
# V Years & Counting

## SCIENCE, URGENCY, AND COURAGE

AVAC | AIDS VACCINE ADVOCACY COALITION – MAY 2002

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More than 8,200 people died of AIDS on September 11, 2001. It was an average day in that regard. In countries across Africa, families were pulling children out of school to care for relatives with HIV/AIDS or to earn money lost when the breadwinner died. In the United States, we continued to witness more friends become infected, more develop mounting resistance to treatments, and more pass away.

We've gotten used to all that. What was *new* in public health last year was the fear of bioterrorism. The public was alarmed and the Bush Administration hurriedly secured an enormous supply of treatments for anthrax and proposed a sixfold increase in bioterrorism funding, to $1.7 billion in 2003.

Without real public urgency, vaccines will have no hope of ending the AIDS pandemic. More funding is needed of course; increased industry involvement too. But at this juncture in AIDS vaccine research, progress depends as much on courage and impatience from the public — even widespread alarm about what the future holds — as it does on the insights and hard work of dedicated scientists.

This year the scientific news was both good and bad. Merck showed promising early results in humans with its DNA/Adenovirus vaccine candidates, other researchers had hopeful data to report, and there were more AIDS vaccine products in production than ever before. But there was also worrisome news: in one of eight monkeys that had been controlling infection following vaccination, the virus mutated around the vaccine and the animal died. Then came word that poor immunogenicity data had led the NIH-funded HIV Vaccine Trials Network (HVTN) to decide against an efficacy trial of the ALVAC candidate vaccine.

What does all this add up to? The truth is, five years away from the date former President Bill Clinton set as a goal for finding an AIDS vaccine, no one knows if any of the current experimental vaccines will work. No one even knows for sure what immune response a vaccine needs to elicit to prevent HIV disease.

The only way to obtain answers is to ask tens of thousands of altruistic and courageous volunteers to participate in dozens of trials. The only way to obtain answers is to invest hundreds of millions of dollars to fund these trials. Not one trial, but a number of small and large human trials will be needed to develop a safe, highly effective vaccine to prevent AIDS. Along the way, even trials that don't lead us directly to an efficacious product may

help scientists learn how to make better products. In less than a year, the world will hear the results of the first efficacy trial of an AIDS vaccine. Whatever the news, we must ready ourselves for more clinical testing to come.

Getting more human data to drive the AIDS vaccine field requires many things. It requires regulatory agencies and companies helping to move more products off the bench and into Phase I trials. It requires supporting clinical infrastructures around the world, and having the will to run with efficacy trials when products demonstrate safety and promising immune responses. It requires addressing the long-standing concerns many groups have with biomedical research. And it means doing a better job of recruiting Americans of African, Latin, and Asian Pacific Island descent, Native Americans, adolescents, and others into trials.

But human trials are not a panacea in AIDS vaccine research. More research and product development is needed as well. Many scientists are skeptical about the vaccine candidates now available for testing. Breadth and duration of immune responses remain nagging challenges. And all the enthusiasm about vaccines that may be able to *control* disease has obscured the continuing inability to elicit antibody responses that could be necessary to *prevent* HIV infection from taking hold. New paradigms in vaccine design may be needed.

AIDS is a national and international emergency. It is a catastrophe. A fitting response requires not only a high level of public and private investment but also widespread public pressure, even outrage. It is essential that large numbers of voters and taxpayers mobilize to insist that developmental and clinical research move forward as rapidly as possible, even though the odds of succeeding may be uncertain.

**Who needs to hear the public demand faster action on AIDS vaccines?**

- *Elected officials in countries rich and poor:* they must provide significantly more funding for global health, resources for establishing clinical trial sites around the world, and incentives to galvanize industry expertise.
- *Regulatory agencies:* they must move more swiftly and decisively to work with investigators, evaluate products for human trials, and build global regulatory capacity.
- *Scientists:* they need to hear that the public stands behind them and demands that they push to develop and test safe products.
- *Industry:* corporate leaders must understand their moral responsibility to address today's great global health challenges and expand research efforts on infectious disease, including AIDS vaccines.

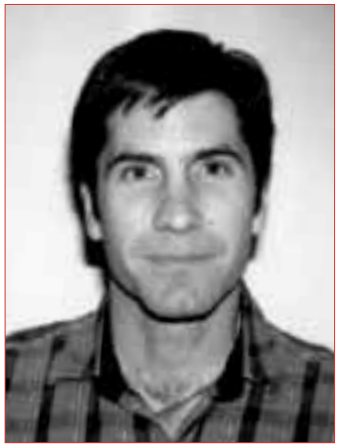
- *Research funders:* they need to stimulate healthy competition and diverse scientific efforts in order to advance multiple vaccine approaches simultaneously.
- *Governments, foundations, and aid agencies:* they need to prepare now to ensure global accessibility to new AIDS vaccines for all those at risk.

This report reviews some of the major issues involved in promoting accelerated, ethical AIDS vaccine research and delivery. *Five Years and Counting* looks different than our earlier reports. It is less a review of what's happened and more of a prospectus on what is urgently needed.

AIDS vaccine research and development will almost certainly be a longterm endeavor, and it must be pursued in the context of a comprehensive response to the pandemic. In many ways, AIDS vaccine research can help blaze a trial in health care delivery today. As clinical trial sites are expanded, there will be opportunities to deliver desperately needed prevention and treatment. Health care services provided as part of vaccine trials can be coordinated to improve health care access for whole communities. Communities that participate in AIDS vaccine research are making an enormous contribution to global health; they deserve tangible benefits.

The commitment and passion of hundreds of scientists and the courage of thousands of volunteers was required to get this far in the marathon search for an AIDS vaccine. Five years after an American President challenged the scientific community to reach the finish line within a decade, more of us need to be courageous and passionate so that this dire race can be completed and won as soon as possible.

Chris Collins
Executive Director — AVAC



# II Clinical Trials at the 5–Year Mark: *Climbing Heartbreak Hill*

**NIH AND EFFICACY TESTING: ONCE MORE, TO THE BRINK**
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Five years ago, on May 18, 1997, President Bill Clinton challenged American scientists to make the development of an AIDS vaccine the 21st Century's first great triumph. Simply by saying this, he moved HIV vaccine research higher on the national to-do list than it had ever been. But even advocates and scientists who welcomed this burst of attention were skeptical about Clinton's goal of developing a vaccine in a decade—a time-line that seemed unreasonably short to most knowledgeable people in the field of vaccine development. The first AVAC report, released in May 1998, put it bluntly: "Unless more is done, the President's challenge will not be met."

Much has changed since then: Clinton is in retirement, 9–11 has divided all of life into "before" and "after," the nation is fighting a war on terrorism, and AIDS vaccines have slid lower and lower on the national agenda.

On the other hand, much remains the same: HIV continues to spread at the alarming rate of nearly 14,000 new cases each day, public health experts still believe that preventive AIDS vaccines are urgently needed, and the failure to move more candidates into clinical trials remains a major impediment to having a safe, effective vaccine.

AVAC takes no joy in still being right. Unless more is done to advance development and testing of AIDS vaccines, the challenge will not be met.

Dozens of potential vaccines have made it to Phase I safety studies. About 15 products are now entering this early part of the race and another, a DNA-MVA combination backed by the International AIDS Vaccine Initiative (IAVI), has recently moved into expanded trials. The middle section of the course, where Phase II trials are required, thins out considerably: in 20 years, the only two candidates that have come this far are various iterations of gp120 or canarypox. In the home stretch of vaccine development, the

Phase III trial, there is only one lonely runner. VaxGen has parallel efficacy studies nearing completion in the United States and Thailand. *(See "Lessons from the World's First Efficacy Trial.")* VaxGen isn't going to hear the footsteps of other candidates behind it until the end of this year at the earliest.

**In late February, three major developments related to clinical trials were announced in a single, carefully worded press release from the National Institutes of Health (NIH):**

- Based on interim data from a Phase II trial, the NIH-sponsored HIV Vaccine Trials Network (HVTN) jettisoned plans for a future Phase III study it had been planning.
- A Phase III trial organized by the U.S. Military and Thai collaborators will go forward, although not quite so soon as expected.
- The Department of Defense HIV research program will be transferred to NIH effective October 1, 2002.

**All three have important, long-range implications for the future of HIV vaccine science.**

### NIH AND EFFICACY TESTING: ONCE MORE, TO THE BRINK

This is the second time NIH has deferred on a Phase III study, first based on results in the lab, then on results in humans. The first time was in 1994, when National Institute of Allergy and Infectious Diseases (NIAID) Director Tony Fauci decided against efficacy testing for two gp120 vaccines (with concurrence from an advisory committee). This time, the brakes were applied by a group of academic scientists who are the core leadership of the HVTN, which was created in 1999 to be an autonomous, university-based network. Its budget stands at $43.5 million for the current year.

In the words of a glossy educational brochure produced last year, "HVTN's goals are straightforward. The Network conducts all phases of clinical trials, from evaluating candidate vaccines for safety and the ability to stimulate immune responses, to testing vaccine efficacy." Although HVTN was intended to run trials with thousands of volunteers, the 25-site, multi-national network currently has only about 525 volunteers enrolled in Phase I and Phase II vaccine trials.

The decision not to move forward with Phase III testing was based on results from a Phase II study evaluating the safety and immune-stimulating properties of a prime-boost strategy using ALVAC (vCP1452), made by Aventis Pasteur, and AIDSVAX® B/B, a VaxGen product. More importantly, this was a practice run for the relatively new ELISPOT assay, which measures cellular immune responses such as those elicited by ALVAC. (Different lab tests are used to measure antibodies stimulated by AIDSVAX.)

### MERCK IN THE SPOTLIGHT

On December 20, 2001, Merck and NIAID announced plans to collaborate on clinical trials of Merck's HIV vaccine candidates. NIAID offered Merck the resources of the taxpayer-supported HIV Vaccine Trials Network (HVTN) in exchange for access to some of the data generated by shared trials. HVTN leader Lawrence Corey told AVAC that the arrangement is mutually beneficial because it gives the Network, made up of academic investigators, the chance to work with a large corporate research team with an international focus.

The relationship allows Merck to access a number of HVTN international clinical trial sites. Teaming up with HVTN also puts Merck in a strong position should it need to collaborate with other companies down the road. In addition, the relationship offers potential benefit to NIH and HVTN, allowing them to compare data across multiple constructs and manufacturers. It remains to be seen whether this important public/private arrangement will cause vaccines to be more affordable or accessible internationally.

