



IAVI Report

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A STEP back?

Additional data released from the STEP trial raises questions about whether the vaccine may have increased the risk of HIV infection

by **Kristen Jill Kresge**

Clinical trials are intrinsically complex, but according to Mark Feinberg of Merck, the 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, a Phase IIb test-of-concept trial of Merck's adenovirus serotype 5 (Ad5)-based vaccine candidate, known as MRKAd5. Since immunizations were stopped in this trial on September 21, investigators, biostatisticians, and clinical trial experts have spent many sleepless nights running assays, analyzing data, and interpreting the results of this pivotal study.

And the results, based on data from all 3,000 volunteers, show that even though the vaccine induced HIV-specific cellular immune responses, they were not effective at preventing HIV infection or in reducing levels of the virus in individuals who became infected despite vaccination. "The immune responses were reasonable," says Mike Robertson of Merck. "The lack of efficacy is not explained by sub-optimal immune responses."

Moreover, there is a trend toward a higher number of infections in vaccinees as the level of pre-existing antibody immunity to the Ad5 vector increases. This Ad5 immunity is due to prior exposure to the naturally-circulating strain of the cold virus, which is used in the vaccine candidate to deliver three HIV antigens: Gag, Pol, and Nef. 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. But in individuals with the highest levels of Ad5 antibody, the imbalance was more pronounced—21 infections in vaccinees compared to 9 in placebo recipients. "This difference is clinically important for at least one subgroup, the high Ad5," 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."

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'Stopping a steam train'

Immunizations and enrollment in a second trial with MRKAd5 have now been permanently stopped, and volunteers in the Phambili and STEP trials are being unblinded

by **Andreas von Bubnoff**

Immunizations and enrollment were stopped permanently on October 23 in a second National Institute of Allergy and Infectious Diseases (NIAID)-sponsored trial called Phambili, or HVTN 503, following the recommendation by the trial's data safety monitoring board (DSMB). Both had

already been suspended a month earlier in response to the futility analysis by the DSMB of the STEP trial. The Phambili trial was a companion study to the STEP trial testing the same clade B MRKAd5 vaccine candidate at sites in South Africa (see *A STEP back?*, above). Phambili's DSMB also

recommended that the study investigators unblind all participants, 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. A similar decision was reached on November 13 for the STEP trial,

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The explanation for this difference is still not clear. There are several possible confounding factors, including race, geographical region, age, and circumcision status of the volunteers. According to Susan Buchbinder of the University of California in San Francisco and principal investigator of the STEP trial, there is mixed data on the protective role of circumcision in men who have sex with men (MSM), the predominant population involved in this trial. In uncircumcised men there were far more HIV infections in the vaccinees while in circumcised men there was an even split of HIV infections in both vaccine and placebo recipients.

But at this stage of the analysis, the trend towards increasing rates of HIV infection among vaccinees persists even after factoring in all of the known potential confounders, says Steve Self, a biostatistician with the HVTN and the Fred Hutchinson Cancer Research Center. “The confounding factors certainly aren’t the full answer,” says Larry Corey of the HVTN.

Researchers are now hard at work trying to determine why the vaccine was not effective and any role it may have had in increasing susceptibility to HIV in some individuals. There is great uncertainty about the evidence that the vaccine may have enhanced the risk of HIV infection but there are some possible biological explanations for this difference, and researchers must now sort out their plausibility.

“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. “Some of those things will take months and some may take longer than that,” says Walker. “We were entering into this thinking that we will find an answer, but even that’s not absolutely guaranteed.”

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 cell-mediated immunity (CMI) and not antibodies against the virus. 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 one of three different HIV genes, *gag*, *pol*, or *nef*. The inserts were from HIV clade B, matching the predominant clade circulating in the areas in which the trial took place. A companion study of MRKAd5 was also conducted in South Africa (see ‘Stopping a steam train,’ page 1).

The original plans for the STEP study only included 1,500 individuals with low levels of Ad5 antibody (less than 200 units, in which a unit is a measure of the antibody concentration required to neutralize Ad5). But after the trial began, data emerged from earlier Phase I and II trials that showed pre-existing immunity to Ad5 did not compromise HIV-specific immune responses to the degree that researchers had 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 high Ad5 antibody titers (greater than 200 units). The majority of the volunteers, 61%, in this second group were women. As a result of this modification, both primary endpoints for the trial—identifying the ability of the vaccine to prevent HIV infection or reduce viral load in volunteers who later became infected—only applied to the low Ad5 titer group. Investigators added an equivalent set of secondary endpoints relating to the group with high Ad5 antibody levels.

Immunizations in the STEP trial were halted on September 21 after the trial’s independent data safety monitoring board (DSMB) reviewed the data for the first time. This interim analysis was triggered by the accrual of 30 HIV infections within the subgroup with low levels of pre-existing immunity to Ad5. The DSMB conducted what is known as a per protocol analysis of volunteers in the sub-group who had received at least two injections of MRKAd5 or placebo, who met all of the specifications of the trial protocol, and who did not become HIV infected within the first three months of the study. The DSMB concluded that based on the breakdown of infections at this time—19 in the vaccine group and 11 in placebo recip-


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Mark Feinberg

	Ad5 antibody titer			
	<18	<18<Ad5≤200	200<Ad5≤1,000	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 titer. Number of HIV-infected individuals, out of the total number of vaccine and placebo recipients, according to increasing Ad5 antibody titer. This data, from the post-hoc analysis of the STEP trial, was presented at the HVTN meeting by Mike Robertson of Merck.

ients—it was futile to continue immunizations because the vaccine was not effective. Based on the trend toward a higher number of infections in vaccine recipients, the DSMB also encouraged the continued follow-up of trial volunteers.

