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Spotlight

A STEP back?

Additional data released from the STEP trial raises many questions

Clinical trials are always complex, but according to Mark Feinberg of Merck, the recent STEP trial may be an extraordinary case in this regard. "I've never seen more complicated data emerge from a study in any field that I've witnessed."

The public got a taste of this complexity at an open session of the HIV Vaccine Trials Network (HVTN) meeting on November 7 in Seattle. There, Merck, along with several representatives from the HVTN and the National Institute of Allergy and Infectious Diseases (NIAID), released mounds of additional data from the STEP trial. This Phase IIb test-of-concept trial evaluated the safety and efficacy of Merck's AIDS vaccine candidate, known as MRKAd5. This candidate uses a common cold virus (adenovirus serotype 5 or Ad5) as a vector to deliver fragments of HIV to the immune system, hopefully triggering an immune response against HIV. Since immunizations were stopped in this trial on September 21, investigators have spent many sleepless nights analyzing data and interpreting this pivotal study.

And the results, based on data from all 3,000 volunteers, show that even though the vaccine candidate induced immune responses against HIV, these were not effective at either preventing HIV infection or in reducing levels of the virus in individuals who became HIV infected through exposure to the virus despite vaccination. In the STEP trial, the study's sponsors revealed in Seattle, there were 49 HIV infections overall in the vaccine group and 33 among those who received placebo as of October 17 (see *Primer*, this issue).

Moreover, researchers reported a worrisome trend towards a higher number of HIV infections among some sub-groups of individuals who received the vaccine candidate, compared to those who received injections of inactive placebo. The vaccine candidate itself did not cause HIV infection but in individuals with higher levels of pre-existing immunity to the Ad5 vector, there tended to be more volunteers who received the vaccine and later were infected with HIV through exposure to the virus (see Table 1, next page). Pre-existing immunity to the Ad5 vector occurs because individuals are exposed naturally to this commonly-circulating cold virus and generate antibodies against it. The levels of antibodies against Ad5 vary greatly between individuals. In individuals with what is considered a high level of Ad5 antibody (≥200), there were 21 infections in vaccinees compared to 9 in placebo recipients. "This difference is clinically important for at least one subgroup," says Keith Gottesdiener of Merck. "I don't really need any statistics to make a declaration that it's an important factor to take into consideration."

The explanation for this difference is still not clear. Steve Self, a biostatistician with the HVTN and the Fred Hutchinson Cancer Research Center who analyzed this data says, "There is great uncertainty about some of these trends." Regardless, researchers are taking it seriously. "When looking at potential harm we have to pay close attention," says Susan Buchbinder of the University of California in San Francisco and principal investigator of the STEP trial.

For many, this was an unanticipated outcome. "It was a surprise to us that there were actually more infections in vaccinees than in placebo recipients," says Mike Robertson of Merck. "We didn't expect that," says Peggy Johnston of the Division of AIDS at NIAID.

There are several possible factors that could contribute to this trend, including geographical region, age, and circumcision status of the volunteers. At this stage of the analysis, the trend towards increasing rates of HIV infection among vaccinees persists even after factoring in all of these potential differences, says Self. But it is possible that there is a yet unidentified difference between the groups

In This Issue

Special coverage of STEP and Phambili trials

	Ad5 antibody levels			
	Low (<18)	Medium-low (<18<Ad5≤200)	Medium-high (200<Ad5≤1,000)	High (Ad5>1,000)
Vaccine	20/382	8/140	14/229	7/163
Placebo	20/394	4/142	7/229	2/157

Table 1. Number of HIV infections according to Ad5 antibody levels. *Number of HIV-infected individuals out of the total number of vaccine and placebo recipients, according to increasing levels of Ad5 antibodies. This data from the STEP trial was presented at the HVTN meeting by Mike Robertson of Merck.*

that received the vaccine candidate or the placebo.

"There are going to be a lot of different hypotheses that need to be tested to try and understand what went wrong; why this wasn't efficacious and why there was a trend toward more infections with vaccine than the placebo," says Bruce Walker of Harvard Medical School in Boston, who is leading a team of scientists who will analyze the data from the STEP trial. But the devil is in the details and until the full analysis of this trial is complete, and maybe even after that, there will be many unanswerable questions. "We were entering into this thinking that we will find an answer, but even that's not absolutely guaranteed," Walker adds.