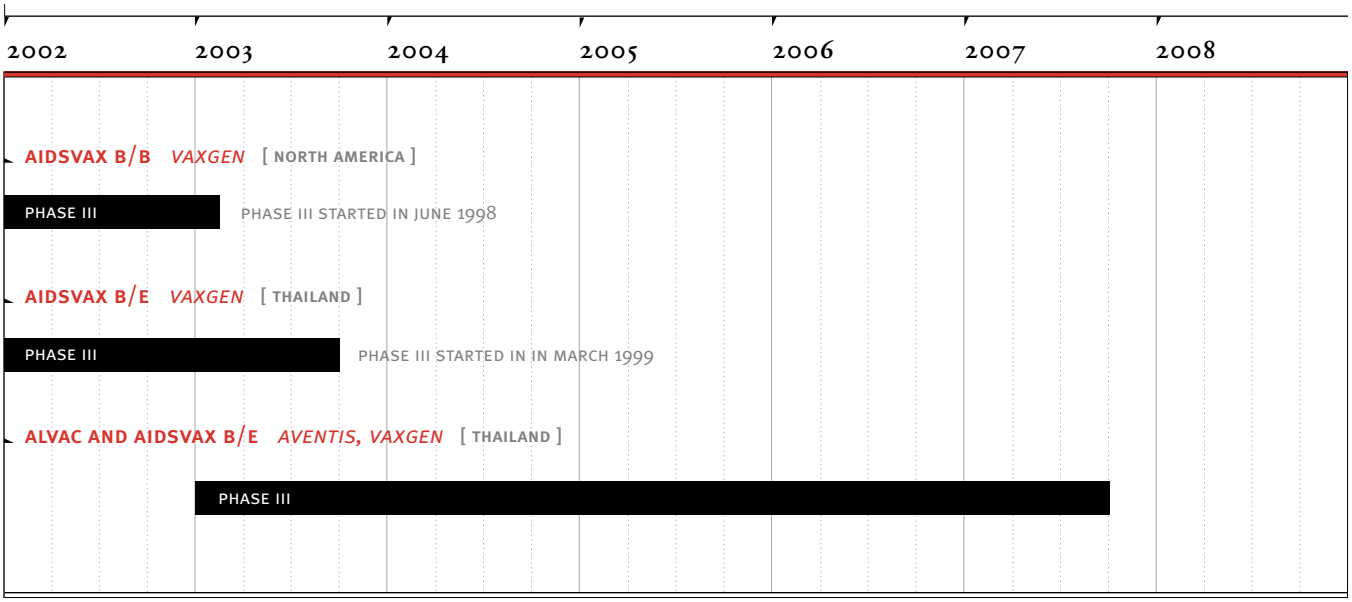
Merck made an even bigger splash in late February, when Emilio Emini, head of the company's HIV vaccine research team, unveiled promising findings from company-sponsored Phase I trials. Results for their DNA gag construct were on a par with those for similar products made by other companies: 20% to 42% of immunized volunteers (about 40 in each group) mounted HIV-specific T cell responses depending on the size of the dose. Most news stories focused on a far smaller trial, in which 36 volunteers received different doses of a gag-bearing adenovirus vector. A 67% CTL response in one subgroup (six of nine volunteers) generated a great deal of excitement with the hope that delay or prevention of HIV disease might be achievable through vaccination.

In positive contrast to older tests for cellular response, which require sophisticated facilities and highly skilled technicians, the ELISPOT could be used in vaccine studies anywhere on the globe.

In the Phase II study, researchers hoped the ELISPOT assay would provide positive results in enough trial volunteers to enable researchers to run a Phase III trial capable of detecting differences between immune reactions to ALVAC in volunteers who were protected and those who were not. If ELISPOT could make this distinction, then investigators could use it in a Phase III study to determine *how* the vaccine worked, if it had, even at a low level — yielding what scientists call a "correlate" of immune protection. This information would have given researchers a roadmap to follow in designing vaccines.

Everyone would like to have an HIV vaccine that is 90% protective, notes HVTN head Lawrence Corey, who runs the program in infectious diseases at Fred Hutchinson

## PHASE III TRIAL TIMELINE




Cancer Research Center and is a professor of laboratory medicine and microbiology at the University of Washington. But since that doesn't seem to be within reach right now, the next best thing would be identifying correlates of protection that inform the design of future vaccines. That was the main goal of the proposed HVTN 501 study. The study was never meant to be a plain vanilla efficacy trial, states Corey, "but an efficacy trial using these two vaccines — one that gave a CTL response and no antibody, and one that gave an antibody and no CTL — that allowed us to probe what we think is the more important question." The search for immune correlates of protection, in other words, figuring out exactly what the body would need to do to fend off HIV, has long been a kind of Holy Grail for academic researchers.

The only problem, of course, is that HVTN 501 is now on indefinite standby. In the Phase II study, HVTN reported, "the percent of volunteers in whom the ELISPOT assay detected an immune response was too low to provide a valid correlates analysis." This disappointing result presented HVTN leaders with a difficult decision. They could wholly redesign their trial as an efficacy trial or they could put the Phase III ALVAC trial on hold in the U.S. HVTN chose the latter route, deciding to focus on future early phase trials of candidates brought forward by Merck, the NIH Vaccine Research Center, Chiron, and other sponsors, while the U.S. military HIV program tests a very similar ALVAC candidate in a straightforward efficacy trial in Thailand.

We think the HVTN decision was justified. But had the ELISPOT readings been better on ALVAC, we would have enthusiastically supported simultaneous Phase III trials in Thailand and the U.S. These two trials — run by HVTN and the U.S. military — would have been complementary — testing different products in different population groups, in countries with different strains of virus. Unfortunately, this was not to be.

For years, AVAC and others have urged NIH to push multiple products forward in parallel Phase II and Phase III trials. Because the products have not been available to test, HVTN now has a large, costly network and no product poised to begin Phase III testing. When NIH previously cancelled a Phase III trial in 1994, the candidates abandoned at the starting line were gp120 vaccines made by Genentech (later spun off to VaxGen) and Chiron. At that time, ALVAC was the handsome stranger on the sidelines. ALVAC (also called "canarypox") was a novel idea with a good pedigree, sponsored by Pasteur Merieux Connaught (PMC, now Aventis Pasteur), a global pharmaceutical powerhouse. Although ALVAC never stimulated more than a middling immune response, the company repeatedly promised to improve this by tweaking the vector's design. At the time, there were valid reasons to work on an improved version of the candidate vaccine. A few other candidates were also undergoing preclinical testing and a larger number were languishing for lack of company or production support, which they have recently received. The fact remains that eight years later, NIH testing networks have advanced no other candidates into Phase II studies.

The point is this: too often there has been merely one candidate AIDS vaccine available anywhere that is prepared to move forward into Phase II or III trials. This speaks not only of the daunting challenges of HIV but also of the failure of public and private sectors to fully engage in the vaccine effort for many years. Finally, there now appears to be a wealth of vaccine candidates in the pipeline for early phase testing. AVAC urges that these be moved forward into clinical testing as swiftly as possible.

NIH's recent decision summons a powerful sense of déjà vu. Just as government hopes were once pinned on canarypox with a gp120 boost, now the taxpayers' eggs are largely in the "DNA plus adeno" basket. The leading embodiment of this hope is a prime-boost strategy from Merck & Co., which made a pragmatic decision to team up with HVTN back in December *(see sidebar)*. Merck's appeal echoes that of PMC back in 1994: each is a major pharmaceutical company with famous scientists on staff. Merck's bright hopes are a DNA prime carrying HIV gag, and a gag-bearing adenovirus boost. They have been tested separately for the most part but recently have been given as serial injections to the same volunteers. In the hands of corporate scientists the results look impressive enough to have garnered Merck a sort of "most favored nation status" with NIH.

In a recent interview, HVTN head Lawrence Corey told AVAC, "The Merck program is the next one, and a large Phase II study is going to start in September." Per Corey, if all goes well, the plan is to have the Merck prime-boost in a Phase III study sometime in 2004.

Even though Merck occupies center stage, Corey insists that HVTN will also advance other products into expanded testing, "Our job is to get a vaccine for the world as quickly as possible. We don't have to do it one at a time; quite the contrary." The second product in line is also a DNA and adenovirus combination from the NIH Vaccine Research Center (VRC). Importantly, the VRC candidate is designed to be "multi-valent" and "multi-clade" in the hopes of being broadly applicable throughout the world. GlaxoSmithKline, AlphaVax, Chiron, Wyeth, Emory University, and others also have protocols in development.

PERSONAL STATEMENT

**DR. PONTIANO KALEEBU, M.D. PH.D.**

*Uganda Virus Research Institute/MRC Programme on AIDS* | *Principal Investigator, IAVI-UVRI HIV Vaccine Programme*
*Steering Committee Member, African AIDS Vaccine Programme* | UGANDA

"Since the first human trials of an HIV vaccine in 1987, it took 12 years to conduct the first vaccine trial in Africa… Since then one other trial has taken place in Kenya sponsored by IAVI and a few other trials are being planned in other parts of Africa… As we plan for vaccine trials it is the obligation of trial sponsors in developed countries and the obligation of governments and institutions in developing countries to put in place and follow sound ethical guidelines… As we participate and conduct HIV vaccine trials in Africa, the road to success will depend on our commitment to conduct ethical research, to protect the volunteers, and to make communities partners in the development."

Meanwhile, in the United Kingdom, IAVI is advancing its DNA and MVA prime-boost combination into an expanded study that will enroll 120 low-risk volunteers. This phase of testing began April 2002 in London. A similar trial in sub-Saharan Africa is expected soon. Other IAVI-sponsored candidates are at earlier stages of development.

As excited as HVTN investigators are about the Merck and VRC prime-boost strategy, two or three years from now they may balk when they face the prospect of an actual

## CREATION OF THE AVAC FUND

In the coming years, the involvement of communities and clinical research sites in the developing world will be greatly expanded. This is where much of the epidemic rages and where AIDS vaccine candidates can be most efficiently and appropriately tested. This reality places additional burdens and responsibilities on parts of the world already overwhelmed by basic social and health needs. In such settings, scientists working on cohort development and vaccine trials often confront critical needs not covered by their budgets. Some of these needs could be satisfied with less than $2,000.

With release of this report, we are announcing creation of The AVAC Fund. It will function as a small-scale "emergency fund" to assist needy clinical sites that require immediate help with purchases such as additional medical or lab supplies not covered by grants or contracts for vaccine research.

Contributions to the Fund will be tax deductible and will be managed separately from AVAC's operating funds. Once the Fund reaches $10,000 in donations, clinical trial sites in resource-limited settings can apply for grants up to $2,000. All AIDS vaccine clinical trial sites in resource-limited countries or needy communities, regardless of sponsor, will be notified when funds are available and informed of application procedures. A committee consisting of HIV vaccine investigators and AVAC Board members will review requests and awardees will be listed on our web site (www.avac.org).