After futility was declared, researchers at Merck and NIAID decided to proceed “cautiously” with a post-hoc 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,” as the trial was not designed to look at different sub-groups separately. When immunizations were stopped, only one HIV infection had occurred within the 1,150 women in the trial and this volunteer received placebo, not vaccine. Since the HIV incidence was so low in female volunteers, investigators conducted all the subsequent analyses on the 1,850 male volunteers only.

The trial investigators also chose to focus on what Robertson calls the “broadest population we could look at,” which is different than the per protocol analysis. This analysis, known as modified-intention-to-treat (MITT), includes volunteers who were infected with HIV during the first three months as well as those who didn’t meet the exact specifications of the trial protocol.

When the individuals who became HIV infected were analyzed according to their level of Ad5 titer, researchers noticed a worrisome trend (see Table 1). In individuals with virtually no pre-existing immunity to Ad5, there were 20 infections in both the vaccine and placebo group. In the group with the lowest level of Ad5 titers, there were 8 infections amongst vaccinees and 4 in placebo recipients, while in individuals with mid-range levels of pre-existing immunity (Ad5 titers between 200 and 1,000), there were 14 vaccine recipients who became HIV infected and only 7 in the placebo group. And in volunteers with the highest Ad5 titers (concentra-

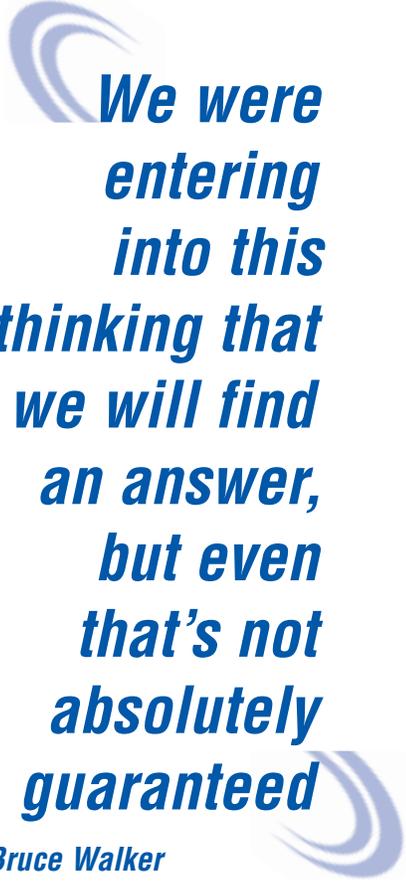
tions of antibody greater than 1,000), there were 7 infections in the vaccine group and only 2 in those who received placebo. “As you move up [into higher levels of Ad5 antibody] there is a trend for the ratio to get higher,” says Robertson.

But Self 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, even if the *p* value is not significant,” says Buchbinder.

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 Robertson. “We didn’t expect that,” says Peggy Johnston of the Division of AIDS at NIAID.

But in 2004 Feinberg co-authored a scientific paper, in his capacity as a researcher at Emory University, issuing a potential warning to the vaccine field, saying “candidate AIDS vaccines may not simply be either efficacious or neutral; they may also have the potential to be harmful.” This study indicated that vaccination of rhesus macaques with a varicella-zoster virus vaccine carrying the simian immunodeficiency virus (SIV) Env protein resulted in an increase in the number of activated CD4⁺ T cells upon SIV challenge (*PNAS* **101**, 13026, 2004). This increased number of proliferating CD4⁺ T cells, in the absence of a balanced CD8⁺ T cell response, led to higher levels of SIV replication and enhanced disease in the vaccinated monkeys. A similar result was not seen in the STEP trial: even though the risk of acquiring HIV seemed to be higher amongst vaccine recipients with high Ad5 antibody titers, there was not a significant difference between the viral loads in this group compared to placebo, suggesting there wasn’t increased HIV replication.

This nonhuman primate study was also done with a different virus vector, which was



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A.

% responders by INF- γ ELISPOT assay at week 8 in STEP trial*		
Male volunteers with Ad5 antibody titers \leq 200		
	HIV+ (n=19)	HIV- (n=143)
Gag	74	76
Pol	63	73
Nef	74	70
Male volunteers with Ad5 antibody titers >200		
	HIV+ (n=13)	HIV- (n=173)
Gag	46	54
Pol	38	47
Nef	46	51

B.

% responders by INF- γ ELISPOT assay in Phase 1 trials*		
Male volunteers with Ad5 antibody titers		
	\leq 200	>200
Gag	61	100
Pol	48	33
Nef	57	58

* A responder is defined as an individual with \geq 55 spot-forming cells per million peripheral blood mononuclear cells (PBMCs).

Table 2. Immune responses to HIV immunogens. Part A shows the immune responses, as measured by INF- γ ELISPOT assay, induced toward HIV proteins included in the MRKAd5 vaccine candidate in both HIV-infected and uninfected trial volunteers. Part B shows the immune responses measured in previously-completed Phase I trials.

replication competent, unlike the Ad5 used in the STEP trial, and with different viral inserts.

Heads or tails

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

The results from the IFN- γ ELISPOT assay show that the immune responses induced by the vaccine were similar or higher in the group with low Ad5 immunity to those seen in previous Phase I and II trials, and only somewhat different in the high Ad5 antibody titer group (see Table 2). These responses did not differ between those who became HIV infected and those who didn't.

In the group with low Ad5 immunity, 79% of volunteers mounted immune responses to at least one HIV antigen included in the vaccine,

while 63% had responses to all three. Far fewer individuals, only 23%, with high Ad5 antibody titers mounted immune responses to all three HIV antigens, but 62% had immune responses to at least one. For now it is still unclear if the vaccine just didn't provide the quantity of T-cell responses necessary for protection, or if they were of the wrong quality. "What was the functionality of the immune responses that were generated?" asks Walker. "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." These results may also impact the future use of IFN- γ ELISPOT assays for assessing the relative efficacy of vaccine candidates (see *Getting it right early*, page 7).

