining these consortia. AVAC urges IAVI, the Enterprise and other consortia to publish their consortia agreements and to open public discussion on ways they propose to overcome these obstacles.

Preclinical Covenant Not to Sue and Later Stage Handling of IP

AVAC supports an approach to IP management to track risks and uncertainties as they evolve throughout the changes in the R&D and product development cycle. Preclinical and early stage IP research risks can be substantially reduced while preserving economic rewards. To that end, AVAC has drafted and offers for discussion a model “Covenant Not To Sue” agreement that any party could opt into. (Read the covenant online at www.avac.org/ip.)

The covenant would suspend the ability to limit an investigator’s freedom to operate only during experimental phases—including for research tools or to overcome the reluctance of manufacturers to provide lots for experimentation—but would not require those signing it to give up any rights to economic reward should the research actually prove to be successful later. (It may be best to avoid using the covenant now for purposes of articulating

royalty issues, but further discussion would be helpful.) If the research proves not to be successful, no one is harmed by having permitted experiments to show that. If the research proves successful, the scope of the covenant may be extended, in some circumstances, to use of materials and samples if data are protected.

An approach like this could be an incentive to help invigorate the pipeline, and we look forward to presenting it more fully for discussion with the research community. Further clinical trial agreements would likely require negotiation, after clinical trials were completed, and while final approvals were being granted, so that rights holders would have adequate value information to allocate and reward contributions of IP. At that last stage, government incentives to purchase vaccine products might help developers to recoup the full costs of their efforts and reduce risk of investment even further.

Harmonization Across Jurisdictions

The importance of freedom to operate and study product candidates for generating data to submit to health agencies—such as the US FDA or the European Agency for the Evaluation of Medical Products (EMA)—is critical to accelerating vaccine development. With an increasingly global effort involving trials of a single candidate conducted on several continents, sponsors will benefit from having consistent rules across jurisdictions. The scope of the US and non-US permission for health agency submitted data should be harmonized as should other IP rules.

Clarity for Research Exemptions

AVAC agrees with the US National Academy of Sciences' recommendation this year that the US government reduce IP research risks for projects

funded by government grants. Federal law already gives unique freedom to operate and chance for royalty when patents are used by the government for its own authorized public use. The National Academy and other experts recommend that the government extend its “authorization and consent” to research carried out by others using government’s funds. To avoid inadvertent problems of compulsory licensing, this should be targeted to early stage projects where there is a chance for public harm if licensing is withheld unnecessarily.

Commitments to Access or Benefits for Populations Where Vaccines Are Tested

To offer every trial participant a direct royalty interest in finally licensed vaccines would be an improper inducement for trial participation and would certainly create a disincentive for research sponsors. However, clinical research *should* recognize and reward the burdens trial participants take on—their loss of control over personal data and samples—and their contributions to advances in knowledge for others. Bioethics principles say that studies should be performed only in populations that stand to benefit from the research. This principle is often discussed in abstract terms, but AVAC believes it should be made more concrete. Planning for trials, particularly in countries where IP rights of participants or researchers are cause for concern, should include publicly acceptable plans early on that provide for both eventual access to final products and improvements in local care, especially for those who participate in trials, regardless of the efficacy of the product being tested.

Protected Data

Trade secret and confidential data are difficult to manage, since once someone outside the confidentiality circle knows the data, it can no longer

effectively be protected. Secure, encrypted and licensed database systems can be set up which will allow authorized users to share trade secret data under carefully controlled circumstances.

AVAC is not naïve about the difficulties and challenges that arise when so many different players, resources and perspectives must be brought to the table. But we believe it is both possible and imperative that the many players come together to confront and overcome the challenges to IP sharing in AIDS vaccine development. E.M. Forster once imagined that a working novelist ideally sits in the middle of the vast, inspiring reading room of the

British Library, borrowing from and simultaneously surrounded by all the other great past and current novelists writing in English. That image of creativity—both individual and shared—is not a bad model for the scientific and asset cooperation needed for AIDS vaccine development.

CHAPTER FOOTNOTES

¹ Bloom, B. "A Perspective on AIDS Vaccines," *Science* 1996 272: 1888-0



DEFINING THE TERMS

A **patent** is not an FDA-type approval to market and distribute a drug or other product. Patents describe rights you acquire to permit you to ask a court to stop someone else from using your invention. They limit the freedom of another to operate or use the invention unless the possessor of the right says it's okay. This becomes more complicated when, as with many vaccines, there are many patents and other rights with multiple owners making overlapping claims.

