AVAC
AIDS Vaccine Advocacy Coalition

AIDS VACCINE TRIALS—GETTING THE GLOBAL HOUSE IN ORDER

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Photo credits: AVAC thanks Mark Boaz and Julia Stout of the International AIDS Vaccine Initiative ('Rwanda' cover photo, page 8); 'South Africa' cover photo courtesy of Health-e News Service, Cape Town, South Africa; Fredrick Sawe, Kericho PMTCT Program (page 15, 23, 24, 26, 30); Seth Greenberg at The Fred Hutchinson Cancer Research Center (page 17, 32).

Cover key: Countries in white have already begun trials; countries in black are scheduled to begin trials.

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EXECUTIVE SUMMARY

In 1997, President Clinton threw down the gauntlet with his challenge to develop an AIDS vaccine in ten years. For seven years, the AIDS Vaccine Advocacy Coalition (AVAC) has counted, and waited, and tracked global progress toward meeting this goal. This year, our countdown ends.

Why have we stopped counting? Certainly not because time is on our side, nor because an effective vaccine is around the corner. Sadly, there will not be a vaccine in 2007 when "ten years and counting" reaches zero. Instead, the timeline for finding an AIDS vaccine stretches years more into the future. The reality is that we are on a long-term mission.

We must do everything we can to define and prepare for this mission so that no more time is lost. This is why AVAC has stopped its countdown. It is time to focus on the long haul, and to set an agenda for sustained and sustainable action that stretches well beyond 2007.

The time for developing and implementing this agenda is now. We need many more vaccine candidates moved into efficacy trials. To do this we need more vigorous pursuit of unsolved scientific questions, more and better products, and more trial sites in the developing world with improved infrastructure and actual capacity to conduct trials. These components of the agenda are separate but closely related.

The field always needs more time and money, but now, more than ever, the AIDS vaccine field needs:

- More flexibility and an open mind to new approaches and ideas.
- Increased collaboration and sharing of resources and infrastructure.
- Improved management of expectations at all levels—globally, nationally and locally.
- Better understanding and articulation of how vaccine research, and a future efficacious vaccine, fit into a comprehensive response to HIV/AIDS.
- Enhanced community participation, especially in the developing world.
- More sophisticated understanding of what it means to be ready for clinical research.

This year's AVAC Report focuses on how the field is readying itself for the road ahead. Several chapters address different aspects of "readiness"—a term that means different things to different people, but that is at the heart of the AIDS vaccine advocacy agenda today. We propose "correlates of trial readiness" to help guide the effort.

These are timely discussions since the past year has seen the topic of large-scale AIDS vaccine trials debated in several forums.

- The disappointing results of the two Vaxgen AIDSVAX studies have been sobering reminders that we are, indeed, facing an extended effort. Nevertheless, these studies have demonstrated that large-scale efficacy trials can be done—and should be done—in developing, as well as industrialized, countries.
- In the face of these discouraging results, a Phase 3 prime-boost AIDS vaccine was initiated with an expected 16,000 volunteers in Thailand, largely financed by the US government.
- A leading group of scientists published concerns about this trial in the January 16, 2004 issue of Science magazine. Important scientific and procedural issues were put on the table about this trial moving forward. These issues need to be vigorously debated and continually reviewed.
- At this year's Conference on Retroviruses and Opportunistic Infections, and later in an article in Nature Medicine, a related debate emerged focusing on the balance between basic science and clinical research. Clearly, we need it all. We need more science and more clinical research, and we need an increase in the quality of both.

  In the face of an ever-growing epidemic, we must improve and enlarge the product pipeline while simultaneously conducting state-of-the-art clinical trials. In developing trial sites and conducting ethical trials, we should not only accelerate the development of an AIDS vaccine, but we can also provide important immediate benefits to communities—improved and expanded voluntary counseling and testing, health infrastructure, primary prevention services and treatment.
- Both the Bill & Melinda Gates Foundation and the National Institute of Allergy and Infectious Diseases (NIAID) initiated efforts to improve coordination within the AIDS vaccine field. The Gates-led Global HIV Vaccine Enterprise was announced in the June 27, 2003 edition of Science, and the NIAID Partnership for AIDS Vaccine Evaluation (PAVE) was announced later that September by Anthony Fauci, NIAID director. Each has highlighted a crucial issue—the need for increased, meaningful collaboration among researchers. Now the various partners must deliver.

As if the science of AIDS vaccines was not challenging enough, all of these political, economic and social issues make the road ahead all the more difficult—but not without hope:

- Over the past year, more new candidates entered into Phase 1 trials than in any single year.
- The different players in the vaccine field are talking with each other about meaningful collaboration.
- The pot of money seems to be increasing, though significant new funding has yet to materialize and budget constraints may lead to shortfalls in the future.

- Ethical and high quality AIDS vaccine efficacy trials can take place—people will volunteer and remain in the trial.
- The world can rally resources and scientific expertise—when it wants to. A prime example is the accelerated search for a vaccine against SARS—a virus that infected 8,098 people and killed 774 worldwide from November 2002 through July 2003. A SARS vaccine candidate has already been identified and tested in mice, and plans are underway for human trial manufacturing.

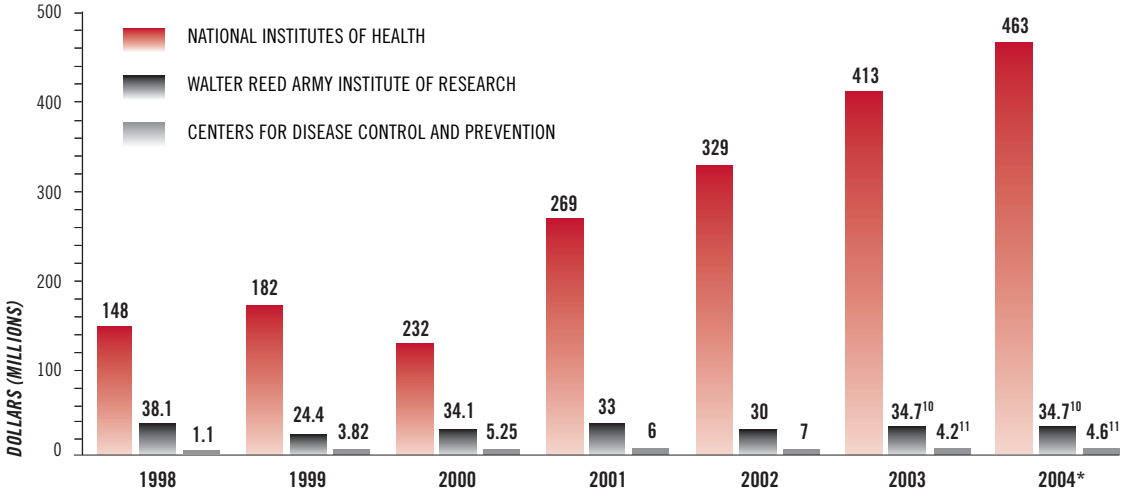
  In the year or so that the world has been responding to SARS, the global HIV/AIDS epidemic killed more than 3 million people, and an estimated 5 million more acquired HIV.

- Although vaccine development is a long-term pursuit, there are many immediate deliverables for communities.

As we increasingly collaborate to make the connections between prevention, testing, treatment and trials to meaningfully engage communities in this "vaccine enterprise," we must ensure a comprehensive and sustainable response to the HIV/AIDS epidemic.

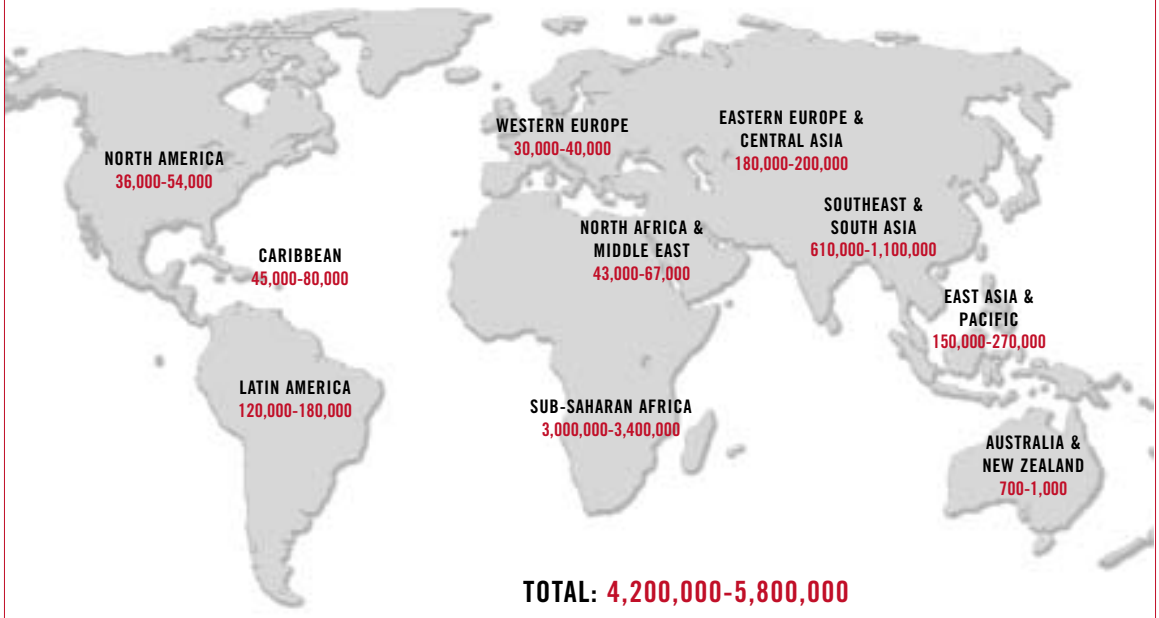
The infrastructure for AIDS vaccine clinical trials, if incorporated into the broader HIV/AIDS agenda, and more importantly, into the overall public health system in a collaborative effort, is certain to build long-term, sustainable capacity for research and service-delivery.

AIDS VACCINE BUDGETS FOR MAJOR U.S. RESEARCH AGENCIES



*Figures for 2004 are estimated and include what used to be WRAIR dollars with NIH dollars because the NIH now oversees the Army's HIV vaccine program. The NIH budget for 2002 includes approximately $23 million for spending on Army HIV vaccine research.

ESTIMATED NUMBER OF ADULTS & CHILDREN INFECTED WITH HIV DURING 2003



Source: Joint United Nations Programme on HIV/AIDS

As we look to the future, AVAC hopes to provide a venue for continued debate and dialogue on these and many other issues—product rationalization; partially-effective vaccine candidates; how and when to engage adolescents in trials; how to ensure that adequate resources get to the "right" products; and who decides which products move forward to large-scale trials. We may not have all the answers, but we want to be sure that the questions get asked and widely discussed.

Most of all, we hope to push for a broad, sustainable response—sustained funding, capacity, infrastructure and realistic expectations—to help us all withstand our long haul from basic science, to product development, through multiple clinical trials and, eventually and most importantly, to a safe, efficacious, accessible and affordable vaccine in use for the people and communities that need it most.

In the end, it is not vaccine trials, or vaccine vials—it is women, men and children and their communities who will finally be protected.

Mitchell Warren
Executive Director

Last year's AVAC report, ***"How do you fight a disease of mass destruction?,"*** documented the inability of trial sponsors to move AIDS vaccine candidates into human clinical trials as rapidly as they had projected in their milestone goals.

This year, we can report substantive progress in overcoming many of the obstacles noted last year:

- The AlphaVax VEE-vectored vaccine, which was originally to have moved into Phase 1 trials in 2000, finally did so in 2003. The vaccine, made with the *gag* gene from the clade C virus that predominates in southern Africa, is being tested in South Africa and the United States. It was the first clade C vaccine to enter human trials. Three more clade C-based vaccines—made by other groups—also began human trials later in the year.
- Three of six vaccines originally scheduled for the clinic in 2002 made it into Phase 1 studies by 2003. These were Chiron's clade B DNA+novel envelope vaccine; DNA+fowlpox clade B vaccine of the University of South Wales; and Wyeth's clade B peptide vaccine. Investigational New Drug (IND) filings have been submitted for the other three products, which are expected to enter Phase 1 trials by July 2004.
- Five of seven vaccines, which had fallen behind plans for Phase 1 testing, have now entered small human studies. These include DNA+IL2; DNA from clades A, B and C; and the DNA portion of a DNA+adenovirus vector expressing genes from clades A, B and C. All three vaccines have been developed by the US government's Vaccine Research Center (VRC). The DNA portion of Wyeth's DNA+IL12 also advanced into a Phase 1 trial in recent months.

Altogether, thirteen vaccine candidates moved into Phase 1 trials in the twelve months since the last AVAC report was issued in June 2003. Even though many entered human trials later than originally projected in the milestone goals, that's still more Phase 1 trials initiated in a single year than in any year since scientists began the quest for an AIDS vaccine.