Searching high and low

The STEP trial—also known as HVTN 502 and Merck V520-023—was co-sponsored by Merck and NIAID. It was a Phase IIb test-of-concept trial of MRKAd5, a candidate that induces cellular immune responses ($CD4^+$ and $CD8^+$ T cells) rather than antibodies against the virus (see *VAX* March 2004 *Primer* on *Understanding the Immune System, Part II*). Antibody responses are how most, if not all, licensed vaccines provide protection. This study involved 3,000 healthy volunteers at high risk of HIV infection at HVTN sites in North and South America, the Caribbean, and Australia. All volunteers were scheduled to receive three shots of placebo or vaccine, which contains a mix of Ad5 vectors carrying different fragments of HIV known as immunogens. A companion study, known as Phambili, with the same vaccine candidate was also conducted in South Africa (see *Removing the blindfold* in *Global News*, this issue).

The original plans for the STEP study only included 1,500 individuals with low levels of Ad5 antibody (less than 200) because researchers thought that having pre-existing Ad5 immunity might hinder immune responses induced by the vaccine candidate to HIV. But after the trial began, data emerged from earlier trials showing that Ad5 antibody levels did not compromise immune responses to HIV as much as was initially expected. In July 2005, seven months after the STEP trial began, the protocol was amended to include a second group of 1,500 volunteers who had what is considered high Ad5 antibody levels (greater than 200).

Immunizations in the STEP trial were halted on September 21 after the trial's independent data safety monitoring board (DSMB) reviewed the for the first time data from volunteers in the sub-group of 1,500 volunteers with low Ad5 antibody levels (see *VAX* June 2007 *Primer* on *Understanding Data Safety Monitoring Boards* and *VAX* September 2007 *Special Report*). The DSMB concluded that based on the breakdown of infections at this time—19 in the vaccine group and 11 in placebo recipients—it was futile to continue immunizations because the vaccine was not effective.

After this, researchers at Merck and NIAID decided to proceed with analysis of the data collected up to that point, according to Robertson, who warns that all these interpretations should be taken "with a big grain of salt." When immunizations were stopped, only one HIV infection had occurred within the 1,150 women enrolled in the trial and this volunteer received placebo, not vaccine. All of the subsequent analyses, including the breakdown of infections by Ad5 antibody levels, were therefore conducted on data collected from the 1,850 male volunteers only.

Heads or tails

Despite the massive amount of data that has already been interpreted and presented on the STEP trial, there is much more work to be done. One of the leading questions researchers will set out to answer is why the vaccine was not efficacious.

The results collected so far show that the immune responses induced by the vaccine against HIV were similar or higher in the group with low Ad5 immunity to those seen in previously conducted trials. The immune responses in trial volunteers were measured by interferon (IFN)-γ ELISPOT assay (see *VAX* August 2007 *Primer* on *Understanding Immunogenicity*). "The lack of efficacy is not explained by sub-optimal immune responses," says Robertson.

Researchers will now look more closely at the immune responses induced by the vaccine candidate. "We had evidence of IFN-γ production but that doesn't tell you if the cells would kill virus-infected cells, so we will obviously be looking a little bit more at the function of the immune responses," says Walker. These results may also shed light on whether or not the IFN-γ ELISPOT assay is a useful tool for assessing the relative efficacy of AIDS vaccine candidates in the future.

Sizing it up

Another issue raised by the STEP trial is the use of Phase IIb test-of-concept trials to evaluate the efficacy of AIDS vaccine candidates (see *VAX* September 2005 *Primer* on *Understanding Test of Concept Trials*). The idea of using trials that are smaller and less expensive than Phase III efficacy trials, which typically involve 10,000 or more volunteers, has become fashionable in the field. These preliminary efficacy trials give researchers a quick read on whether or not a candidate is likely to protect against HIV infection, or to provide some level of partial protection that could limit disease progression in volunteers who become HIV infected through exposure to the virus despite vaccination. The STEP trial was the first to use a Phase IIb trial to evaluate an AIDS vaccine candidate—though similar trials have been used for other vaccines—and it successfully showed that this design can yield earlier results with fewer volunteers than a full Phase III trial. "The STEP study trial design was an enormous success," says Steve Self, a biostatistician with the HIV Vaccine Trials Network (HVTN).