It is a common misconception to equate **intellectual property** only with patents, but IP also includes rights to trade secret and confidential data, materials/samples and even the difficult "know-how" involved in making or finding complex high molecular weight biological proteins in living matter.

An invention can also be **licensed**, which allows others to pay for using the invention, technology or materials.

Often, the owner of a patent places high value on the future revenue potential of the patent, even if it is not being used at the moment. The patent owner may not

grant rights to use it in early stage development, fearing competition or use of their invention to discover another invention that can be patented by someone else. Once a license is granted, it may become more difficult to rein in downstream continued use by others who don't pay them. Vaccines are particularly problematic since they usually only require one or two injections (or inhalations or ingestions), so are not typically big moneymakers like many drugs. In the hope of making the most money from licensing a patented compound or technology, owners may hold back licenses that are needed for development of a promising vaccine candidate.

For AIDS vaccine research to move forward, invigorating ways to allow early freedom to operate is vitally important. In the early period of research, the true value of an invention is least known, and therefore licenses are granted or withheld without knowledge of the eventual reward, or worth, of the product.

PRELIMINARY ANALYSIS OF US PATENT DATABASE– 1985-2001* (approximately 1000 patents)		
MAJOR PLAYERS	NUMBER OF PATENTS	IP PORTFOLIO EMPHASIS
US Department of Health	54	subunits, vectors
Institut Pasteur	40	vectors
Chiron	23	subunits
Connaught	20	peptides, nucleic acids
University of California	19	peptides, proteins
Smith Kline	19	nucleic acids
University of Texas	18	peptides
Virogenetics	15	vectors
University of Pennsylvania	10	peptides, vectors
Genentech	8	proteins

* For general analysis purposes, in 2001 (later supplemented in 2003), AVAC conducted a fundamental search of the United States Patent and Trademark Office issued patents database, literature, news reports and other sources to tally only some basic key components of AIDS vaccines. The number of relevant patents for products, therefore, is really much larger when other general components, processes, techniques and methods are added.

VACCINE CANDIDATE–VIRAL VECTOR PLUS TWO OR MORE SUBUNITS		
VACCINE CONSTRUCT	NUMBER OF PATENTS	NUMBER OF PATENT ASSIGNEES
HIV-1 <i>env</i> , <i>gag</i> , <i>tat</i> , <i>rev</i> or a combination of them	241	96
Vaccinia	21	11
Canary pox	32	5

Note: This information is from a 2001 search of the US patent database and is meant to provide a snapshot of information, not to be an exhaustive search of all possible patents on these components.



In terms of property rights, the scientific challenge of vaccine development includes vaccine components, necessary tools, design criteria and engineering efforts. In 2003, AVAC found that more than 1300 US patents had been issued since 1984 (when the discovery of HIV was patented with a vaccine use claim) to dozens of private, government and academic assignees. Those rights covered only the most significant AIDS vaccine product matter compositions of HIV genes or proteins, useful vectors and sequences. This does not include other patents for manufacturing methods, tools, adjuvants, processes or combinations.

Almost a dozen DNA or live recombinant vectors of one class or another are currently in human trials to study their ability to ferry and insert matter into cells, and more are being studied in preclinical research. Each is different in some ways, but multiple and overlapping rights and ownership claims, including how to make, combine or use them have been made for each. Adding adjuvants or testing a candidate in combination with another adds another factor to the number of theoretical trials of each candidate that could be performed, each portion of which is owned by another entity. Separate ownership may apply to specific formulations or combinations that require licensing or permission even if an investigator retains rights to one of the components by itself. By 2003, AVAC searches had found that 11 separate US assignees laid claim in 21 patents to the basic vaccinia product, 5 assignees with 32 patents to canarypox.

But the vector is only the beginning, simply the “FedEx[®]” carrier for a complex lottery of HIV genetic constructs originating from different isolates, to mimic different HIV clades or recombinant forms, or based on a large number of possible genetic sequences. Even the process of grafting the HIV genes onto the vector is a controversial IP issue: long held basic patents for processes such as Columbia University’s co-transformation technique

or the “Winter II” patent add cost and licensing permissions to every effort.

