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Barcelona 2002: A Retrospective, and a Look Ahead

This issue of the* IAVI Report *is devoted to a collection of articles on key themes in vaccines at the XIVth International AIDS Conference.

BY PATRICIA KAHN

This time around, the world's largest AIDS conference had a very different tone than its predecessor. While Durban 2000 was a turning point in galvanizing global momentum for an all-out response to the epidemic, Barcelona was permeated with the hard reality that the world has not yet risen to that bold challenge, either in terms of political will or committed funding. So once again, this bi-annual gathering was focused on the epidemic's unrelenting spread and the world's woefully inadequate response.

Yet at the same time, the conference spelled out plainly what can be achieved now, by using proven prevention measures and tackling prevention and treatment together rather than pitting them against each other.

"We're still hearing a lot of words, but not the scale," Columbia University economist Jeff Sachs told the audience. "The scale of what's needed has never been more clearly understood. The number of deaths on the line has never been clearer."

"In Barcelona, people were coming to realize that there are no magic bullets in this epidemic," said Jose Esparza, who heads the WHO/UNAIDS HIV vaccine unit. "We have to accept that there are no ideal interventions, and use what is in our hands."

Barcelona also marked the debut of Richard Feachem at the helm of the Global Fund on HIV/AIDS, Tuberculosis and Malaria, on which many hopes are pinned. In a much-anticipated speech, Feachem vowed to fight for a "massive increase" in donations, to support treatment as well as prevention, and to run the Fund in an accountable manner with built-in outcome measurements. He also expects to release multi-year projections of resources needed and anticipated rates of expenditure following the Fund's Board of Directors meeting in October.

We begin our coverage with a brief look at a study released just before the conference, on what a comprehensive response would entail, what it could achieve, and how much it would cost. We also speak with the conference's community track co-organizer, South African advocate Shaun Mellors (p. 10), about the challenges this entails, and about what was and wasn't accomplished at Barcelona.

On the vaccine front, many speakers focused less on recapping progress than on mapping the way forward, identifying gaps and proposing solutions to some of the thorny challenges ahead–topics that provided the meat of a one-day vaccine satellite meeting (p. 2). The main conference offered updates of ongoing clinical trials, reports on newer vaccines in the pipeline (p.15) and presentations on the difficult task of designing efficacy trials for candidates that may be only partially effective (p.7).

Underscoring the growing recognition of links between prevention and treatment, it was striking that some of the most provocative talks for vaccine developers focused on infected people or animals. Topping the list was Bruce Walker's report of an HIV-positive man who became "superinfected" with a second HIV strain, despite an immune response that controlled the first virus—a finding widely portrayed in the press as a major blow for vaccines. Here we take a closer look at the case and its lessons, and at the broader issue of HIV double infections (p.3). Last, we look at a new therapeutic vaccine that's showing some hints of success in chronically infected monkeys (p.13)—where there's been precious little success with immune-based treatments so far.

The Epidemic's Future: Two Scenarios

The international AIDS conferences traditionally begin with an update on the global epidemic, and Barcelona was no exception (see p. 8). But there was a difference: This year, Bernhard Schwartländer (WHO, Geneva) also presented a study on projected numbers of new infections, but with two sets of predictions: one, if the global response remains at today's

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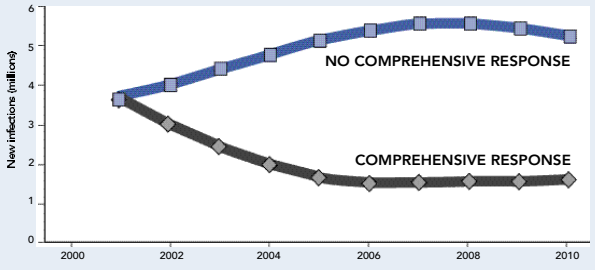
levels, and another, if it scales up to meet the targets set at the United Nations General Assembly Special Session on HIV/AIDS in June 2001. The analysis was based on reviewing the impact of prevention activities in 126 middle- and low-income countries, while the comprehensive response assumed a package of proven prevention and treatment interventions costing about $9.2 billion yearly by 2005. (The study was published in *Lancet* 360:73;2002.)