Many people praised Merck for deciding to evaluate their candidate in a Phase IIb test-of-concept trial and for planning an early analysis by the data safety monitoring board. "It enabled us to get an answer as quickly as possible," says Peggy Johnston of the Division of AIDS, part of the National Institute of Allergy and Infectious Diseases (NIAID). "That, in hindsight, proved to be an excellent decision." Andrew McMichael of Oxford University agrees. "Maybe we should do more [such] trials rather than the full blown 10,000-person Phase III trial."

But some argue that even smaller trials, an idea known as screening-test-of-concept or STOC trials, could provide preliminary efficacy data for candidates faster yet. This novel clinical trial concept has been championed by IAVI as a way to conduct rapid, less costly trials in far fewer volunteers. An article describing the design of STOC trials was recently published in the scientific journal *AIDS.* These trials would involve 500 to 1,000 volunteers in areas with high HIV incidence, compared to the 3,000 participants in the Phase IIb STEP study or the 8,500 volunteers in the original plans for the PAVE 100 trial. "We at IAVI feel that it's important to move quickly and be as efficient as possible in collecting clinical data to guide the field," says Pat Fast of IAVI.

But the STOC trials will also provide more limited information than can be collected from larger Phase IIb studies. The current STOC design would not allow researchers to determine if a candidate protects against HIV infection. It would only allow researchers to detect a difference in viral load in volunteers who do acquire HIV, despite vaccination.

"If we think that there may be differences in acquisition of infection, then that's not the design to do," says Johnston. But many researchers think the best possible hope for AIDS vaccine candidates that induce cellular immune responses, and not antibodies against HIV, is a reduction in the quantity of virus or viral load in vaccinated individuals if they become HIV infected. Especially now, given the results of the STEP trial. Still some are cautious. "We still don't know if the basic assumption is correct," says José Esparza of the Bill & Melinda Gates Foundation. "After the current results, we need to be extra careful with our assumptions."

Ian Gust of the University of Melbourne and a member of IAVI's board of directors, says that both Phase IIb and STOC trials have validity, but he views the use of STOC trials as an attempt to move the field forward as rapidly as possible.

There are also many additional studies planned. Researchers will analyze the viruses that infected some of the volunteers and see how they varied from the HIV immunogens included in the vaccine candidate. This work may help researchers determine if this candidate failed because the immunogens selected did not protect against diverse strains of HIV. There are also plans to sequence the genomes of the volunteers to identify any genetic characteristics that might have enhanced susceptibility to HIV or, conversely, provided protection to placebo recipients. "Some of those things will take months and some may take longer than that," says Walker.

Researchers are now also hard at work trying to determine any role the vaccine may have had in increasing susceptibility to HIV infection in some individuals. There is great uncertainty about this, but there are some possible biological explanations and researchers must now sort out their plausibility. Julie McElrath of the Fred Hutchinson Cancer Research Center plans to continue studying the $CD4^+$ T cell responses induced in the volunteers that became infected with HIV to see if these provide any clues.

Broader strokes

Based on the complexity of the data generated by this trial, it may be a while until the results are fully understood. For now, most agree it is too early to close the door on vaccine candidates that induce cellular immune responses. "[The] STEP results proved that this product failed and should not be construed as indicative that all adenoviral vectors or other viral vectors will fail," says Johnston.

But until any possible association between Ad5 immunity and increased susceptibility to HIV is ironed out, most researchers are urging caution. "Any further trials of adenoviral vectors should be done very cautiously," says Johnston.

PAVE 100 was the next Phase IIb test-of-concept trial on tap with an Ad5-based candidate—it was scheduled to begin just weeks after Merck and NIAID announced that immunizations in the STEP trial were stopped. The original plans for this NIAID-sponsored 8,500-person trial were to test the safety and efficacy of a prime-boost combination of two vaccine candidates administered sequentially. One uses DNA to deliver HIV immunogens and the other uses an Ad5 vector, which is slightly different than Merck's, to deliver a different set of HIV immunogens. Both of these candidates were developed at the Vaccine Research Center (VRC), part of

NIAID, and the trial was planned in collaboration with the HVTN, IAVI, and the US Military HIV Research Program (USMHRP). This same regimen was also to be tested in a Phase II trial, known as V002, conducted by IAVI in Rwanda, Kenya, Uganda, and Zambia. After immunizations in the STEP trial were halted, the opening of both of these trials was postponed.

