



DATELINE **2011**

LOCATION **Kiev, Ukraine**

Masha, a study nurse at a clinical trial site in Kiev, is sixty-three years old. This makes her nearly a statistical anomaly in a part of the world that has seen life expectancy decline as health care services faltered in post-Soviet Union times.



It also means that she can remember when the first prevention research sites were established in her city; and how long it took to establish trust with the injection drug users, commercial sex workers and migrants; and how it was yet more difficult to establish a community advisory mechanism that brought leaders from these socially-stigmatized groups together with scientists and clinicians to discuss those first protocols.

In those days, she never thought the clinic would be in the position it is in now: having to turn down protocols because the site is already functioning at capacity.

She thinks back over the past few years: as part of an international trials network, Masha and her team have recruited volunteers for a follow-up test-of-concept study of a candidate that showed some efficacy in preventing heterosexual transmission.

Initially, volunteers wanted the vaccine regardless, and said that it would be unethical to have placebo-controlled trials. However, after community educators talked about the statistical uncertainty around the result, and about the different modes of transmission of HIV, these attitudes changed, and the study was launched.

But now there are several new candidates that have emerged as a result of basic science initiatives that were launched in 2006. No one knows whether these new strategies will work, but there is excitement about the animal study data; Masha has picked up the optimism of her colleagues at scientific meetings. She's been hoping that their site could start a safety trial of one of these candidates sometime soon.

But at a meeting today, the team looked at its resources and its plans for the year and decided it couldn't be done. The site has been supported for its trial-specific activities, but not for overall growth and expansion that would allow it to easily add another study. And the resources are stretched too thin on the test-of-concept trial already.

How did this happen, Masha wonders? And is it the case elsewhere in the world? Or was there an organized effort to build trial site capacity in line with the anticipated needs as new candidates emerged? She hopes so—just as she hopes that the studies that do happen include injection drug users and their partners. It's a position she would rather not be in: she cannot help test the hypothesis at her own already over-taxed trial site. Instead, she will have to wait and find out.

02. Reports from the Frontlines: Learning from Last Year's Clinical Trials

As we look back on this year's clinical trials of new prevention technologies, we are struck by a field that is teeming with activity and yielding insights at an invigorating rate.

Taking stock of this activity means taking a step back: lessons are coming from AIDS vaccine trials, but they are also coming from microbicide studies and from the array of other new prevention research endeavors discussed in greater length in chapter 4. This is especially true for areas of community involvement, ethical discussions, infrastructure, staffing and capacity building.

But there are also issues that are specific to AIDS vaccine trials. These include decisions about which candidates move forward into trials; how to sequence trials (of the same candidate and of candidates in the same class) and related investments in manufacturing; and selection of study endpoints, particularly for vaccines that might work by reducing the severity of disease progression.

This year brought developments on both fronts—some new, some familiar but newly-urgent, and some open questions. Taken together, they serve as signposts for where the field should (and should not) be heading in the coming years.

Calculated risks in trial sequencing

Last year we reported that the STEP study, a test-of-concept of Merck's adenovirus candidate, which is being run by Merck and the National Institutes of Health HIV Vaccine Trials Network (HVTN), doubled its enrollment from 1500 to 3000.

Even with the size increase, the single trial remains a test-of-concept which will, at best, give an indication of whether there is a trend towards efficacy that would then be re-confirmed in subsequent trials.

This year, Merck and the HVTN decided to begin preparations for a second test-of-concept trial which is known as HVTN 503. This trial is planned for South Africa and will test the same candidate, and include a possible study among adolescents (see chapter 3).

This decision is a risk, in that HVTN 503 will go forward before any conclusive data have been analyzed from the ongoing STEP study. More precisely, it is a calculated and exemplary risk. Merck's Ad5 vaccine is the lead candidate at the moment. The sequencing of the STEP and 503 means that we will minimize any delay in gathering additional data, should STEP indicate that the candidate has some efficacy.

HVTN 503 will also shed light on whether a vaccine that is based on epitopes that are conserved across clades but based on a single subtype (B) is immunogenic and effective in the South African setting, where subtype C predominates.