The AVAC Fund is a direct and tangible way to assist AIDS vaccine clinical trial sites in communities that are struggling with the devastation of AIDS and to reward their heroic efforts in the search for a vaccine. Contributions can be made by credit card on our web site (www.avac.org) or through the mail. Please call us with any questions about the Fund.

Phase III study. The Merck combination doesn't aim to prevent HIV infection but instead aims to suppress viral load so that disease does not appear and transmission is less likely. Given this situation, the endpoints of an efficacy trial will need to be redefined and public support will be crucial in moving forward.

### THAI TRIAL GOES FORWARD/MILITARY HIV RESEARCH MOVES INSIDE THE BELTWAY

For over a decade, scientists from the Walter Reed Army Institute of Research (WRAIR) have laid groundwork for large-scale testing of HIV vaccines in Thailand. Vaccine preparedness studies and Phase I and II trials have been carried out by U.S. and Royal Thai Army scientists, leading academic investigators, and Thai public health officials. Encouraged by WRAIR scientists, Chiron-Biocine (now Chiron Vaccines), Pasteur Merieux Connaught (now Aventis Pasteur), and later Genentech (now spun off to VaxGen) were the first companies to match vaccine candidates to the predominant HIV subtypes found in Southeast Asia. Chiron withdrew from the collaboration in 1998. By the end of this year, the remaining collaborators plan to launch a Phase III study of an Aventis canarypox vaccine (vCP1521) with a VaxGen gp120boost (AIDSVAX B/E).

While progress has been underway in Thailand and while WRAIR has been building vaccine collaborations in several African countries, the Pentagon has tried on several occasions to close down this highly regarded HIV program. WRAIR supporters in Congress and the advocacy community (including AVAC) have continually intervened to win needed funding increases and keep the program going.

This time, however, there was an unstoppable order from the Bush Administration's Office of Management and Budget. The OMB ordered the Department of Defense (DOD) to move four medical science and technology programs to NIH effective October 1, 2002. Among them is the WRAIR AIDS vaccine program, sent packing without its base funding of about $24 million and without its $11 million "plus up" from friendly members of Congress. The WRAIR program is admired for being highly directed, for partnering successfully with industry and foreign governments, and for supporting the sites and staff necessary to carry out large-scale trials around the world. Many people in the field are at least relieved that it is being transferred to NIH, rather than shut down entirely.

The timing for the move appears auspicious because the present head of the NIAID Division of AIDS (DAIDS) is Edmund C. Tramont, a retired Army colonel who founded the military retrovirus program 16 years ago. Tramont brings private-sector vaccine experience as well as military know-how to DAIDS, which has tremendous resources and all the weighty trappings of bureaucracy. He says that "the objective is to keep the military program as intact as possible." Whether this can be effected depends on a

### GOVERNMENT RESEARCH CENTER UP AND RUNNING

In October 2001, one year after the Dale and Betty Bumpers Vaccine Research Center (VRC) moved into its sparkling new headquarters on the NIH campus, director Gary J. Nabel announced that the VRC's first experimental HIV vaccine was being tested in volunteers. Today, that study is well underway at the NIH Clinical Center and Nabel's team is collaborating with the HIV Vaccine Trials Network (HVTN) to expand testing. The Network's leaders say that VRC products are in line right behind Merck. AVAC applauds this impressive beginning for VRC. The Center's work is testament to what is possible in the public sector when the necessary resources, leadership, and a mandate to show tangible results are in place.

Some participants in the discussions about a VRC/HVTN partnership optimistically predict that the VRC's first candidate vaccine could be in a Phase II study by early 2003. Veteran vaccine developers are skeptical about such a timetable, given that the Center's first product has been tried in only 21 volunteers and that delays in manufacturing and regulatory approval are inevitable. Nabel refuses to set a date but says that VRC and HVTN are "working as hard as possible to reach Phase III."

Nabel says the Center's goal is to create broadly protective vaccines that are "multi-valent" and "multi-clade" and to ensure that they are accessible and affordable to the world. Exactly how this goal will be realized is unclear. In all likelihood, any successful vaccine created by the VRC would be licensed to a major company.

Like Merck, the VRC is working on a prime-boost strategy that combines DNA and adenovirus delivery systems. The Center's DNA vaccine, now in Phase I study, contains genetic material for two key HIV proteins, gag and pol. It is being manufactured by the California company Vical, where DNA technology licensed by Merck also originated. Next in line is an adenovirus vector that will encode three HIV proteins (gag, pol, and nef) as well as envelope proteins from as many as three clades of HIV (A, B, and C). The contract manufacturer for this vaccine is GenVec, a Maryland company that has previously made adenovirus vectors for gene therapy. The HIV adenovirus product has yet to be tested in human volunteers.

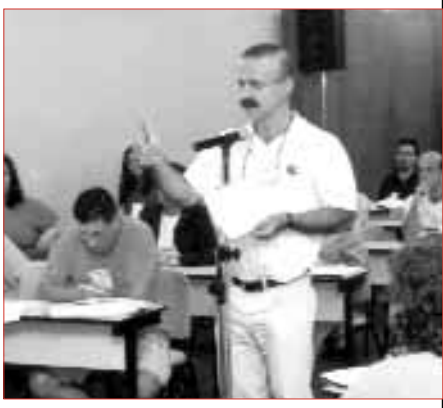
Memorandum of Understanding that NIH and DOD are negotiating now. There are delicate personnel and programmatic questions involved such as which NIH administrators will supervise which military officers. It is likely that some top people are not going to like what they are offered and some scientists down the ranks could find that their services are no longer needed by the bigger, richer NIH.

If the merger goes well, Tramont expects the military division of NIAID to become "a linchpin for international studies," which has not been a strongpoint of the NIH HIV vaccine program so far. Col. John McNeil, who has led the Thai collaboration for the past decade, also takes a guardedly optimistic view, "It's very important for our organization to maintain its identity and philosophy, which has allowed us to work the way that we have.

PERSONAL STATEMENT

**JORGE BELOQUI** | *Advocate* | BRAZIL

"I have been involved in vaccine activities since 1991… Prevention and care are the two sides of a strategy against AIDS, interpreted within a context of human rights… [The highest] standard of care should be provided to volunteers, [including] counseling, access to condoms and syringe exchange, and triple therapy for people infected in vaccine trials… AIDS vaccine awareness has risen and there are enough funds for vaccine research to warrant ethical and scientific excellence. Facilitating access is very important, and should be negotiated in the beginning. To transfer technology to developing countries is perhaps the easiest way to provide access."



If that can be accomplished in the context of a larger, coordinated effort with DAIDS, that could be unbelievably powerful." In a letter to NIH and DOD leaders, AVAC forcefully underlined the need to retain the "operational independence" of the WRAIR team.

The immediate challenge is to keep momentum going for the Phase III study in Thailand. The WRAIR program was transferred with an empty wallet and NIH has agreed to supply $24 million to keep it going for the current year. In addition, Tramont told AVAC that NIH is committed to funding the Thai efficacy trial, which he estimates will cost $40–$60 million. The Phase III study is now slated to begin in the fourth quarter of 2002. If all Thai and U.S. regulatory approvals come through in a timely manner, McNeil says that 16,000 community residents from two provinces, Rayong and Chon Buri, will be enrolled over 12 months. Military investigators and HVTN scientists are discussing the possibility of adding a cohort of intravenous drug-users to the protocol who might be recruited by an HVTN site at the Research Institute for Health Sciences in Chiang Mai, Thailand. As this report went to press, the outcome of these negotiations was not yet known.

Final results from the Thai Phase III will not be available until after the study ends in 2007. What happens then hinges on many scientific, political, and economic unknowns. If the vaccines are efficacious, McNeil and others predict that the Thai FDA will approve them for clinical use. Most scientists interviewed by AVAC did not believe, however, that the U.S. FDA would license these vaccines based on findings from a single efficacy study – conducted overseas with candidate vaccines matched to an HIV type not commonly found in the United States. Even if the prime-boost approach demonstrated a surprisingly

high level of protection in Thailand, it would probably not be available to U.S. communities until additional trials are run, an estimated 2 to 4 years after the Thai trial ends.

## LESSONS FROM THE WORLD'S FIRST EFFICACY TRIAL

In November 2002, the world's first Phase III trial of a vaccine to prevent AIDS will draw to a close. This study of the VaxGen AIDSVAX B/B enrolled more than 5,400 at-risk gay men and heterosexual women in the U.S., Canada, and Holland. Trial volunteers are receiving seven blind shots of either AIDSVAX B/B or placebo and are being followed for 36 months. In October 2001, an interim review of 24 months worth of trial data resulted in a recommendation that the trial continue to its scheduled conclusion. This did not mean that the vaccine had failed or that there was evidence of protection — merely that there was not yet enough data to reach a statistically significant conclusion regarding efficacy at that time. The company expects to announce results of the trial during the first quarter of 2003. Showing foresight (and characteristic optimism), VaxGen recently formed a joint venture with three South Korean companies to build manufacturing plants for AIDSVAX.

An ongoing, parallel Phase III study in Bangkok enrolled approximately 2,500 injection drug-users who participate in a government methadone-treatment program. The protocol was the same as the U.S. trial except that the vaccine was AIDSVAX B/E, a product designed for use in Thailand. Final results from this collaboration with the Bangkok Vaccine Evaluation Group are expected later in 2003. When the study is complete, VaxGen and its Thai collaborators will have demonstrated that a U.S.-made vaccine can navigate the regulatory processes of two countries to generate data suitable for licensure filings.

The first requirement for any vaccine is that it be safe. No safety problems have surfaced after more than a decade of testing gp120 vaccines, such as AIDSVAX, in volunteers. Moreover, risky behavior apparently declined during the trial, confounding predictions by some that a false sense of security would make vaccine trial volunteers more likely to engage in risky sexual or drug-using behavior.

The big question, of course, is how effectively the vaccine blocks HIV infection. Final results may show that AIDSVAX had no protective effect or protected just some of those who were vaccinated, so that the rate of HIV infections in the vaccine group was at least somewhat lower than in the placebo group. Few scientists expect AIDSVAX or other first-generation HIV vaccines to protect everyone, and many predict the trial will find the vaccine had little or no efficacy.

If the U.S. trial shows that the vaccine protects at least 30% of immunized volunteers, VaxGen would probably not seek FDA approval until results from the Thai study are known at the end of 2003. Given the pace of FDA review and the demands of large-scale

manufacturing, a successful VaxGen product would probably not arrive in clinics until 2004. If its efficacy is low, important discussions will ensue concerning how and in what populations it may be safely deployed.

In addition to showing whether two specific vaccines can protect against infection or alter the course of disease, the world's first Phase III HIV vaccine trials should yield vital lessons about study planning and preparation, infrastructure needs, ethics, recruitment, and community and public-sector support. For those determined to slow the global AIDS pandemic, a major benefit of the VaxGen experiment is that it proves that large-scale clinical trials can be successfully implemented in motivated, at-risk populations in the U.S. and beyond. Already the VaxGen study has demonstrated high retention rates and evidence of strong commitment on the part of the volunteers.