"There are substantial differences between the Merck product and the VRC product," says Gary Nabel, director of the VRC. One difference is the prime-boost combination of two different candidates. In both preclinical and clinical studies, researchers at the VRC report that this combination induces different immune responses than when an Ad5-based candidate is administered alone.

But when the latest data from the STEP trial was released at the HVTN meeting, researchers began grappling with additional questions about how, or if, to proceed with the PAVE 100 trial. Some groups, including the AIDS Vaccine Advocacy Coalition (AVAC), are now advocating that other efficacy trials should be postponed until "definitive conclusions" can be drawn about the results of the STEP trial. But many researchers think it is still imperative to test other candidates. "I certainly feel there are ways to go forward safely, but we have to do that together," says Scott Hammer of Columbia University and chair of the PAVE 100 protocol team.

Hammer and his colleagues on the PAVE 100 team will be meeting soon to discuss possible changes to the trial design. "It has to be amended in light of the STEP trial," says Hammer. "We do not have the details of that amendment in place. The regimen won't change, but the study design might." Some possible alterations might involve the populations enrolled in the trial or the way the data is monitored while the trial is underway to ensure the safety of the volunteers.

Conference Coverage

Giving it their best shot

Researchers gathered recently to discuss the challenges of developing and delivering life-saving vaccines

You've probably heard the parable about the man who was upset that he had no shoes until he met someone without feet. This came to mind during a meeting held October 8-13 in Cape Town, South Africa that brought together vaccine researchers from different disciplines to discuss developing and delivering life-saving vaccines throughout the world. Commiseration, as well as a sense of shared commitment, pervaded the meeting as researchers from various fields shared ideas and approaches to developing vaccines against three of the world's biggest killers—tuberculosis (TB), malaria, and HIV/AIDS.

This inaugural Keystone Symposium on the Challenges of Global Vaccine Development explored many of the common challenges and creative approaches, as well as some of the overlap in the strategies being investigated to combat all three diseases. The conference, which was held in conjunction with the annual meeting of the Bill & Melinda Gates Foundation's Grand Challenges in Global Health initiative, also had an added focus on efforts to successfully deliver vaccines. Tachi Yamada of the Gates Foundation says that although the foundation has always been committed to discovery, "we also have to think about how to deliver these exciting new products."

Boosting spirits

The gathering for the Keystone conference occurred just a few weeks after the initial announcement that Merck and the National Institute of Allergy and Infectious Diseases (NIAID) stopped immunizations in a large Phase IIb test-of-concept trial, known as the STEP study, because Merck's adenovirus serotype 5 (Ad5)-based AIDS vaccine candidate (MRKAd5) was not effective. At the same time, enrollment and immunizations in the Phambili or HVTN 503 trial, which was testing the same vaccine candidate in South Africa, were suspended—they have since been stopped entirely (see *Removing the blindfold* in *Global News*, this issue). These were some of the most hotly discussed issues both in and out of the meeting.

Carolyn Williamson of the University of Cape Town told the audience assembled for her plenary session that AIDS vaccine researchers, "really have to go back to the drawing board." But those from other disciplines were able to provide some fresh perspective. "I wouldn't be too downbeat," says Adrian Hill of Oxford University, who is currently developing possible vaccine candidates against malaria. "We've had candidates fail for malaria about 15 times."

Recently, there was some good news in the malaria vaccine field. The most advanced of a slew of candidates is being developed by GlaxoSmithKline Biologics in Belgium, and a recently completed Phase II safety study in Mozambique showed that it was 65% effective at protecting infants from malaria (*Lancet* **370**, 1523, 2007). Phase III efficacy studies with the candidate, known as RTS,S or Mosquirix, will begin next year, and if similar results are observed, the first potentially licensable malaria vaccine may be available as early as 2011 (see *VAX* May 2005 *Spotlight* article, *Malaria vaccines: Renewed promise*).

But over the last few years, researchers working on malaria vaccines have also developed a heightened interest in using viral vectors to target the disease during a different stage of the parasite's lifecycle when cellular immune responses are critical to controlling disease progression.