In the best-case scenario, where both trials show efficacy, there will be important lessons to learn about how to explain these sequencing decisions to various audiences. And in a situation where there is indeterminate or no efficacy, the field will have an opportunity to re-orient itself to new directions, based on the data.

FIGURE 4

COUNTRIES CONDUCTING PREVENTIVE AIDS VACCINE TRIALS (AUGUST 2006)



With the stakes as high as they are in the epidemic, a gamble on positive results is the right decision. This is the kind of forward-looking risk-taking that the field needs and should embrace.

At the same time, we must prepare for the ethical questions that may arise when and if a product that shows signs of efficacy in a test-of-concept trial is moved into a phase III study.

Various community constituencies have questioned whether a placebo-controlled trial of a product showing indications of benefit can be justified, and this concern needs to be addressed immediately.

Moving forward with a collaborative trial

The Partnership for AIDS Vaccine Evaluation, or PAVE, has continued its work on a collaborative trial of the Vaccine Research Center’s (VRC) DNA prime/Adenovirus-vector-based boost vaccine strategy. The three-part phase II trial of the combination has begun in the Americas, where the sites are being run

by the HVTN; in East Africa, where the International AIDS Vaccine Initiative (IAVI) and the US Military HIV Research Program (USMHRP) are running sites; and at HVTN sites in South Africa.

PAVE is testament to the fact that entities with different organizational cultures, funders, protocols, and approaches to everything from assays and blood draw procedures to precise definitions of adverse events can work together on a single trial. “This required a lot of negotiation and several inches of paperwork to arrive at a compromise,” says Assistant Director for HIV/AIDS Vaccines at NIAID, Peggy Johnston. “What is underestimated is the amount of time [that collaborations take].”

The VRC candidates contain *env* genes from multiple subtypes—another potential strategy for a vaccine that is effective around the world. Conducting trials in multiple regions is a critical first step to testing this hypothesis. A trial with the geographic spread of the current Phase II could not have easily been conducted

The Division of AIDS of the National Institutes of Health (DAIDS) houses various networks that fund assorted HIV/AIDS-related clinical trials across the world—and is the largest funder of vaccine and other prevention studies in the world.

All of the AIDS-related clinical trial networks funded by DAIDS have time-limited funding from grants, which generally last five years. This year, as part of the ongoing “recompetition” process, DAIDS considered applications from existing and proposed networks, all seeking funding for the next seven years.

The six networks were announced in June and will each address a different priority: vaccines (HVTN); microbicides (MTN); other prevention research (HPTN); maternal, pediatric and adolescents (IMPAACT); strategic initiatives (INSIGHT); and therapeutic clinical trials (ACTG.)

Clinical trial sites and research organizations around the world were able to apply to one or more of these networks, and so could potentially work with multiple networks at the same time doing different types of studies. Under this arrangement, DAIDS—which has its own, increased centralized budget for trials activities—offers a lump sum to a site, which covers core operations for all of the networks that it is working with. Each network then funds the direct protocol and study operations costs for the site. Sites were free to apply to as many networks as they liked, and the networks could approach promising sites as well.

This arrangement is one strategy for realizing the vision of “pluripotent” or multifunctional sites which can do multiple types of research simultaneously or in sequence. It’s a vision that has gained a lot of traction in conference-room conversations about clinical trial-site capacity. In theory, it offers a cost-effective approach to maintaining sites, using trained staff and infrastructure effectively, and ensuring that there is less “down time” between trials.

But how does the reality look on the ground?

As a first step towards answering this question, AVAC spoke to seasoned investigators in South Africa about how their sites are faring under this system.

At press time, most sites were waiting to hear the outcomes of their applications, and most had applied to more than one network, in hopes of broadening from areas of proven experience (be it prevention of mother-to-child transmission, ARV delivery, vaccines or microbicides) into newer activities.

Overall, we heard good news and some cautionary notes. There was broad consensus that multi-tasking was a cost-effective approach, but there was also concern that some essential activities might be under-funded. Most sites also felt that they would need to find additional funding resources for trial-related activities from a limited local and international pool.