Six of the Phase 1 trials of new products were launched as part of the US government's HIV Vaccine Trials Network (HVTN). Both the network and the Division of AIDS (DAIDS) deserve credit for overcoming the delays noted by AVAC last year. In addition, HVTN expanded its Phase 1 testing of Merck's clade B adenovirus- vectored vaccine (Ad5 *gag*) to sites in Peru, Thailand and the United States in trials that are expected to enroll 435 volunteers.

Merck also launched the first Phase 1 trial of the multigene version of its Ad5 vaccine, which expresses the *gag*, *pol* and *nef* genes of clade B. A trial to test the multigene approach—which the company views

as its lead candidate—began last May and has now enrolled more than 188 volunteers in the United States toward a goal of 273 by June.

The International AIDS Vaccine Initiative (IAVI) also stepped up the pace compared to last year. It deserves credit for putting two new vaccines into Phase 1 trials over the past twelve months, and for adding South Africa to the countries where its DNA+MVA vaccine is being tested.

One of IAVI's new products makes use of adeno-associated virus (AAV) as a recombinant vector to deliver the *gag* gene from Clade C. The product, developed in collaboration with Columbus Children's Research Institute and Targeted Genetics Corp., is being tested in small safety trials in Belgium and Germany. Another new product, developed by AIDS researcher David Ho and colleagues at the Aaron Diamond AIDS Research Center and Vical, Inc., is a DNA plasmid multigene clade C vaccine being tested among 45 volunteers in the United States.

During the past 12 months, IAVI also extended human testing of its clade A DNA+MVA vaccine to South Africa. The vaccine was already in human trials in the United Kingdom, Kenya and Uganda.

Despite the inability of the AIDSVAX gp120 vaccine to demonstrate overall protection from infection in two Phase 3 trials last year, the US Army—whose AIDS vaccine program is now part of the National Institute of Allergy and Infectious Disease (NIAID)—and the Thai government successfully launched the world's largest Phase 3 trial in Thailand last October. The trial, which is to enroll 16,000 people, is testing Aventis Pasteur's canarypox-vectored vaccine as a prime, followed by VaxGen's clade E AIDSVAX as a boost. Scientists hope that the two vaccines in combination will have a protective effect even though AIDSVAX alone did not.

Still, AVAC notes that not much headway has been made in solving some of the key problems described in last year's report. In particular, manufacturing snafus continue to rain on the parade to the clinic, with two vaccines using modified vaccinia Ankara (MVA) posing hard-to-solve problems.

The problems were so frustrating that last year the VRC abandoned a 2002 milestone to test its MVA vaccine candidate. Another MVA vaccine—developed by Bernard Moss and colleagues at NIAID—is still delayed by manufacturing difficulties. Also a 2000 milestone, the vaccine was to enter human trials in the first quarter of 2001.

Likewise, batch-release problems have delayed another 2002 milestone, Chiron's clade C DNA+envelope boost. A Phase 1 trial was to begin the first quarter of 2005, but manufacturing problems have now delayed the start date.

Similarly, a Phase 1 trial of the GlobeImmune yeast-vectored vaccine, a 2003 milestone, has been delayed by the need to remanufacture the product to meet good manufacturing practices (GMP) standards.

To solve manufacturing problems, the AIDS vaccine field will have to diagnose problems earlier, pool talent to address the challenges, and come up with sufficient funds to support whatever improvements are necessary.

Key to the effort will be a commitment to share information. One vehicle could be the US government's new Partnership in AIDS Vaccine Evaluation (PAVE), set up last fall. PAVE aims to bring together US government agencies, and government-funded organizations involved in AIDS vaccine research and development, to forge coordinated planning efforts.

PAVE has already made notable progress toward the development of common assays for use in AIDS vaccine evaluation. It has also set up a new laboratory to look at the stability of vectors to deliver the genes used to make AIDS vaccines. Now PAVE needs to focus on additional manufacturing issues. For the consortium to achieve its full potential, all US agencies, as well as the International AIDS Vaccine Initiative, need to fully participate.

A broader initiative, the Global HIV Vaccine Enterprise established by the Bill & Melinda Gates Foundation (see page 43), can also provide a forum for evaluating manufacturing issues, along with myriad other questions involving both pre-clinical and clinical research.

Hopefully, both forums will not only ask the tough questions, but also serve as venues to develop creative solutions to problems.

The treatment agenda is the pull mechanism; community education is the push mechanism. Both are necessary components of readiness for AIDS vaccine trials.

—Nzeera Ketter, the International AIDS Vaccine Initiative

AIDS vaccine trials readiness and what it will take to get there

The house needed work. Although a very comfortable residence by Rwandan standards—spacious rooms, tiled floors, a woven straw ceiling—it was a long way from an immunology lab. The windows let in dust and damp from the afternoon rainstorms; debris sifted down from the plaited straw ceiling, settling into the deep crevices between the tiles. The power came and went intermittently.

Still, the small white house was the best available option. It sat close by Projet San Francisco (PSF), a long-standing research project in Kigali, Rwanda. And so, the team from PSF and the International AIDS Vaccine Initiative (IAVI) turned it into a laboratory center for AIDS vaccine clinical trials. This meant pouring cement over the tiled floor, putting in air conditioning units, freezers, buying a generator, a back up generator and yet another back up system. It meant flying in a British technician to install a safety hood; waiting patiently when a crucial piece of equipment, the centrifuge, went missing for ten days in an international air freight hangar; installing freezers and radio controlled temperature monitors; and waiting for the arrival of liquid nitrogen from the country's one supplier, a cattle-breeding operation that used it to freeze bull semen.

By the time the work was done and Rwandan laboratory technicians had begun their training, IAVI had spent twenty-one days and roughly $250,000 and involved people and products from four countries. It was a feat of coordination and creativity. And "it was less than twenty-five percent of the work that we needed to do to get the site ready," says Nzeera Ketter, director of efficacy trials at IAVI, who rattles off a laundry list of other activities from building roof tanks to ensure a reliable water supply, to translating informed consent documents into French and Kinyarwanda to be signed by the forty-five people to take part in a trial of an experimental AIDS vaccine.

There is nothing remarkable about this house. Today, transformations like the one that took place in Kigali are going on around the world as part of a massive readiness effort aimed at building research capacity for AIDS vaccine clinical trials.

But while these activities are far more widespread than they have ever been, they are not enough. The world is not prepared for the next five to ten years of AIDS vaccine trials, and readiness efforts suffer from a lack of funding and collaborative planning. These problems threaten to slow the search for an AIDS vaccine.

What lies ahead?

Just what is the AIDS vaccine field getting ready for? It depends on whom you ask.

In June 2003, the authors of a commentary in the journal Science called for a global vaccine enterprise (see page 43) and projected that, to keep pace with the expanded AIDS vaccine pipeline, 5,000 volunteers per year would be needed to conduct Phase 1–2 trials and another 30,000 would be needed each year to conduct Phase 3 trials. In September, Emilio Emini, then head of Merck & Co.'s vaccine development program, and Gary Nabel, head of the US government's Vaccine Research Center, said that 50,000 to 100,000 trial volunteers would be needed over the next five to ten years.

These numbers are rough calculations. The uppermost figure is based on the assumption that the field will launch one Phase 3 AIDS vaccine trial per year from 2005–2010—a projection that reflects extreme optimism. It's a best-case scenario and the best-case scenario has never happened in the AIDS vaccine field.

A more likely scenario is that the next several years will bring multiple small and intermediate-size (Phase 2b) trials. These "proof-of-concept" trials might be less than half the size of Phase 3 trials. In most cases, they would not be able to provide definitive answers about whether a product works or not, but they would provide much-needed clues about product efficacy that could help vaccine developers decide whether to go on with Phase 3 trials—or go back to the drawing board.

While Phase 2b trials would be smaller than Phase 3 trials, they would still require thousands of volunteers. And so, regardless of the precise figures, the warning stands: The present capacity for large-scale clinical trials is far less than what is needed for multiple medium and large-scale trials in the coming years.

Consider these sobering facts:

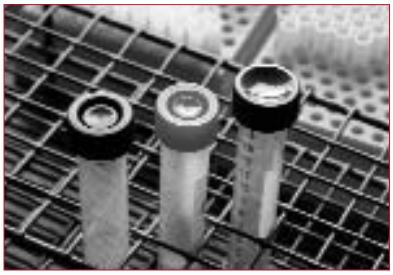
- In all of sub-Saharan Africa, there are only two immunology laboratories outside of South Africa that meet the international "quality assurance" standards required for AIDS vaccine trials.
- Experienced principal investigators at Phase 1 trial sites around the world are reporting slow rates of enrollment.
- Few cohorts have well-characterized HIV prevalence and incidence rates—data that is necessary in order to plan large-scale efficacy trials.

The US government's HIV Vaccine Trials Network (HVTN) currently has the capacity to enroll about 13,000 people at existing sites, says Judy Wasserheit, director of the core HVTN operations center in Seattle. (By contrast, the US Army/NIAID and Thai government are enrolling 16,000 people into a single Phase 3 trial of a prime-boost vaccine regimen.) Other networks are also developing sites, but the emerging capacity still is unlikely to meet the field's needs.

"We'll be lucky to pull off two Phase 3 trials in the next five years," says VRC's Nabel.

These grim prognoses may be correct. However, it is also possible that, should a truly promising candidate come through the pipeline in the next few years, the world would rally to find the resources needed to test the product.

The more difficult and likely scenario is that there will be multiple trials—including Phase 1, Phase 2b, and Phase 3 trials—over the next ten years. These trials will gather data on vaccine candidates that will help guide the design of even better products down the road. "We can think of efficacy trials as the last step in a relay race—but I would say this is a conservative and potentially risky approach," said Susan Buchbinder, head of HIV research programs at the San Francisco Health Department, at this year's Conference on Retroviruses and Opportunistic Infections. Buchbinder recommended that efficacy trials be seen as experiments whose results will enrich the field even if they do not lead to licensure.



Readiness for this long haul cannot be achieved on short notice or sustained by enthusiasm for a specific product. It requires willing and ready communities and multiple trial sites that are both well-sustained and flexible enough to adapt to changes in plans—be it a cancelled trial or a call for rapid scale-up when a candidate shows unexpected promise. The best, if not the only, way to build this type of readiness is by integrating research activities into existing public health systems so that sites do not stand alone and apart, but rather strengthen and partner with services for the community at large. This type of readiness is needed—and lacking—today.

Redefining readiness

The concerns about readiness come at a time of increased scrutiny of large-scale AIDS vaccine trials. In January 2004, twenty-two leading American AIDS researchers, writing in Science, questioned the scientific merits of the Thai prime-boost trial. The leadership in the US House Government Reform Committee seized on the critique and recommended that the Thai trial be de-funded, diverting the monies to shore up the cash-strapped AIDS Drug Assistance Program (ADAP), which provides antiretroviral drugs to uninsured or under-insured Americans. This swap almost certainly will not come to pass. However, it is a warning of conflicts that could arise in the future, particularly as both ADAP and the National Institutes of Health confront funding battles over the next few years.

In March 2004, in an open letter in Nature Medicine, Harvard AIDS researcher Ronald Desrosiers argued that more pre-clinical research was needed before vaccine candidates were advanced to prime-time clinical trials. "The major difficulties blocking development of an effective vaccine against HIV-1 are fundamental scientific questions, not issues of manufacturing, numbers of sites, international site preparation or validated testing procedure," he wrote.

Desrosiers makes important points about the state-of-the-science of AIDS vaccines, but his views, which he also presented at the retroviral conference in February, can be oversimplified as a duel that pits "basic science" against "empirical" science in clinical trials. In fact, basic science involves empirical experiments and clinical trials include basic science.