Researchers, including Hill, have tested various viral vectors in prime-boost combinations, including MVA and fowlpox-vector-based malaria vaccine candidates. When clinical trials were conducted in the UK and the Gambia with the fowlpox/MVA

prime-boost combination, these candidates induced high levels of immune responses in human volunteers. But when this same strategy was tested in a Phase IIb clinical trial in Kilifi, Kenya, it showed no efficacy. Hill says the immunogenicity of the vaccines was markedly lower in areas where malaria transmission occurs more frequently (see *VAX* August 2007 *Primer* on *Understanding Immunogenicity*). He speculates that this may be a recurring problem for malaria vaccines in high-burden areas, where the vaccines could potentially have the greatest impact.

Following this failure, researchers set out to find a better prime-boost combination. This led them to explore using adenovirus as a vector. "Adenovirus vectors have in many ways been the high-flying vectors," says Myron Levine of the University of Maryland. Hill's group at Oxford compared the immunogenicity of different serotypes of human adenoviruses with simian, or monkey, versions and found that a serotype of adenovirus that infects chimpanzees (AdCh63) induced even better immune responses than human Ad5.

Hill is currently preparing to begin a Phase I safety trial to test an AdCh63/MVA prime-boost combination in humans. "There's a lot of interest in adenovirus vectors for malaria at this moment," says Hill. Chimpanzee adenoviruses have also been of keen interest to AIDS vaccine researchers, but as of yet, no candidates have been advanced into clinical trials.

Before and after

Without question, there are still substantial scientific challenges facing the development of new vaccines against the most pervasive global health threats. "Science is the critical ingredient for success," says Regina Rabinovich of the Gates Foundation, who provided the opening keynote address at the Keystone conference. "You can't get there without it."

But science is not the only barrier. There are other challenges that occur after effective vaccines are licensed for public use, including manufacturing capacity and vaccine production, as well as vaccine delivery and administration. "Finding a new way of creating a vaccine is only half the issue," says Duncan Steele of the World Health Organization (WHO). Despite high-flying success stories of late, like the licensure of effective vaccines against human papillomavirus (HPV; see *VAX* February 2006 *Spotlight* article, *Cervical cancer vaccines*), there are still many issues to resolve about how best to deliver these vaccines to the world's poorest people. If these aren't worked out before vaccines are licensed, it can result in a sometimes lengthy lag time between the introduction of vaccines in rich and poor countries.

> ***I wouldn't be too downbeat. We've had candidates fail for malaria about 15 times.***
>
> **Adrian Hill**

Immune responses to vaccines can also vary in different populations, so even when a vaccine is delivered successfully, it still may not provide optimal protection to everyone—there is documented evidence of vaccines inducing varying levels of antibody responses in different regions of the world. For this, critical lessons can be learned from the delivery of already licensed vaccines. Overall, vaccines that are administered orally tend to induce greater immune responses in industrialized nations.

The responses induced by the live oral cholera vaccine are just one example of this phenomenon. Greatly diminished immune responses to this vaccine have been observed in Brazil, in children of low socioeconomic status in Peru, and in Indonesia, where a higher dose of the vaccine is required to achieve similar levels of immunity. For rotavirus, several of the earlier live oral candidates failed to work at all when tested in developing country populations (see *VAX* July 2006 *Spotlight* article, *Vaccines enter battle against an intestinal virus*).

But some vaccines work better in developing countries, Levine says. The vaccine against haemeophilus influenzae type b, or Hib, a bacteria that can cause a potentially fatal brain infection in children, is one example of this phenomenon. Only 10% of US infants reach the level of antibodies required for protection against Hib after a single vaccination, while 29% of infants in Chile reached this antibody level after one shot. Based on this observation, the government funded a study to evaluate fractional or partial doses of the vaccine, which at its full dosage cost more than all of the vaccines that were currently part of the country's immunization program.

This study showed that in Chile there was no difference between administering a third, a half, or a full dose of the Hib vaccine. The Chilean government never used fractional doses of Hib vaccine because its cost was eventually covered by the Global Alliance for Vaccines and Immunization (GAVI), now the GAVI Alliance. But this case suggests it may be possible to get equivalent protection in some populations with less vaccine and, as the cost of newly-licensed vaccines soars, this could translate into substantial savings. Levine suggested that studies to quantify the level of antibody required for protection for new and expensive vaccines, like those against HPV, are vital so that determinations about the dose required for protection can also be made.

One thing that is certain is the massive public health benefit that vaccines can have. Since the creation of GAVI in 2000, the WHO estimates that the introduction of vaccines in developing countries has prevented 2.6 million deaths. But these dramatic effects come with a hefty price tag. The WHO and the United Nations Children's Fund (UNICEF) estimate that GAVI will require between US$226 million and $778 million between 2011 and 2015 to continue funding vaccination programs in its target countries.