Projected global new adult HIV infections with and without a comprehensive response



Source: Adapted from Lancet 360:73;2002 and B. Schwartlander plenary lecture

The result was stark and simple (see figure): without a comprehensive response, another 45 million people will become infected by 2010; with it, 29 million of these infections (nearly two-thirds) can be prevented. The analysis also found that a one-year delay in mobilizing a response will cost 5 million of these preventable infections; a three-year delay, half of them.

Other speakers referred repeatedly to this blunt message. For example, Helene Gayle of the Bill and Melinda Gates Foundation, pointed to a 1993 WHO projection that spending $1.5 billion on prevention could halve the number of new infections by 2000 and save $90 billion in related costs. "Will we continue to wait until the cost has doubled, tripled, quadrupled and tens of millions more lives are lost?" she asked. "Ultimately, we will pay now or pay later." ◆

VACCINE SATELLITE: LOOKING AT THE BIG PICTURE

For the first time since the International AIDS Conferences began in 1983, this year's event featured an official satellite meeting on vaccines. "AIDS Vaccines for the World: Working Together to Accelerate Development and Delivery,"* attracted over 375 people from 61 countries and a wide range of sectors, reflecting the diversity of conference participants. The agenda mirrored this breadth, with presentations on progress—as well as the gaps and challenges ahead—from the scientific, political and community perspectives.

A full report is available at www.iavi.org/barcelona. Here we highlight some of the key themes and viewpoints that emerged.

The Bottom Line: Political Commitment

The need for greater political support of vaccine development was one of the most frequently-raised themes, underscoring its key role in virtually all stages of the vaccine effort.

That tone was set in the meeting's first presentation, given by Kapil Sibal, Member of Parliament in India. Sibal belongs to a bipartisan group of Parliamentarians working to draft legislation supporting a comprehensive national response to HIV/AIDS, establish the necessary financial mechanisms and build a supportive, rather than punitive, legal framework that protects human rights and combats stigma. "If we don't do something, we'll have an epidemic [like sub-Saharan Africa's] on our hands," he said.

Paolo Teixeira, director of Brazil's National STD/AIDS Programme in the Ministry of Health, described the infrastructure supporting the country's widely-hailed response to the epidemic, and that now provides a foundation for vaccine trials—from nation-wide health care clinics and diagnostic labs to surveillance and ARV distribution networks. Brazil also has many active AIDS NGO's, a robust research community and a national vaccine plan.

Early commitment and a national vaccine plan were also key factors in enabling Uganda to host Africa's first AIDS vaccine trial (in 1999-2001), according to David Apuuli, Director-General of the Ugandan AIDS Commission. With this experience in hand, as well as clinical trials infrastructure and trained personnel, the country has now revised its vaccine plan to further define procedures and standards for trials and to help prepare for future access. Still needed, said Apuuli, are more international partnerships and funding to expand vaccine activities.

While national vaccine plans are becoming increasingly common in the developing world, the Canadian government's announcement just prior to Barcelona that it will prepare a vaccine strategy makes it the first industrialized country to do so.

Even in the scientific sessions, political commitment was a frequent theme. For example, VaxGen president Don Francis criticized the widespread "can't do" attitude towards AIDS vaccines in politics and media, and the lack of social value placed on vaccines. "If the world really cared, we'd have more candidates," he said. While the cost of making and testing vaccines is high (VaxGen's product has cost US $200 million), Francis pointed out that this is a small fraction of the $18 billion spent annually in the US on AIDS treatment and care.