There are also many additional studies planned. Researchers will sequence the viruses that infected the volunteers to look at whether or not the HIV epitopes included in the vaccine

anti-Ad5 antibody titer	HIV incidence rate (%)	
	vaccine	placebo
<18	4.0	4.0
19 – 200	4.4	2.2
201 – 1000	6.1	3.0
>1000	4.4	1.2

Table 3. HIV incidence rates during STEP trial. This table shows the HIV incidence observed in vaccine and placebo recipients during the STEP trial, according to Ad5 antibody titer.

antigens were present in the infecting virus strains. This work will be done in cooperation with Francine McCutchan of the US Military HIV Research Program and might provide valuable information about why the vaccine didn't work. It may also help elucidate whether a single vaccine candidate can provide sufficient antigenic coverage for the exceptional diversity of HIV.

There are also plans to do whole genome sequence analyses of some of the volunteers to identify any genetic components that might have enhanced susceptibility to HIV or, conversely, provided protection to placebo recipients. "Part of the problem is there are actually very few samples that are available," says Walker. "We just don't have that many so we are going to have to make decisions about what we prioritize."

The next question to tackle is whether or not the vaccine enhanced susceptibility to HIV infection. Julie McElrath of the Fred Hutchinson Cancer Research Center says this is "the question on everyone's lips." One possible explanation is that with the adenovirus there is increased activation of CD4⁺ T cells expressing the CCR5 coreceptor, thereby creating more target cells for HIV, says Walker. McElrath has found that individuals with high Ad5 antibody titers do have higher levels of activated, CCR5 expressing CD4⁺ T cells in peripheral blood. However, within this group there is no difference between vaccine and placebo recipients. "The whole thing is puzzling," Walker adds.

There is also some evidence that HIV-specific CD4⁺ T cells can migrate to the male genital tract—researchers have detected them in both peripheral blood and seminal fluid samples, according to Danny Casimiro of Merck. McElrath plans to further study the CD4⁺ T cells in both the rectum and lower male genital tract and will also investigate if the CCR5⁺, activated CD4⁺ T cells in vaccinees are more susceptible to HIV *in vitro*. "There is a hint of

something going on here but these are very preliminary studies," she says.

Broader strokes

McElrath raised two other questions in Seattle that she and others, who are busy analyzing the STEP data, will also attempt to address: is this observation specific to Ad5? And could there be a similar issue with other viral vectors? "We have no clear clue about that but we will try to address this in the best way we can," says McElrath.

Feinberg emphasized that the way the STEP trial is handled has implications that extend far beyond this single vaccine candidate. "We have to work together. It's easy for that to sound like a platitude but it's not," he says. "If we don't do this right, the whole field will come apart at the seams and we can't allow that to happen." Merck and NIAID were openly seeking input from various investigators, advocates, and community members at the HVTN meeting, making it abundantly clear that they see issues, like the ongoing analysis of data, as a collective decision and undertaking.

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. "Researchers will need to carefully consider whether enrollment of individuals with existing immunity to that adenovirus serotype can be justified from a safety perspective, at least until the STEP results are better understood." And based on the complexity of the data generated by this trial, it may be a long road. For now, most agree it is too early to close the door on CMI-inducing vaccines. "One trial does not mean the concept is not correct," says Corey. 

Andreas von Bubnoff contributed reporting to this article.



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and now all volunteers in this trial will also be unblinded.

When Phambili was suspended in September, it was at a much earlier stage than the STEP trial. At the time, Phambili had enrolled only 801 volunteers of a planned total of 3,000, 58 of whom had received all three vaccinations. Still, as news of the suspension reached the Phambili trial sites in September, 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 the Phambili trial. At that time, the trial sites were enrolling as many as 50 volunteers a day.

The process of unblinding the Phambili trial began immediately after the DSMB’s decision was released on October 23. Gray says it took only 16 days to unblind all participants after the initial announcement. In what she compared to a “military operation,” the volunteers were contacted by radio, cell phone short message service (SMS), and phone. All volunteers are still being encouraged to return for study visits. Gray says the decision to unblind volunteers in the Phambili trial made sense because the 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.

One goal of the Phambili trial was to see if the candidate vaccine would be effective in areas with HIV subtype C, the most common clade circulating in South Africa. The Phambili trial was also conducted for the most part in heterosexual volunteers and was to enroll 60% women, far more than in the STEP trial, which originally aimed for one quarter of the volunteers to be women. Women are at a very high risk of contracting HIV in South Africa, and while the STEP trial primarily involved men who have sex with men (MSM), the Phambili trial could have helped researchers determine the efficacy of this candidate in women.

When Phambili was suspended it had enrolled approximately 45% women, compared with 38% in STEP. But the HIV incidence rate among women in the STEP trial was very low—only one of the 83 HIV infections through October 17 occurred in a female volunteer. The reasons for this discrepancy are currently unclear. “We don’t have enough data from this study to say anything about vaccine effects in women,” says Susan Buchbinder of the University of

California in San Francisco and principal investigator of the STEP trial.

Following the unblinding of the Phambili trial, there was also some discussion about how the Phambili and STEP trial results would affect other AIDS vaccine trials in South Africa. On November 14, South Africa’s Health Minister, Manto Tshabalala-Msimang, said that all HIV vaccine trials would be put on hold, pending review of the STEP and Phambili data, according to Elise Levendal of SAAVI, who was present at a meeting with the Minister that day.

But there are currently no trials in South Africa that have ongoing immunizations, Gray says. A Phase I trial is planned for next year to test DNA- and MVA-based candidates, developed by Carolyn Williamson of the University of Cape Town, in a prime-boost regimen. That trial, Williamson says, is currently under regulatory review with the FDA. “I am hoping that the issues will be resolved so as not to slow down the testing of this vaccine,” Williamson says.

