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AIDS Vaccine 2007: An advocates' (opinionated and selective) meeting report

This year's AIDS Vaccine Conference didn't get much attention from mainstream media. A handful of newspapers from Seattle, where the meeting was held, published broad articles peppered with familiar sound bites: an AIDS vaccine is, potentially, a critical tool for ending the epidemic; the first data from [test-of-concept trials](#) will provide important insights for the field; enduring scientific challenges mean that we are still many, many years from having a candidate that approaches [sterilizing immunity](#).

Notably, some of these well-known themes were packaged under new headlines. One [Seattle Times article](#) ran with a headline which suggested that the focus for AIDS vaccines had shifted to "stopping transmission." This refers to the hope that a vaccine which lowered viral load could reduce the likelihood that someone who was immunized and later became HIV positive would pass the virus to his or her partner. Has the field really shifted its vaccine-related goals to reducing infectiousness? Not yet. (This was one of the topics on the agenda at a meeting on vaccine endpoints that AVAC attended in Paris this month). It is critical that we track, and work together to influence the ways that media outlets package and, inevitably, simplify complex messages about what we can and cannot expect from current generations of AIDS vaccines.

Turning away from the headlines, to the Seattle conference itself. AVAC, along with nearly a thousand other participants attended sessions which contained far more detail than any of the news coverage. For all the added specificity, the themes we heard were, by and large, familiar. The major sessions included reports on work on antibodies, variations on viral vector based candidates with no major breakthroughs to speak of. This isn't surprising—it's the reality of the slow and steady chipping away at major scientific challenges that the field has committed itself to over the past few years.

In this meeting report, we do a whirlwind tour through some of the major areas discussed at the meeting and then zero in on the two talks that we think defined the meeting by grappling, head on, with challenges that all of us in the field of AIDS vaccines are going to face in the coming months.

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Vaccine strategies

Oral abstract sessions (in which speakers have 15-20 minutes to present their work) on vaccine concepts and design, and on clinical trials, provided updates on ongoing work, including human clinical trials and basic scientific efforts.

Presentations on antibody-related projects described how various teams are trying to fine-tune our pictures of the structure of HIV proteins* and the [neutralizing antibodies](#) that bind them. Others described work with viruses that are isolated shortly after people have become infected. In both instances, the goal is to generate pictures of what the virus looks like when it is vulnerable to neutralization, so that we can develop antibody-inducing [antigens](#) for future vaccines. But, as usual, there are no new antigens even approaching human trials—a reminder of the long and uncertain road that lies ahead.

Turning to reports on what *is* in human trials: here, too, most conference talks covered familiar territory. Several presentations provided safety and immunogenicity data from Phase I studies of newer candidates. All these candidates were variations of viral vector with or without DNA prime strategies, with vectors including modified vaccinia Ankara virus (abstract [OA02-01](#); [OA02-02](#)) and fowlpox (abstract [OA02-02](#)). Reports from animal studies included explorations of live-attenuated measles virus vector and BCG (Bacille Calmette Guerin).

Some presentations looked at the different ways that we can measure [immunogenicity](#). Various measures of the breadth, specificity, and functionality of immune responses are increasingly being used to better define what we mean by a vaccine being “immunogenic.” As in previous meetings, the emphasis was on measuring the “polyfunctionality” of [T cells](#) induced by vaccines. Many traditional assays (tests) of T cell function have measured cell secretion of a substance called interferon gamma, using this as an indicator, or [surrogate marker](#) of, cell activity.

Polyfunctionality refers to T cells’ ability to perform multiple key functions, including secretion of other substances, in addition to interferon gamma. (For more explanation on this topic, [see this report](#) from the Treatment Action Group (TAG).) Although arguments can be made about what and how to measure, the fact remains that until there is a vaccine that shows efficacy, we will not know which assays are most useful. If there is an efficacy finding, the field will be able to link specific types of immune responses with some form of vaccine-related benefit, thus identifying a correlate of protection.

Among the familiar topics, there were some newer points of interest. These included reports from non-human primate studies of a vaccine delivery strategy called electroporation, which uses controlled levels of electrical current in the administration of the vaccine. These studies suggest that this method leads to increased immune responses, compared to traditional injection of the same vaccine.

In addition, there was a suite of presentations on therapeutic vaccines—a topic which has received limited attention from the field. Several posters also provided updates on the first pediatric vaccine trial, which was launched in October 2006. The trial aims to assess the safety and immunogenicity of vaccine candidate ALVAC-vcp1521 in infants; the next step could be to evaluate whether a neonatal vaccine reduces infants’ risk of acquiring HIV through breastfeeding.