In face of the skepticism expressed by Desrosiers and others, AIDS vaccine trial networks need to apply more scrutiny in deciding what products to advance into Phase 2 and Phase 3 trials—and do a better job of explaining why it is important to be prepared to conduct trials:

- **Well-designed trials are a necessity**. Even though animal models may help identify promising (and not-so-promising) AIDS vaccine strategies—it's only by testing potential candidates in people that scientists can learn for sure whether they are safe and effective.
- **Clinical trials cannot be confined to the industrialized world**. Although large-scale AIDS vaccine studies will undoubtedly take place in the United States and Europe, sites in developing countries, such as the one in Kigali, are going to play a crucial, if not defining, role in AIDS vaccine development. Conducting AIDS vaccine trials in developing, as well as developed, countries is the only way to gather information about the effects of HIV genetic subtypes and/or co-infection with other endemic diseases on vaccine efficacy.
- **Trial infrastructure must be created.** In developing countries—some of which spend as little as $10 a year per person on health care—AIDS vaccine clinical trial infrastructure must either be built from scratch or grafted onto often rudimentary public health clinics or a handful of long-standing research efforts such as Rwanda's Projet San Francisco or Uganda's Rakai Project.
- **Efficacy trials cannot be done overnight.** Experienced trial planners say that it takes two to three years to establish incidence and prevalence data—an effort that costs about $1 million per year. A large-scale efficacy trial can take another three to five years to enroll and complete, at an estimated cost of more than $100 million.
- **Clinical trials are just one element of the vaccine development process.** Although clinical trial capacity is one of the most visible and tangible aspects of readiness, many other areas require equal resources and attention. These include: community mobilization and outreach efforts to build political

will among leaders and policy makers in countries where trials may take place; manufacturing capacity and "process development" to ensure that a candidate vaccine can be made in large quantities; and regulatory capacity for scientific and ethical review in developing countries. These tasks must be pursued simultaneously since gaps in any area can stall or halt vaccine clinical research.

The AIDS vaccine field must sharpen the timelines for completing these activities and improve understanding of the skills, resources and materials needed to complete them. Gaining the support of village chiefs in South Africa has as much in common with a flow cytometer to measure HIV-specific immune responses as high school sex education does with the "air-burst" machinery to test condom strength. All are essential in pursuit of a common goal, yet the technical skills required for each task do not transfer to the other.

The kaleidoscopic nature of readiness, however, cannot deter the AIDS vaccine field from clearly defining the goals and activities involved in preparing for international trials. A working group to strengthen clinical trials capacity, convened by the Bill & Melinda Gates Foundation's Global HIV Vaccine Enterprise, has identified four areas of focus: scientific and human resources; research infrastructure; research subjects; and policy maker/opinion leader support for research.

For each focus area, the group has named at least three "challenges," or action items. These run the gamut from: "assist communities in preparing for AIDS vaccine trials through community education and establishment of community advisory boards and other participatory mechanisms" to "establish supply, maintenance and utility systems to support state-of-the-art clinical and laboratory facilities and IT capacity at AIDS vaccine trial sites in developing countries." (See chart page 50.)

These challenges are broad. Now the group needs to develop a strategic plan to meet the challenges and secure widespread consensus among key players to implement the plan. The clinical trials working group will address only some aspects of readiness. Others working groups, including those focused on basic science, manufacturing and product development, are also coming up with plans. If the Global HIV Vaccine Enterprise is able to mesh all plans into an overarching blueprint for readiness, it will make a significant contribution to the field.

Such a blueprint will also help the AIDS vaccine field dovetail its efforts with those in related fields, and with other readiness efforts aimed at the developing world. This includes the European Developing Countries Clinical Trials Platform (EDCTP), which is focusing on clinical trials capacity in sub-Saharan Africa, including vaccines, microbicides and non-vaccine prevention strategies expected to enroll more than 40,000 volunteers in developing countries between 2005 and 2010. Even more capacity will be sought for antiretroviral treatment programs which are on the horizon in many developing countries.

By setting priorities and goals for readiness and sharing them with other research efforts, the AIDS vaccine field can help formulate a readiness agenda that distinguishes between cross-cutting and field-specific items.

All research activity in the developing world would benefit from the following:

- Clinical laboratories that meet international quality assurance (QA) standards for analyzing blood chemistry.
- Viral load measurements and CD4 cell counts.
- Expanded regulatory capacity, including ethics.
- Scientific review capacities with the human resources and technical expertise to review protocols at an ever-increasing rate.
- Voluntary testing and counseling centers—the crucial "square one" for everything from TB screening to antiretroviral drug (ARV) delivery to prevention counseling to enrollment in trials of vaccines and microbicides.
- Laboratories that meet international QA standards for analyzing immune responses to vaccines.
- Manufacturing capacity that comes on line in a timely way, as vaccine trials expand to more people.
- Ongoing outreach and education at multiple levels about challenging concepts—partial efficacy, clade, attenuation of disease—of AIDS vaccine development today.

Learning from—and building upon—the past

In getting ready for large international AIDS vaccine trials, history should not be forgotten. Each of the trials started to date is testament to successful readiness activities—from slaughtering a goat as part of a pre-trial celebration in South Africa's Soweto township to the innumerable "dry runs" that make a trial's standard operating procedures second nature to its lab technicians.

Past preparedness studies also provide valuable lessons about how to engage various communities. In 2000, the Hlabisa preparedness project in rural KwaZulu-Natal Province in South Africa implemented model practices for a "participatory approach" to AIDS vaccine community preparedness. The Hlabisa team started by using digital technology to map the area, pinpointing the location of every homestead, church and meeting place for basket-weavers, sewing circles and other social groups. This process paved the way for a mobile clinic and outreach unit while also ensuring that the research team members were familiar faces to every community member.

Before that, the US-based projects Linking Communities and Scientists (LinCS) and Jumpstart both used focus group discussions and one-on-one interviews to gather the first data on awareness and attitudes about AIDS vaccine research among researchers and target populations, including men who have sex with men, injection drug users and women at risk via heterosexual exposure. Medical anthropologist Kate MacQueen, who helped lead LinCS from the US Centers for Disease Control and Prevention says, "The project generated a lot of acceptance among researchers that they were going to have to sit at the table with these communities—to learn from them and take their contributions."

In 2004, the AIDS vaccine field must draw on the lessons of the past and become strategic, clear and coordinated in the approach to readiness. Just as there are aspects of trials that must be managed "in house" by each sponsor, there are also places where networks can and must work together. Each trial network does not need to develop its own clinical laboratories, voluntary testing and counseling centers, and community mobilization strategies. Some resources can be built jointly and "owned" by the field. This is the only way to ensure that the race to readiness does not become a scramble, and that we are neither duplicating efforts nor losing sight of specific priorities.

The global house

The story of the house that became a lab is the story of readiness for AIDS vaccine trials in developing countries. There are serviceable structures throughout these countries—buildings, clinics, research teams, regulatory authorities and community groups mobilizing to fight HIV and AIDS—but almost all need considerable work in order to become viable components of clinical trials needed to evaluate AIDS vaccines in humans.

The keys to success, whether in Kigali or Rio de Janeiro, are the same. Someone has a plan and the ability, resources and control to see it through. People executing the plan arrive at the right time and receive the resources they need to complete their tasks. When problems arise—as they always do—the plan and the people executing it need to be flexible enough to find creative solutions.

Seen in this light, it is entirely possible to get the global house ready for AIDS vaccines. It is a task that should not be delayed.

Correlates of Readiness

For the better part of the last decade, the AIDS vaccine field has been searching for immunological correlates of protection—specific immune-system markers that might indicate whether a person was protected from HIV infection or HIV disease, such as the number of particular types of white blood cells.

But quite apart from the science, the AIDS vaccine field also needs to establish correlates of trial readiness—a checklist of specific, quantifiable goals that AIDS vaccine trial networks can use to determine whether they are ready to conduct large AIDS vaccine trials in developing countries. To start the dialogue, AVAC has developed its own checklist of readiness correlates.

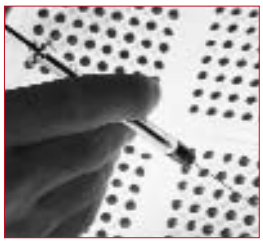
Readiness for recruitment into Phase 1 and Phase 2 trials

More Phase 1 AIDS vaccine trials were launched in 2003 than ever before (see page 5). And while these trial launches are to be applauded, it is no time to become complacent. As the participants themselves attest, it will be difficult to maintain or pick up this pace for additional Phase 1 trials or larger efforts.

Enrollment is a key bottleneck for sites that are up and running. "No matter how big a pool of volunteers you have, you just need more," says Efthyia Vardas, a principal investigator at the Soweto Vaccine Evaluation site in South Africa, which launched two Phase 1 preventive AIDS vaccine trials this year.

Vardas and her colleagues developed an innovative pre-screening protocol that recruited potential vaccine trial volunteers from Sowetan voluntary counseling and testing (VCT) centers, and offered them the opportunity to join vaccine discussion groups (VDG). Groups met for six sessions and provided a comprehensive introduction to AIDS vaccines, and the risks and benefits of trial participation.

This protocol ran for two years and recruited 350 volunteers, more than half of whom remained throughout the entire VDG process. However, when it came time to enroll the trials, there were only thirty-two eligible volunteers. The others had changed their mind, lost interest, or had lab abnormalities that rendered them ineligible for participation. A small percentage also failed to correctly answer key questions on the site's "assessment of understanding" tool.



These numbers bear out estimates that ten volunteers may need to be screened for every one that is enrolled in an AIDS vaccine trial. Even state-of-the-art sites, such as the Soweto unit—with a vibrant, active community advisory board, innovative outreach programs, and a comprehensive approach to providing care and treatment for all individuals (HIV-positive and HIV-negative) who volunteer—may lose more than ninety percent of trial recruits.

This phenomenon is not confined to the developing world. Halfway around the world in Baltimore, the Johns Hopkins University vaccine trials unit is also feeling the crunch when it comes to enrolling volunteers for Phase 1 trials. In the 1990s, the site recruited the largest number of volunteers for the North American and European AIDSVAX Phase 3 trial of any site in the study.

But Johns Hopkins investigators are now anxious that tried-and-true strategies of recruiting volunteers through newspaper and radio advertising may not be enough to supply volunteers for five Phase 1 trials slated for the coming year. "We need a paradigm shift," principal investigator Clayton Harro told the site's community advisory board (CAB) in March. "We used to be asked to enroll five or six people per study at our site; now we're being asked to enroll fifteen or twenty." Some CAB members suggested the site take the "shoe-leather" approach to recruiting—"barbershopping" through word of mouth at hubs of community activity.

Not all sites are experiencing this pinch. Many trials are enrolling swiftly in many different parts of the world. Nevertheless, reports by experienced recruiters of challenging times ahead should not be ignored.

What will it take to increase enrollment for Phase 1 trials? Vardas says the key is strengthening VCT services: give people incentive to learn their HIV status by offering treatment and care if infected; high quality prevention counseling—including the option of participating in prevention research on vaccines and microbicides—if not infected. This is why Vardas and her Soweto team recently dug in their heels when the hospital tried to move the adult VCT clinic out of the vaccine center.

"If there is not enough treatment at the site, then there won't be enough people coming through the voluntary and counseling testing centers. Which means there will not be enough people who know their status and can be screened for vaccine trials," agrees Ketter. "The treatment agenda is the pull mechanism; community education is the push mechanism. Both are necessary components of readiness for AIDS vaccine trials."

As treatment initiatives roll out in developing countries, it will be important to link vaccine trials to antiretroviral drug (ARV) programs, and to position VCT centers as entry points for a whole range of services. The Bush Administration's new AIDS relief program for sub-Saharan Africa and the Caribbean, and other treatment initiatives such the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Clinton Foundation, and initiatives through the World Bank, offer an unprecedented opportunity to accelerate readiness, not just for AIDS vaccine trials, but also for treatment and other prevention trials.

Correlate 1: VCT centers linked to treatment, care and clinical trials.

Correlate 2: VCT counselors educated about AIDS vaccine research and trained to incorporate referrals to vaccine trials into post-test counseling for all HIV negative individuals.

Readiness for recruitment into large-scale trials

One of the biggest missing pieces in the readiness puzzle is the lack of cohorts with well-characterized incidence and prevalence rates of HIV infection. Without a reliable sense of how many infections occur in a community in a given year, there is no way of knowing whether a candidate vaccine has helped reduce the rate of new infections. This data must be collected before a large-scale trial can begin. Since the AIDS vaccine field is evaluating vaccines that may work by slowing the rate of disease progression, it is also important to understand the dynamics of viral load and CD4 cell counts in HIV-infected people in the community where the trial will take place.

Cohort development also provides initial information about rates of recruitment and retention. It is also a hands-on training opportunity for nurses, counselors, lab technicians and physicians who may go on to work on the trial. And perhaps most importantly, it is an opportunity for community mobilization around vaccines that paves the way for rapid recruitment once a trial has been mobilized.

Although there are a number of cohorts currently being developed for large-scale trials of AIDS vaccines and microbicides, more are needed. Incidence rates among potential trial participants can drop as they did in Thailand before the launch of the prime-boost trial. Political instability can arise. Community priorities can change. If the field wants to conduct large or even mid-size AIDS vaccine trials, it needs to invest in cohort development and find a way to do this across networks.

Correlate 3: New cohorts developed with an inter-network plan for collecting and sharing prevalence and incidence data.

Correlate 4: Shared documentation of site assessment and readiness protocols used to collect epidemiological data with a coordinated effort to translate experience to date into concrete estimates of sample size, capacity needed for future trials.