The holy grail of a product that would work either partially or completely across many isolates of HIV would yield the most benefit. Some trials—the HVTN/Merck vaccine or the NIH/VRC prime boost—are based on that quest. Only the VRC, as a government entity, has the complete flexibility, i.e. absence of profit pressure, to donate the property rights it develops to the public domain. It is possible that a few different vaccines will be needed for different HLA types or populations, the composite of rights to which are separately owned. In any successful vaccine, it is likely that methods of producing the materials, incorporation, the product itself, method of delivery into the body, or method of using it as prime or boost may all be separately owned rights and require permission to use collectively.

These are only a few of the complex IP issues that may inhibit vaccine discovery. There are literally thousands of possible complex rights and combinations to assemble and test AIDS vaccines.

There are many other issues that potentially complicate the IP for any one vaccine candidate. Rights to sequence data or HLA type samples from past trials are a rich mine of trade secret information to help with new vaccine design. Individual trial volunteers in the US relinquish their rights to condition sample use or data derived from their participation during the informed consent process of a trial, but in some countries—Brazil, Thailand, South Africa—individual ownership or control rights are not easily stripped. Most likely, a successful vaccine candidate will be tested in multiple countries, each with different laws governing IP. Should investigators or clinical sites that conduct trials benefit financially or become co-owners or co-inventors of any aspects of a product? These and other issues will need to be addressed.



The copyrighted, peer-reviewed publications of articles reporting research and study results are also intellectual property. This year, NIH addressed public and community access to those articles, which can be very costly (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-022.html> and <http://www.nih.gov/about/publicaccess/>). New grant policy guidelines request that government funded investigators deposit research manuscripts as soon as possible but no later than within 12 months after acceptance for publication in the internet accessible PUBMED Central database (<http://www.pubmedcentral.nih.gov/>). (US nonprofit or privately funded researchers are not addressed.) This policy may increase community and trial participant access to complete research results but will succeed only if scientists support the program by contributing their studies promptly. Some traditional authoritative journals, like the *Proceedings of the National Academy of Sciences* (PNAS), facilitate participation by means of their online access policies (<http://www.pnas.org/cgi/content/full/101/23/8509>).

On May 19, 2005, the UK's Wellcome Trust went further, requiring that the 3500 papers published each year through its funding must be deposited in a public digital archive within six months of publication (http://www.wellcome.ac.uk/doc_WTX025191.html). A broad, open access policy is also the subject of consultation by the Research Councils UK (<http://www.rcuk.ac.uk/access/cover.asp>).

AVAC calls on all NIH and other publicly-funded vaccine scientists to lead by example and post manuscript or publication materials with the government as soon as possible. Intramural researchers within NIH especially have few constraints on their ability to implement the policy to the benefit of community and trial participants. Other foundations could follow The Wellcome Trust lead. For further information go to: <http://www.taxpayeraccess.org>.

Links to all of these documents and websites can be found at <http://www.avac.org/ip>.

FOR MORE INFORMATION

- + A longer paper on intellectual property issues, AVAC's "Covenant Not to Sue," and other IP resources are online at <http://www.avac.org/ip>
- + The National Academy of Sciences recommendations are in "A Patent System for the 21st Century" at <http://www.nap.edu/html/patentsystem/81-129.pdf>

05



DON'T SHOOT THE MESSENGER: AN UPDATE ON TENOFOVIR RESEARCH



DON'T SHOOT THE MESSENGER: AN UPDATE ON TENOFOVIR RESEARCH

In the last year, controversies surrounding clinical trials of tenofovir have managed to bring a remarkable number of festering issues in international clinical research to public attention. This was going to happen sooner or later. Whether it was in Cambodia, Thailand or Cameroon, people being recruited for tenofovir trials began demanding the same benefits already afforded volunteers in rich countries. Act Up Paris got involved, two trials were shut down, and the list-serve equivalent of a food fight broke out among AIDS activists. By spring of this year, research that just about everyone agrees holds real promise was coming to a standstill. (Tenofovir is being tested for safety and efficacy as pre-exposure prophylaxis—a once-a-day pill that might reduce the likelihood of HIV infection.)

People were arguing about different things, all of them with broader implications for health research. One issue is the ambiguous definition of the word “community.” Is it people enrolling in a trial, the surrounding population, NGOs in the region or nation, activists 4000 miles away? How are all those voices to be heard and responded to in a meaningful way?