Staffing was a major concern. Because staff funding is often related to specific protocols, salaries have to be apportioned across different projects and sometimes even different funders, as no single funder is really prepared

to support entire, long-term staff structures. Instead, they prefer to pay for part of an individual staffer's time. The result is a juggling act, which can sometimes fall short. One investigator, who, like many interviewed, asked to speak anonymously, said that this could become a "huge problem." Another site reported losing a fairly senior and experienced investigator as a result.

Another area of concern was capacity development—the catch-all phrase which includes developing, training (and re-training) staff; maintaining and expanding infrastructure; and building and sustaining strong relationships in the community and at multiple levels of government and the media.

Here, too, human resource issues loom large. "Capacity development will need further funding from the outside," says Glenda Gray of the Perinatal HIV Research Unit at the Chris Hani Baragwanath Hospital in Soweto. "No one is willing to pay to develop scientists or researchers. We will need to be innovative to ensure that capacity development occurs."

Gita Ramjee of the South African Medical Research Council says that the sites that are best positioned to become multifunctional are ones that already have strong capacity, raising the question of whether and how new, additional capacity can best be developed. "The [DAIDS] funding will be for research within clinical trial sites with trained staff and infrastructure," she says.

Other areas of concern include long-term and essential issues of social marketing and communication about the site's activities, HIV research and services such as counseling, testing or treatment. Community mobilization, recruitment and retention are also time- and labor-intensive and can be under-funded through protocol-specific budget lines, as well.

"The big issue is that funding occurs on specific protocols, so money only flows when you are enrolling or have activated a protocol. There is very little money to develop sites' community relations. Sometimes it can take up to 18 months to get real community buy-in and no one is prepared to pay for the preparations sites need to do before trials are started," says Gray.

Balanced against these concerns is the over-riding sense that working with the NIH is a truly collaborative exercise, and that there are many benefits—from training opportunities and infrastructure development to information exchange with colleagues in other countries—that come from working within the DAIDS networks.

Given the range of trials that are ongoing or planned for the coming years, it will be critical to build on these strengths and to pay close attention to unmet needs, including ongoing community work, development of new sites, and expanded relationships with existing treatment and care infrastructure. Addressing these issues is critical to making the idea of multifunctional sites a credible and sustainable reality.

"But," says Gavin Churchyard, a principal investigator at Aurum Health Research, which is working in South Africa's mining communities, "our complaints are small in comparison to the good work being done with the networks and the NIH. It is mostly a very positive experience."

FIGURE 5

ESTIMATED NUMBER OF ADULTS AND CHILDREN NEWLY INFECTED WITH HIV, 2005



by any single partner, since each has focused its efforts in a particular region. For this reason, PAVE's work to date and in the planned PAVE 100 trial (whose test-of-concept protocol is in collaborative development) is a strong example of where collaboration is a wise and necessary choice for moving forward.

Trouble-shooting in the Thai Prime-Boost Trial

In late 2005, the Thai Prime-Boost trial of Sanofi Pasteur's ALVAC vCP1521 and VaxGen's AIDSVAX enrolled its last volunteer, reaching its target number of 16,402 volunteers from Chon Buri and Rayong provinces in Thailand; all immunizations were completed at the end of July 2006.

One of the most important lessons to be learned from this trial—aside from the simple statement: it can be done—is that collaborative trouble-shooting can help address problems that emerge after the trial is underway. In the early part of 2006, the trial was seeing worryingly low retention rates of 88 to 90 percent says Nelson Michael, a principal investigator from the USMHRP.

The low retention rates (which reflect per protocol attendance at study visits) were attributed to higher-than-expected levels of migration from the rural provinces where the study population was drawn from, to the capital city of Bangkok.

To address this issue, the trial team worked with the Thai Ministry of Public Health (which has provided clinic space for the trial site activities) to add study site facilities to clinics in the Bangkok area and to train outreach teams to help trace volunteers who do not return for follow-up. As of July 2006, retention was up to 95 percent—a sign that the intensified and collaborative strategy had worked, says Michael.