Correlate 5: Epidemiological studies and cohorts in populations that have proven hard to reach—women at heterosexual risk; intravenous drug users; young gay and bisexual men of color.

Correlate 6: Funding and supplies for cohort building infrastructure—including steady supplies of HIV rapid test kits; outreach teams equipped with cars and bikes to follow up with cohort members; ongoing vaccine-related staff development for epidemiological study staff.

Readiness to manufacture and supply candidate vaccines

A vaccine trial cannot happen without a product. Obvious as it is, this statement bears repeating since the field has serious shortfalls in manufacturing capacity that could slow or imperil large and mid-size trials.

"Readiness for large-scale trials is not going to happen if it is piece-meal," says Emilio Emini, now head of vaccine development at IAVI. "It's not going to happen without integration. You can't spend hundreds of millions of dollars on site preparation without hundreds of millions of dollars on product development and manufacturing plans."

On the manufacturing front, Emini says that a key missing piece is "translational research," which he explains as "how you take a good idea and move it into clinical trials." This expertise, largely based in the pharmaceutical industry, is what turns promising lab experiments into candidates, and what turns small-scale production processes into industrial-scale processes.

What's the cost of not investing in this expertise? At the least, delays in clinical trials will result; at the worst, derailment of a product. "We've had promising candidates fall off the map because manufacturing was done sloppily," says Edmund Tramont, head of DAIDS.

Correlate 7: Dedicated AIDS vaccine production plant capable of manufacturing sufficient quantities of vaccines for small and mid-size trials.

Correlate 8: Financial incentives for more industry experts to conduct translational research for the AIDS vaccine field.

Readiness for long-term relationships with sites and communities

Many of the preparedness studies of the 1990s were not directly linked to clinical trials. While an AIDS vaccine trial did eventually take place in Philadelphia—a LinCS site that involved injection drug users—this was the exception rather than the rule. Today, four years since implementing its preparedness project, South Africa's Hlabisa district is still waiting for its first vaccine trial.

The 21st century model for AIDS vaccine trials readiness activity should, in most cases, link readiness work to actual clinical trials. "We don't need any more (stand-alone) preparedness studies," says Steve Wakefield, who oversees community education for the HVTN. "People know that research happens. Our money needs to be going into trials and trial-related activities. Site preparation needs to be tied to a specific, research-related agenda."

This does not mean that community outreach and education should fall by the wayside, but that these activities should be linked to preparedness work that achieves scientific goals, such as prevalence and incidence studies, or even Phase 1 vaccine trials. This is the only way to maintain long-term relationships with communities, and to ensure that the field has the flexibility to conduct the trials it needs—when they are needed.

This means that AIDS vaccine trial sponsors must be ready to work with ARV scale-up programs, with other fields (such as microbicides), and with studies of behavioral interventions and harm reduction strategies to ensure that research projects do not vanish from communities simply because an appropriate vaccine candidate is not available.

It may not be an easy task. Plans will change, products will fall by the wayside and funds may be in short supply. But if trial sponsors are to maintain the trust and support of people willing to donate time, energy, input and blood to a research effort, they need to find ways to keep the infrastructure open.

Correlate 9: High percentage of active sites operating with flexible research agendas and minimal "downtime" between projects.

Readiness for staffing and supporting developing-country trials

The AIDS vaccine field has come a long way from the time it was accused of focusing exclusively on clade B candidates from the industrialized world. More trials are happening in developing countries than ever before—and the majority are testing candidates based on locally-relevant strains.

However, the field still has miles to go to ensure that developing countries are equal partners in research. There is an urgent need for local medical and laboratory professionals. "If we want to do trials in developing countries, there is still a shortage of scientists," says Punnee Pittisuttitham of Mahidol University in Thailand, a member of the Global HIV Vaccine Enterprise working group on clinical trials capacity. The same goes for regulatory authorities, including ethical and scientific review bodies. Regulatory capacity is growing in many developing countries—but not at a rate that allows it to keep pace with research activity.

Correlate 10: New PhD, RN and MD degrees awarded to people from developing countries each year who remain in or return to their home countries to participate in research projects.

Correlate 11: Number of developing country regulatory authorities, including ethical and scientific review boards, institutional review boards and data safety and monitoring bodies that have the training, resources and administrative support to review multiple protocols from fields of research—including AIDS vaccine trials—each year.

Readiness for a series of efficacy trials and partial efficacy

A key component of readiness is managing expectations around trials and eventual candidates. Unlike most vaccine trials in the past, the current crop of AIDS vaccines moving toward large trials is not expected to protect people from infection. Instead, these vaccines are more likely to ameliorate the progression of HIV to AIDS if a vaccinated person becomes infected. To determine the vaccine's impact, volunteers will need to be followed over a long period of time, perhaps their lifetime. This represents a significant paradigm shift—one that will require considerable education of trial participants and communities in which trials occur.

What's more, there is no guarantee of success and a high likelihood that one—or possibly all—of the candidates in the pipeline will fail to show efficacy that warrants licensure and large-scale distribution. "We're not going to get it right on the first try. We could spend all this money and conduct all these trials and still fail to find an effective product," says VRC director Nabel.

The role of efficacy trials is also changing. If proposed Phase 2b trials go forward, then the AIDS vaccine field will be preparing for a series of intermediate-size trials that would not necessarily be geared towards licensing a vaccine. More than ever, the field will need to explain to communities that AIDS vaccine research is an iterative, stepwise process of testing and refining concepts in human trials, as well as in the laboratory. Put simply, products may fail but trials do not as long as they are ethical, scientifically relevant and give back to the community.

The AIDS vaccine field cannot do enough work to ensure that these concepts are well understood by diverse audiences—from politicians to funders to community leaders and trial participants. To do this, AIDS vaccine researchers need to develop and share tools to build and measure community understanding. The field needs to document and share lessons from trials such as the VaxGen Thai study in which the product did not show efficacy but the country remained engaged, recently launching a Phase 3 trials of the prime-boost approach.

Correlate 12: Media stories, political speeches and community dialogues that accurately articulate the nature of the search for an AIDS vaccine.

Readiness for global collaboration

When the history of AIDS vaccine development is written, people are not going to write a chapter on IAVI and a chapter on VaxGen. They will write about the stages the field went through and the approaches that emerged at different points in the search. Hundreds of years down the line, history books may simply say, it took "X" number of trials to find an AIDS vaccine.

ANTICIPATED HIV-RELATED TRIALS IN DEVELOPING COUNTRIES 2005-2010

Phase II/B and Phase III Trials

Technology	Trials	Countries	Volunteers
AIDS vaccine trials	5	15	44,000
Non-vaccine HIV prevention trials, including microbicide trials	10	12	52,000

Source: Judith N. Wasserheit, director, HIV Vaccine Trials Network (HVTN), Seattle, Wash. Numbers are estimates as of January 2004 based on informal analysis of planned trials in developing countries. Estimates are minimum because not all groups could be contacted and additional trials are in development.

Today the field does not fit this narrative. Trial sites are "owned" by individual networks, as are capacity-building efforts on many fronts. To ready itself for the realities of global research, the field must find ways to bridge gaps between trial sponsors and work in concert more often, and more effectively.

One opportunity to do this is via the restructuring—or "recompetition" process—at the National Institute of Allergy and Infectious Diseases. This planned assessment of US networks—including HVTN, the HIV Prevention Trials, and the Pediatric and Adult AIDS Clinical Trials Groups—offers a major opportunity to bring fresh ideas and more effective network configurations to the table. But if this process is not handled with sufficient input from all vested interests, including community advocates and scientists from outside existing networks and from the developing world, then it runs the risk of alienating key players and thereby undermining the goal of collaboration.

The nascent Global HIV Vaccine Enterprise is another opportunity. Some of the most productive areas for collaboration may be in training of developing country researchers; investment in central clinical laboratories for blood chemistry, viral load and CD4 cell monitoring; and in sharing of lessons learned.

While Enterprise members are optimistic about the targeted use of new resources, some are also wary of competition that might arise as various networks attempt to "own" specific activities or projects that may receive Enterprise funding (see page 43).

The success of trials in the developing world will also hinge on availability of ARV treatment. It is the promise of these life-saving medicines that brings people through the doors of VCT centers to learn their HIV status. Readiness efforts, therefore, must include authentic collaborations between international and in-country leaders of ARV scale-up initiatives—such as the Global Fund to Fight AIDS Tuberculosis and Malaria, and the President's Emergency Plan for AIDS Relief (PEPFAR)—and vaccine trial sites.

At the present time, "PEPFAR does not map to existing vaccine trial sites," says HVTN's Wakefield. "There is no one coordinating country-to-country to make sure that this money flows to places where large-scale trials are underway." Wakefield says that this type of coordination "could create an enabling environment for research."

Treatment and care need to be a part of the overall strategy to get sufficient numbers of trial volunteers and to meet ethical obligations to provide treatment and care to those who become infected during the course of a trial (see facing page).

Correlate 13: Community, developing world, and non-NIAID stakeholders whose substantive input is taken into account during recompetition process.

Correlate 14: PEPFAR or GFATM-sponsored ARV programs in communities engaged in vaccine research, and existing vaccine trial sites that share capacity with ARV scale-up programs.

In general, the research project should leave low-resource countries or communities better off than previously or, at least, no worse off. It should be responsive to their health needs and priorities in that any product developed is made reasonably available to them, and as far as possible leave the population in a better position to obtain effective health care and protect its own health.

—Council for International Organizations of Medical Sciences, International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2002.

VACCINE TRIALS: LEAVING COMMUNITIES BETTER OFF

What will poor communities in developing countries get out of agreeing to take part in AIDS vaccine clinical trials? The question is vexing, especially since the road to an effective vaccine is looking longer than once anticipated and the prospect of a vaccine that prevents HIV infection, as opposed to HIV disease progression, is not on the immediate horizon.

Given the long haul ahead, AIDS vaccine scientists, who are rushing to line up international vaccine trial sites in developing countries, need to focus on a key issue: How they can leave poor communities better off for having taken part in a trial even if the particular vaccine being tested turns out not to work or to be only partially effective.

As Seth Berkley, President of the International AIDS Vaccine Initiative (IAVI), puts it: "Communities participating in AIDS prevention and treatment trials, whatever the results, are contributing knowledge that is a global public good and should benefit in return."[1]

No more safari research

Fortunately, the world has moved a long way from the "safari research" that used to be conducted by Western scientists in poor countries. It is no longer considered ethical for researchers to parachute into impoverished communities, collect their data, and then leave without the community reaping any tangible benefits for having taken part in the study. Such an approach would violate international ethical guidelines,[2] and politically savvy communities in the developing world would no longer accept it anyway.

But how, exactly, can AIDS vaccine researchers contribute to the health and welfare of poor communities where vaccine trials will be conducted?

Much attention over the past year has focused on the provision of antiretroviral drugs (ARVs) to trial participants who become infected during the course of a trial. This is a critical issue—and a difficult one—since these drugs can dramatically reduce mortality rates from HIV, but they are not yet widely available in the developing countries where vaccine trials will be conducted. However, the major trial networks—including the US government's HIV Vaccine Trials Network (HVTN) and the former US Army-sponsored network, IAVI, and the South African AIDS Vaccine Initiative (SAAVI)—have now all committed to making ARVs available as needed to trial volunteers. And they have laid plans for funding mechanisms (typically, an insurance fund) to pay for the drugs.

Important details—such as how long the drugs will be provided, whether infected family members will also qualify, and whether there will be an effort to provide ARVs to entire communities—remain to be worked out. But there is consensus among the trial sponsors that these life-extending medicines will at least be offered for free to trial participants who have breakthrough infections. That is an important advance—and one that is not likely to break the bank. Only a small percentage of trial volunteers are expected to become infected during a trial and ARVs likely won't be needed until people develop symptoms, which could take as long as 10 years. By then, ARVs are expected to be much more widely available in the developing world.

ARVs are just one benefit

Providing access to antiretroviral drugs for trial participants, however, is just one way that AIDS vaccine researchers can leave poor communities better off. There are myriad benefits that AIDS vaccine trials can bring to host countries and to specific communities within those countries.

Ideally, specific benefits will be determined at the grassroots level as AIDS vaccine researchers engage with national and community leaders and with members of the community advisory boards (CABs), which advise local trial units. Each community may want and need something different.