Several years ago VaxGen joined forces with collaborators from the Centers for Disease Control and Prevention (CDC) to learn as much as possible from this unique trial. At six domestic sites, VaxGen and CDC recruited 800 volunteers who are not in the vaccine trial but who agreed to come to the clinics and undergo the same interviewing and counseling as trial participants. This research will provide a valuable context for understanding sexual and drug-related behavior reported by trial volunteers. Researchers can also compare rates of new infection in the two groups and will be able to determine what strains of HIV are circulating in these areas.

CDC has also undertaken important qualitative research on trial volunteers' attitudes, knowledge, and reasons for enrollment. In addition, interviews with trial-site staff will be used to spot hallmarks of highly successful clinical sites — important knowledge for future Phase III trials.

VaxGen and its collaborators also expect to review data for evidence of "social harms" related to volunteering for a vaccine trial, such as discrimination. Although few participants have reported such detrimental effects, some have noted adverse changes in personal relationships or difficulty obtaining health insurance. The studies will also seek to confirm that participant privacy and other rights were protected at all the trial sites.

Lessons from the pioneering VaxGen trial will be indispensable when HVTN, IAVI, or any other sponsor begins recruiting volunteers for Phase III trials of the future.

# III Community Call to Action

## ISSUES FOR ACTION
## WHAT INDIVIDUALS, COMMUNITIES, AND ORGANIZATIONS CAN DO
## SHARED ADVOCACY IN THIS PANDEMIC

The AIDS vaccine movement depends on public engagement, which so far has been weak. Engagement needs to take many forms. Individuals can volunteer to participate in trials. Affected communities and their organizations must insist on ethical research and take an active role in the process. Most importantly, the general public must come to see AIDS vaccines as *everyone's* issue — not a need restricted to communities of gay people or drug users. It is essential that a broad spectrum of citizens support clinical trials that will answer important research questions and advance the field. The public must also demand accelerated research efforts, additional funding, and global access to a vaccine.

Greatly increased public demand for AIDS vaccines would move the process at every level — from the research lab, to the World Bank, to the rural clinic. Expanded activism can, and *must*, work in solidarity with global AIDS prevention and treatment efforts.

**We ask you to incorporate advocacy for AIDS vaccines into your work and your life.**

### ISSUES FOR ACTION

Many crucial issues in AIDS vaccine research are highlighted throughout this report. Here is a quick summary:

**Protecting trial participants:** People who volunteer for AIDS vaccine trials are making a significant contribution to global health research. Participants deserve protection from harm, including a guarantee that they will be provided medical care and compensation for any injury caused by a candidate vaccine. Governments and researchers must also do everything possible to prevent discrimination against people who volunteer for trials. Congressional legislation may be proposed later this year to expand protections for AIDS vaccine trial participants. Watch for this legislation and demand the protections. Vaccine trials must provide high-quality behavioral prevention interventions to help volunteers protect themselves from infection. Access to AIDS treatment is extremely poor in

resource-limited countries, and vaccine trials must be used as opportunities to expand HIV treatment. Ideally, this would happen in an integrated fashion so that vaccine trial participants who become infected — as well as others in their communities — will have access to treatment.

**Accelerating ethical research:** A series of clinical trials involving tens of thousands of people throughout the world will likely be needed to find an AIDS vaccine. Public support for these trials is essential. A diverse enrollment is crucial — including people of color and adolescents. U.S. voters need to support funding increases for AIDS research and serve notice to their representatives that the current focus on bioterrorism must not undermine efforts to combat the world's major infectious scourges — AIDS, tuberculosis, and malaria. The public needs to urge Congress to pass the *Vaccines for the New Millennium Act*, which will provide incentives for private-sector research on vaccines to combat these worldwide killers. Pressure is needed to support accelerated regulatory consideration of candidate AIDS vaccines in the U.S. and Europe, and to increase regulatory capacity in resource-limited countries.

**Involving and educating communities:** Clinical trials can only succeed when at-risk communities are involved in their planning and implementation. Communities need to be educated about the promise and the limits of AIDS vaccines. Information, training, and resources must be provided in a manner that respects local cultures and in language that people can understand. Politicians and policy makers must be educated about the value of vaccines — and their place in a comprehensive approach to HIV/AIDS. Public dialogue, education, and outreach are essential elements in vaccine research and delivery.

**Ensuring global vaccine access:** People in the developing world historically wait a decade or longer to receive a needed vaccine after it has been licensed for use in industrialized nations. This history must not be repeated with AIDS vaccines. The public must press for faster delivery of vaccines and treatments to poor countries through increased funding for the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the Global Alliance for Vaccines and Immunization (GAVI). Overall, greater global spending is required to strengthen health care infrastructures in resource-limited countries. Countries participating in vaccine research must demand up-front agreements securing vaccine access should a candidate vaccine being tested in their country prove effective. The public must demand that government officials and donor organizations commit, *in advance*, to purchase AIDS vaccines as soon as they become available. Also needed is support for public-sector efforts to bolster manufacturing capacity for AIDS vaccines. Partially efficacious vaccines may be considered for licensure within the next two years. Communities must demand "100% access" and "100% personal choice" in the delivery of these vaccines. A special

liability system must be created to provide rapid compensation to anyone harmed by a licensed HIV vaccine — a program that would benefit consumers and industry alike.

### WHAT INDIVIDUALS, COMMUNITIES, AND ORGANIZATIONS CAN DO

You and the organizations you are part of can make a real difference in the quest for an AIDS vaccine. *What can you do?*

**Consider Volunteering for a Trial:** AIDS vaccine research is being conducted in cities large and small around the world and there will be more trials in the future. You may check out a list of current trials on the IAVI web site (www.iavi.org) or the HVTN web site (www.hvtn.org), contact the AIDS Clinical Trials Information Service by calling 1-800-TRIALS-A or visiting their web site (www.actis.org), or write AVAC (avac@avac.org) for information about trials near you. Remember that AIDS vaccine trials are not for everybody and you should fully inform yourself of the potential risks and benefits of participation before entering a trial.

**Join a Community Advisory Board (CAB):** There are CABs at each AIDS vaccine research site and they make important contributions to the design and conduct of trials. For more information on CABs near you, contact the sources in the paragraph above.

**Advocate:** Write or call your members of Congress and ask what they are doing to accelerate ethical research on AIDS vaccines and to promote better global health. Urge them to co-sponsor the bipartisan *Vaccines for the New Millennium Act* (H.R. 1504 and S. 895) in Congress and support advance commitments to buy AIDS vaccines for global use when they become available. (We've found that an effective strategy is to place direct calls to Congressional offices in Washington, emphasize that you are a constituent, and ask to speak with the staff person who handles health issues.) Call your state lawmakers and urge them to look into innovative approaches such as those taken in states including California and Georgia *(see "New Roles for State Governments in the U.S.")*. Contact AIDS and health organizations in your area and ask what they are doing on behalf of AIDS vaccines.

**Make AIDS vaccines part of your mission:** If you are a staff member or supporter of an AIDS organization, health advocacy group, or civic organization, make sure that AIDS vaccines are part of your group's mission. Incorporate AIDS vaccine issues *(like those summarized above in "Issues for Action")* into your group's advocacy agenda and education efforts. Contact AVAC (avac@avac.org) for more detail on policy and advocacy issues.

**Contribute money, time, or take a ride:** The AVAC Fund *(see page 11)* provides small-scale but immediate support to clinical trials sites in needy countries or communities. You can make a contribution to the Fund on the AVAC web site (www.avac.org). Many research institutes and advocacy organizations (including AVAC) accept donations and

need volunteers. AIDS Vaccine Bike Rides that benefit specific research institutions are held every year in various locales. (Know, however, that although these long-distance rides have raised millions of dollars for research, more than two-thirds of the money raised actually goes for expenses associated with the rides themselves.)

**Become a member of AVAC:** Visit our web site (www.avac.org) or mail in the form on page 43 of this report to become a contributing member of AVAC. You'll receive regular updates and a copy of our annual report. And you'll be helping us push for accelerated ethical AIDS vaccine research and global vaccine access.

## SHARED ADVOCACY IN THIS PANDEMIC

Treatment, behavioral prevention intervention, and needle exchange are the current bulwarks in the fight against AIDS. At some point, vaccines will become another vital tool to control the AIDS pandemic — but they won't do it alone. Vaccines will be used along with other interventions including safer sex practices, effective treatments for those living with HIV, and perhaps, someday, one or several microbicides for prevention. (A microbicide is a cream, gel, or other formulation being developed to prevent HIV/AIDS and other sexually-transmitted diseases through topical application to genital surfaces.)

Today, AIDS vaccine research is intertwined with AIDS care, prevention, and research in many ways. There will be times when advocates for vaccines, microbicides, and treatments can best work alone on issues of specific concern to them, but there are many opportunities to work together toward common goals.

- **Health care infrastructure:** Vaccine research and development will require a substantial investment in health care and research infrastructure in the developing world. Resource-limited communities in which vaccine trials will be conducted are the *same* communities that need health care clinics and research capacity to implement HIV treatments or evaluate a candidate microbicide. Improved infrastructure will be essential for a sustainable local response in the future. Vaccine, microbicide, and treatment advocates must join forces to ensure that the United States and other wealthy countries invest in building health care and research capacity in the world's poorest nations.
- **Product procurement and pricing:** Developing a vaccine is only one step toward ridding the world of HIV/AIDS. Unless vaccines are affordable and widely accessible, they will have little effect on the epidemic. The current debate about the high prices of AIDS drugs in the developing world is a battle that vaccine and microbicide advocates can join. Understanding how drugs can be made accessible to the world's poorest countries, while allowing companies to recoup their costs and satisfy their

PERSONAL STATEMENT

**JOE WRIGHT** | *Advocate* | USA

"Many community advocates instinctively distrust and avoid HIV vaccine research… But for community people to ignore the search for an HIV vaccine puts a hugely important project in the wrong hands. Not only does HIV vaccine research itself need both criticism and support from people outside of science, but we also need to start planning for how we would make an eventual HIV vaccine part of the larger fight against AIDS. When a vaccine arrives, individuals and local communities will be the ones to decide whether to take it, and whether our behavior will support or undermine its benefits… each of us who needs to be protected against HIV must see it as our vaccine – a thing not of distant technocrats, but a part of our most personal aspirations. That is not something that happens overnight. It is something that must start now."

shareholders will help pave the way for future pricing and distribution of vaccines and microbicides. Working together, advocates can encourage policy makers and industry executives to devise a tiered pricing system that allows higher prices in the United States and Europe to subsidize lower prices in Africa, Asia, and South America. But lower prices for poor countries will only go so far. Advocates must work together to ensure that the Global Fund to Fight AIDS, Tuberculosis and Malaria along with other multi-lateral organizations and donor nations, marshal the billions needed to provide treatments today, and vaccines and microbicides when they become available.