Many of the concerns with tenofovir trials had to do with volunteer benefits and protections:

- + If people become HIV infected while enrolled in a trial as a result of risky behavior or exposures that they cannot avoid, should they be provided treatment for HIV above and beyond what is available to their neighbors who are not trial volunteers?
- + If they are physically harmed by the product being tested, should they receive care and compensation?
- + If the product they are helping test is licensed for use, should they receive that product even if their government or health insurer won't pay for it?

- + If trial volunteers are being recruited for research because they practice a particular risk behavior, should they receive the best proven measures to help them reduce their risk of acquiring HIV infection from that behavior (e.g. clean needles for injection drug users?)

While the ethical deliberations continue, the reality is that most of these issues are becoming questions of how to implement delivery and benefit programs, rather than win philosophical debates. One thing globalization is doing is making it much harder to justify double standards in health research. That does not mean that, in the future, a clinical trial in Abuja will look exactly like one in Atlanta, but it does mean the bar for participant rights and protections is rising rapidly in the developing world.

Very soon, the path of least resistance will be to forgo the ethics debates and provide the benefits above... but... *creatively*. Each of these benefits present thorny logistical challenges, like guaranteeing delivery of care years after a trial has closed down, or getting around legal prohibitions without putting the research site at risk of a police raid.

Individual sponsors and research teams cannot be expected to solve all the inequities in the communities where they do research. There has to be a partnership with governments, donors, NGOs and civil society to solve these problems.


Tenofovir is the messenger of changing expectations in clinical research. If everyone involved can figure out how to address the issues that have been raised in the last year, they will be laying the groundwork for more expeditious—and much more sustainable—health research for years to come.

In March of this year AVAC issued a special report on tenofovir research: *Will a Pill a Day Prevent HIV?* In it, we called for:

- + Better coordination between the disparate trials and multiple sponsors, in part to assure that there is adequate statistical power in the studies to move toward licensure of the product in multiple countries and settings (should tenofovir prove safe and efficacious as PREP).
- + Discussion among sponsors and public health leaders as to whether additional—perhaps larger—research studies are needed in order to license the product for use, including in populations not enrolled in current studies. (If additional studies are needed, planning should begin now, rather than waiting for the current trials to produce data.)
- + Protections and benefits for trial participants at all trial sites that include treatment for HIV infection, high quality prevention interventions (including clean needles in IDU populations) and compensation for physical harm caused by participation in research.
- + Identification of public policy and health worker training priorities to help make tenofovir globally accessible if it is widely licensed for use.
- + Development of communications and social marketing strategies to prepare for announcement of trial results and, perhaps, integrate the product into HIV prevention packages.
- + More engagement from Gilead, the manufacturer, to plan for manufacture and delivery on a global scale.

We reiterate these recommendations now. In the six months since we issued our report, trial sponsors have been (understandably) focused on keeping their studies afloat, rather than addressing the longer term questions. In May, the International AIDS Society convened a multi-stakeholder consultation in Seattle on behalf of tenofovir trial sponsors. This meeting was an important step toward addressing the ethical, operational and communications issues at hand. One very good idea to come out of the meeting was to create a “global stakeholders group” that would promote ongoing monitoring, dialogue and coordination among different studies and between researchers and civil society. Such a group could—and, we think, should—address many of the recommendations above.

CURRENT TENOFOVIR PREP STUDIES				
STUDY LOCATION	POPULATION GROUP	SPONSOR	STUDY GOAL	EXPECTED RESULTS
Ghana	High-risk women 400 volunteers	Family Health International	Safety and efficacy	2007
Malawi	High risk men 500 volunteers	Family Health International	Safety and efficacy	2007
Botswana	Young adults 1200 volunteers	Center for Disease Control & Prevention	Safety and efficacy	2007
Thailand	Injection drug users 1600 volunteers	Center for Disease Control & Prevention	Safety and efficacy	2007
United States	Men who have sex with men 400 volunteers	Center for Disease Control & Prevention	Safety	2007
Peru	Men who have sex with men 400 volunteers	National Institutes of Health	Safety and efficacy	2008

 CANCELLED TENOFOVIR PREP STUDIES				
STUDY LOCATION	POPULATION GROUP	SPONSOR	STUDY GOAL	WHEN CANCELLED
Cambodia	High-risk women	National Institutes of Health	Safety and efficacy	2004
Nigeria	High-risk women	Family Health International	Safety and efficacy	2005
Cameroon	High-risk women	Family Health International	Safety and efficacy	2005