Advocacy: "Principled Leadership and Angry Activism"

Addressing the need to increase political commitment, several speakers spelled out some concrete steps. David Patterson of the Canadian HIV/AIDS Legal Network (which held a satellite meeting the previous day; see www.aidslaw.ca), urged greater links between vaccine and treatment advocates, emphasizing their common issues—such as commu-

**held on 6 July 2002 at the Hotel Arts, Barcelona, with 18 sponsors from 5 continents; coordinated by IAVI.*

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Superinfection: What Does It Mean for Vaccines?

BY PATRICIA KAHN

Barcelona introduced a new word—and a new worry—into the common AIDS parlance: superinfection. In one of the conference's most widely-discussed presentations, Bruce Walker (Massachusetts General Hospital, Cambridge) described the case of an HIV-positive man who became infected with a second, closely related strain—despite having strong cellular immune responses that were controlling the first virus without drugs. The finding set off alarms, in the press and the corridors, that it could portend dim prospects for developing an HIV vaccine (at least one based on cellular immunity) that protects against even minimally divergent strains.

Walker's wasn't the only report of superinfection, although the others went relatively unnoticed. In one (Abs. #ThOrA1381), Stephanie Jost from the University of Geneva described a man who became superinfected with a clade B virus about two years after initial infection with an A/E strain. (This finding, first reported at the Retrovirus Conference in Feb. 2002,* was since published in *New Eng. J. Med.* 347:731; 2002.) And a Thai-CDC collaboration found two potential cases of superinfection in IDUs, each involving a second subtype (#TuOrC1194; *J. Virol.* 76;7444; 2002), although the methodology used could not completely rule out simultaneous transmission (or two separate transmissions occurring close in time). But none of these three patients was found to have immune responses that recognized the new strain at the time of superinfection—in contrast to Walker's patient, where cross-recognition was clearly present.

From a public health perspective, the take-home message is straightforward: Superinfection can occur, and can lead to worsening of disease—making safe sex precautions essential for HIV-positive individuals.

But for vaccines, the lessons are more ambiguous. Alongside the question of failed immune protection, it's unclear whether this reflects what would happen with a vaccine. Nor is it known whether superinfection (especially with a virus of the same clade) is a rare event, or far more common than people have realized. While the first question is largely unanswerable in the short-term—and Walker spelled out some caveats about extrapolating to vaccines—data on the frequency of superinfection should emerge from an ongoing study in Tanzania (#MoPeC3509).

*Abs. #757W at www.retroconference.org/2002

Superinfection with a Same-Clade Virus

According to Walker's talk and information from Marcus Altfeld, who carried out this work with Todd Allen in Walker's lab, the superinfection case involved a male patient who was participating in an ongoing trial of structured treatment interruption. He had begun HAART shortly after becoming infected and interrupted for the first time about 18 months later; virus rebounded immediately, and he resumed treatment. During a second interruption he controlled virus much better, maintaining low loads (~1,000) for about 6 months and CD4 counts in the 700-900 range.

But then virus suddenly spiked again, and the patient developed symptoms typical of acute HIV infection, including fever, lymphoadenopathy and fatigue. After another few months of treatment, a third interruption led to immediate viral rebound.

Then came an unexpected finding. Analysis of virus from these two spikes revealed what looked like a different strain than the original one—also clade B, but diverging by about 12% at the protein sequence level. Even with sensitive (PCR-based) techniques, the new strain couldn't be detected in blood samples taken before the spike that occurred 6 months into the second interruption. Consistent with the patient's report of an un-protected sexual exposure around that time, the researchers concluded that this represents a superinfection.

The immunological findings were also striking: At the time of superinfection, the patient had strong, broad T-cell responses to HIV—over 25,000 spot-forming cells per million PBMC, measured by Elispot analysis for interferon-gamma-producing cells. What's more, these were directed against more than two dozen different HIV epitopes spread across the viral genome. After superinfection, about half of these responses persisted, and they turned out to recognize epitopes present in both viruses; there were even three new CD8 responses detected, all specific to the second virus.

Yet this wasn't enough to prevent the second infection. "I anticipated, as did others," says Walker, "that this level of immunity would be cross-protective."