- **Regulatory capacity:** In many developing countries there is either no counterpart to the U.S. Food and Drug Administration, or there is only a rudimentary system for approving drugs, vaccines, or medical devices for testing or sale. Vaccine, microbicide, and treatment advocates all have an interest in enhancing regulatory capacity in the developing world. Expanded regulatory capacity will facilitate local decisions about hosting clinical trials and will expand each country's ability to assure safety in the conduct of these trials.
- **Research:** AIDS research is a multi-disciplinary undertaking, drawing on fields including immunology, virology, infectious disease, clinical trial design, process science, behavioral research, and other scientific areas. Vaccine research depends on investment in all of these — and what happens in the vaccine realm impacts other

parts of AIDS research. For example, the prospect of vaccines that do not prevent infection but rather delay its impact has clear implications for treatment in the future. Researchers who work on ostensibly different problems, such as vaccines or microbicides, may share a need for expanded access to non-human primates for preclinical studies. The AIDS community must continue to support comprehensive expansion of AIDS research rather than pit one type of research against another.

- **Industry involvement:** Much of the world's expertise on drugs and vaccines resides in the private sector. Government has a responsibility to provide cooperative agreements, technology transfer, funding, and incentives to facilitate and encourage private industry research on AIDS prevention and treatment. Vaccine, treatment, and microbicide advocates must all support expansion of private-sector research.
- **Ethics:** Trust is the foundation of clinical research. Clinical trials of vaccines, microbicides, or drugs can be sustained only if they are ethical. Concerns such as informed consent, community involvement, and provision of adequate care for volunteers apply to all types of AIDS research. Advocates for prevention and treatment have a shared interest in these issues.

- **Debt relief:** Developing countries cannot mount and sustain an effective response to AIDS if they must sacrifice health and education funds to repay or service debt to rich nations and institutions. If developing nations are to establish independent health care and research capacity, rather than rely permanently on donor support, they must be enabled to spend their resources on their own citizens rather than payments to foreign banks and governments.
- **Community education:** The cooperation of communities and their leaders is essential for the conduct of vaccine research as well as the eventual deployment of viable products. Early and repeated educational efforts will be needed to ensure that people are informed not only about clinical trials but also about what AIDS vaccines can and cannot accomplish in terms of disease control. Integrated educational approaches that offer a full description of the biomedical and behavioral approaches to HIV/AIDS will be more successful than educational efforts that tell only part of the story.

# IV Vaccines on a Global Scale



The scientific research dollars of the industrialized nations will probably fuel global HIV vaccine research and development around the globe for many years to come. And while more resources are needed to defeat the AIDS pandemic, we are seeing progress on research in resource-limited countries as clinical trials get underway in Thailand, Uganda, and Kenya.

These trial efforts, by definition, are partnerships involving one or more sponsor organizations, the host government, one or more host institutions, and a number of trial sites. Although the ideal would be partnerships among equals, too often the reality is that some partners are more equal than others. But as relationships between sponsors and hosts evolve, it appears that the balance of power is becoming more balanced.

## THE ESSENTIAL ROLE OF GOVERNMENTS IN COUNTRIES WITH LIMITED RESOURCES

Years from now, after an AIDS vaccine has reached millions of people, what story will historians tell? We hope this narrative will be very different from histories of other vaccines and therapies that did not reach poorer countries for years or decades. One of the chief differences with AIDS vaccines will likely be the central role that resource-limited countries play — in sponsoring trials, creating research and regulatory infrastructures, training staff, manufacturing products, and educating their populations.

An AIDS vaccine is not something rich countries will develop and then hand off to the rest of the world. Several resource-limited countries have already emerged as leaders on AIDS vaccine research. The Thai government, for example, has long been a strong participant in AIDS vaccine clinical research. Early on, Thailand confronted the epidemic and provided targeted prevention. With assistance from the World Health Organization

(WHO) the Thais developed an AIDS national plan and set up infrastructure that would be needed for clinical trials. Academic medical centers, the Royal Thai Army, the Bangkok health department, and the Ministry of Public Health all collaborated with vaccine researchers. Readiness studies identified target populations and assessed their willingness to participate in trials. Thailand, of course, is an industrializing nation, with more resources than many severely affected countries.

Other nations, less wealthy than Thailand perhaps, need to implement policies that will expedite trials of AIDS vaccines appropriate for their populations. Some countries, such as India and Brazil, have additional strengths such as high-quality manufacturing capabilities. They could play an important role by producing vaccines for their own use and for other countries with limited resources.

In some countries, lack of clinical trial infrastructure or regulatory capacity is the chief impediment to advancing HIV vaccine research. But in many others, lack of political will is a central factor. This can manifest as denial of the severity of AIDS, lack of understanding about the human and economic value of vaccines, or distrust of clinical research and outside researchers. In countries with limited resources, strong leadership is needed to speak out about the importance of AIDS vaccines, participate in planning, ensure ethical trials, accept technical assistance and financial support from the outside, and negotiate plans for widespread access to a vaccine. Strong leadership is also needed from wealthy countries and international research funding institutions. They must be willing to dedicate funds for clinical trial operations and infrastructure even in areas where there are difficult political or other challenges.

In *IAVI Reports*, Jean-Louis Excler, former chief of HIV vaccine clinical development at Pasteur Merieux Connaught (now Aventis) has suggested a "regionally-focused, integrated approach," among countries with financial barriers. Excler proposes that countries in a geographical region set up a task force to "formulate a clear, specific vaccine development plan." This is a goal the Joint United Nations Programme on HIV/AIDS (UNAIDS) has also been working toward. Excler argues that little progress can be made without strong leadership, which he calls "the definitive gap" in AIDS vaccine development.

## RE-EVALUATING ETHICS

The AIDS epidemic rages mainly in developing countries while the reservoir of scientific research is located in rich, industrialized nations. Clinical trials are where the two approach one another. A uniform ethical code is the bridge that joins them — in ways designed to protect the more vulnerable members of the partnership from harm and exploitation. Over the years these relationships have been guided by various ethical

## ESTIMATED NUMBER OF ADULTS AND CHILDREN NEWLY INFECTED WITH HIV DURING 2001


[ TOTAL: 5 MILLION ]

**Sources:** Joint United Nations Programme on HIV/AIDS (**UNAIDS**) and World Health Organization (**WHO**).

guidelines in use around the world. As more developing countries prepare for clinical trials, incorporating solid guidelines — at the insistence of developing countries — is essential to the globalization of HIV vaccine research.

In the past, developing countries have been understandably reluctant to be the first to test the safety of drug and vaccine candidates that have been created elsewhere. In response to these concerns, it became common practice to insist that products first be tested in their country of origin. But this standard has its limits for AIDS vaccines. It could result, for instance, in situations where researchers in resource-limited countries are precluded from overseeing the Phase I testing of vaccine candidates developed specifically for their population's use.

Recognizing the need for revision, framers of ethical texts are responding. Point 8 in *Ethical Considerations in HIV Preventive Vaccine Research*, the UNAIDS guidance document published in 2000, states that there may be situations where developing countries choose to conduct Phases I/II because "conducting Phase I/II trials in the country where the strain exists may be the only way to determine whether safety and immunogenicity are acceptable in that particular population, prior to conducting a phase III trial." Similarly, the *International Ethical Guidelines for Biomedical Research*

## CIPRA: THE NEW ARCHITECTURE FOR INFRASTRUCTURE

For years, HIV/AIDS reports by AVAC and other organizations have lamented the lack of infrastructure for conducting clinical trials in developing countries. In June 2000, the U.S. Government put some of its HIV/AIDS research dollars toward addressing this issue when it launched the Comprehensive International Program of Research on AIDS (CIPRA), a NIAID-funded program with a current annual budget of $15 million.

CIPRA evolved to address problems with the traditional NIAID approach to supporting international research, which consisted mainly of short-term grants and contracts paid through U.S. academic institutions. When those contracts ended, the US investigators' involvement ended too. "This is not a sustainable model," said Rodney Hoff, a senior epidemiologist in the Vaccine and Prevention Research Program at NIAID and coordinator of the CIPRA group.

CIPRA's goals are "to provide long-term support to developing countries to (1) plan and implement a comprehensive HIV/AIDS prevention and treatment research agenda relevant to their populations, and (2) enhance the infrastructure necessary to conduct such research." What sets CIPRA apart from earlier programs is that *only* researchers in developing countries can apply for CIPRA grants. The three-tiered grant program is also structured to be flexible enough to engage countries with ongoing research programs as well as those starting from scratch, Hoff told AVAC. For researchers less experienced in applying for international grants, CIPRA provides grants for writing grant proposals — a level of help U.S. investigators are not offered when they apply to NIH.

Local team-building is a key aspect of CIPRA. Preparing a CIPRA application drives researchers to seek out colleagues in their home and regional institutions, forging relationships that contribute greatly to sustainability. Ironically, previous funding mechanisms sometimes pushed developing-world researchers to have closer associations with their counterparts in industrialized countries than with their colleagues down the hall. CIPRA also encourages researchers to connect with their governmental ministries.

The first CIPRA awards have been made to researchers in Trinidad and Tobago, Peru, China, Zambia, and the Russian Federation. And thanks to CIPRA energetically getting the word out, many researchers around the world are working on applications for upcoming funding cycles. AVAC supports this innovative effort, which for the first time puts researchers in developing countries in the driver's seat.

*Involving Human Subjects* issued in 1993 by the Council of Biomedical and Behavioral Research (CIOMS), the ethics text used in a number of countries, is currently being revised to reflect the research needs of developing countries.

## REVVING UP THE REGULATORY PROCESS

Since most vaccines in the global pipeline are sponsored by American companies, the US Food and Drug Administration (FDA) exerts a strong influence on what is tested worldwide. In many regards the FDA is an admirable agency, staffed by conscientious scientists who have the unenviable task of weighing the risks and benefits of experimental products presented for their review. It is distressing then, that such a pivotal agency is so overextended, short staffed, and under funded. And it is a matter of great concern that the FDA Center for Biologics is essentially a passive and reactive organization, apparently unwilling or unable to take active steps to prepare for the Investigational New Drug (IND) applications coming their way. Moreover, many of the new products are from biotech and new industry sponsors who lack experience with FDA Regulatory Affairs and who often find the IND process almost unfathomable.