The process of unblinding the STEP trial is now also underway, following an announcement from Merck and the HVTN on November 13. An oversight committee comprised of leadership from Merck, NIAID and the HVTN made the final decision, according to Buchbinder, who says this decision was reached after discussing two options: unblinding all volunteers or offering unblinding to all participants while creating a voluntary blinded follow-up arm. Peter Gilbert of the Statistical Center for HIV/AIDS Research and Prevention (SCHARP) in Seattle calculated that if at least 40% of all the STEP trial volunteers remain blinded, the statistical power of the trial would still be intact. But according to Buchbinder there was substantial uncertainty that investigators could learn significantly more from the subgroup likely to remain in blinded follow up. “There were many benefits to unblinding all study volunteers,” she 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.”

Buchbinder says that before the official decision to unblind, some STEP volunteers had already requested unblinding, an option available to all volunteers at any time.

Kristen Jill Kresge contributed reporting to this article.

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**Susan Buchbinder**

Getting it right early

The STEP trial offers lessons for future preclinical/clinical AIDS vaccine development

By Simon Noble

The reverberations are still being assessed, the data is undergoing analysis, and researchers are still discussing and debating next steps, but after the failure of Merck's adenovirus-based vaccine candidate (MRKAd5) some familiar questions are already being rehashed as to what can be done differently to develop the next generation of vaccine candidates.

Animal model

Like virtually all animal models of human disease, there are differing opinions as to which of the various animal models most faithfully recapitulates HIV infection in humans. "Animal models are animal models. The key word is model," says Emilio Emini, head of vaccine research and development at Wyeth. "All models are approximates," says Stanley Plotkin, executive advisor at Sanofi Pasteur, "it is not unusual in vaccine development to find that a vaccine doesn't work as well in humans as it does in animals."

One of the many issues that AIDS vaccine researchers have wrestled with in recent years concerns the fine specificities of the various non-human primate (NHP) and simian immunodeficiency virus (SIV) models. Viruses like the pathogenic SIVmac239 have been used extensively in challenge studies to test vaccine concepts, but this has been viewed as a particularly stringent test because it replicates to high peak viral loads and more rapidly causes disease in rhesus macaques than HIV does in humans. Some years ago hybrid simian-human immunodeficiency viruses (SHIVs) were constructed to try to provide a more reasonable challenge for a vaccine concept to protect against. The most commonly used is SHIV-89.6P, which contains *tat*, *rev*, and *env* genes from HIV. But the pathogenesis of this hybrid virus is markedly distinct—it causes rapid and almost complete loss of CD4⁺ T cells in macaques, elicits neutralizing antibodies, and uses CXCR4 rather than CCR5 as a coreceptor when infecting cells. Paradoxically, SHIV-89.6P challenge has proven relatively easy to protect against with many vaccine approaches, resulting in preserved CD4⁺ T cells and greatly reduced viremia.

Since the halting of immunizations in the STEP trial, the fact that MRKAd5 was most notably successful against SHIV-89.6P chal-

lenge in NHPs (*Nature* **415**, 331, 2002) has been a point of discussion. A similar vaccine candidate—the Merck Ad5 backbone encoding only Gag, rather than the Gag, Pol, and Nef included in MRKAd5—was ineffective against an SIVmac239 challenge when administered alone, and only marginally effective when accompanied by a DNA prime vaccination (*J. Virol.* **79**, 15547, 2005).

Strong opinions on the relative veracity of the SIV or SHIV challenge models have been expressed in the past. "The field as a whole has preferred the SIV model," says Gary Nabel of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID). "We have always felt that SIV is probably a better approximation of human disease." Indeed, John Moore of Cornell University and Mark Feinberg of Merck warned some time ago that "SHIV-89.6P may be a sheep in wolf's clothing, with the potential to lead the AIDS vaccine development effort down the wrong path" (*Nature Medicine* **8**, 207, 2002).

The results of the STEP trial have only reinforced this position for some researchers. "We've already learned some pretty important things from this trial. For one, we have learned that the SHIV model does not have very good predictive value," says Tony Fauci of NIAID. When more data from the STEP trial was released at the HIV Vaccine Trials Network (HVTN) meeting in Seattle on November 7, the discussion again turned to the predictive value of the NHP model. Jeff Lifson of the National Cancer Institute in Maryland said, "The NHP data strongly correlated with these results."

David Watkins of the University of Wisconsin, Madison says, "This shows that the monkey model is highly relevant, but only with a rigorous SIV challenge, not a SHIV-89.6P challenge. We had the fond hope that it might be easier to protect humans than it was to protect monkeys against rigorous SIV challenge, but that proved not to be the case."

Assessing assays

Another question raised by the STEP trial is the validity of the current assays used to gauge immunogenicity. There has been increasing opinion in recent years that the



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**John Moore &
Mark Feinberg**



**We have
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and rigorous
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preclinical
assessment
of vaccine
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before they
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expensive
and lengthy
Phase IIb or
III trials**

David Watkins



interferon (IFN)- γ ELISPOT assay is not really up to the job of assessing the relative efficacy of vaccine candidates. The problem is that ELISPOT simply measures a T cell's ability to secrete IFN- γ (or other soluble factor) and this does not reliably correlate with any particular biological function of that cell. "An ELISPOT is an easy first check of immunogenicity. I think no one is satisfied that by itself it is the only assay one should do," says Peggy Johnston of the Division of AIDS, part of NIAID.

In the STEP trial, high levels of immune responses were induced by MRKAd5 to the HIV antigens and these responses were similar overall to those reported in Phase I and II trials (see *A STEP back?*, page 1). In the group with low levels of pre-existing immunity to Ad5, 79% of participants generated immune responses at a level greater than 55 spot-forming cells per million peripheral blood mononuclear cells (PBMCs), as measured by IFN- γ ELISPOT assay, to at least one of the HIV antigens included in the vaccine. In the 1,500 volunteers with high titers of antibody against Ad5, 62% generated responses to at least one antigen. Danny Casimiro of Merck presented data at the HVTN meeting showing that even though the vaccine was not effective, it did induce high levels of T cells secreting IFN- γ and interleukin (IL)-2. Watkins says this trial once again indicates that "immunogenicity is not efficacy."