Unraveling Protection and CD8 Responses

The finding that it wasn't resonated strongly with vaccine developers, who routinely evaluate CTL-based vaccines by the same T-cell responses that Walker's group measured. "These data challenge our notions that magnitude and breadth translate into protection," says Kent Weinhold of Duke University (Durham), who heads the central immunology laboratory of the HIV Vaccine Trials Network. "They tell us that we need to look more deeply at parameters of cellular immunity. This really opens our eyes that protection is much more complicated."

That view is also beginning to emerge from studies on what constitutes an effective (viremia-suppressing) response in infected people. For example, Mark Connors of NIH has compared CD8 responses in a group of long-term non-progressors (LTNP) who meet stringent criteria (infected for 13 years or more; viral loads below 50; normal CD4 counts) to those in progressors, all without HAART. His findings: even patients with high viremia and progressive disease have high numbers of HIV-specific CD8 cells, while LTNP have similar levels but narrower, more focused responses (*PNAS* 97:2709;2000). Other research-

> *"These data challenge our notions that magnitude and breadth of T-cell responses translate into protection."*
> *—Kent Weinhold*

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◀**SUPERINFECTION** *continued from 3*

ers, including Mike Betts and Louis Picker (*J. Virol.75: 11983;*2001), Marylyn Addo in Walker's group and Merck's John Shiver also have recent data showing a lack of correlation in infected patients between levels of HIV-specific CD8 cells (measured by interferon-gamma production) and the ability to control viremia.

So it's back to the "holy grail" question: what defines a protective response—or, as Walker reworked the question in his talk, what correlates with loss of viral control? Part of the answer may involve having responses to the "right" epitopes, which several labs are working to identify. Connors is looking for qualitative or functional differences between protective and ineffective responses, focusing on differences in the ability of CD8 cells from progressors versus LTNP to divide (*Nature Immunol.*, in press). Others are looking at markers that might further define protective cells among interferon-gamma-producing CD8 populations (see *IAVI Report,* Mar-Apr 2002, p. 15), and at CD4 help. "The fact that most of the vaccines being tested rely on CD8 responses make this qualitative difference very important to understand," says Connors.

Do These Findings Translate to Vaccines?

All this still leaves the underlying questions of why Walker's patient could not stave off a second infection, even across a relatively small strain difference, and whether this predicts that the same might happen with vaccines. Walker raised several caveats, and other researchers offered some of their own.

One is that "we are dealing with an HIV-infected person who most likely has immune deficiencies," says Altfeld, and even subtle damage could impair his ability to make fully functional responses. Looking specifically at T-cell help, there were signs of a downward trend in the patient's CD4 levels (from 1,000-1,300 during treatment to 700-900 before superinfection), although Altfeld said this did not reach statistical significance.

Another key point is that immunity established by vaccination before HIV exposure is very different from that induced by active infection—which could mean differences in qualitative properties and/or responses to specific epitopes. "If the same degree of broad immunity were induced by a vaccine in an uninfected person, it might be much more effective," said Walker.

Primatologist Mark Lewis (Southern Research Institute, Frederick) raises a very different point, asking whether protection has truly failed. "We don't expect CTL-based vaccines to block infection," he says, and therefore the superinfection "wasn't at all surprising. But we don't know what the outcome of this patient will be. Is his immune response going to change his ultimate disease course?" [As of mid-September 2002, Altfeld said the patient is off treatment after a fourth round and controlling viral load—but with an elevated setpoint of 10,000-40,000.] Going a step further, "Isn't this what we'd expect without neutralizing antibodies in the mix?" asked another researcher.

How Common Is Superinfection?

Another crucial question, from both vaccine and public health perspectives, is how often superinfection occurs. "A single case tells us that it's possible to become infected despite broad CTL responses," says Walker. "It doesn't tell us how likely this is." To date there have been only sporadic reports of double infections, although the huge number of HIV recombinant strains—both those in circulation and the much larger group of strains unique to one or a few people—suggest that this may not be rare at all. But there has been no systematic surveillance up to now, and no clarity on whether these double infections reflect transmission of two strains at one time (or shortly after one another) or true superinfections, with a second infection occurring after the first one is well-established.