Global News

Removing the blindfold

On October 23, immunizations and enrollment in a second National Institute of Allergy and Infectious Diseases (NIAID)-sponsored trial called Phambili, or HVTN 503, were permanently stopped based on a recommendation from that trial's independent data safety monitoring board (DSMB). Phambili's DSMB also recommended at this time that study investigators unblind all participants (see *Primer*, this issue), telling them whether they received vaccine or placebo, and counsel them about the possibility of an increased susceptibility to HIV infection due to the vaccine (see *Spotlight* article, this issue). The vaccine candidate cannot cause HIV infection, and it is too soon to determine if there is any real link between the receipt of the vaccine candidate and an enhanced risk of HIV infection in some individuals, but investigators are proceeding cautiously.

The Phambili trial was a companion study to the STEP trial testing the same vaccine candidate, developed by Merck, at sites in South Africa (see *Spotlight* article, this issue). One goal of the Phambili trial was to see if the candidate vaccine, which included clade B HIV fragments to induce an immune response against the virus, would be effective in areas where the most commonly transmitted virus is clade C HIV (see *VAX* July 2006 *Primer* on *Understanding HIV Clades*). The Phambili trial was also conducted for the most part in heterosexual volunteers—unlike the STEP trial which enrolled primarily men who have sex with men—and was to enroll mostly women, who are at very high risk of contracting HIV in South Africa.

The Phambili DSMB had already suspended the trial a month earlier, immediately after further immunizations in the STEP trial were halted. At this time only 801 volunteers of a planned total of 3,000 were enrolled, 58 of whom had received all three vaccinations. Still, as news of the suspension reached the Phambili trial sites it felt like "stopping a steam train," says Glenda Gray of the Perinatal HIV Research Unit at the University of Witwatersrand and principal investigator of this trial. At that time, the sites throughout South Africa were enrolling as many as 50 volunteers a day.

The DSMB recommended permanently stopping immunizations and enrollment and unblinding volunteers after carefully analyzing data from the STEP trial. Following this decision, Gray and her colleagues set out to unblind and counsel all 801 volunteers. Once underway, Gray says it took only 16 days to complete the process. In what she compared to a "military operation," all volunteers were contacted by cell phone or short message service (SMS). Announcements were also made on the radio, alerting trial volunteers to come to the study sites for further information. Gray says the Phambili trial was at such an early stage it would not have yielded any substantial information, even if the participants who were already enrolled were kept blinded. All volunteers are still being encouraged to return for tests and study visits.

> ***There were many benefits to unblinding all study volunteers, including the clarity with which we could deliver risk-reduction counseling messages and for building trust with the study volunteers and the broader community.***
>
> **Susan Buchbinder**

Merck, NIAID, and the HVTN also decided to unblind volunteers in the STEP trial shortly after this issue was discussed publicly at the annual HVTN meeting in Seattle on November 7 and the unblinding process is now underway at sites throughout North and South America, the Caribbean, and Australia. According to Susan Buchbinder of the University of California in San Francisco and principal investigator of the STEP trial, investigators had considered keeping a subset of individuals blinded, who voluntarily chose not to know if they received vaccine or placebo. But there was substantial uncertainty that investigators could learn that much more about the vaccine candidate from this type of follow up. Before the official decision was announced, some STEP volunteers had already requested to know if they received vaccine or placebo, an option available to all study volunteers at any time.

"There were many benefits to unblinding all study volunteers," Buchbinder says, "including the clarity with which we could deliver risk-reduction counseling messages and for building trust with the study volunteers and the broader community."

Global HIV Vaccine Enterprise appoints executive director

The Global HIV Vaccine Enterprise announced the appointment of Alan Bernstein, founding president of the Canadian Institutes of Health Research (CIHR), as its executive director on October 11 at the Keystone Symposium on Challenges of Global Vaccine Development in Cape Town, South Africa. Bernstein will establish the permanent administrative offices of the Enterprise in New York City with US$20 million in funding from the Bill & Melinda Gates Foundation over the next four years, and an additional $7 million over the next seven years from the National Institute of Allergy and Infectious Diseases (NIAID).