Researchers have begun to develop improved assays that accurately reflect biological function—such as *in vitro* lysis of HIV-infected target cells and consequent virus inhibition, for instance—to better assess vaccine candidates in preclinical and clinical development. "The ELISPOT really only scratches the surface," says Emini, "we know the science has moved well beyond the ELISPOT." Casimiro says these assays will be conducted with the samples from the STEP trial to look at the cytolytic potential of the T cells induced by MRKAd5 and their ability to neutralize virus.

Watkins draws a parallel with neutralizing antibodies. "You might have binding antibody, but if you don't have neutralizing antibody it will be very difficult to protect. The same is probably true with CTLs [cytotoxic T lymphocytes]; ELISPOTs are the equivalent of measuring antibody binding to envelope, but we really don't have an assay for CTL efficacy. We desperately need the equivalent of a neutralizing antibody assay."

Some researchers have balked at the prospect of abandoning the well-established and validated ELISPOT assay, but Watkins's opinion is that "just because it's difficult doesn't mean it's not the right thing to do. We've got to find better assays, and production of cytokines is not the way to go—we need functional assays."

Rick Koup of the VRC thinks ELISPOT assays are still critical if "you want to know if your vaccine is stimulating a T-cell response," and says it is impossible to say definitively whether or not viral suppression assays will better evaluate efficacy until there is a candidate that is shown to be effective and suppresses virus *in vitro* but doesn't give a strong ELISPOT response.

"We really can't say at this point," says Fauci, "maybe we need better ELISPOTs, but right now the relationship between ELISPOT intensity and outcome is not known. We need a comparison, this is only one trial." José Esparza of the Bill & Melinda Gates Foundation concurs that researchers are in a Catch-22 situation, saying that "the only way to know which lab assay correlates with protection is after conducting a successful efficacy trial."

Future strategies

Beyond the finer points of animal models and immunological assays, some researchers have expressed opinions on what the STEP trial might mean for future preclinical and early clinical vaccine development strategies. Moore says that researchers will "have to demonstrate that their favorite vaccine is better than what has gone before; we can argue about what 'better' means, but there is no point in advancing immunogens or vaccines that don't do any better than the ones that have failed."

"We have to be a lot more honest and rigorous about the preclinical assessment of vaccine candidates before they go into expensive and lengthy Phase IIb or III trials," says Watkins. He says the STEP trial "tells us that if you're not protecting against SIVmac239 with autologous challenge, then don't even bother going into the clinic." He also thinks novel approaches will be paramount. "We need creative, radical new ideas—to use a football metaphor, running up the middle is not going to work, we need to be creative in our play-making. Those discoveries are going to have to come from basic research labs; the big science approach is not going to be effective, or at least it will be more difficult." 

Giving it their best shot

Researchers from many areas of vaccine development gathered recently to discuss the challenges of developing and delivering life-saving vaccines

By Kristen Jill Kresge

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 from 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, many of whom don't usually attend the same conferences, 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 was an experiment in its own right, according to conference co-chair Margaret Liu of the Karolinska Institute. It 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 also held in conjunction with the annual meeting of the Gates Foundation's Grand Challenges in Global Health initiative, 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."

One thing that is certain is the massive public health benefit that vaccines can have. Since the genesis in 2000 of the Global Alliance for Vaccines and Immunization (GAVI), now the GAVI Alliance, the World Health Organization (WHO) estimates that the introduction of vaccines in developing countries has pre-

vented 2.6 million deaths.

Just one year after the vaccine against haemophilus influenzae type B (Hib) was introduced in Mali through the GAVI Alliance, there was a 67% reduction in mortality due to Hib and a 32% reduction in all hospitalizations in the country. 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 and \$778 million between 2011 and 2015 to continue funding vaccination programs in its target countries.

Boosting spirits of AIDS vaccine researchers

The gathering for the Keystone conference occurred just a few weeks after the 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 taking place in South Africa, were suspended—they have since been stopped entirely (see 'Stopping a steam train', page 1). 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, "We really have to go back to the drawing board." But while many AIDS vaccine researchers were still reeling from the news, 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 can-



***I wouldn't
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malaria
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times***

Adrian Hill



**Three
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That's not
enough to
give you
protection
against
malaria
either**

Adrian Hill



didates fail for malaria about 15 times.”

Data analysis for the STEP trial is proceeding rapidly, but for now it remains unclear why MRKAd5 was not effective (see *A STEP back?*, page 1). The immunogenicity data analyzed so far shows the vaccine induced the expected levels of immune responses. But Hill expressed doubt that the low quantity of T cells generated by this vaccination strategy could ever be sufficient to fend off HIV. “Three hundred or 400 T cells against HIV aren’t enough to give you protection,” he says. “That’s not enough to give you protection against malaria either.” Hill thinks a vaccine candidate should induce three to four times as many T cells to provide some protection against HIV.

Many researchers at the meeting spoke favorably about the pursuit of a prime-boost strategy for AIDS vaccines. “The Merck vaccine was in fact three shots of a single structure,” says Gustav Nossal of the University of Melbourne and conference co-chair. For some time now the idea of using a heterologous prime-boost combination of different vaccine constructs has been gaining favor in the AIDS vaccine field, and after this latest development it seems to have become the battle cry. “Prime-boost got a big boost from this negative result,” added Nossal, referring to the STEP study.