FORMAL COORDINATION NEEDED NOW

Whether it be through this stakeholders group or some other process, it's imperative that there be more formal coordination of tenofovir research. We applaud the limited coordination efforts that are already taking place, but now *statisticians, research teams (from Family Health International, the Centers for Disease Control and Prevention, and the National Institutes of Health), along with international public health planners and regulatory agency representatives, need to sit down and chart a course for accelerated testing and rapid global licensure and delivery to diverse populations in the event tenofovir is safe and effective as PREP.* We need to better understand what the current studies will tell us, about which populations, and whether additional studies should be initiated now.

A Centers for Disease Control and Prevention (CDC) analysis has determined that their studies (in Botswana and Thailand) may be considered statistically conclusive as pivotal studies to license the product for use as prevention only if the true efficacy of tenofovir is high. A low level of efficacy would only demonstrate proof of concept—indicating some effect of tenofovir but not providing adequate data to label the product for prevention. We know from studies on use of partially effective vaccines that prevention products with relatively lower efficacy can still produce substantial public health benefits. But as it stands, a proof of concept result at a lower level of efficacy would require that still more studies be planned, recruited and run. That would mean year's more wait. Can the other tenofovir studies be added to a meta-analysis with increased statistical power? Would that data be adequate to license the product in all the highest risk groups? These questions need further study, and soon.

FOR MORE INFORMATION

- + AVAC's tenofovir report, *Will a Pill a Day Prevent HIV?* is online at <http://www.avac.org/pdf/tenofovir.pdf>
- + AVAC's *AIDS Vaccine Handbook* has more information about clinical trials and is online at <http://www.avac.org/handbook/>

06



ADVOCATES' WORK IS NEVER DONE



“The goal of developing a vaccine is revealing itself to be even more challenging and time-intensive than anticipated.”

SETH BERKLEY, IAVI¹

ADVOCATES' WORK IS NEVER DONE

Every year, AVAC tries to give an objective assessment of where the field stands. In our first years, that was easy; so little was being done, and the areas of lack were large and easy to identify.

More recent AVAC reports have tackled ever harder issues, including those we've written about this year:

- + Where are we, really, on the road to a vaccine? (We don't rightly know.)
- + Will a more coordinated effort like the Enterprise help? (It's too soon to say.)
- + Will new sources of investment be useful? (If they materialize, it will depend upon how well they're used.)
- + Can intellectual property and access to data be optimized to advantage? (Probably so.)

This has always been a difficult field. We know even better now that we're unlikely to get any lucky breaks. We'll have to do it the hard way.

In each of our reports, we try to make helpful recommendations, sometimes from the sidelines and sometimes for advocacy. That is trickier this year as we've become ever more involved ourselves. Our staff and our board members have become active and positive influences, we hope, at HVTN, IAVI and the Enterprise.

PESSIMISTS, AGNOSTICS—BUT HARDLY AN OPTIMIST IN SIGHT

A year ago, at Bangkok and after, people were using the fact that there's not going to be a vaccine for

years as evidence to support renewed focus on microbicides as well as other biomedical prevention, traditional prevention, treatment and care. The talkers were somewhat ahead of the doers, however, who have been moving forward at their own deliberate pace. The facts are few and separated (we'll look at those in a moment), and so it is an exercise of creative imagination to try and connect the dots or project any turn of events.

The question is not who to believe but what can we hang our hats on? We believe we can hang our hats on the following points:

- + The approaches currently in development are almost exclusively vectored genes. Add-ons may be critically important (DNA, traditional and biologically active adjuvants, newer envelope constructs). We are still following a path that began well more than fifteen years ago with vaccinia as a vector—chasing after adequate cellular immunity in a fairly large number of variations.
- + We have yet to solve any of the basic questions that would help direct our efforts (animal protection, sources of known immune control, correlates of protection). We certainly do not know if we're measuring what we need to measure. In fact, we're probably not.
- + Extraordinary time frames appear unreachable. Every approach takes years to get to the clinic, iterations before moving from small safety and immunogenicity trials, and hurdles before efficacy can be evaluated. Think in terms of ten years per approach, or thereabouts, with virtually nothing falling by the wayside.