Sharing experience of problem solving is essential: while trial administrators may be reluctant to air their issues in public forums, making case studies of where issues arose and were addressed will only improve future endeavors. While we cannot conduct trials simply for the sake of this type of information, we should make every effort to gather and disseminate it widely.

RECOMMENDATION: Ensure that the various strategies for current trials and plans for future ones are shared at a meeting of a reconstituted Enterprise Clinical Trials Working Group, to ensure that lessons are learned, capacity needs are anticipated, and decisions about when and how to conduct and sequence trials are not made in a vacuum by any single sponsor.

Addressing the issue of vaccine-induced seropositivity

Many AIDS vaccine candidates include synthetic viral components that can cause a positive reaction in standard HIV diagnostic tests (which look for antibodies against the virus, rather than the virus itself). This phenomenon of “vaccine-induced seropositivity”—in which an uninfected volunteer tests positive for HIV antibodies—is a challenge that the field has faced, in theory, for several years.

But until recently, the issue has garnered little attention: trials were small enough to allow case-by-case attention to volunteers; or the candidates did not induce responses that made seropositivity an issue. The current Ad5 candidates may be changing this. Both the Merck and the VRC candidates are significantly more immunogenic than previous candidates. Most HIV tests detect antibodies generated against *env*. Merck’s Ad5 candidate does not contain *env*; the VRC’s candidate does.

The seeds of a solution may lie in the work of Hana Golding of the US Food and Drug Administration, who this year published a paper about HIV SELECTEST, a new assay that identifies antibodies against sequences of HIV that are not part of most current HIV vaccine trials.¹

This is welcome news. But it is only a first step. Issues of regulatory approval, cost, manufacturing capacity, and existing testing algorithms at national and site level must be addressed before SELECTEST can be considered a complete solution.

RECOMMENDATION: Develop a timeline with milestones for validating SELECTEST as a useful tool for addressing vaccine-induced seropositivity, securing approval, and moving to widespread, affordable access where needed.

Pregnancy

At the biannual Microbicides 2006 meeting in Cape Town, South Africa, much attention was given to higher-than-expected rates of pregnancy among women volunteers, particularly in the five ongoing efficacy trials of six products that are being conducted in multiple sites in sub-Saharan Africa and elsewhere. Sites are reporting rates of pregnancy as high as 64 pregnancies per 100 person-years.

These rates of pregnancy come among volunteers who are counseled about the need to use contraception and avoid pregnancy for the period of immunization; the data are ample evidence that these messages cannot overcome many other factors affecting women, including inability or unwillingness to use hormonal contraception or other highly-effective methods.

In some instances, women may decide to join the trial if they are planning to get pregnant, since the general level of medical care is greater than that available to the general community.

Since women who remain pregnant cannot continue using the study product (none of the candidates in development have undergone sufficient reproductive toxicity screening), they are removed from the active study protocol, although they continue to be followed up. This means a lower sample size and, by extension, the potential for reduced statistical power in the trials.

There are multiple options for addressing this challenge, from expanding the study cohort once the trial is underway, to enhancing on-site delivery of contraception, to targeting post-partum women, who may be most interested in family planning to space children.

¹ Human Immunodeficiency Virus (HIV) Vaccine Trials: a Novel Assay for Differential Diagnosis of HIV Infections in the Face of Vaccine-Generated Antibodies. *Journal of Virology*, Mar. 2006, p. 2092–2099.

RECOMMENDATION: AIDS vaccine trial planners and advocates should actively engage the issues related to pregnancy, contraception, and women’s reproductive choices that have been highlighted by recent microbicide trials. AIDS vaccine trials historically have enrolled fewer women than men in many parts of the world. Addressing these issues in consultations with communities, local health authorities and international advocates could prove to be an important step towards facilitating women’s participation in these trials.

Making investments to reaching the “right” populations

The past year brought reports from scattered trial sites—including microbicide studies in Ghana and Nigeria, and a behavioral intervention among injection drug users in Russia—of instances in which the incidence among trial volunteers was lower than expected or predicted by study planners, with the result that the site lost its statistical power to answer the study question.

