

GETTING THE GLOBAL HOUSE IN ORDER

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 global house

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 Efthya 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.

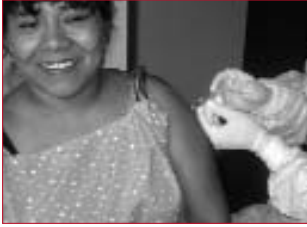
Correlate 7: Dedicated AIDS vaccine production plant capable of manufacturing sufficient quantities of vaccines for small and mid-size trials.

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			
<i>Phase II/B and Phase III Trials</i>			
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.