In the past, we have often taken the position that a real measure of progress is the number of efficacy trials started and finished, simply because they give definitive answers about what will prove efficacious. Today, two efficacy trials have been finished and two are underway. No matter what one thinks of these experiments, each in its time was—and is—considered the best shot at testing an important approach. Should one of those approaches, or the related approach of the VRC, demonstrate any activity, we may continue down the same road, refreshed with the notion that it's leading somewhere worthwhile.

We have also used the number of Investigational New Drug Applications (INDs) submitted to the US FDA for testing vaccine products as one indicator of progress. As of July 2004, the FDA had allowed 63 INDs, 17 of which came in the period from January 2003 to July 2004, a fairly robust pipeline, if we are looking only at numbers. Since then, several others also have been submitted. These numbers only include vaccines that sponsors submit for planned US testing, so it is a useful, but not complete measure of all products worldwide.

However, the numbers of vaccine candidates or trials is not a good reflection of the health of the overall endeavor.

HOW OUR ANALOGIES PLAY TRICKS ON US

The idea that a full pipeline of ideas or products would help us get to a vaccine has dominated the big picture thinkers like IAVI and NIH and led them to fund a large number of development projects. Each project has had its own scientific rationale and milestones, but they have been based, for the most part, on relatively few scientific premises: proteins, peptides, DNA vaccination and a variety of safe viral vectors, particularly MVA. Along the way, and unfortunately before there is hard evidence, much confidence has melted away. Ideas are easier to conceive than to actualize.

Now, people have begun to worry about both the quality of the projects in the pipeline and the cost of carrying them all forward. As we stated in reply to an article in *Nature Medicine* in August of this year, in which CHAVI and the Vaccine Enterprise were questioned, more of the same is beginning to look like a foolish way to proceed.²

David Baltimore has asserted, “If everything broke right, we might have a partially successful vaccine in five years. But realistically, it will be 10 years or more before we might expect we can protect people against

“Time and again, high hopes have given way to crushing disappointments, and the field has been roiled repeatedly by bitter disputes about the best way to move forward. If the different players worked in isolation, as private companies often do, the tensions might not matter much. But in the world of international vaccine research, there’s a constant tussle for resources and influence among government agencies, universities, drug companies, health ministries, networks of clinics and the communities that agree to participate.”

JON COHEN IN “MILITARY VACCINE STUDIES: ON TRIAL”³

HIV with medicine....A simple conclusion would be that no vaccine is possible. And in fact, we can't prove that that's wrong, but scientists luckily are optimists. The need is so obviously great that people will simply not accept that answer. Although the amount of activity in the field is high, there is no clear pathway to success. AIDS provides challenges on such an enormous scale that their solution requires the perturbation of business usual."⁴

It is those very perturbations that have made 2004-5 such an interesting period, but it is far too early to make any final judgments.

At AVAC, we have begun thinking about vaccine development more as a manufacturing process than as a pipeline. The amount of time from product design to delivery is long and can only be pressured or expedited to a certain degree. Researchers must design the best models possible, and the emphasis must be as much on quality as quantity. Even with more attention to design, it is true that, as with any product, an accurate evaluation can only be made once the model is out of the planning stage and in production. From time to time, and using one's best judgment, new projects must be started down the line, and problems must be addressed in the process.

We at AVAC have also been great believers in setting milestones and tracking against them. If developers said they'd have their concept into Phase I or Phase III trials by a certain year, we tried holding them to it. Not only did very few ever meet their milestones, we discovered that virtually everyone had unreasonably optimistic expectations that did not account for the complexities of the process or for the inevitable snags that arose. The lessons learned from these experiences must not be ignored. It would, no doubt, be very useful to examine those painful experiences and learn about common mistakes made in establishing processes and making projections and use that information as a reality check in the future.

We must review all projects to date with this more experienced and unbiased eye, learn from the mistakes as well as the successes of each, and establish best of class practices that help all of us move forward. If ten years, give or take, from bench to proof of concept is a realistic time frame, then let's concede that the clock runs only that fast and make sure it runs more or less on time along the way.