The prime-boost strategy furthest along in development is a DNA candidate followed by a boost with an Ad5 vector-based candidate, which is slightly different from the one developed at Merck, both encoding multiple immunogens (*gag/pol* fusion construct and *env*) from several HIV clades. This candidate was developed at the Vaccine Research Center at NIAID. Gary Nabel presented data on this prime-boost regimen and summarized the differences between it and MRKAd5 (see *What next?*, page 13).

But Nabel faced some tough questions. Hill pointed out that the immune responses, as measured using the interferon (IFN)- γ ELISPOT assay, induced by the VRC’s DNA/Ad5 candidates against the HIV genes *gag*, *pol*, and *nef*, were of a similar magnitude to those induced by MRKAd5. He therefore questioned whether just the inclusion of the HIV *env* gene would really be sufficient to induce a significantly different magnitude of immune responses. Nabel

says he expects inclusion of *env* will make a difference, not only in the magnitude of immune responses but also by improving the quality of these responses. He also argued that this is the reason to test these candidates in the planned Phase IIb test-of-concept trial, known as PAVE 100, which has been delayed until more data from the STEP study is analyzed and researchers can sort out any possible association between the level of pre-existing immunity to Ad5 and enhanced susceptibility to HIV infection. “The clinical trial now becomes the experiment,” says Nabel.

Other prime-boost AIDS vaccine regimens were also discussed. Williamson presented data in nonhuman primate studies with a prime-boost combination of the VRC’s DNA plasmid vaccine encoding Gag, Rev, Tat, Nef, and Env clade C HIV proteins and a modified vaccinia Ankara (MVA)-based vaccine, developed at the University of Cape Town, carrying the same immunogens. All eight baboons that received three immunizations with the DNA candidate followed by two booster immunizations with the MVA vector had immune responses to SIV and were considered responders based on results from the IFN- γ ELISPOT assay. All of the baboons generated responses directed towards *gag* and *nef*, while six of the eight had responses to *env*. Williamson says this prime-boost regimen elicited a high magnitude and breadth of both CD4⁺ and CD8⁺ T cells, and therefore warrants evaluation in human volunteers. A Phase I safety trial of this DNA/MVA prime-boost regimen conducted by the South African AIDS Vaccine Initiative (SAAVI) was scheduled to begin later this year, pending approval from the US Food and Drug Administration and the Medical Research Council of South Africa, but all vaccine trials have been placed on hold by the South African Health Minister following the news on the Phambili trial (see *‘Stopping a steam train’*, page 1).

A different DNA/MVA prime-boost regimen is also being tested in an ongoing Phase I trial in Dar es Salaam, Tanzania by researchers at the Karolinska Institute in Sweden, in collaboration with the Walter Reed Army Institute of Research (WRAIR). Britta Wahren of the Karolinska Institute provided a progress report on this trial and says that so far 57 volunteers have already received at least one dose of the DNA vac-

cine candidate or placebo and 21 have already completed all three doses. Administration of the MVA boost, which was developed by researchers at WRAIR, is expected to begin in the first volunteers later this year.

Presentations on these similar, but different, prime-boost regimens prompted multiple questions on how these combinations would stack up in a head-to-head comparison. Without comparative studies it is difficult to know how any of these regimens would compare to MRKAd5, because they all include different immunogens and many also use different nonhuman primate models for preclinical evaluation. Researchers also use different criteria to determine immunogenicity. This makes it nearly impossible to establish which of the current strategies is the most immunogenic, and on several occasions during the meeting, researchers outside the AIDS vaccine field asked why comparative studies aren't conducted as part of preclinical evaluation. "Some people really don't want to compare their vaccine to each other's," says Liu. Nabel says there are several complications to doing these types of studies, but added that the VRC has created a standardized HIV Env insert that is available to all researchers and can be used to eliminate at least one of the variables between experiments.

The bandwagon

It's not only HIV researchers who are exploring prime-boost regimens—they are currently in vogue in other fields as well. 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 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.

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 it is released from the liver into the

blood. At this stage of malaria, cellular immune responses are a critical component in controlling disease progression or eliminating the parasite.

Researchers, including Hill, have tested DNA plasmid vaccines alone and in combination with MVA vector-based candidates, as well as a heterologous prime-boost combination of a fowlpox vector-based candidate and an MVA candidate. In mouse studies, the fowlpox/MVA prime-boost regimen was the most protective, generating CD8⁺ T cells that correlate with protection against malaria, using the IFN- γ ELISPOT assay. Clinical trials conducted in the UK and the Gambia also showed high levels of immune responses in human volunteers, but when this prime-boost regimen 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. Children with high quantities of parasite in their blood had the lowest immune responses to the candidates. Hill speculates that this may be a recurring problem for malaria vaccines in high-burden areas, where the vaccines could also have the greatest impact.

Following this failure, researchers set out to find a better heterologous prime-boost regimen and because more T cells correspond to better protection, Hill says, he and others tried to identify vectors that could induce even higher levels of cellular immune responses. 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. "This [the outcome of the STEP study] does not mean adenovirus would not be a great vector encoding other antigens."

Hill's group at Oxford compared the immunogenicity of different serotypes of human adenoviruses with simian versions and found that chimpanzee adenovirus serotype 63 (AdCh63) was even more immunogenic than human Ad5. A prime-boost regimen with the AdCh63, followed by an MVA-based candidate encoding TRAP (a multiple-epitope fusion protein from the sporozoite stage of the parasite) induced 3,000 IFN- γ producing T cells per million peripheral blood mononuclear cells (PBMCs) in rhesus macaques.



**Adenovirus
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vectors**



Myron Levine



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



Hill is currently preparing to begin a Phase I trial to test this AdCh63/MVA prime-boost regimen in humans. This will mark the first time a chimpanzee Ad has ever been tested in human volunteers. “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. This vector may hold even greater interest in the future, based on the results from the STEP trial.

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 in the opening keynote address of the Keystone conference. “You can’t get there without it.”