Concerned that a regulatory bottleneck could choke the flow of products eligible for global clinical trials, AVAC has been pursuing ways to work constructively with the FDA. Since July 2001, AVAC has met twice with FDA representatives. Unfortunately, as this report goes to press there has been no demonstrative progress in three areas in which AVAC believes the FDA can take a more active role — namely administrative improvements, information sharing, and scientific guidelines.

The FDA mission gives the agency significant power. And for whatever reason, the agency discourages criticism and resists making formal changes, although we have recently seen positive signs of a more cooperative attitude. Additional funding and political support are justified, especially given the large funding increases that we are currently seeing for product development.

If this is where we are today, what will happen tomorrow when we actually have successful vaccines? How will they be licensed? The first ones to prove their worth in clinical trials will probably be reviewed by the FDA or an equivalent regulatory body such as the European Medicines Evaluation Agency (EMEA). If so, chances are the regulatory bodies in resource-limited countries will take their lead, to a large extent, from the regulatory bodies in the developed countries.

However, it is possible that after analyzing the risks and benefits of a product, the FDA may decide against licensing a vaccine for use in the U.S., whereas a developing country may see the vaccine as being beneficial for its population and decide to go it alone. But to license a product without FDA or EMEA backing requires that a developing country have confidence in its own regulatory capacity and the necessary political will. Rotavirus vaccine is a cautionary tale. When rare but serious side effects from the vaccine were identified in the U.S., the vaccine was taken off the market. This action precluded

use of the very effective Rotavirus vaccine. And many would argue the benefits far outweigh the risks in many countries.

Countries typically have a regulatory body but many lack experience in licensing new products. Building the regulatory capacity anticipated for the future has to start now. One possibility, according to Michael Isbell, a senior policy advisor at IAVI, is to foster regional collaboration and dialog. Isbell believes that although countries may not be prepared to relinquish their rights to make their own regulatory decisions, countries in the region that have greater regulatory capacity could reach out to their less experienced neighbors and disseminate information and assistance.

There has recently been a growing recognition of the need to harmonize regulatory processes across countries. WHO has held two meetings on regulatory issues, one focusing on vaccines and another on microbicides, and the organization is working with many countries to assess and expand their regulatory capacities. In addition, several countries are discussing approaches to regulatory harmonization in their own regions.

There is also an International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (called ICH). This body is made up of government regulators and drug industry representatives from the U.S., the European Union, and Japan working to "make the international drug regulatory process more efficient and uniform." This effort is primarily in the interest of pharmaceutical companies and countries that can pay top Dollar, Euro, or Yen for drugs or vaccines.

Other innovations are also possible. In geographical areas where the demographics and viral subtype are the same, several national regulatory authorities might join forces to evaluate clinical evidence of safety and efficacy and decide to register successful vaccines on a regional basis.

## PARTNERSHIPS: THE NEW BUSINESS MODEL TAKES HOLD

Partnerships are becoming the organizing principle in AIDS vaccine research and this is good. The challenges presented in the quest for an AIDS vaccine — from scientific unknowns, to clinical complexities, to steep manufacturing costs — all call for teamwork. Partnerships between the public and private sector hopefully draw on the strengths of both, and ideally accelerate research and product delivery.

The partnership proliferation makes increasing sense at this stage in AIDS vaccine research. It highlights the maturation of research efforts and the progression toward more concerted product development. It also signals the importance of bringing multiple areas of expertise, capability, and interest to bear on AIDS vaccines.

PERSONAL STATEMENT

**JENIFER EHRETH, PH.D.** | *Aventis Pasteur* | FRANCE

"My first study in the area of HIV was 15 years ago... A worrisome development since then has been the divide between the AIDS advocacy community and companies that search for solutions... I hope to see better coordination among all interest groups. The best solutions can be found when there are fewer adversaries and more partnerships keeping in mind the best interests of patients."

Partnerships are the way of the future but they do raise issues for vaccine advocates. More partnerships mean more research entities to be held accountable. Care is needed to ensure that partnerships do not inhibit healthy competition, interfere with parallel development of multiple products, or discourage risk-taking and the expeditious advance of products.

Most importantly, if the public sector provides funding, research tools, and trial sites to private industry, advocates need to ask what the public gets back, particularly in terms of expanded access to a vaccine that proves effective. Early signs indicate that valuable, though limited "give back" or "access" provisions can be negotiated, but that industry players — particularly the largest drug companies — are exceedingly wary of these agreements. There is some irony here, since it is wholly to the private sector's advantage to find new ways to secure global AIDS vaccine access while making a profit. If the company that makes an AIDS vaccine fails on global access they have only to lose — in the form of missed opportunities for expanded markets, international respect for patents, and public opinion.

## MANY HANDS SHAPE THE VACCINE INITIATIVE IN BOTSWANA

Throughout this report we discuss the challenges facing resource-limited countries as they grapple with the complexities of clinical trials. A particularly interesting approach is emerging in the Republic of Botswana, where the Harvard AIDS Institute and the Government of Botswana have come together to form a joint enterprise—the Botswana-Harvard Partnership for HIV Research and Education (BHP).

Botswana, famed for great wildernesses such as the Kalahari Desert, nestles between South Africa, Namibia, Zimbabwe, and Zambia. The democratically governed country boasts the highest gross domestic product in Africa, high literacy levels, and a state-sponsored health care system. These assets give the country a boost in establishing its vaccine initiative. Botswana also has the highest HIV-infection rate in the world with almost 40% of the population infected. The potential decimation facing the nation has galvanized the Botswana Government and its leader President Festus Mogae. "We are the most hideously affected country in the world and we had to do something about it," Mogae said.

Botswana's collaboration with the Harvard AIDS Institute began in 1996. There are now several HIV/AIDS related programs and studies underway in Botswana. One program, the KITSO AIDS Training Program, supported by the Merck and the Bill and Melinda Gates Foundations, provides current AIDS care information and training to physicians, nurses, and counselors. A drug-resistance study, supported by legislation passed in January 2002, will provide antiretroviral treatments to 120,000 people during its initial three-year phase. In addition, the largest private-sector employer, The Debswana Mining Company has provided free AIDS treatment to HIV-infected employees for more than a year. The four centers established for treatment are also designed to be future vaccine trial sites.

Further evidence of the Government's commitment to HIV research is joint sponsorship with the Harvard AIDS Institute of the new Botswana-Harvard HIV Reference Laboratory, a state-of-the-art laboratory located in the capital Gaborone that opened in December 2001. The 25,000 square foot facility is dedicated to conducting research on clade C, the viral subtype prevalent in Africa.

A vaccine initiative has always been on the Botswana-Harvard Partnership agenda. In June 2001, Max Essex, chair of the Harvard AIDS Institute took sabbatical leave and spent seven months in Botswana setting up the infrastructure needed to conduct vaccine trials. So where does the BHP vaccine initiative stand at the moment?

Tonya Villafana, site director for the BHP vaccine initiative, arrived with Essex last summer. Working closely, they established a Community Advisory Board and started "doing all the things you need to do to prepare for vaccine trials," said Villafana in an interview with AVAC. For the immunologist and public health scientist, this meant developing a protocol for a vaccine-preparedness study scheduled to start this year. This study, coordinated with the NIH-sponsored HVTN, of which the Botswana site is also a part, will deal with myriad infrastructure-related issues.

Rupert Hambira was a member of the fledgling CAB before becoming senior community education advisor to the vaccine initiative. Reverend Hambira, a minister in the United Church of Christ, sees his job as community mobilization. As such, the role of the Advisory Board, comprised of members from all sections of Botswana society including a traditional healer, will be very participatory. This is especially important as decisions in Botswana are made by consensus. Reverend Hambira's Community Education Plan will use all communication means available—education materials, annual AIDS-related events, the media, churches, trade unions, and so on—to make sure everyone in Bostwana learns what the vaccine initiative is and why it matters.

While much is fine about the Botswana initiative, there are still hurdles to overcome. Informed consent and autonomy are challenging issues for program administrators in a society where elders and authority figures traditionally hold sway. And as yet, the site has no idea which vaccine it will test first—one of the BHP candidates in development or an HVTN candidate. Another pressing challenge is building medical capacity. Botswana has no medical school, although the Government has recently purchased twelve facilities at a medical school in South Africa. Also, regular traffic must flow between Botswana, Harvard, and other centers for the purposes of training and education. For now, most of the scientific leadership comes from Harvard. There is a need to invest in the training of African scientists and find ways to keep them engaged in this country's quest for an HIV vaccine. Villafana acknowledges that capacity building is something the initiative is working very hard on at the moment. As she points out, Botswana and not the Harvard AIDS Institute, must eventually take ownership. Right now, the vaccine initiative is ready to start. The will of the Government is behind it. The will of the people of Botswana is behind it.

# V U.S. Government



## THE NATIONAL INSTITUTES OF HEALTH

The AIDS vaccine research effort needs more than money: it requires willingness to take risks, rethink paradigms, and plan for the long haul. The National Institutes of Health has the resources. But is NIH agile enough to meet the challenge? In the global exploration for an HIV vaccine, the gravitational pull of NIH grows increasingly stronger. The HIV vaccine budget is slated for a 24% increase in the coming fiscal year. Soon NIH will swallow whole the U.S. military's highly regarded HIV vaccine research program. The new NIH Vaccine Research Center (VRC) is moving forward rapidly with its own products, and partnerships with industry and academic centers are on the increase.

With more resources and a larger share of the research enterprise comes growing responsibility for NIH to lead the field. The optimistic view is that this concentration of expertise and resources results in integrated, intensified efforts. The fear is that the NIH AIDS vaccine effort becomes a black hole, sucking in more dollars but avoiding healthy scrutiny, and failing to take necessary calculated risks or challenge old business models. In recent years, NIH has demonstrated willingness to adapt its funding mechanisms to accelerate HIV vaccine product development. The HIV Vaccine Design and Development Teams and the Integrated Preclinical/Clinical AIDS Vaccine Development program are notable examples of this. In Fiscal Year 2003, the Division of AIDS will request proposals for a new program, a Master Contract for Preclinical Development. This initiative will enhance vaccine and microbicide development resources by supporting critical preclinical safety evaluations, product production for at least one candidate per year, and microbicide screening. The continuing leadership of Dr. Peggy Johnston has been key. Yet important challenges — and the need for more accountability — remain.