That's exactly what Francine McCutchan (Henry M. Jackson Foundation, Rockville), Michael Hoelscher (University of Munich) and collaborators are now studying in Tanzania, a country with three major clades in circulation. They first carried out a pilot study involving 100 infected, high-risk women ("bar girls"), says McCutchan, and found that an astonishing 45% harbored unique inter-clade recombinants—each of which must have arisen from a double infection, either in the women themselves or in a proximal sexual contact.

To pin down the frequency of inter-clade double- and superinfections, they also established a cohort of 600 bar girls in the context of the HSIS Bar Workers Health Project, (presented by Oliver Hoffman (≠MoPeC3509). Recruited without regard to HIV status, initial HIV prevalence was 68%, with an incidence after one year of 14.1 infections/100 person-years. Now two years into the three year study, the women continue to be monitored every three months for HIV infection, and blood samples collected for later analysis. Key questions: are double infections found, and if so, when do second infections tend to occur relative to first ones? And can people who become doubly infected be distinguished immunologically from those who don't?

Looking Ahead

Studies like these should help resolve whether superinfection represents a common event or a fascinating but rare curiosity—although they don't yet tackle the question of superinfection within clades, which Altfeld hopes researchers will start looking for now in the wake of the attention this issue has received.

But vaccine developers don't all seem as fazed as initial reports implied. "As nicely worked up as this is, it's a case report in one individual," says primate researcher Jeff Lifson (National Cancer Institute, Frederick). "I wouldn't discount something as important as preventive vaccines because of one patient. It's certainly sobering, but by itself not enough to make me get my nihilist hat back on." ◆

Barcelona Sessions Spark Full Discussion of Partially Effective Vaccines

BY EMILY BASS

Is the AIDS vaccine glass half full or half empty? With a host of animal studies on candidates that fail to protect against infection but delay or prevent disease, it can be difficult to tell—especially since it's not known whether results from animal studies are predictive of what will be seen in humans. But some of the most talked-about presentations in Barcelona clearly reflected a "glass half full" outlook as they highlighted the potential benefits of partially-effective vaccines that, while far from perfect, could still have an enormous public health impact on the AIDS epidemic.

The potential usefulness of partially effective vaccines was driven home most recently by a WHO report issued in March entitled *The Epidemiological Impact of HIV/AIDS Vaccines in Developing Countries*, which provided a meta-analysis of several mathematical models that simulate the impact of partially-effective vaccines. There are many variables in these scenarios, including what proportion of the population is immunized, how long vaccine protection lasts, and what stage the epidemic has reached in a given region. The report concluded that there is a compelling case for seeking these imperfect tools: Hypothetically, a vaccine with 50% efficacy over 10 years given to 65% of all adults could reduce HIV incidence by 25 to 60%. And other studies have shown that even a 30% efficacious vaccine could have a significant impact on reducing new HIV infections in certain contexts.

Partial efficacy is a difficult concept to define—especially when it comes to vaccines, which are widely perceived to provide more or less complete protection. As the discussion in Barcelona and the WHO report revealed, there are subtle distinctions that will have to be part of public health messages around experimental and licensed vaccines. In fact, the term "partially effective" can refer to two different vaccine effects. First, it can be used to describe vaccines that protect only some of the people who are immunized, rather than nearly everyone. Alternatively, it can describe vaccines that do not protect against infection but work instead by delaying or reducing disease in those who become infected.

In practice, it may be very difficult with HIV vaccines to make clear distinctions between these different categories. The current crop of candidates that induce cellular immune responses recognize and kill already-infected cells, and it is considered unlikely that they will efficiently block infection. But it could turn out that they protect at least some people from detectable infection, due to the interplay between vaccine, genetics, route and frequency of exposure and other variables. It's also possible that sexual exposure to HIV in a vaccinated person could result in a local infection that does not spread systemically, and is therefore never detectable in the bloodstream by viral load measurements. Or a local infection could be completely eliminated by the death of infected cells. People who are infected and clear or contain the infection would not, technically, be completely protected from infection, although it would appear this way by most standard measures.