These reports underscore the need to invest the time and energy required to reach the right populations for prevention trials: those who are at high-risk of infection and therefore in high need of new interventions.

In many instances, the same factors that contribute to individuals’ vulnerability to HIV infection also present challenges from a trial planner’s perspective. High-risk women in the United States—who remain largely overlooked in many arenas of prevention research—are one example. AIDS continues to spread among poor women, often with substance-abuse problems, whose addictions can lead to homelessness, incarceration, and instability that complicate follow-up.

The key to addressing these issues is building relationships with communities of potential AIDS prevention trial volunteers. This takes time, energy, and an authentic commitment to creating an environment of mutual trust at every level—from the study team and the clinic space, to the attitudes of political, community and media leaders.

It also requires that sites take a context-specific approach to their recruitment efforts. In the case of the STEP study, each site has developed its own approaches, which range from street-based campaigns using former commercial sex workers to internet-based campaigns for San Francisco’s gay men to outreach to individuals who test HIV-negative at a voluntary counseling and testing center in Haiti. Successful sites have also been able to build trust by responding to rumors circulating in the community: when word went around in San Francisco that the vaccine candidate might contain live HIV, the site developed a simple ad campaign focusing solely on this issue—and saw its outreach numbers jump.

This approach appears to be working. As of mid-2006, the STEP study had met its target for recruiting high-risk volunteers, and was, if anything, exceeding its projected rate of “events,” says Mike Robertson of Merck.

“We emphasize to our sites that since this is an event-driven study, it’s not just about getting bodies through the door [to enroll]...but to focus on getting high-risk people,” Robertson explains. An event-driven study is one in which enrollment and follow-up continues until a threshold number of events—in this case, new infections—have occurred. In other trial designs, a specified number of people are followed for a pre-determined amount of time.

RECOMMENDATION: Document and disseminate best practices in innovative epidemiological survey techniques to identify “hotspots” of incidence recognizing that this is an on-going process; fund and support projects for the resource-intensive work of reaching and retaining particularly vulnerable groups.

The need for consensus on “good community practice”

This item is last on this list but is first among AVAC’s own priorities. As we look at the state of the field and the array of scientific, ethical and logistical questions that are being raised by current trials in multiple fields,

we feel more strongly than ever that a consensus on “good community practice” is long overdue. This new “GCP” would be a universal document that would help the scientific community and communities “in the field” ensure that every trial that is initiated meets agreed-upon criteria for substantive and sustainable engagement with the issues.

In the next year, AVAC commits to playing an active role in developing a draft set of “GCP” guidelines.

To do this, we will start by engaging in dialogue with a wide array of stakeholders including researchers, community members, service providers and international decision makers. We began this process with a skills-building session in Toronto, and we are already using the insights and ideas from that initial collaborative step to move the process to the next level.

Putting it all together

From closely-spaced test-of-concept trials, to collaborative efforts, to trouble-shooting in the largest AIDS vaccine trial to date, the field is experimenting with different ways of working to evaluate candidates. At the same time, other research endeavors are providing relevant findings about reaching and working with various communities.

We must plan today with an eye towards the issues that will emerge in the future. Decisions about trial sequencing will only get more complicated as data from other prevention trials emerge (see chapter 4).

Nor will it be easy to interpret the data from the current test-of-concept trials—even if it is positive. The Merck candidate is being evaluated in trials that look at viral set point. But the field lacks validated endpoints for vaccines that aim to prevent disease progression. (It takes too long and would raise ethical issues to track infected volunteers without treatment over time; yet viral set point or peak may or may not be a useful indicator of a vaccine’s impact on long-term health outcomes.) VRC head Gary Nabel says that PAVE is considering memory cells as a surrogate marker of efficacy. This, too, has yet to be validated.

And so we must plan now so that we have capacity, community buy-in, and clear pathways to evaluate candidates that show different kinds of efficacy in initial trials. At the same time we must also plan for the time, several years from now, when a new generation of candidates begins to emerge from CHAVI and CAVD initiatives. Will capacity be there? Will communities be engaged and willing to participate in the full sequence of trials—from Phase I through efficacy—once again?