But science is not the only barrier. Along with the scientific challenges, there are others 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) and rotavirus, there are still many issues to resolve about how best to deliver these vaccines to the world’s poorest people. Many of these issues aren’t resolved before vaccines are licensed and this accounts for the sometimes lengthy lag time between the introduction of vaccines in rich and poor countries.

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. For this, critical lessons can be learned from the delivery of already licensed vaccines. There is documented evidence of vaccines inducing varying levels of antibody responses in different regions of the world. Overall, vaccines that are administered orally tend to induce greater

immune responses in industrialized nations in agreement with the hygiene hypothesis, which postulates that in richer countries there aren’t as many enteric viruses or bacteria competing for the immune system’s attention.

“The ‘normal’ gut is very different in developing and industrialized countries,” says Levine. “In kids in developing countries the innate immune system is turned on full volume,” he adds. As a result, the vaccine gets “laughed at.” 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.

But so-called conjugate vaccines—those made by joining an antigen to a protein—typically work better in developing countries, Levine says. The Hib vaccine is one example of this phenomenon. While only 10% of US infants reach the required level of serum antibodies against Hib after a single vaccination, 29% of infants in Chile reached the same 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 expanded program on immunization.

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 introduced these fractional doses of Hib vaccine because its cost was eventually covered by GAVI. 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 a 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. 

What next?

As data analysis proceeds on the STEP trial, some future trials are placed in a temporary holding pattern

By Kristen Jill Kresge

Science is an empirical process. “We had a hypothesis, we tested it, and it didn’t work,” says Emilio Emini, head of vaccine research and development at Wyeth, referring matter-of-factly to results of the Phase IIb STEP trial, which showed Merck’s adenovirus serotype 5 (Ad5) candidate was not effective.

After the sudden failure of MRKAd5, many are wondering what will happen next with the string of other cell-mediated immunity (CMI) candidates that are in various stages of clinical testing or preclinical development—many of which use an adenovirus vector, albeit in slightly different form than Merck’s. Some of these candidates contain different immunogens and are also being tested in heterologous prime-boost regimens, unlike Merck’s, which involved multiple immunizations with the same vaccine. Other candidates use different serotypes of Ad, including Ad35, Ad26, or a chimeric version of Ad5. “They [different serotypes of Ad] are probably as different as two other viral vectors altogether,” says Dan Barouch of Beth Israel Deaconess Medical Center in Boston. These differences may result in better immunogenicity and a higher likelihood of efficacy, and researchers make several arguments as to why they should also get a fair trial. “[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 Peggy Johnston of the Division of AIDS, part of the National Institute of Allergy and Infectious Diseases (NIAID).

PAVE 100 was the next Phase IIb test-of-concept trial on tap—it was scheduled to begin just weeks after Merck and NIAID announced that immunizations in the STEP trial were stopped. This NIAID-sponsored 8,500-person trial aims to test the safety and efficacy of a heterologous prime-boost combination of DNA and Ad5 vector-based vaccine candidates that were developed at the Vaccine Research Center (VRC), part of NIAID, in collaboration with the HIV Vaccine Trials Network (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. The start of both of these trials was immediately delayed.

“There are substantial differences between the Merck product and the VRC product,” says Gary Nabel, director of the VRC. One difference is the heterologous prime-boost regimen. In both preclinical and clinical studies, researchers at the VRC report that the DNA vaccine candidate appears to effectively prime the immune system, resulting in an enhanced immune response following the boost vaccination with Ad5. The exact mechanism for this is unknown (see *One-two combination, LAVI Report*, May-June 2007), but Nabel says this combination “elicits a quantitatively and probably qualitatively different immune response,” including more diverse CD4⁺ T-cell responses and an increased magnitude of CD8⁺ T-cell responses than when Ad5 is used alone.

Nabel also points to the differing efficacy between MRKAd5 and the VRC’s DNA/Ad5 combination when evaluated in the SIV/nonhuman primate (NHP) model. In this model, he says, “The Merck vaccine really doesn’t work,” whereas the VRC’s DNA/Ad5 candidates promoted long-term survival in SIV-infected non-human primates and suppressed viral load during the early stages of SIV infection (*Science* **312**, 1530, 2006).

But when the latest data from the STEP trial was released at the HVTN meeting on November 7, researchers began grappling with additional questions (see *A STEP back?*, page 1). For now it is too soon to determine if there is any real link between enhanced risk of HIV infection and receipt of the MRKAd5 vaccine in some individuals. 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. But many researchers think it is still imperative to test other candidates that induce different immune responses. “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.

The opening of the PAVE 100 trial is still postponed and the protocol 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



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Peggy Johnston



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Scott Hammer



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 monitoring of the data collected while the trial is underway to ensure the safety of the volunteers.

"I am confident that the team will come up with a plan that will have equipoise and participant safety and scientific integrity all wrapped into it," says Hammer. This revised trial plan will then be sent to an oversight committee for review and comment. "The go, no go decision is not in our hands," says Hammer. "[It] is in the hands of the Division

of AIDS at NIAID. Peggy [Johnston] and Tony's [Tony Fauci, director of NIAID] office [make] the ultimate decision."

"[We are] looking very carefully at the differences between products," says Johnston. "As we decipher the immune responses that are made by this vaccine [MRKAd5] in humans, we can then have a better comparison with other products in the pipeline and make a best assessment whether the differences are sufficient for moving ahead," she adds. 

Andreas von Bubnoff contributed reporting to this article.