The bottom line from an advocate’s perspective: the timelines for antibody-inducing vaccines are long and uncertain—and need to be honestly communicated. And, as AVAC argues in this year’s [AVAC Report](#) (also launched at the meeting), we need to make truly novel approaches a top priority: selective testing of potential “me-too” products (another DNA-MVA, for example), a focus on [live-replicating vectors](#), and swift follow-up on innovative delivery strategies and [adjuvants](#) that could improve current candidates. Some of this is happening—but more needs to be done.

Clinical trials

Clinical trial capacity, conduct, community engagement, and other issues were addressed in a handful of abstract-driven sessions and plenary speeches at last year’s AIDS Vaccine Conference. In this year’s meeting, the official program corralled these topics into poster discussion sessions, with a single symposium covering a wide variety of topics.

Future meetings should consider allocating session time for more extensive discussion of topics such as pregnancy rates and contraceptive use among women trial participants (abstract [P06-31](#) and abstract [P07-12](#)) and vaccine-induced seropositivity, which was addressed tangentially in an interesting poster ([P06-04](#)) on a Thai-led survey of test-kit use among health centers in areas where the Prime-Boost trial was taking place.

Issues related to social and behavioral science, community involvement and the overall conduct of clinical trials were discussed at satellite sessions, including "Connecting the Dots in AIDS Vaccine R&D" sponsored by AVAC, the [HVTN](#) and [NIAID](#), and "Expanding Capacity and Promoting Regional Networking to Accelerate HIV Vaccine Development in Developing Countries" hosted by the [African AIDS Vaccine Programme](#). (For presentation downloads see left column.)

An IAVI-sponsored session also held before the opening ceremony discussed the rationale for establishing local laboratory reference ranges (“normal” ranges for various blood chemistry analyses) in advance of launching screening and recruitment efforts. Here, the issue is that when reference ranges from the US or Europe are used as the basis for screening those interested in joining a trial in Africa, many potentially-eligible participants may be excluded simply because what is “normal” blood chemistry in the US is not “normal” in the developing world. For more information, see <http://iavi.org/viewfile.cfm?fid=46429>.

Although they deal with quite disparate topics, both the Thai presentation on surveys of test-kit usage and the IAVI meeting on lab ranges underscore the need for trial sponsors to invest in research on context-specific issues in advance of launching major studies.

Also of interest: Updates on ongoing clinical trials (Step, Phambili, and the Thai Prime-Boost study, abstracts [P06-03](#); [P06-41](#)), which touched on retention rates, community engagement strategies, and rates of risk behavior. Regarding the last, a poster from the Step study ([P06-07](#)) reported on trends in the rates of risk behavior (drug use, number of sexual partners, rates of unprotected anal or vaginal sex) among trial participants, 66% of whom had been followed for

six months at the time of analysis. Overall, self-reported high-risk sexual activities and drug use decreased from baseline to week 26. In a smaller group of participants, who had been followed out to one year, risk behaviors rose slightly after their initial decrease—but did not exceed baseline levels.

The bottom line for advocates: The Step, Phambili, and Thai Prime-Boost trials are all on track in terms of enrollment, retention, and incidence rates to give us answers in the next two years. Risk behaviors in the Step study are following a trend similar to [what was reported in the VaxGen study](#): with risk behaviors dropping after enrollment, then rising slightly—though not exceeding baseline levels.

Talks to remember

Was there anything newsworthy? Absolutely. Two presentations—one by Mark Feinberg of Merck’s Vaccine Division, and one by Scott Hammer, from Columbia University and the chair of the protocol committee for the planned PAVE 100 trial—laid down gauntlets for the AIDS vaccine field. Both Feinberg and Hammer covered familiar ground regarding planning for future trials and for potential efficacy data. These topics are not entirely new. They’ve been the subject of lots of discussion in recent months and received significant attention in this year’s AVAC Report. However, these presentations were singular in their explicit formulation of upcoming challenges.

Feinberg’s presentation, “*From Test-of-Concept to Global Access: Needs and Questions Moving Forward*,” took a long, hard look at the issues that might arise following the announcement of test-of-concept trial results.

The vaccine could show impact on viral load but not on prevention of infection. No other vaccine has ever been licensed on the basis of this kind of effect and, as Feinberg described in great detail, the pathway to getting to licensure of such a vaccine is overwhelmingly vague.