As early as July 1996, in a report called *Social Issues Over the Long Haul of Human Trials*, Chris Collins talked about redefining success. He said that "sustaining public support for vaccine research while communicating the complexity of the research task will require a delicate balance of honesty and optimism."⁵ (Little did we know that we'd have to exercise the same balanced approach with scientists themselves.) He also noted, "However realistic it is, this 'delayed gratification' definition of success can only become widely accepted by the public and affected communities if they have faith in the integrity of researchers and research efforts." We doubt, when Chris concluded, "Today, building trust in researchers is more important than generating blind enthusiasm," that it would come to mean not only building trust *in* researchers by outsiders, but also *within, among and by* researchers themselves.

We must also seek new and energetic colleagues on both the science and advocacy sides of the struggle. Gary Nabel, director of the VRC said it best: "Young investigators are critical to the success of the field. If you accept the idea that this disease is not going to disappear overnight, we need to ensure that the right people are involved as the efficacy trials are done, whether it's in five years or in twenty years. Young investigators should recognize that there is no more important problem in biomedical research than this problem, for several reasons.

Number one, the scientific questions that underlie it are fascinating and they will uncover basic biology relevant to immunology, virology, genetics and evolution. Secondly, by working on this problem you are contributing to an effort that will have perhaps the greatest impact on human health on this planet. It's important for us to get that message out; this is a unique opportunity to address the scientific challenges and to meet a public health imperative. In an age where scientific trainees are reading in the newspapers about the excitement of stem cell, neurobiology, or genetic research, it's important to understand that the energy and excitement in our field is perhaps even greater. We are in the midst of an incredible renaissance in the field of HIV vaccines. The science and technology that we can apply now to advance the field is unprecedented.”⁶

WHAT WE CAN COUNT ON KNOWING, AND WHEN

Here, roughly, is our estimate of how progress in the field should play out in the next five years:

In 2005-6 the Enterprise Secretariat, Center for HIV/AIDS Vaccine Immunology, and the new Gates initiatives for three key areas of vaccine R&D will be funded.

The large number of candidates that had been funded by NIH, IAVI and SAAVI for development, particularly various DNAs, MVAs, and novel vectors and adjuvants should have completed initial Phase I testing, giving us some indication of their relative immunogenicity compared to other products that have already moved forward, and to each other.

Clinical trials networks should be more integrated for doing a variety of studies and multi-country tests of microbicides, vaccines and PREP.

In 2007, the VRC envelope containing, multi-clade DNA Adeno5 prime boost regimen should make it into an international efficacy trial.

In 2007-8, news should be forthcoming on the Thai Canarypox-gp120 and the Merck Adeno5 trials. These results will almost certainly tell us if we're on the right track toward a partially effective CTL-based vaccine, or if that hypothesis is worthless or requires major innovation to be made workable.

In 2008-10, it's reasonable to expect tangible results from the initiatives currently in development. Judging from the talk at scientific meetings about these proposals, their size and interdisciplinary character should allow for real and substantial progress

“Vaccine development for HIV has been notable for its sophisticated use of modern molecular engineering techniques, both for the production of protein antigens and for the design of viral vectors. However, if I may be irreverent, it must be said that our application of advances in immunoregulation has been disappointing, to say the least. In principle, we are using immunization techniques that might have been employed 50 years ago with products that could not have been available even 5 years ago.”

WILLIAM PAUL, JULY 1996, FORMER DIRECTOR OF THE NIH OFFICE OF AIDS RESEARCH⁷

“We’re trying to get the immune system to clear this infection, which it wouldn’t naturally do, so you can’t do this blindly and empirically. We must understand how this fundamentally works and manipulate the system. The critical issue is fundamental understanding. This, in the end, will serve us well.”

EMILIO EMINI⁸

in our knowledge about vaccine immunology, animal experiments and even more complex and sophisticated approaches to vaccine design.

The Enterprise will have either fulfilled its promise as a generator of more strategic and collaborative R&D, or not. Investigator-initiated research and scientific inquiry will have closed a few doors and opened more in the exploration of viral dynamics, immune responses, pathology, epidemiology and behavioral research—as it has consistently continued to do.

WHAT WE CAN DEMAND/EXPECT/INSIST ON IN THE WAY OF PROGRESS

We must be systematic on a larger scale while still leaving space for novel ideas. The field seems to be maturing into this posture.

Following is a basic, no-frills list of expectations based on the assumption of increased funding and collaboration:

- + Better immunology.
- + More robust and varied assays.
- + Mechanisms for testing multiple hypotheses widely.

- + Plenty of ideas and experimental data to prime the field with new ideas for making vaccines.