The Global HIV Vaccine Enterprise is an alliance of independent organizations with a shared scientific plan that focuses on accelerating six areas of AIDS vaccine research: vaccine discovery, laboratory standardization, product development and manufacturing, clinical trials capacity, regulatory issues, and intellectual property. The idea of the Enterprise was first proposed in 2003 by a cadre of leading HIV researchers as a

way to promote collaboration in the field. But the "core of the enterprise is science," said José Esparza of the Gates Foundation.

To date, the organizations of the Enterprise have raised $750 million to achieve the objectives of the scientific plan. The new executive director of this effort needs to see that this funding, and the science it supports, is deployed in innovative ways, said Esparza. "We are convinced Alan is the ideal choice," he added. "As the head of the Enterprise, Alan Bernstein will bring his passion and expertise to the challenge of developing an HIV vaccine."

Bernstein most recently presided over the $1 billion budget of CIHR, the Canadian equivalent of the US National Institutes of Health, and was a member of the scientific board of the Grand Challenges in Global Health Initiative, sponsored by the Gates Foundation. Bernstein, whose scientific experience is not within the AIDS vaccine field, views his being an "outsider" as a strength because he can bring fresh perspective.

He emphasized the need to coordinate efforts within the field and get funding agencies, industry, and regulators working together. Bernstein said he recognized that getting the scientific community to work together on an issue of global importance is a hefty task and he compared the efforts to develop an AIDS vaccine to the campaign to tackle global warming. "As a group we've received hundreds of millions of dollars," said Bernstein. "The world is watching us."

He also referred to the recently reported results from the STEP trial as a "wake-up call" for the field. "It's going to be a long journey. We need to learn from the STEP trial and all other trials before and after that. The Enterprise will accelerate the development of a vaccine, [and] make the dream of a vaccine a reality," Bernstein said. "I think it's doable and I'm looking forward to it."

New funding focuses on innovation in global health

The Bill & Melinda Gates Foundation announced a new grants program called the Grand Challenges Explorations Initiative at the Keystone Symposium on the Challenges of Global Vaccine Development, held October 8-13 in Cape Town, South Africa (see *Giving it their best shot*, this issue). This initiative will foster innovative approaches to the greatest global health challenges by funding academic or independent research and discovery efforts in several areas of public health.

The Gates Foundation has committed US$100 million to the program over the next five years and will issue grants of $100,000 to selected applicants with the aim of encouraging the best minds to explore novel approaches to the world's greatest health challenges. "This is not about making money; this is not about publishing," said Tachi Yamada of the Gates Foundation. "It's about delivering to patients."

This initiative will also attempt to break down the interdisciplinary boundaries of research. "Innovation is a word that is misused by most," said Yamada. "They mean what I'm doing, not what you're doing.

Another guiding principle of the Explorations program is speed. Applications require no advanced data and are limited to two pages. They will be reviewed quickly and grants will be delivered within three months. The initial target areas for the grants will be announced early next year and proposals, which will be reviewed by experts in the areas of science and technology, will be accepted starting early- to mid-2008. Grantees will be expected to take on big questions and big risks and share information as soon as it's available, according to Yamada.

In September, IAVI launched a $10 million initiative focusing specifically on AIDS vaccine research and development. This program, known as the Innovation Fund, will identify and fund small- and medium-sized biotechnology companies working on innovative technologies that may have applications in AIDS vaccine research. The need for pioneering approaches to AIDS vaccine design became even more apparent after Merck's leading candidate, MRKAd5, failed to provide any degree of protection against HIV infection or to control viral load in individuals who became HIV-infected despite vaccination in a large Phase IIb test-of-concept trial called the STEP study (see *Spotlight* article, this issue).

"Let's face it, 25 years after the advent of HIV/AIDS and there's still no vaccine," said Yamada. "As a funder of this work we have to be willing to fail. But when we have success, we should be ready to invest very, very heavily in that success."

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IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 24 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it. For more information, go to www.iavi.org.

What are randomized, controlled, double-blind clinical trials?

A clinical trial is a research study conducted in human volunteers. Clinical trials are designed to decisively answer specific questions about vaccines or new therapies, such as whether they are safe and effective. Clinical trials are conducted in phases, starting with small Phase I studies that look primarily at safety, and progressing to large Phase III clinical trials, which are designed to show whether or not a vaccine or other medical technology is effective at either preventing or treating a disease. These trials lead to the licensure of a vaccine or therapy for public use. Other intermediate studies, such as Phase IIb test-of-concept trials, can also be used to give initial indications of efficacy (see *VAX* September 2005 *Primer* on *Understanding Test-of-Concept Trials*). The final stage of evaluation, Phase IV, occurs after a vaccine or therapy is licensed and is being used by large numbers of people, but these studies are not always required or completed.