One of the major gray areas has to do with [regulatory authorities](#). Feinberg identified a number of questions, including, what kinds of data will different regulatory authorities in developing and developed countries want or need? As he explained, if the vaccine does show impact on viral load, it could still take years of follow-up to determine whether this translates into a “clinical benefit” in terms of slower disease progression. Tracking vaccinated individuals’ CD4 cell counts after infection could be an alternative—but would such a [surrogate endpoint](#) (i.e., preserved [CD4 cell](#) count as indirect evidence of slower disease progression) be acceptable for regulatory authorities?

Other tough questions will arise in ethical arenas. And here, neither AVAC nor any other group doing education and messaging can afford to be complacent. All of us have done hard work, together and separately, on explaining what a test-of-concept trial can and cannot tell us (see [box](#) and [table](#) from AVAC Report 2007 for more info); underscoring the need for additional studies to confirm any positive results; and outlining the questions about durability and clinical benefit of a viral-load effect, which will remain when these initial trials end.

But despite much work having been done, we must all be prepared for global attention from a wide range of stakeholders who may or may not be familiar with these messages, once the trial results are released. If there is a positive finding, there will be questions about why the vaccine cannot move quickly to licensure without additional trials; why it is (or is not) being given immediately to all people in the communities where the trial took place; and whether the strategy should become a placebo for all future studies.

These are questions that the relatively insular AIDS vaccine research field has not answered internally—and which will almost certainly take center stage if there is a positive result. Right now, we're not ready with the answers—not at AVAC and not in the broader field. There is critical work to be done in ethical discussions, community forums, communication planning, and future trial designs in the coming months. And all of this should be done in a coordinated manner. As Feinberg said, “Ideally, an effective coalition should be established before it is needed.”

Feinberg went on to explore issues that might arise if a partially-effective vaccine were licensed. Who would pay for its delivery, he asked—even if Merck were to make the vaccine available at cost in poor countries, there would still be tremendous costs associated with programs for delivery.**

The other presentation that made us sit up and take notice was made by Scott Hammer, the protocol chair for the planned PAVE 100 trial, which currently aims to enroll 8,500 people to test a DNA-adenovirus-based prime-boost vaccine strategy under development by the NIH's Vaccine Research Center (VRC).

Hammer's talk was the most detailed attempt we've seen to quantify the ways that HIV prevention trials may have to change as new prevention technologies come on line. Using the projected sample size, incidence rate, and gender breakdown for the PAVE 100 study, Hammer showed theoretical projections of what might happen if various new interventions were introduced. For example, he showed how trial size would jump if 80% of men enrolled were circumcised (as opposed to the 40% circumcision rate in current trial projections): the trial size might jump from 8,500 to 9,945 participants, he said. Introduction of HSV-2 treatment for prevention would also reduce incidence and, therefore, necessitate larger trials: here, the shift could be from 8,500 to 11,305 participants.***

These were initial, illustrative calculations, which will likely change over time and as more information becomes available. But they're an absolutely critical element of planning for future prevention trials. Without a clear idea of changes in sample size, and, by extension, trial cost, we cannot make accurate estimates of resources needed for large-scale efficacy trials.

The bottom line for advocates: Now is the time for developing these positions—and for accelerating preparation for good, bad, or indeterminate news from today's vaccine trials. One point of intersection between Hammer and Feinberg: the question of when and how new prevention strategies should be added to trial protocols. We're already seeing a variety of approaches to male circumcision—and an unfortunate lack of clear policy coming from any major research sponsors. This is not an area for ad hoc decision making. Just as the field should

have a clear and public consensus on ensuring access to ARVs for trial participants, it should also have a clear and community-informed approach to redefining the standard of prevention in light of new research findings. In the AVAC Report launched at the conference, we presented our own position, which you can read at http://avac.org/pdf/reports/2007_Report/section_2.pdf.

* In the standard schematic drawing of HIV, there are “spikes” that stud the surface of each viral particle. These spikes are proteins, which are large molecular compounds. Proteins found on the surface of HIV include gp120 and gp41. Both have complex structures and play key roles in viral infection of target cells. The structure and composition of viral proteins are determined by viral genes. In viruses, as with people and all living things, genes are the blueprint for life’s design.

** AVAC agrees that this is an important question to raise; we hope that Merck will make explicit tiered-pricing commitments part of all of its future-oriented AIDS vaccine planning, as the lack of a clear pricing structure for its HPV vaccine continues to be a hurdle in resource-poor settings.

*** In communication following the conference, Hammer stressed that these are preliminary estimates and should be used and cited as such.