The other softer stuff is going to be harder to make happen: more advocacy and better government assistance with regulatory, rights and policy incentives. So AVAC and other advocacy groups have their work cut out for them if we, and they, are to keep pace and fulfill these critical ancillary needs. They take politics, really good human-to-human communication, good journalism and commitment—all even harder to marshal and measure than scientific inquiry. That’s the messy stuff where human nature tends to get in our own way.

REAL REASONS FOR OPTIMISM

In addition to change, we need to maintain forward motion. On the whole, in our opinion, things don’t so much need to change as they need to get going and keep going. This is not the easiest position for an advocacy organization to adapt. It lacks the drama of things going wrong or things undone. It becomes very difficult to maintain a sense of urgency and avoid taking potshots or second guessing those who are following a plan of action that takes a very long time.

For those of us who were rebellious youths, the job of cheerleader is not a comfortable one. But that’s

what the field seems to need right now. These cheerleaders must be people who understand the need and who can maintain a sense of urgency in the face of very slow progress and regular setbacks. That enthusiasm may be the only measure of progress we have for a very long time to come, especially given the implacability of the virus and the universe.

Scientific, advocacy and political will are outposts that need to be colonized, tended, watered and warmed. For better and worse, we are the caretakers, here to nourish them day after day, season after season, year after year.

CHAPTER FOOTNOTES

- ¹ Berkley, S. Annual letter to friends of IAVI. December 20, 2004.
- ² Snow, B. "Reply to 'One for the Money.'" *Nature Medicine*. August 1, 2005.
- ³ Cohen, J. "Military Vaccine Studies: On Trial." *MIT Technology Review*. January 2005.
- ⁴ Groshong, K. "Caltech President Sounds Off on AIDS: Says Vaccine Remains Years Away." *Pasadena Star-News*. January 11, 2005.
- ⁵ Collins, C. *Social Issues Over the Long Haul of Human Trials*. Monograph Series Occasional Papers #2. July 1996.
- ⁶ Noble, S. "Immunology and AIDS Vaccines: An Interview with Gary Nabel." *IAVI Report*. September 2004–November 2004.
- ⁷ Paul, W. "Untapped Opportunities: Marshaling Immunoregulatory Advances for HIV Vaccine Development, OAR. July 8, 1996.
- ⁸ As quoted in Kahn, P. *AIDS Vaccine Handbook*. AVAC. 2005.

FOR MORE INFORMATION

- + *Social Issues Over the Long Haul of Human Trials* is online at <http://avac.org.phtemp.com/lib/libVT3.htm>
- + AVAC's *AIDS Vaccine Handbook* is online at <http://avac.org/handbook/>
- + An *IAVI Report* interview with Gary Nabel is online at <http://www.iavireport.org/Issues/1104/GaryNabel.asp>



Founded in 1995, the non profit AIDS Vaccine Advocacy Coalition (AVAC) seeks to create a favorable policy and social environment for accelerated ethical research and eventual global delivery of AIDS vaccines as part of a comprehensive response to the pandemic. This work is guided by the following principles:

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

AVAC CURRENTLY FOCUSES ON FOUR PRIORITY AREAS:

- 01** Develop and advocate for policy options to facilitate the expeditious and ethical development, introduction and use of AIDS vaccines and other new prevention technologies.
- 02** Ensure that rights and interests of trial participants, eventual users and communities are fully represented and respected in the scientific, product development, clinical trial and access processes.
- 03** Monitor the AIDS vaccine field and mobilize political, financial and community support for AIDS vaccine research as part of a comprehensive response.

- 04** Build an informed, action-oriented global coalition of civil society and community-based organizations exchanging information and experiences.

In May 2005, we published the second edition of the **AIDS Vaccine Handbook** as a core element of our effort to marshal and sustain public involvement in global AIDS vaccine efforts. This completely revamped and international edition provides an overview of the key scientific, policy, social, ethical and economic challenges, and of the diverse experience gained around the world over the past two decades. The easy-to-read, lively essays are written by people involved in this work as community educators and advocates, trial staff and volunteers, scientists and researchers, and policy-makers and journalists. AVAC hopes this new handbook serves well as a resource and reference guide—and that it motivates people to take action! The handbook is available online at www.avac.org/handbook, and printed copies can be ordered from the National Prevention Information Network at <http://www.cdcnpin.org/>.

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