To stimulate the dialogue, AVAC offers this checklist of ways that vaccine trials can leave communities better off:

- **Voluntary HIV testing and counseling.** Since vaccine trials involve HIV negative volunteers, people have to be tested for HIV before they can participate in a trial. As many AIDS vaccine researchers are now doing, the screening process should be used as an opportunity to introduce rapid HIV-testing kits to the community, and to teach local people how to administer tests and how to counsel those who test positive.
- **Support groups for those who are HIV positive.** In much of the developing world, AIDS carries more social stigma than it does in the industrialized world. By helping set up support groups for people who test HIV positive in trial screenings or turn positive during a trial, AIDS vaccine researchers can provide emotional support to people with HIV while helping to break the silence and prejudice surrounding the disease. While no substitute for broad educational programs, access to ARVs and treatment for opportunistic infections, group support can provide a pathway to testing and treatment not sought for fear of societal penalty.
- **Prevention of mother-to-child transmission (MTCT).** Short-course nevirapine helps prevent the transmission of HIV from infected mothers to their newborns. AIDS vaccine researchers can partner

with local health officials to provide this simple and inexpensive regimen and educate HIV positive pregnant mothers about its life-saving potential. Health care should extend beyond that to include provision of ARVs for these mothers on an on-going basis. Mothers must also be counseled about the complex issues surrounding the risks and benefits of breastfeeding in resource-poor settings.

- **Antibiotics and medicines to combat malaria and TB.** Quite apart from antiretroviral drugs, many communities in the developing world have little access to standard antibiotics and medicines to fight two leading killers—malaria and tuberculosis. As many research groups are now doing, AIDS vaccine trial units in developing countries should provide these medicines to trial participants. Vaccine trial units should also make treatments available for other sexually transmitted disease (STD) infections, which, if left untreated, can greatly increase the risk of people contracting HIV.

- **HIV prevention programs.** AIDS vaccine researchers are ethically required to educate clinical trial volunteers about what HIV is and how to keep themselves from becoming infected. Vaccine trials offer the opportunity to expand HIV prevention efforts into the larger community. Community advisory boards play an important role in this effort. If male and female condoms are not widely available in the community, vaccine researchers can use their leverage with public health officials and international aid agencies to provide them at no cost.

- **Professional training.** Vaccine trials can be an opportunity to expand the number of medical professionals—doctors, nurses, technicians, social workers and others—in short supply in many developing countries. Trials cannot proceed without trained professionals—and the people best able to understand and respond to the needs of a community will come from the community. Trials can offer not only on-the-job training, but also the chance for classroom and laboratory training at associated academic institutions in the host country or abroad.

- **Shared laboratory facilities.** Many AIDS vaccine trials research teams will be setting up laboratories to conduct tests on blood samples drawn from trial volunteers. Depending on what's being measured, these labs may use sophisticated equipment and a wide range of assays. In poor communities without access to advanced testing facilities, these labs might also provide services such as antibody tests, T-cell counts and viral loads to help public health officials treat HIV-infected people and track the epidemic in the local area.

AIDS vaccine researchers can provide certain benefits directly or they can link up with others who can provide them. Most importantly, scientists need to make certain that whatever is put in place to improve public health infrastructure can be sustained after the trials end.

A chilling example of what can happen without that commitment comes from an HIV prevention study in Zambia by researchers from the University of Alabama, Birmingham. During a temporary hiatus in the program due to a funding glitch, mortality rates among trial participants doubled. The reason was not diminished access to ARVs; none were provided to trial volunteers as part of the study. Rather, scientists attribute the jump in death rates to the fact that participants no longer had access to the TB and malaria medicines provided at the site.[3]

Some ethicists argue that providing these benefits offers an unfair inducement for people in poor communities to take part in AIDS vaccine clinical trials. If so, that would be a violation of international ethical guidelines. However, as Ruth Macklin, biomedical ethicist at Albert Einstein College of Medicine in New York, points out, the unfair inducement argument is relevant only when benefits offered during a trial provide an incentive for an individual to take risks that he or she would otherwise not take.[4]

In the case of AIDS vaccines, however, the medical risk of participating in an AIDS vaccine trial appears to be minimal. No product in the research and development pipeline is made with whole HIV so the vaccine cannot give someone HIV.

The larger issue is more related to social risk rather than medical: Will participation in a vaccine trial, for instance, stigmatize trial participants? For women in particular—who have little power in many traditional cultures—participation could mean ostracism from the family, loss of financial support and even physical abuse. That risk scenario is even more reason for AIDS vaccine researchers to ensure that trial sites have effective community-wide HIV education programs.

Kericho: A model program

While AIDS vaccine sponsors have launched a number of initiatives to improve public health at various trial sites in the developing world, a particularly outstanding effort is underway on the highlands of western Kenya. In a district known as Kericho, the United States Army Medical Research Unit (USAMRU) is engaged in a comprehensive effort to prepare for a large-scale trial of the US government's DNA vaccine against clades A, B and C of HIV.

The trial site is a large tea plantation owned by the British-based James Finlay & Co. Ltd., a global tea conglomerate. About 18,000 Kenyans work at the company, either as pickers or tea processors. Virtually all live in company housing and receive medical care at the company hospital. An average picker makes the equivalent of $1.65 a day based on the weight of tea picked. An estimated fifteen percent of all the workers are infected with HIV.[5]

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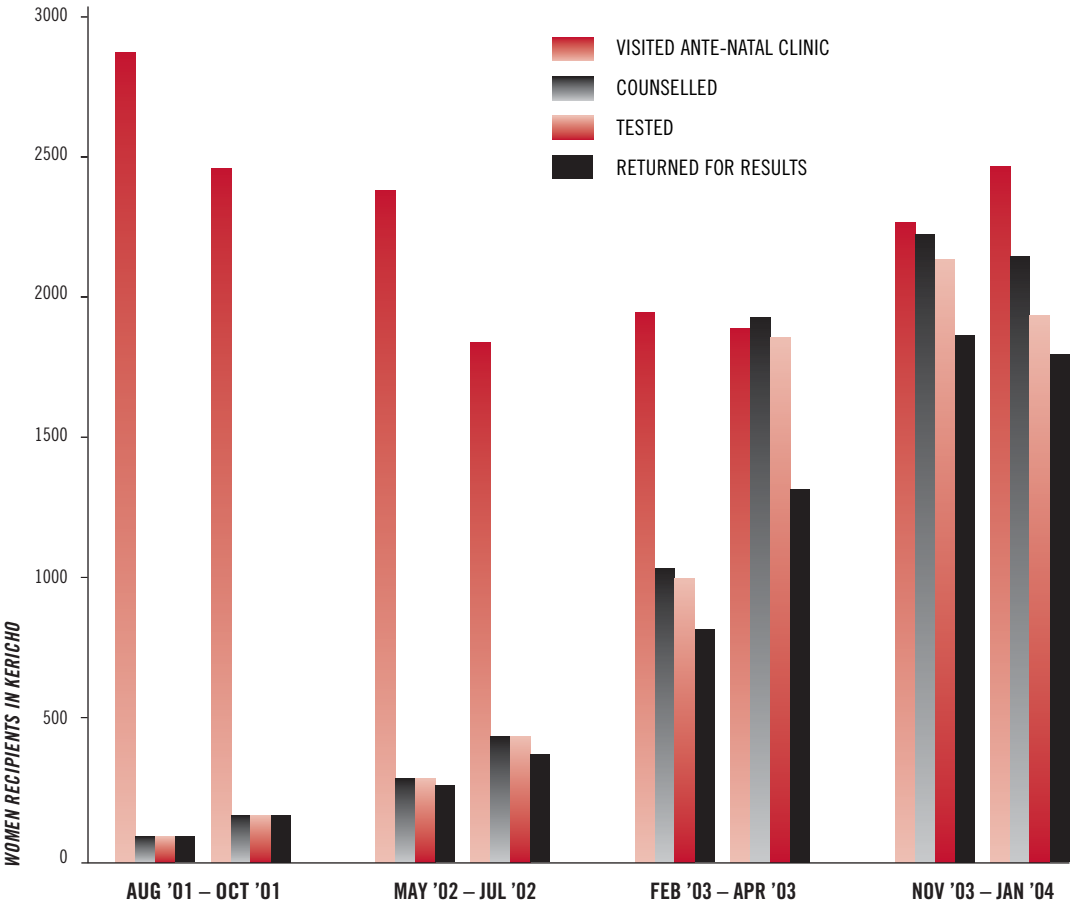


Source: Kericho Prevention of Mother-To-Child Transmission of HIV Infection Program (March 2004)

Under the leadership of Merlin Robb, of the Henry M. Jackson Foundation, and Col. Deborah Birx, director of the US Army's AIDS vaccine research program, scientists from the US and Kenya have teamed up to enlist senior management of Finlay and residents of Kericho in preparation for a trial of the Vaccine Research Center's multi-clade DNA vaccine. If the vaccine works, it could reduce the incidence of HIV disease among tea workers while also boosting worker productivity.

The site team—which launched its effort nearly four years ago before any particular vaccine candidate had been selected for testing—views improvements in public health for the entire Kericho community as integral to the trial itself. "Our effort is to get a handle on this disease—whether we do vaccine research,

primary prevention or treat disease," said Fredrick Sawe, a Kenyan obstetrician and gynecologist on the research team. "The end is the same. We are trying to stop this disease in its tracks."

To that end, the vaccine researchers have conducted a community-wide education program to teach people about behaviors that put them at risk of HIV infection. The message has gone out not only in conventional brochures, but also in rap performances and condom distributions at pre-game soccer shows, and at "barazas" or traditional community meetings, where research staffers perform dramas about HIV prevention in both Kiswahili and English.

Until the research team came along, nobody had a handle on the prevalence and incidence of HIV infection in the area. Last year, the team recruited 3,000 volunteers and tested them for HIV. After six months, volunteers were tested again to determine the incidence of new infections.

With funding from the Elizabeth Glaser Pediatric AIDS Foundation, the team also brought the first program to prevent mother-to-child transmission (MTCT) to Kericho. As part of that effort, it built the community's first ante-natal clinic on the grounds of the Kericho District Hospital. The clinic now offers short-course nevirapine to HIV positive mothers—and the same regimen is provided at twenty-two other centers upgraded as part of the program.

In setting up the MTCT program, researchers trained fifty-six nurses and counselors to implement the program, which includes post-test counseling for mothers who test positive or negative for HIV. Another thirty-six people were trained to do rapid HIV antibody testing.

So far, the team has not been able to provide ARVs at the site beyond the short-course neviripine provided for HIV positive mothers and their newborns. By 2008, however, it hopes to have the capacity to offer ARVs to approximately 30,000 people in the Kericho district and in a neighboring district where workers have family members.

Who pays?

How ARV therapy for vaccine trial volunteers will be paid for has not yet been determined. Under federal regulations, the National Institutes of Health, which now oversees the Army's AIDS vaccine research program, cannot use federal research dollars to fund treatment unless it is the focus of a particular study. A logical funder would be the President's Emergency Plan for AIDS Relief (PEPFAR), the State Department bilateral program that will pump some $9 billion of new US funding into AIDS treatment, prevention and care in twelve African countries, including Kenya, over the next five years. The program has agreed to provide an initial $2.9 million to the site, but additional dollars are needed if drugs are to be provided more widely in the community as Army researchers have proposed.

The advent of generic ARVs opens an opportunity for the Bush administration's new program to provide treatment for large numbers of people. However, the administration has balked at providing generics—a decision that needs to be reconsidered as the program rolls out.

The Finlay Co., which stands to achieve productivity gains from a healthier workforce, is currently underwriting the cost of upgrading health-care infrastructure on the plantation and adding nurses and other medical personnel. If the Army can demonstrate the benefit of providing ARVs to the HIV-positive workforce, Finlay will likely pay for the medicines, says Col. Birx. Such an approach has been adopted by gold-mining conglomerates in South Africa.

In order to extend the ARV program to all in the Kericho area who need them, however, additional funds need to come from PEPFAR. The site might also qualify for treatment dollars from the Global Fund to Fight AIDS, Malaria and Tuberculosis. However, the Global Fund is struggling to finance projects already approved and may be reluctant to pay for ARVs when the much-better financed PEPFAR program has already targeted Kenya for stepped-up treatment dollars.

Such Catch-22 situations are likely to arise at other trial sites. They speak to the need for more flexibility from both US and international agencies dealing with the AIDS pandemic, as well as closer collaboration among all players—trial networks for both prevention and treatment trials; bilateral/multilateral AIDS relief programs; and the public/private sector, particularly the Bill & Melinda Gates Foundation whose Global HIV Vaccine Enterprise initiative might set aside funding of ARV provision to entire communities where vaccine trials will be conducted.

Success in using AIDS vaccine trials to leave poor communities better off, however, is not just a matter of money. Fundamentally, it's attitude. Instead of doing research *on* communities, scientists need to do research *with* communities. Instead of narrowly focusing on trial outcomes only, scientists need to care about the overall health of individuals and their communities.

In Botswana, Harvard scientists have it right—testing an AIDS vaccine in the context of a national ARV program, largely funded by philanthropies. As Richard Marlink, executive director of the Harvard AIDS Institute puts it, "We commit to the health of Africa, not to a single project or proposal."[6]

While not even Harvard is rich enough to provide health care for all of Africa, the intent is on the mark.