### AMBITIOUS GOALS

Since 2000, NIAID leadership has been setting and regularly revising milestones for its own HIV vaccine research program. As of April 2002, these milestones call for nine

## NIH VACCINE PROGRAM

| 2001 | 2002 | 2003 |
|---|---|---|
| Canarypox into Phase 1 in Caribbean | — | NIH (Moss) MVA into Phase 1 (Q1) |
| VEE replicon into Phase 1 (delayed) | VEE replicon into Phase 1 (Q3) | Chiron DNA + env Protein (Clade B) into Phase 1 (Q1) |
| MVA + Fowlpox into HIV + children on HAART (delayed) | MVA + Fowlpox into HIV + children on HAART (Q3) | Chiron DNA + env Protein (Clade C) into Phase 1 (Q4) |
| p55 particle into Phase 1 (dropped) | Emory DNA into Phase 1 (Q3) | — |
| Canarypox Phase 2b (cancelled) | U So Wales DNA + Fowlpox (IL12; IFNg; CladeB) into Phase 1 (Q3) | U So Wales DNA + Fowlpox (Clades A/E Recombinant) into Phase 1 (Q3) |
| — | Wyeth DNA into Phase 1 (Q3) | — |
| — | Wyeth Peptides into Phase 1 (Q4) | Wyeth IL12 DNA into Phase 1 |
| — | Epimmune CTL DNA into Phase 1 | Epimmune HTL Protein into Phase 1 (Q2) |
| VRC DNA (Clade B) into Phase 1 | VRC DNA (Multi-Clade A/B/C) into Phase 1 (Q3) | VRC DNA (Multi-Clade A/B/C) into Phase 2 (Q1) |
| — | VRC DNA IL2/Ig into Phase 1 (later in Q3) | VRC Adeno (Multi-Clade A/B/C) into Phase 1 (Q2) |

**Source:** NIH, April 2002

PERSONAL STATEMENT

**PAISAN TAN-UD** | *Thai Network of People Living with HIV/AIDS (TNP+)* | THAILAND

"With 1 million people living with HIV/AIDS and 300,000 already dead, Thailand certainly recognizes the importance of clinical and vaccine research and trials related to alleviating the toll of HIV. Yet the issue of researchers' responsibility to the community is totally under-addressed… The public, including people living with HIV/AIDS, is rarely educated by scientists and researchers about the meaning and implications of research and trials, not to mention the ethical dimensions… We must as a community work harder to ensure protections for research participants."

candidate HIV vaccines to be in Phase I trials within the calendar year with seven additional products entering Phase I in 2003, including those created by the VRC. As in years past, NIAID has set ambitious goals — and this is the key value of milestones. That there are often delays in meeting ambitious milestones is not the issue. Milestones are an important goal-setting and tracking tool, making the complex world of NIH-sponsored research more transparent. We will continue to monitor NIH achievement and we applaud NIH for moving aggressively to get more candidate vaccines into Phase I.

### MONKEYS, CLADES, AND ANTIBODIES

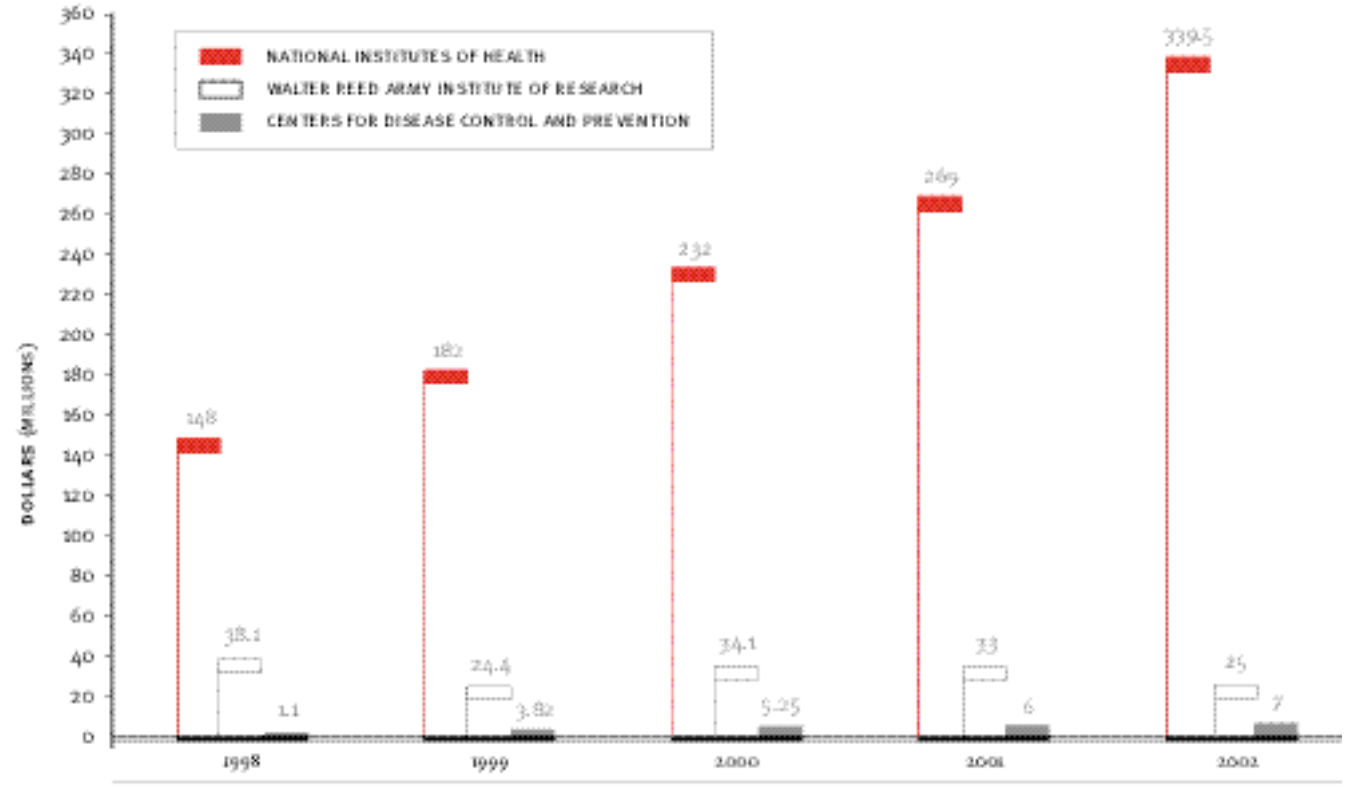
Each year at NIH, the Office of AIDS Research (OAR) re-evaluates, with outside input, its priorities for AIDS vaccine research two years in advance. Looking over the priorities for 2002 — a more robust pipeline, expanded human trials, improving immunologic assessment, and increasing the supply of rhesus macaques for animal testing — there is evidence of progress. The plan for 2003 expands on the macaque supply issue and adds two new key priorities:

- Develop vaccine candidates that are capable of creating antibody responses against a broad variety of HIV isolates.
- Develop strategies to ensure that HIV vaccines are licensed and available for adolescents when they become available for adults.

For years, the limited supply of macaques has been an exasperating impediment to accelerated HIV vaccine research. The National Center for Research Resources has been roundly criticized for not moving decisively to address the issue. The problem stems, in part, from decisions in the 1990s to discontinue support for macaque breeding colonies because these animals were overabundant at the time. Failure to anticipate increasing need for macaques for AIDS and other biomedical research has led to the current predicament, which makes larger and more definitive monkey trials costly and difficult (if not impossible). Burgeoning research on bioterror will only magnify the demand for animals.

Since Spring 2001, NIH has taken several steps to address the shortage of primates, including funding sites for animal breeding, establishing an interagency working group to develop an action plan, surveying researchers on their needs, and doing a census of animals. There is some interest in looking at alternative — and more accessible — species for primate research but switching animals would entail different delays as customized assays and challenge stocks are developed. AVAC hopes that expanded efforts of NIH to address the monkey shortage will result in increased availability of primates for a broad range of health research. Unfortunately, most of the solutions take time and will not remedy the crunch in the immediate future.

## AIDS VACCINE BUDGETS FOR MAJOR U.S. RESEARCH AGENCIES




**Sources:** NIH Office of AIDS Research, WRAIR, CDC.

An issue of increasing importance is understanding the significance of HIV clades in vaccine immunity, and ultimately, in protection. As more HIV vaccine candidates become eligible to enter Phase III trials around the world, it will be essential to know whether a vaccine that is effective against an HIV strain that predominates in one country will protect against different strains elsewhere. For example, if the approaching Thai trial of ALVAC were to show that the vaccine is effective, it would not be clear whether people in many other countries, including the United States, could benefit from the vaccine.

### CENTERS FOR DISEASE CONTROL HIV VACCINE PROGRAM

The HIV Vaccines Section of the Centers for Disease Control is a relatively small program that continues to provide important services that help advance AIDS vaccine trials. The Section is now conducting social, behavioral, and biomedical research as part of the two VaxGen Phase III trials; doing epidemiologic research to prepare for future trials;

developing a clinical and epidemiologic trial site in Cote d'Ivoire; conducting field site development in Kenya; and collaborating with Emory University to develop an HIV vaccine for use in Africa. The Section also sponsored a workshop in January 2002 on the use of a partially effective AIDS vaccine — the kind of preparation that is needed at this stage. All this is valuable work, accomplished on a meager budget.

But there is much yet to be done by this agency with ultimate public health responsibility. Important challenges include: incorporating vaccine education more fully into the CDC Community Prevention Planning network; designing behavioral research to capture the concerns of diverse populations in the U.S. rather than relying on findings from a single trial in a relatively homogeneous group; and partnering with the HIV vaccine public education efforts that NIH is now leading. In addition, the agency could start tooling up to deliver vaccines, such as Hepatitis B vaccine, to people at high risk. It could also intensify its efforts to support state and local government capacity to accurately diagnose HIV infection in an era when vaccine-induced immune responses will be more commonplace.

*The Department of Defense HIV vaccine program and the FDA are federal government entities discussed elsewhere in this report.* *(See page 12 "Thai Trial Goes Forward/Military HIV Research Moves Inside the Beltway" and page 27 "Revving up the Regulatory Process.")*

### WHO'S WHO?

Although the White House has finally nominated an NIH director and a potential Surgeon General — the Office of AIDS Research, CDC, and FDA still have no one at the helm. Perhaps of greater concern than empty seats are the litmus tests that will be applied to potential nominees. Conservative requirements on issues like abortion, stem-cell research, sex education, and needle exchange will effectively eliminate many first-tier candidates for these posts. Scientists who do pass conservative muster may not be in the best position to address an epidemic that strikes poor people, the gay community, and drug users. Appointees who survive such a politically biased process may have difficulty gaining respect from many academic scientists.

The AIDS Vaccine Research Committee (AVRC), better known as "The Baltimore Committee" continues to meet periodically and offer recommendations to NIAID, OAR, and NIH on scientific issues, which are taken seriously, and sometimes on programmatic issues, which may or may not be. We think this is because the Committee's role, responsibilities, and relationship to NIH have always been somewhat unclear. AVRC was recently officially re-named the AIDS Vaccine Research Working Group (AVRWG) since it apparently never had standing as a formal government committee. AVAC hopes that this prestigious body will work with NIH leadership to re-evaluate its mission, utility, and accomplishments — finding a more useful role within NIH.