The best way to determine if a vaccine or therapy is effective is to test it in a randomized, controlled, double-blind clinical trial. This type of trial is often referred to as the gold standard in medical research and provides the strongest evidence for the efficacy of an experimental product. Clinical trials of AIDS vaccine candidates are conducted in this manner to determine whether or not they are effective at protecting people from HIV infection or have some degree of partial efficacy that limits disease progression in individuals who become HIV infected even after receiving the vaccine (see *VAX* May 2007 *Primer* on *Understanding Partially-Effective AIDS Vaccines*).

Taking control

A controlled clinical trial compares the vaccine candidate or therapy being tested to either the best available treatment for that disease or, in the case of a preventive technology like a vaccine, against an inactive substance known as placebo that has no biological effect. AIDS vaccine candidates are tested in placebo-controlled trials—one group of volunteers is given the experimental vaccine candidate, while another group, called the control group, receives placebo. This allows researchers to detect any differences between the two groups regarding safety or efficacy.

For safety, it is valuable to compare any possible side effects in individuals who receive the vaccine candidate with those in volunteers who receive an injection of an inactive substance. The efficacy of an AIDS vaccine candidate in protecting against HIV infection is determined by comparing the number of individuals who become HIV infected—through exposure to the virus in their community—in each group. To say whether or not a vaccine candidate is partially effective, researchers compare the quantity of HIV in the blood, known as the viral load, in individuals from the two groups who become HIV infected through natural exposure to the virus during the trial.

Researchers can conclude whether a vaccine candidate is effective or not by looking at the difference between the vaccine and placebo recipients in either the total number of newly HIV-infected individuals or in their viral loads. If there is no difference, researchers can conclude that the vaccine candidate is ineffective. This was determined recently in the Phase IIb test-of-concept trial, known as the STEP trial, of Merck's AIDS vaccine candidate (see *Spotlight*, this issue).

Randomization

Whether a volunteer in a clinical trial receives the vaccine candidate or placebo is determined completely randomly by a computer program. However the randomization process involves more than simply dividing volunteers into two groups. For the results between the vaccine and placebo recipients to be truly comparable, the composition of these groups must be similar. For example, if the vaccine group involves only women, and the placebo group involves only men who have sex with men, the results between the two groups aren't comparable because it is impossible to rule out whether or not the route of HIV transmission may have affected the efficacy of the vaccine candidate.

Several factors must be considered during the randomization of volunteers, including sex, age, race, and geographic location. In AIDS vaccine trials, volunteers are also randomized based on behavioral factors that put them at increased risk of HIV infection, such as number of sexual partners. If the distribution of different factors is equivalent between the vaccine and placebo groups, a trial is randomized properly.

However there are always some factors that researchers can't account for during the randomization process. These are called confounding factors because they are not distributed evenly between the two groups and therefore can bias the results. Statistical analyses of completed clinical trials can sometimes help explain the effects of such confounding factors.

Blinding

Another factor in the design of clinical trials that adds credibility to the results is double-blinding, which requires that neither the volunteers nor the researchers know who is receiving the vaccine candidate or placebo. Double-blind trials give more accurate results because individuals do not alter their behavior based on whether or not they are receiving the vaccine candidate. But some trials, such as those that offer a surgical intervention like circumcision, can obviously not be blinded and are referred to as open trials.

Several precautions are taken to keep trials blinded. Volunteers in a vaccine trial are assigned code numbers and staff members at a clinical trial site are only given a syringe labeled with that individual's code number. The pharmacist at the site, who prepares the syringes containing either the vaccine or placebo, only has access to the volunteer's code number and does not see any of the trial volunteers. Also, the placebo formulation is given in the same quantity as the vaccine and is made to look identical.

Researchers and volunteers usually do not find out who received vaccine or placebo until all volunteers finish their study visits and the trial is considered complete. Sometimes, such as in the STEP and Phambili trials, researchers decided to unblind volunteers before the trial is technically complete (see *Removing the blindfold*, this issue).