As AIDS vaccine trials roll out around the world over the next five to ten years, that's exactly the mindset the AIDS vaccine field as a whole needs to adopt—in Africa as well as in impoverished communities of eastern Europe, Asia, the Caribbean and Latin America. Without volunteers from these communities willing to roll up their sleeves and be inoculated, no effective AIDS vaccine will ever be developed for anyone.

If we had a vaccine and it was only approved in those over 18, we would be missing at least 25 percent of the new infections in the United States and many more internationally.

—Bret Rudy, director of the adolescent HIV clinic at Children's Hospital of Philadelphia

ADOLESCENTS: THE MISSING COHORT

Adolescents[7] make up a significant percentage of people infected with HIV around the world. But in nearly two decades of clinical research, adolescents have generally not been included in human trials of AIDS vaccine candidates. Almost all candidates have been tested in people over the age of 18.[8]

Unless adolescents are included in clinical trials, they likely won't have timely access to an effective AIDS vaccine when one is developed and licensed. That would not only deny young people of an important HIV prevention tool, but it would also hamper efforts to stop the AIDS pandemic.

"If we had a vaccine and it was only approved in those over eighteen, we would be missing at least twenty-five percent of the new infections in the United States and many more internationally," says Bret Rudy, director of the adolescent HIV clinic at Children's Hospital of Philadelphia and a national leader in HIV prevention for adolescents.

As it gears up for large international trials over the next five to ten years, the AIDS vaccine field needs to be more deliberate about addressing the issue. The following steps need to be taken now:

- **Strategic plans.** Sponsors of clinical trials—including the US government's HIV Vaccine Trials Network (HVTN), the International AIDS Vaccine Initiative (IAVI), the South African AIDS Vaccine Initiative (SAAVI), and European Vaccine Effort Against AIDS (EuroVac)—need to develop strategic plans for the inclusion of adolescents in clinical trials. It may be too soon to begin enrolling adolescents, but plans to do so must be in place.
- **Regulatory advice.** The US Food and Drug Administration (FDA) needs to hold an informal meeting with AIDS vaccine trial sponsors to discuss the minimum criteria for an adolescent indication of an AIDS vaccine proved efficacious in adults. Without such guidance, it will be difficult for trial sponsors to develop intelligent plans. Similar meetings should occur with regulatory bodies in other countries such as South Africa. A key issue is whether regulatory bodies will require a Phase 3 study involving adolescents in order to approve an adolescent indication.
- **Coordination with existing prevention programs.** No vaccine trial that includes adolescents can be conducted without strong HIV prevention programs specifically targeted at youth. A number of youth programs exist or are being created in both the developed and developing world. AIDS vaccine trial sponsors need to link up with these programs now so they can include them in their strategic plans.

- **Learn from private-sector experience with other STD vaccines.** Important new ground is being broken by GlaxoSmithKline in testing a vaccine against genital herpes among adolescents, and by Merck & Co., testing a vaccine against human papilloma virus among adolescents. AIDS vaccine developers need to pay attention to these path-setting trials of STD vaccines among young people. Both firms have important lessons to pass on about the inclusion of adolescents in AIDS vaccine trials.

The potential benefits to youth of an AIDS vaccine

Of course, everyone will benefit from development of an effective AIDS vaccine, but adolescents especially so because they represent such a large proportion of people infected with HIV.

In sub-Saharan Africa, for example, about ten million of the region's thirty million people living with HIV are between the ages of 15 to 24. Among the young people, two-thirds are girls or young women.[9] "Adolescent girls in high-prevalence countries in Africa are at significantly higher risk of acquiring AIDS. In some communities, as many as 20 percent of the girls aged 15 to 19 are infected compared to 5 percent of boys the same age,"[10] says the US State Department in its new five-year $15 billion plan to combat AIDS in sub-Saharan Africa and the Caribbean.

In the United States, a recent study by the Centers for Disease Control and Prevention (CDC) estimates that approximately 15,000 of the 40,000 new HIV infections reported to public health officials in 2000 were among young people aged 15 to 24.[11]

Given the number of youth at risk, it would be unethical not to enroll them in clinical trials of an AIDS vaccine from which they could greatly benefit. Although international guidelines call for the protection of children from abuse in medical research, the guidelines are equally insistent that children should not be excluded from research that could benefit them.

As the Society of Adolescent Medicine observes, "The interests of justice demand that adolescents not be exploited for the benefit of others, but also that adolescents not be excluded from participation in research that may have direct or indirect benefit."[12] AIDS vaccine trials are an important case in point.

The challenges of enrolling adolescents

It is one thing to endorse the enrollment of adolescents in AIDS vaccine clinical trials and another to actually enroll them. The challenges include getting the informed consent of parents while honoring the privacy rights of the adolescent; fear that youth taking part in AIDS vaccine trials will engage in risky behaviors; the social risks associated with of vaccine-induced seropositivity; and the recruitment and retention of young people, who characteristically live busy and unstructured lives or who may be alienated from the medical system.

Issues are complex for any type of vaccine testing in adolescents. But for AIDS vaccines, there is added complexity. HIV is a sexually transmitted disease that carries enormous social stigma, particularly in the developing world, and among racial minority youth in the United States who are among those most at risk.

Working through these issues will take clear thinking, collaboration with young people and organizations that represent them, and political courage in the face of a growing conservative ideology promoting an abstinence-only approach to HIV education among young people attending US public schools. "Yes, there are challenges, especially ethical and logistical challenges," says Craig Wilson, professor of pediatrics at the University of Alabama at Birmingham and chair of the US government's Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). "But the overriding ethical imperative is that we have an HIV vaccine that can be given to adolescents."

What follows are key challenges and AVAC recommendations.

Ethics

Under both international and US guidelines,[13] children—including adolescents—are regarded as a "vulnerable" population that must be accorded special protections from exploitation and physical or emotional harm during the course of a clinical trial.

For adolescent girls, there may be additional vulnerabilities. "In some cultures, adolescent girls may not be able to exercise true autonomy in light of gender norms and the influence of their parents or partners," the World Health Organization advises in its guidelines on conducting vaccine trials among children in developing countries.[14]

Because of these and other vulnerabilities, ethical guidelines lay out certain protections for children that extend beyond what is required for adults. Extrapolating from these, it is possible to infer what practices Institutional Review Boards, which must approve clinical trials, are likely to require in order for adolescents to participate in AIDS vaccine trials:

- Adolescents themselves must agree to take part in the clinical trial.
- At least one of the adolescent's parents (or guardians) must give their fully informed consent for the adolescent to take part in the trial.
- The community in which the trial takes place should discuss and agree on the inclusion of adolescents before adolescents are enrolled.
- No vaccine should be given to adolescents unless it has first been given to a sufficient number of adults to insure that it is safe.
- Large numbers of adolescents should be enrolled in a vaccine trial only when it appears that the particular vaccine candidate being tested in adults shows promise of working in Phase 2 studies.

While it may take time and effort to implement such safeguards, they are all do-able. Indeed, most can be met with good planning and quality counseling and education programs—a practice to which leading trial networks already adhere.

The most daunting challenge is likely to be securing informed consent of the parent while also protecting the privacy of the adolescent. The consent process may force adolescents to tell their parents—and researchers—whether they are sexually active. In some cultures and some families, an admission of sexual activity could have adverse consequences for the adolescent.

But there are ways around the problem. If it were unnecessary to enroll adolescents in Phase 3 trials—which are conducted among people at high risk of HIV—there would be no need to screen young people for trial participation based on sexually active status. Trials could be conducted among adolescents generally, no matter what their risk.

On the other hand, if adolescents need to be enrolled in Phase 3 trials, researchers can determine whether a young person is sexually active short of asking directly. For instance, a previous STD diagnosis might be an enrollment requirement; or for young women, a previous pregnancy.

In some communities, the average age of sexual debut may be so low that researchers can simply assume that enough adolescents are sexually active in a particular population to include them in a clinical trial. For example, a University of Cape Town survey conducted among 500 youth aged 13 to 18 in Masiphumelele—an informal community south of Cape Town—found that fifty percent of the youth were sexually active by the age of fourteen, the majority knew about HIV but did not use condoms, and most had multiple sex partners.

Whatever approach is taken will largely depend on whether Phase 3 trials will be necessary for adolescents. That's why it's so important that the FDA and other regulatory bodies step forward now to share their thinking on the issue in a consultation with AIDS vaccine trial sponsors.

There is precedence for such consultation. Last year, the FDA met with AIDS vaccine developers to broadly discuss the criteria the agency would need to approve a therapeutic AIDS vaccine to treat people who are already infected.[15] A similar meeting should now convene to discuss complex regulatory issues related to adolescent indications for an AIDS vaccine tested primarily in adults.

By the age of 22, one in four South African women has HIV. In South Africa's Tembisa township, a 21-year-old mother with HIV nurses her six-week-old baby, who is also infected.

Source: Survey of 11,904 South African youth aged 15 to 24 by the Reproductive Health Research Unit at the University of Witwatersrand, 2004.

Photo courtesy of Mujahid Safodien, *The Johannesburg Star.*

Discouraging risky behaviors

Another big challenge to overcome is concern that adolescents, if enrolled in AIDS vaccine clinical trials, could view participation as a green light to engage in risky behaviors, such as having unprotected sex with multiple partners.

So far, in the two Phase 3 trials of AIDSVAX—the only vaccine that has yet completed large efficacy tests—this has not proven to be a problem among adults. However, it may be a problem among adolescents who are just becoming sexually active.

With well-executed youth-oriented HIV prevention programs, however, this concern can be overcome. Such programs already exist or are in the making in fifteen US cities involved in the federal government's Connect-to-Protect program, which is targeting specific neighborhoods for stepped-up HIV prevention among adolescents.

The program, which will run five years, uses demographic data to locate the most HIV-impacted neighborhoods in the targeted cities, many of them African American, and then mobilizes community-based organizations in an intensive campaign to prevent HIV among adolescents in those areas.

"Don't expect families to let their healthy, HIV-negative children roll up their sleeves and get inoculated if all you've got to offer the community is a vaccine that might work in some distant future," says Audrey Smith Rogers, director of the maternal and child division of the National Institute of Child Health and Human Development, which is overseeing the program along with the CDC. Rogers adds, "But the community might accept it if it's one component of a much broader HIV prevention agenda."

Adolescent trials should also be conducted in conjunction with enhanced HIV prevention activities targeted at youth in developing countries. Such activities will be rolling out in the most impacted countries in sub-Saharan Africa and the Caribbean over the next five years under the bilateral PEPFAR program. Prevention initiatives have also been launched through the Global Fund.

In South Africa, the Kaiser Family Foundation's "loveLife" initiative represents the world's largest HIV prevention program for youth. Vaccine researchers could locate adolescent trial units near the network of youth centers that loveLife has set up across the country. That would ensure that HIV prevention was an integral part of adolescent trials.

Vaccine seropositivity

Another key challenge is explaining to adolescents and parents that, if participants are in the active arm of a trial, they will likely test HIV seropositive on standard assays—even though they are not actually infected with HIV.

While possible vaccine-induced seropositivity discrimination is a concern for adults, it may be more of a concern for adolescents who are just embarking on adult life. At issue may be a young person's ability to enter military service, for instance, or, in the case of adolescent girls in sub-Saharan Africa, to marry and remain a valued member of a family unit. The very fact of participating in an AIDS vaccine trial may subject young people to stigma and discrimination among friends, family, and others.

AIDS vaccine researchers need to make sure that systems are in place to verify that a positive test stems from vaccine-induced antibodies, rather than an actual infection. Also, needed are programs to combat discrimination against anyone enrolled in an AIDS vaccine trial—whether they test HIV seropositive or not.

Each community will need to decide what measures will work best in the local context. One option may be an ID card specifying that the adolescent has taken part in a trial and may test positive on HIV antibody tests, though is not infected. Additional measures could be a special office where trial participants, including adolescents, can take their complaints if they experience discrimination; and a concerted effort to provide test kits at vaccine trial sites that can distinguish between vaccine-induced positivity and an actual infection.

Recruitment and retention

Recruiting HIV-negative adolescents into AIDS vaccine trials—and retaining them—will also be a challenge. Given the importance of peer pressure, many young people may not want to be enrolled in a study that involves a disease associated with homosexuality, intravenous drug use and what some people regard as sexual promiscuity. Many youth may not want to participate for fear they will have to talk with their parents about sex. Others may be too busy to keep clinic appointments, while some may lead complex lives marked by homelessness, drug use, incarceration and frequent changes of address.

Among some youth, deep mistrust of government-sponsored medical research may exist because of past ethical lapses, such as the infamous Tuskegee syphilis study involving African-American adults who were denied penicillin while US government scientists studied the course of their syphilis infection. The study ended in the 1970s, but its legacy lives on in the African-American community.