# VI Vaccines as Intellectual Property

Science has experienced something of a gold rush since the day in 1957 when Edward R. Murrow asked Jonas Salk: "Who owns the patent on the polio vaccine?" Salk answered, "Well, the people, I would say. There is no patent. Could you patent the sun?" Now we live in a world where there will be no vaccines without patents. Intellectual property, for better and worse, is what drives investment, innovation, and industry. It is increasingly a territory riddled with claims, potential blocks, and licensing costs. So, AVAC has become concerned about the ramifications of the rights for AIDS vaccines.

As of September 2001, AVAC legal advisors were able to identify over 1000 issued patents in thirteen selected HIV-specific vaccine component categories. These are held by numerous assignees including government, academic, and industry holders. Many more related specific compounds, methods, and processes are known to exist. Every one of these patents holds some potential for limiting cross-experimentation and for their owners to pursue claims for royalties — as complex vaccine approaches move forward. A vision of this potential impact was seen last year in a public glimpse into the rights connected with the Merck approach of DNA vaccine with adenoviral boost. Basic DNA gene-delivery technology is licensed from Vical Incorporated in the United States by Merck but many other groups are developing DNA vaccines without such licenses. Vical's European patent

PERSONAL STATEMENT

**DR. MORENIKE FOLAYAN** | *Obaemi Awolowo University* | NIGERIA

"The mortality and morbidity rates for infectious diseases in developing countries have remained high because of the inability of most citizens to pay for the cost of treatment, even where the cost of treatments has been as low as $0.50 as in the case of malaria… Less than a century after the development of vaccines for diphtheria, whooping cough, polio, smallpox, and chickenpox, many doctors in the developing countries read about these diseases in the pages of textbooks. They are hardly diagnosed anymore. This is the same hope we in the West African sub-region look forward to with the development of an HIV vaccine."

for its core naked DNA technology to deliver nonviral genetic material, including use as part of a vaccine, was successfully opposed by six other companies and found to be not valid for European applications.

Merck's adjuvant technology is licensed from CytRx Corporation. Their product also uses an adenoviral vector boost, the validity of which appears so far unchallenged. However, last year when Introgen Therapeutic was issued a broad patent for producing adenovirus vectors (U.S. Patent No. 6,194,191), its Vice President for Intellectual Property was quoted as saying, "We expect that companies will have an interest in talking to us once they have picked themselves up off the floor." Everyday, these news items impact the business decisions of companies and investigators with interesting scientific ideas. They must continually assess whether they can afford to go forward with their ideas and whom they will have to pay if they're successful.

Although many vaccine candidates are in progress, the complex arrangements involving cross-licensing and other means to secure required intellectual property from a large number of entities — each seeking royalty shares — may increase development costs significantly and slow innovation and research. The proliferation of patent applications for small, perhaps trivial, improvements to existing technologies and the issuance of patents covering broad biotech applications garnered the scrutiny of the Chairman of the Federal Trade Commission. In a speech last November, the Chairman expressed grave concerns about the permissiveness of the U.S. patent system and its potential to block use and extension of technologies.

In addition, patent infringement risks and challenges rise with the number and complexity of rights needed for HIV vaccines — products that require a higher degree of property right assignment and licensing than many other complex technologies.

Some of the increased cost-and-risk impacts attributable to complex intellectual property arrangements for HIV vaccines may be mitigated by carefully constructed "patent pools" or consortia open to the broad class of government, university, and private owners of the numerous elements required for HIV vaccine research. Patent pools for biotechnology research have received encouragement recently from the U.S. Patent Office. There are several considerations in constructing a pool that enhances research potential, minimizes risk, and optimizes reward for participants while helping to lower costs of a final efficacious vaccine. AVAC invites interested parties to discuss these possibilities with us in more detail as we strive for viable means to initiate patent pooling for HIV vaccines.

# VII New Roles for State Governments In The U.S.

## AN EASY "YES" FOR STATE LAWMAKERS

## IN GEORGIA, THE ROAD LESS TRAVELED

At this writing the American economy seems to be on the upswing from a mild recession, although state and local budgets typically recover more slowly than the national picture. Additionally, all but a handful of states prohibit deficit spending, meaning that many states are cutting budgets despite the positive signs of growth. Yet there is much that states and localities could do to help AIDS vaccine research. Georgia, for example, is one of many states trying to catch the biotech wave in innovative ways. Most states highly regulate their insurance and Health Maintenance Organization (HMO) industries. As seen with California in the example below, this regulatory role presents valuable and tangible opportunities that do not involve state appropriations. These are areas of advocacy that could yield useful results and help speed AIDS vaccine development.

### AN EASY "YES" FOR STATE LAWMAKERS

A novel piece of California AIDS legislation clicked into place on the first day of 2002, although when it will actually have an impact on public health remains to be seen. This new California law requires that all HMOs doing business in the state, including the giant public employee plan called CalPERS, purchase a federally approved HIV vaccine as soon as one is available and offer it to their enrollees. The idea is to stimulate vaccine development by guaranteeing companies that their product will sell in the largest state market for health insurance.

The legislation was written by Senator John Vasconcellos, a Democrat representing the Silicon Valley, with input from long-time AIDS physician Marcus Conant of San Francisco. With strong support from Senator Jim Battin, a Republican from LaQuinta, the bill passed easily in the Assembly and Senate. There was little reason to vote against it: the bill provides an incentive to business, is likely to save lives, and required no budget appropriation. Recognizing that a single state does not a marketplace make, Vasconcellos and Battin are encouraging other states to pass similar bills. In January the senators wrote to party leaders and health committee chairs in both chambers of all state legislatures,

PERSONAL STATEMENT

**SANDRA WEARINS** | *Trial Participant and Educator* | USA

"There are many reasons why I am a vaccine participant, however, the three most important are: First, I could not ask other people to let us inject them with an experimental vaccine if I was not willing to roll up my own sleeve. Second, when I conduct educational presentations within the community, I am often asked if I am a participant. When I answer yes, I feel that the community is more apt to listen to me and trust what I say. Third, participating in the trial allows me to share my personal experience with potential volunteers. I want to effect change in my tribe, the Lumbee, and the world I live in. There is a saying in the Tuscorora tribe that "the decision I make today will affect seven generations." Participating in a vaccine trial to prevent HIV is not for my benefit, but for the benefit of future generations."

emphasizing that a vaccine is a lower-cost alternative to expensive medications that private insurers and state and federal programs already purchase for HIV/AIDS patients. (In the same vein, state legislation on access to Hepatitis B and other vaccines makes sense.)

As *5 Years and Counting* went to press, bills modeled on the California legislation have been introduced in Hawaii and Rhode Island, and similar language added to an existing piece of legislation in Illinois. Lawmakers in Nevada and North Carolina have also expressed interest in following in California's footsteps. The National Conference of State Legislatures spotlighted the new law in the March issue of its magazine *State Legislatures*, and is considering organizing an educational session on HIV vaccines for their next annual meeting.

## IN GEORGIA, THE ROAD LESS TRAVELED

Back in 1990, Georgia state lottery proceeds helped launch a program that has become a key player in HIV vaccine research and development at Emory University in Atlanta. By the end of 2002, the Emory Vaccine Center and its spin-off company, GeoVax, hope to begin Phase I testing of a construct developed by DNA-vaccine pioneer Harriet Robinson. The Center was created with help from the Georgia Research Alliance (GRA), a non-profit organization that started with money from the lottery but is now funded by the Georgia legislature and private foundations. Each year, Georgia lawmakers appropriate $30–35 million for the program that promotes a wide range of science and technology endeavors.

GRA set out to make Georgia a leader in technology-driven economic development and its modus operandi is providing tools that researchers at universities and start-up companies can use to turn ideas into products. "Our money acts as a catalyst," says program manager Kathleen Robichaud. Instead of using peer-review to award grants for specific research initiatives, GRA recruits top faculty members for its member universities and determines which expensive facilities — such as X-ray crystallography or nuclear magnetic resonance (NMR) laboratories — would be helpful to scientists working on many different projects.

In the case of the Emory Vaccine Center, the GRA "eminent scholar" program helped lure immunologist Rafi Ahmed to the university where he heads the Vaccine Center and in turn, recruited Robinson and other important researchers. Over the past decade, GRA spent $6 million renovating facilities and purchasing costly high-tech equipment that aids the search for vaccines against HIV, malaria, and now cancer. Today the Center attracts about $15 million each year in National Institutes of Health funding and last year received $1.5 million from the Pallotta organization's AIDS Vaccine Rides.

The Georgia experience is an important reminder that state governments can play a part in vaccine development, giving a boost to candidate vaccines that have not gotten sufficient backing from sources such as NIH grants or contracts, pharmaceutical companies, or venture capitalists.

## BECOME A MEMBER OF AVAC TODAY...

You can help support AVAC's work by joining our network of individuals interested in promoting accelerated, ethical HIV vaccine research. If you've found this report worthwhile, please help us continue the work.

**In return, we will send you:**

- The AVAC newsletter updating you on AVAC and HIV vaccine research and policy issues from a community and consumer perspective
- Timely policy alerts advising you of action you can take to help HIV vaccine research
- A copy of our annual report

**There are two ways you can join AVAC:**

- Visit our website at www.avac.org
- Mail this form with your check to:

AVAC, 101 West 23rd St., #2227 New York, NY 10011

NAME _____

ADDRESS _____

PHONE _____ E-MAIL _____

___ $20 Basic Membership
___ $50 Individual Membership
___ $250 Supporting Membership
___ $500 Sustaining Membership
___ $1000 AVAC Benefactor
___ $250 Organization/Business Member
___ Other Amount $_____

___ I'm not able to contribute now but would like occasional updates on AVAC's work
___ I'm interested in volunteering
___ Do not include my name on lists of AVAC members

**It would help us develop more useful benefits and reach others who support HIV vaccine research if you could answer two questions. Please check all that apply. Thank you!**

### HOW DID YOU HEAR ABOUT AVAC?

___ Internet
___ Colleague or friend
___ AVAC report
___ Media
___ Other_____

### HOW ARE YOU INVOLVED IN HIV VACCINE WORK?

___ Industry/private research
___ Government research
___ Government policy
___ Community Advocacy
___ Study Participant
___ Financial support

The AIDS Vaccine Advocacy Coalition is a 501c3 organization. Contributions are deductible to the extent allowed under law by the Internal Revenue Service. For specific information on tax deductibility, please contact AVAC. AVAC does not accept contributions or grants from governmental or pharmaceutical industry organizations.

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## ABOUT AVAC

The AIDS Vaccine Advocacy Coalition (AVAC) was founded in December 1995 to accelerate the ethical development and global delivery of vaccines against HIV/AIDS. We provide independent analysis, policy advocacy, public education and mobilization to enhance AIDS vaccine research and development.


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