As difficult as it is to define and tease apart these different vaccine effects at a hypothetical level, it's even more daunting to design trials that detect them. HIV-positive individuals can remain healthy and asymptomatic for five years or more—longer than the duration of current (and planned) Phase III trials. To evaluate vaccines for licensure, planners therefore have to rely on surrogate markers such as viral load, rather than on clinical symptoms of disease. They'll also have to reach consensus with regulatory agencies on how much of a decrease in viral load, sustained for how long, is significant in terms of health benefits and reducing transmission risk. And even with viral load as an accepted surrogate, they will have to do long-term follow-up studies to determine whether viral load effects translate into changes in disease progression in vaccinees as compared to matched controls. Duration of immunity is another key consideration, since immune defenses could wane over time, as they do with many vaccines. And vaccinees may be exposed to different subtypes or new strains of HIV that are not recog-

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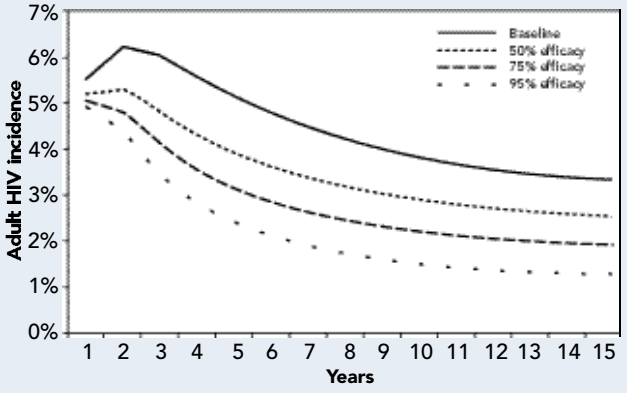
Effects of vaccine efficacy in HIV transmission in rural Zimbabwe



Source: World Bank Policy Research Working Paper 2811, The Epidemiological Impact of an HIV/AIDS Vaccine in Developing Countries*, March 2002.*
Graph reflects assumption that incidence has peaked due to saturation in highest risk groups and condom use.

◀**PARTIALLY EFFECTIVE VACCINES** *continued from 5*

nized by vaccine-induced responses, leading to a change in the degree of protection afforded by immunization.

Math Models Help Plan Ahead

Faced with these real world challenges, it's not surprising that some of the most discussed presentations in Barcelona were trial simulations. Roy Anderson, Geoff Garnett and colleagues (Imperial College, London) are developing models that look at shifts in key variables—such as HIV incidence in the trial population, number of volunteers, and viral load reductions—depending on the level of efficacy a trial seeks to detect (Abstract #WeOr136). The goal, Anderson says, is to design trials that will give clear answers to questions about how well a vaccine protects against both infection and disease progression.

Among other things, this requires choosing realistic endpoints and efficacy thresholds from the outset and then powering trials to detect them. Aiming too high can lead to ambiguous results—which could result in overlooking potentially useful candidates. That's what happened with a malaria vaccine, Spf66, tested in children in Kilombero, Tanzania in 1994. The Kilombero trial was powered to detect a vaccine with 50% efficacy. But when the study data was unblinded, researchers found what appeared to be 31% efficacy—a level that could nevertheless have a profound impact on malaria in this hard-hit area. However, the result was ambiguous, since it was below what the trial was powered to detect and yielded wide confidence intervals (range of uncertainty). In other words, the vaccine could actually be significantly more or less effective than 31%.