Despite these sensitivities, Merck and GlaxoSmithKline are demonstrating that it is possible to recruit large numbers of adolescents into clinical trials of vaccines aimed at preventing infection with two other sexually transmitted diseases—human papilloma virus (HPV), the leading cause of cervical cancer and a cause of genital warts, and herpes simplex virus (HSV) type 2, which causes genital herpes and genital ulcers.

Admittedly, these viruses don't carry the same stigma as HIV, nor do they typically represent a health pandemic. Still, the fact that they are sexually transmitted viruses means that testing vaccines against

these infections among adolescents is not as simple as enrolling youth to test vaccines against such common childhood diseases as measles and mumps.

In face of the challenge, Merck has managed to enroll between 5,000 and 6,000 adolescents, aged 9 to 18, in a Phase 3 trial of its HPV vaccine. All told, the vaccine is being tested among 25,000 people in thirty countries. Likewise, Glaxo recently initiated several studies of its HSV vaccine, which will enroll approximately 7,000 young people aged 10 to 17.

Both companies have turned to large pediatric practices in developed countries to recruit volunteers. Glaxo has also recruited from public schools in Canada for trial participants. Merck has enrolled adolescents at trial sites in both developing and developed countries—including the U.S., Canada, the United Kingdom, Colombia, Peru, Mexico, Thailand and the Philippines—through recruitment efforts at large public health clinics, private clinics and non-governmental organizations working in working-class and migrant communities.

Before enrolling adolescents, both companies consulted widely with experts on adolescent health. "It's very difficult to explain the studies to a ten or eleven-year-old," says Gary Dubin, the Glaxo physician in charge of the clinical development program. To best do that, the company developed a youth "informed assent form," in which a youngster gives his or her written approval to take part in the trial. This was supplemented by age-appropriate educational brochures and a website catering to pre-teens. Of course, parents were also asked to sign consent forms.

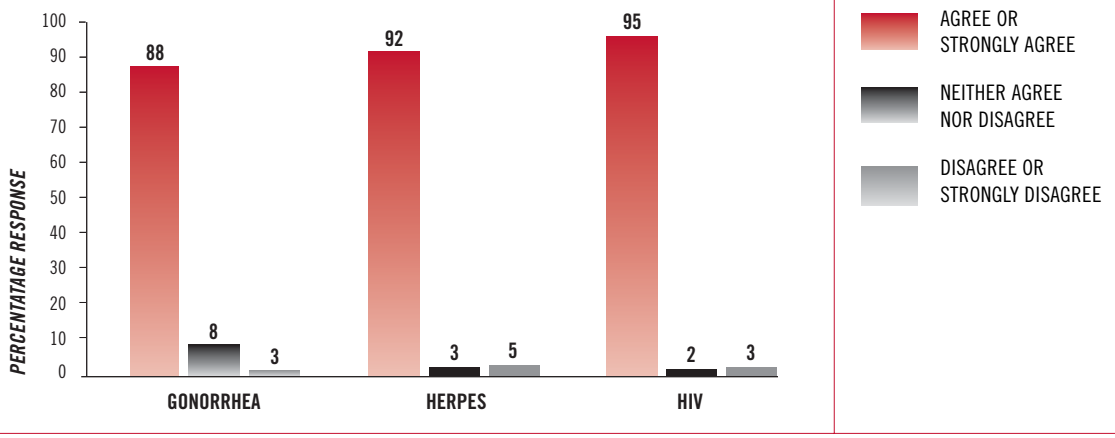
Merck developed a strategy aimed at helping take the stigma out of HPV by depicting it in brochures, posters and booklets as a medical problem that can lead to cervical cancer, not as an infection freighted with undertones of sexual promiscuity. "This took it out of the realm of an STD and made it into just another disease that people get," explains Eliav Barr, senior director of the HPV vaccine clinical research program. Barr said recruitment was strongest in developing countries because of relatively high prevalence of cervical cancer.

The experience of these companies provides helpful lessons for the AIDS vaccine field as it moves toward the inclusion of adolescents in clinical trials. Undoubtedly, Glaxo and Merck, both of which are developing AIDS vaccines as well, will make use of their STD trials experience to consider inclusion of adolescents in their HIV trials. Other trial sponsors need to draw on the companies' accumulating experience and glean from it information that will better inform the AIDS vaccine field.

If we make it, will they come?

Fast forward to the day that the world finally has an effective AIDS vaccine, licensed for use not only in adults, but also in adolescents. Will parents and their teenagers go for it?

ACCEPTABILITY OF POSSIBLE STD VACCINES AMONG PARENTS OF TEENAGERS



Source: Gregory D. Zimet, Indiana University Schools of Medicine and Nursing. Based on a survey of 156 parents of adolescents in the U.S. Unpublished data, expanding the cohort to more than 300 parents, show similar acceptance rates.

That was the question asked by Gregory D. Zimet and colleagues at Indiana University Schools of Medicine & Nursing as part of a federally-funded study to examine predictors of parental acceptability of STD vaccination for their adolescent children. The study involved interviews with 156 parents of adolescents aged 12 to 17 who accompanied their children to appointments at urban adolescent health clinics and primary-care pediatric offices.

In the survey, parents were asked to record their responses to a statement about the acceptability of vaccines against gonorrhea, genital herpes and HIV/AIDS. For HIV/AIDS, the statement was: "If a safe and effective vaccine for preventing HIV/AIDS was available, I would get my child vaccinated." Parents were asked to respond on a five-point scale, ranging from ""strongly disagree" to "strongly agree."

The responses—at least among this cohort of American parents—were overwhelmingly positive. And of the three vaccines, the vaccine for HIV/AIDS had the most support. (See chart this page.)

Of note, Zimet found important factors that predicted a favorable response: whether the parents themselves had experienced an STD infection, the degree to which the parent believed that their adolescent child was vulnerable to an STD infection in the next five years, and the anticipated negative effect on their child of learning they had contracted an STD. The one factor that predicted less acceptance of the vaccine was the fear that it would lead the teenager to engage in unsafe sexual activity. "The influence on sexual behavior—more partners and less use of condoms—is a real disincentive," Zimet explained. "For HIV vaccine researchers, it's a justifiable concern to anticipate."

Transferring concepts for HIV-1 vaccines into clinical applications has lagged. There is an urgent need to create and systematically evaluate more candidate vaccines and the pace of development of new HIV vaccine candidates needs to be accelerated.

INVOKING THE ENTERPRISE

In a June 27, 2003 Science magazine Policy Forum, Richard Klausner, Executive Director for Global Health at the Bill & Melinda Gates Foundation, along with twenty-three additional authors (including Chris Collins, then Executive Director of AVAC) address "The Need for a Global HIV Vaccine Enterprise."

By coincidence, that issue of Science also features a ravishing cover illustration of how Myosin V carries biochemical cargo within cells by taking nanometer-size steps along actin filaments, placing "one foot over another"—a lesson in biochemical tightrope walking that might be taken to heart by the twenty-four authors and the loose organization developed since then to make such an enterprise a reality.

Their thesis is that there is still a need for a high-quality collaborative AIDS vaccine research system that goes well beyond the high-quality—but separate—research projects that we have today.

- The world awaits the development of an effective preventive vaccine.
- Transferring concepts for HIV-1 vaccines into clinical applications has lagged.
- There is an urgent need to create and systematically evaluate more candidate vaccines, and the pace of development of new AIDS vaccine candidates needs to be accelerated.
- The best engine for solving major scientific challenges in AIDS vaccine research is the creativity of individual scientists working together in multidisciplinary problem-solving consortia, adequately resourced and linked to vaccine development capabilities.
- Thus, a well-coordinated global enterprise does not exist and must be created.

This case has been made by many over the course of the epidemic, but never before with such unanimity or from such well-funded and well-placed principal authors. Therein lies its appeal and its power. That and a certain sense of fatigue and frustration with the scientific community's level of uncertainty after more than a decade of hard work.

The importance of the four-page article cannot be overestimated. It signals a new level of collaboration and a call to radically increase planning, funding and cooperation in the long-term effort to develop an effective AIDS vaccine. Because of the prominence of the Gates Foundation in global health and its demonstrated willingness to use its wealth to put major new resources into projects it supports, many hope that this declaration heralds a new, higher level of activity and progress commensurate with the overwhelming importance of this issue.

Perhaps drawing on Klausner's experience as former Director of the National Cancer Institute—where large cooperative medical research consortia are common—the article cites the model of acute lymphocytic leukemia (ALL), where cure rates improved eight to ten fold, to 80–100 percent, through a coordinated and iterative program of preclinical developments. That kind of gradual advance required a centralized coordinated clinical trial and laboratory evaluation system, and substantial medical and political support. Because of the scope and toll of the HIV pandemic, however, the article recommends a much faster and better-funded response.

The inescapable fact that there is still this need after more than a decade of work and hundreds of millions already invested seems unassailable. Yet, the promise of big and desperately needed new investments across the AIDS vaccine board has generated lively and contentious public and private comment in the ensuing months while work has proceeded under the informal auspices of the Gates Foundation to move what is now known as "the Enterprise" forward.

AVAC believes that the key to success of this enterprise will be if its sponsors remain unsatisfied with incremental improvements across the field—and instead strike a balance of exploratory and developmental research with bold funding decisions that finance genuine gaps in the current programs. That would truly energize the effort, not just inside the small world of AIDS vaccines research, but for the outside world as well.

The all-star team

To begin to understand the Enterprise, it helps to first take a look at the original authors. Seven are listed before the names go alphabetical:

- Klausner and Helene Gayle of the Bill & Melinda Gates Foundation.
- Seth Berkley, President of the International AIDS Vaccine Initiative (IAVI).
- Four leaders from the National Institutes of Health (NIH) and its programs: Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID); Larry Corey, Principal Investigator of the NIH-funded HIV Vaccine Trials Network (HVTN); Gary Nabel, Director of the Vaccine Research Center (VRC); Barton Haynes, Chair of the AIDS Vaccine Research Working Group (AVRWG).

Additional luminaries include: David Baltimore, former AVRWG Chair and Harold Varmus, former NIH Director; Julie Gerberding, director of the Centers for Disease Control and Prevention (CDC); Michel Kazatchkine, director of the French Agence Nationale de Recherches sur le Sida (ANRS);

Peter Piot, Director of the Joint United Nations Programme on HIV/AIDS (UNAIDS); Jose Esparza, then Director of the World Health Organization (WHO) HIV Vaccine Program who has since moved to the Gates Foundation to work on this project; and a wide range of scientific and international leaders in the field. In fact, the list of authors and their affiliations fill more than five column inches of Science small print.

Thus, this is a wide-ranging group headed by the leaders of the largest and most influential AIDS vaccine development programs in the public sector. If this group says there's a need for a Global HIV Vaccine Enterprise, that's saying something. These are the very people we've entrusted with developing such a vaccine, and the very people who have the power and resources to influence it most.

A loose but grand structure is proposed

In the article, the authors say they hope to prompt an international dialogue about options to achieve the goal of developing a safe and effective AIDS vaccine in the shortest time possible by defining basic principles for the Enterprise. The authors present a number of ideas:

- AIDS vaccine development centers.
- Vaccine science consortia.
- Development of dedicated HIV-1 vaccine manufacturing capacity.
- Establishment of standardized preclinical and clinical laboratory assessment.
- Expansion of an integrated international clinical trials system.
- Optimizing interactions among regulatory authorities.
- Coordinating international AIDS vaccine development.

The authors invoke the Human Genome Project model, saying that the time is right for the major scientific and product-development leaders, and stakeholders involved in the global AIDS vaccine development enterprise to come together in an analogous way—with particular attention to international aspects and with full participation of the developing world where the pandemic rages.

With the caveat that this enterprise should consider multiple structural models to accomplish its goals, the authors propose developing a road map for this new Global HIV Vaccine Enterprise that 1) prioritizes the scientific challenges and product development efforts, 2) sets a rapid implementation plan, and 3) identifies the resources needed. That work is now underway.

Progress to date: brave new world

In August 2003, the authors invited about sixty key researchers to a retreat at Airlie House in Virginia to further develop the enterprise concept. There, five working groups defined their portion of the Enterprise, two co-chairs were identified for each group, and a coordinating committee was announced (see page 50). A report and terms of reference for making the blueprint were made available to participants so they could continue their work.

The Airlie House meeting was a way to get further input from experts in each of six areas—vaccine discovery, product development, measurements, manufacturing, clinical trials capacity, and global regulatory and licensing—share those ideas, and begin to explore what initiatives would move the field forward. The retreat stated a "moral commitment" of participants to work in alliance and participate in implementation of a strategic plan. It also began to vet a set of ideas for initiatives that could fundamentally transform what people are able to accomplish themselves and together. This is exciting stuff for those who advocate for an AIDS vaccine.