Sizing it up

Another issue raised by the STEP trial is the use of the Phase IIb test-of-concept trial to evaluate the efficacy of AIDS vaccine candidates. The idea of using these smaller, less expensive trials has become fashionable in the field as a way to get a quick read on whether or not a candidate is likely to protect against HIV infection or provide some level of partial protection that could limit disease progression. 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 Ad5 candidate in a Phase IIb test-of-concept trial and for planning an early analysis by the data safety monitoring board, which gave decisive information on the efficacy of the product even faster. "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 smaller trials, an idea known as screening-test-of-concept or STOC trials, could provide preliminary efficacy data for candidates that induce cell-mediated immunity even faster than Phase IIb trials. This novel clinical trial concept has been championed by IAVI as a way to conduct rapid, less costly trials in

far fewer volunteers (*AIDS* 21, 2259, 2007). 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 PAVE 100. "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. Emilio Emimi of Wyeth calls the concept of STOC trials a "nice design" but warns that "you can't cut the corners too tightly."

"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 cell-mediated immunity candidates that don't elicit neutralizing antibodies is a reduction in 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. "I don't think IAVI should reflect the prevalent or most conservative point of view," he says. —KJK

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 (see *Giving it their best shot*, page 9). Bernstein will establish the permanent secretariat of the Enterprise in New York City. The Bill & Melinda Gates Foundation will provide US\$20 million over the next four years for activities of the secretariat, and the US National Institute of Allergy and Infectious Diseases (NIAID) has committed \$7 million over the next seven years.

The Global HIV Vaccine Enterprise is an alliance of independent organizations united by a 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. But the “core of the enterprise is science,” said José Esparza of the Bill & Melinda Gates Foundation.

To date, the constituent organizations of the Enterprise have mobilized \$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.

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. Since the inception of this virtual consortium, the interim secretariat was held by the Gates Foundation. In 2006, Adel Mahmoud was announced as Chief Executive of the Enterprise but his appointment never came to fruition.

“We are convinced Alan is the ideal choice

[for executive director],” said Esparza. “He is an internationally renowned scientist. 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 views the fact that his scientific experience is outside the AIDS vaccine field as a strength. “I’m not an HIV researcher. I’m also not a vaccinologist,” said Bernstein, who sees being an “outsider” in the field as an advantage because he can bring fresh perspective.

Bernstein said the job of the Enterprise is 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; he compared the efforts to develop an AIDS vaccine to the campaign to tackle global warming. He suggested that involving more young researchers and generating new ideas is more important than seeking harmony in the field, which is seen by many as the primary focus of the Enterprise. “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 and spoke about prospects for developing an AIDS vaccine in the wake of this trial. “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.”

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The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996 and operational in 24 countries, IAVI and its network of collaborators research and develop vaccine candidates. IAVI's financial and in-kind supporters include the Alfred P. Sloan Foundation, the Bill & Melinda Gates Foundation, the Foundation for the National Institutes of Health, The John D. Evans Foundation, The New York Community Trust, the James B. Pendleton Charitable Trust, The Rockefeller Foundation, The William and Flora Hewlett Foundation; the Governments of Canada, Denmark, Ireland, The Netherlands, Norway, Spain, Sweden, the United Kingdom, and the United States, the Basque Autonomous Government as well as the European Union; multilateral organizations such as The World Bank; corporate donors including BD (Becton, Dickinson & Co.), Continental Airlines, Google Inc., Henry Schein, Inc., Merck & Co., Inc. and Pfizer Inc; leading AIDS charities such as Broadway Cares/Equity Fights AIDS and Until There's A Cure Foundation; other private donors such as The Haas Trusts; and many generous individuals from around the world. For more information, see www.iavi.org.

New funding focuses on innovation in global health

Recently two new funding initiatives geared towards fostering innovation within the AIDS vaccine field, and beyond, have been announced by IAVI and the Bill & Melinda Gates Foundation.

In September, IAVI launched a US\$10 million initiative to actively identify and fund small and medium-sized biotechnology companies that are developing innovative technologies in an effort to bring these novel applications to bear on the research and development of an effective AIDS vaccine. This new funding mechanism, called the Innovation Fund, was announced at the annual meeting of the Clinton Global Initiative in New York City. The Innovation Fund is being co-funded by IAVI and a grant from the Bill & Melinda Gates Foundation.

In October, at the Challenges of Global Vaccine Development Symposium, the Gates Foundation announced its new innovation program, called the Grand Challenges Exploration Initiative, which will fund academic or independent research and discovery efforts in several areas of public health. The Foundation has committed \$100 million to the program over the next five years and will supply 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."

Both of these new initiatives will 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." IAVI's Innovation Fund will target unconventional and unproven concepts from areas beyond those currently being investigated within the AIDS vaccine field. A panel of expert advisers will comb through promising technologies in diverse fields, such as cancer immunology and therapeutics and monoclonal antibody engineering, to search for the most promising and creative ideas. "We created the

Innovation Fund to bring the best and the brightest minds from outside the field to AIDS vaccine development," says Seth Berkley of IAVI.

Another guiding principle of both efforts is speed. IAVI's Innovation Fund will seek to identify and fund roughly 15 to 20 companies over the next three years with seed money that will help grantees quickly determine whether these technologies are feasible for AIDS vaccine research. The Fund will also conduct rapid evaluations of the potential technologies, awarding grants within just eight weeks.

The Grand Challenges Exploration program will review and deliver grants within three months of receiving applications, which will require no advanced data and be limited to two pages. The initial target areas for the grants will be announced early next year and proposals for this initiative, 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.

The grants issued by IAVI's Innovation Fund will focus primarily on areas that IAVI has identified as the major obstacles to AIDS vaccine development. They include technologies that address how to induce broadly neutralizing antibodies against HIV; how to identify and deliver HIV immunogens capable of inducing immune responses that can control HIV infection; and how to stimulate immune responses in mucosal tissues, which are a primary entry point for the virus during sexual transmission.

The need for pioneering approaches to AIDS vaccine design became even more apparent after Merck's leading AIDS vaccine candidate, MRKAd5, failed to provide any degree of protection against HIV infection or to modulate viral load in HIV-infected individuals in a large Phase IIb test-of-concept trial called the STEP study (see *A STEP back?*, page 1). "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."