Now work is underway to elaborate and hone the working groups' ideas into specific proposals and initiatives that can be agreed upon—defined well enough to be achievable in predictable time frames, yet open ended enough to be amenable to the scientific process of change and development. Not a Manhattan Project, not a man-on-the-moon drive, not an empire building exercise. Something more like the Human Genome Project, whose members have been advising and consulting with the group. A kinder, gentler form of big science.

Not terribly long after the publication of this report we can look forward to an articulated plan with state-of-the-art scientific goals, programmatic recommendations, and—everyone hopes—a new influx of funds and activities. That, after all, is what the original article (and all this work) calls for.

Invoking the Enterprise

While all this has been going on, a number of individuals have mentioned or talked about the Enterprise publicly and from varying angles. Though nothing has been formally announced, these invocations give a good indication of the machinations and adjustment inherent in such an endeavor—and the sense of apprehension and importance it evokes.

First, Anthony Fauci. In his plenary and press conference on AIDS Vaccine Policy and Science at the Vaccines 2003 Conference in New York last September, Fauci unveiled the new government AIDS vaccine collaboration, Partnership for AIDS Vaccine Evaluation (PAVE). Also announced were inter-agency agreements among the US Department of Health and Human Services agencies, which, Fauci

said, would in turn embrace other public and private sector partners that he specifically and particularly included as "an important component of the recently proposed Global HIV Vaccine Enterprise." This complex, ungrammatical, and somewhat contradictory relationship of including and being included illustrates the ambiguities of how the largest investor in AIDS vaccine research and development, the biggest most powerful government in the world, and the largest private foundation funded by the world's richest man are engaging with each other.

Next up was Klausner, invited to speak to the HIV Vaccine Trials Network at its October full group meeting in Seattle. In a way, it was the mirror image of Fauci's speech. The Gates Foundation Global Health Executive Director, first author of the Enterprise vision, was presenting it to a group of government investigators and sites already engaged in a variety of clinical trials of private industry and public/private/academic product-development partnerships. Clearly the HVTN participants had concerns about the inclusiveness of the Enterprise, since it is largely a top-down effort to remake AIDS vaccine research and development. Klausner spoke with enthusiasm about how the work of clinical networks could be enhanced, and how more and better products could be developed with feedback from clinical trials while feeding into them—another complex two-way relationship.

The Conference on Retroviruses and Opportunistic Infections at San Francisco in February was the next opportunity to continue the public discussion about the yet largely undefined Enterprise. This meeting draws researchers and clinicians who are more involved in HIV disease progression and treatment and more sanguine about AIDS vaccines. There are always a number of vaccine sessions, however, and the two most prominent invoked the Enterprise, which at this stage was being developed behind closed doors.

Ronald Desrosiers of the New England Regional Primate Research Center at Harvard Medical School, whose arguments have been described in earlier chapters of this report, took to the podium and delivered a sharp critique of the AIDS vaccine field. Desrosiers is, in fact, an active and valuable member of the Enterprise planning group; as is Susan Buchbinder, head of HIV programs at the San Francisco Health Department, who gave a balancing plenary at the same meeting on the lessons learned and future directions of AIDS vaccine efficacy trials—the other end of the so-called research and development pipeline. She concluded her talk by invoking the Enterprise with a doctored picture from *Star Trek*. She expressed hopes that it would help make iterative, mid-size efficacy trials an integral part of product screening, refinement and scientific development—as an alternative to larger, hit-or-miss licensing trials more appropriate for a more mature field.

Then most recently, and a full eight months after the original article, Science published two letters from eminent, non-contributing European scientists responding to two very different aspects of the original

Enterprise piece. The Nobel-winning immunologist, Rolf Zinkernagel from the Institute of Experimental Immunology in Zurich, flat-out states that we have no idea how to make a vaccine against a group of diseases that includes HIV—so an influx of investment would serve no purpose "if current accepted paradigms are not drastically changed," which is not unlike Desrosiers' perspective. Even more extremely, Zinkernagel proposes that this is such a long-term scientific task that the epidemic needs to be controlled by behavioral, therapeutic and epidemiological means. A similar argument was made by Chip Schooley at the Conference on Retroviruses in a talk on the future of antiviral therapy subtitled, "What If There Is No Vaccine?" In fact, a new clinical trial is even testing use of the anti-viral tenofovir as a prophylactic medication.

Hans Wolf from the University of Regensburg, Germany, takes issue with the need for a new enterprise at all. He describes the efforts of the European Commission to organize AIDS vaccine research and development and proposes that the United Nations serve to coordinate existing efforts.

Apparently, no good idea goes unopposed—and the buffeting that the proposed Enterprise is undergoing may be a sign of its vitality. Yes, the authors reply, "the development of an HIV vaccine is one of the most complex scientific challenges that modern biomedical research is confronting." Yes, success "will depend on the ability of all," and yes, they are "delighted that this international dialogue is taking place."

AVAC's history with the Enterprise

Chris Collins, then Executive Director of AVAC, was asked to sign on to the Enterprise article and had input on its final form. He also attended the Airlie House meeting. Immediately following, AVAC formally made the following points to the organizers:

As a citizen's advocacy group, AVAC believes several additional points are particular concerns, offered in the spirit of collaboration and with our offer to help in any way we can. Our thoughts fall into three categories: the social context, leadership on clinical trials, and engaging industry. We discuss them in this order because we believe the social context and clinical trials will be the keys to introducing new products down the road and maintaining and enhancing public and private interest and support.

1. **The social context.** Success in AIDS vaccine research is sure to require sustained public support for research as well as recruitment and retention of volunteers for years to come. Attention to the social context is crucial. AVAC believes at least four principles are important to success: fostering high standards for clinical research, leaving tangible benefits for communities, involving civil society and operating with an appreciation of global access issues.

2. **Leadership on clinical trials.** Clinical research on current promising products needs to be accelerated even as the (AIDS vaccine) enterprise is breathing new life into product development. The practical

and scientific benefits of obtaining efficacy data on cellular immunity mediated vaccines as soon as possible cannot take second place while we hunt for a more perfect vaccine. Like the Salk and Sabin controversy, this would be a waste of scientific energy and credibility.

One deficit in the field is relative lack of pressure—from the public, politicians, public health leaders, and sometimes scientists—to run efficacy trials. The Enterprise can remind the world about the risk-reward of clinical research in this field and the need to take decisive actions in order to get results. The Gates Foundation is known for its pragmatic approach to health emergencies and, in the case of AIDS vaccines, support of genuinely iterative efficacy trials is the most immediate and practical current activity.

3. **Engaging industry.** Industry representatives have emphasized the potentially crucial convening role of the Enterprise as a place to discuss assay and other research standardization that can make data more comparable across the field. That would be an excellent entry point for further collaboration. Also there is the concept of the Enterprise itself: if it is positioned as a visible global leader in health research, the Enterprise can produce public relations benefits for companies that participate.

The Enterprise as envisioned would bring much needed collaboration, energy, attention and resources to AIDS vaccine research. AVAC encourages the Enterprise to also make a contribution on the policy, legal and regulatory issues involved in moving forward.

AVAC invokes the Enterprise

We at the AIDS Vaccine Advocacy Coalition would now like to invoke the Enterprise ourselves by making the following additional points:

- If we really want to get an AIDS vaccine faster, this kind of cooperation and influx of funds has to happen.
- Its success will require giving up some autonomy on the part of each and every organization involved, and in pulling new researchers, ideas and energy into the system.
- The entire AIDS vaccine (small E) enterprise needs to reestablish its sense of urgency similar to what we've recently witnessed for SARS, avian flu, and BSE.
- The AIDS vaccine enterprise needs to acknowledge and take account of its place and proportion in relationship to other AIDS control and global health efforts. The Gates Foundation Global Health program is the ideal convener for such a sea-change among vaccine researchers.
- The role of private money needs to be tempered with public, academic and consumer input.

In March, AVAC talked with Helene Gayle who has direct responsibility for the project at the Gates Foundation. She says that every meeting toward the Enterprise gives "the sense that this is so necessary" and she's very pleased that it is energizing the scientific community about the overwhelming importance of this issue.

We can look forward to a fall announcement of the Enterprise plan. If it's a compelling plan, is a platform for sharing, and there's a sense it can accelerate the effort, it will be impossible to ignore the Gates Foundation and others who have already joined into the process. Now more than ever, especially in the face of current doubts and uncertainties, such an enterprise is necessary. Courage, verve and legitimate optimism are the order for the day.

Stay tuned.

THE GLOBAL HIV VACCINE ENTERPRISE STEERING COMMITTEE

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LABORATORY STANDARDIZATION
David Montefiori, *Duke University*
Giuseppe Pantaleo, *University of Lausanne*

REGULATORY/LICENSING/IP
Gladys Monroy, *Morrison & Forester LLP*
Helen Rees, *University of the Witwatersrand*

CLINICAL TRIALS CAPACITY
Nzeera Ketter, *IAVI*
Judith Wasserheit, *HVTN*

HVTN – HIV Vaccine Trials Network
NIH – US National Institutes of Health
IAVI – International AIDS Vaccine Initiative
VRC – Vaccine Research Center

[1] Formerly of the WHO-UNAIDS HIV Vaccine Initiative
[2] Formerly of Merck & Co.

FOOTNOTES

1 Berkley, S., "Thorny issues in the ethics of AIDS vaccine trials," The Lancet, vol. 362, p. 992, Sept. 30, 2003.

2 The Council for International Organizations of Medical Science (CIOMS), in its ethical guidelines for biomedical research, states: "In general, the research project should leave low-resource countries or communities better off than previously or, at least, no worse off. It should be responsive to their health needs and priorities in that any product developed is made reasonably available to them, and as far as possible leave the population in a better position to obtain effective health care and protect its own health." 2002.

3 Allen, Susan, poster presentation, AIDS Vaccine 2003 Conference, New York, Sept., 2003.

4 "Ethics, Antiretrovirals and Prevention Trials: An Online Debate," IAVI Report, vol 7, no. 3, Sept. 2003–Jan. 2004, p. 8.

5 Fox, Matthew P. et al., "The Impact of HIV/AIDS on labour productivity in Kenya," Journal of Tropical Medicine and International Health, vol. 9, no. 3, pp. 318-324, March 2004.

6 Lecture, University of Pennsylvania Center for AIDS Research, Feb. 19, 2004.

7 The World Health Organization defines adolescents as youth aged 9 to 19, which includes preadolescents. For HIV vaccine research, this is the most useful definition because ideally a vaccine should be given before a young person becomes sexually active. US government agencies and UNAIDS classify adolescents as youth and young adults aged 15 to 24.

8 Safrit, Jeffery, "HIV Vaccines in Infants and Children: Past Trials, Present Plans and Future Perspectives," Current Molecular Medicine, 2003, vol. 3, p. 303. Of the 110 AIDS vaccine trials that had been completed by 2003, only two included children as part of their focus, Safrit reports.

9 Lewis, Stephen, Special UN Ambassador to Africa on HIV/AIDS, keynote address, 11th Conference on Retroviruses and Opportunistic Infections, Feb. 8, 2004, San Francisco, CA.

10 US Department of State, 2004, "The President's Emergency Plan for AIDS Relief: US Five-Year Global HIV/AIDS Strategy," p. 25.

11 Weinstock, H., Berman, S., Cates, W., "Sexually Transmitted Diseases Among American Youth: Incidence and Prevalence Estimates, 2000," Perspectives on Sexual and Reproductive Health, vol. 36, no. 1, January/February 2004.

12 Society of Adolescent Medicine, "Guidelines for Adolescent Health Research," Journal of Adolescent Health, 2003, vol. 33, p. 398.

13 The moral foundation for the ethical conduct of medical research involving human subjects has evolved from the Nuremberg Code (1947), the Universal Declaration of Human Rights (1948), and the Declaration of Helsinki (1964) issued by the World Medical Association. In the US, the guiding document is the federal government's "Belmont Report" (1978) issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Globally, the guiding document is the International Ethical Guidelines for Biomedical Research Involving Human Subjects (1993) issued by the Council for International Organizations of Medical Sciences (CIOMS.) Additional guidance on vaccine research in particular has been provided by the Joint United Nations Programme on HIV/AIDS (UNAIDS) in "Ethical Considerations in HIV Preventive Vaccine Research (2000) and by the World Health Organization (WHO) in "Ethical Considerations Arising from Vaccine Trials Conducted in Paediatric Populations with High Disease Burden in Developing Countries," (2002).

14 WHO, op cit., p. 16.

15 The Washington, DC meeting of April 2003 was hosted by the Forum for Collaborative HIV Research based at George Washington University.

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