The ongoing VaxGen trials in Thailand and the US illustrate the interplay between efficacy thresholds, HIV incidence in the cohort (numbers of new infections every year) and the numbers of volunteers needed to measure protection against infection. (VaxGen's vaccine is the only one in the clinical trials pipeline aimed at inducing antibody responses that might block infection.) To detect a minimum of 30% efficacy, the Thai trial (based on an incidence of 4 new infections per 100 person-years) had to enroll about 2,500 volunteers, while the US trial, with a lower expected incidence of 1.5% annually, recruited over twice that number (5,400 individuals). And in the upcoming Phase III trial prime-boost trial (canarypox with gp120) in Thailand, which is powered to detect 50% efficacy, the much lower incidence rates in the study population will require enrollment of 16,000 volunteers.

Since surrogate endpoints like viral load will most likely be used to make decisions about vaccine licensure, Anderson says that long-term, post-licensing studies are crucial. Gathering five or even eight years of post-immunization follow-up data is a monumental task. But without it, he warns, there won't be enough information about duration and nature of effect to make strategic

IAVI Outlines R&D Plans for Next Two Years

At the Barcelona meeting, IAVI released its Research and Development Agenda 2002-2004 (enclosed with this issue of the *IAVI Report* and available at www.iavi.org). The Agenda is a blueprint for activities in several key areas and encompasses issues ranging from pre-clinical development to large-scale manufacturing of a licensed vaccine.

The first area of focus is identifying and addressing some of the obstacles to vaccine development. On the pre-clinical front, the key hurdle IAVI will tackle is the lack of candidates able to induce antibodies that neutralize a broad range of primary HIV strains. Solutions will be sought through the recently-established Neutralizing Antibody Consortium, founded by IAVI in 2002 to accelerate progress on a variety of approaches and to foster close collaboration among leading labs working on the problem from different angles.

A second set of obstacles concerns the eventual manufacture and rapid delivery of a licensed vaccine. The R&D agenda lays out plans to invest in developing new technologies that will be needed to mass-produce, as cheaply as possible, hundreds of millions of vaccine doses based either on DNA or on viral vectors. A related goal, to be pursued together with regulatory bodies and global health organizations, is the creation of a regulatory template that identifies core requirements which an AIDS vaccine must meet for licensure.

Another focus is broadening the clinical pipeline. Here, IAVI will continue to work on developing candidates that induce broader and more durable cellular immune responses, by optimizing designs for DNA vaccines and viral vectors systems, including modified vaccinia Ankara (MVA; already in human trials), Semliki Forest Virus (SFV) and adeno-associated virus (AAV). Studies in rhesus macaques will play a major role in evaluating these candidates. In addition, IAVI is planning clinical studies to help determine whether mucosal immunity is necessary for protection. Here, the strategy is to compare a DNA vaccine delivered by bacteria given orally (which is likely to induce mucosal responses) with the same vaccine injected as naked DNA, which is not expected to induce these responses. Work on these candidates will emphasize HIV subtypes prevalent in the most afflicted regions and involve intellectual property agreements that permit eventual technology transfer to developing countries and keep prices to a minimum.

The Agenda also outlines plans for moving the most promising candidates into large-scale efficacy studies. Important milestones include advancing a DNA-MVA candidate vaccine (now in Phase I/II trials) to Phase III trials by the end of 2004 and identifying two other "second generation" candidates for accelerated clinical development, with the goal of starting efficacy trials by 2007. IAVI's core immunology laboratories for evaluating blood samples from human and non-human primate studies will provide a standard foundation for IAVI trials, and for the broader field. **—PK**

decisions about who should get highest priority for vaccination and when—i.e., high-risk groups, versus general population or adolescents. It will be an ongoing decision-making process, since public health officials will likely make one set of decisions following licensure, and then review and re-evaluate them as follow-up data on long-term health and protection effects come in.

One Trial, Two Goals

Building on the complexity of evaluating vaccines based on surrogate markers, Michael Hudgens of the HIV Vaccine Trials Network (HVTN) also presented modeling work on the thorny task of designing trials that yield conclusive data about a vaccine's efficacy in preventing both infection (termed VEs) and disease (VEp) (WeOrD1298). The HVTN model, developed by Steve Self (HVTN) and others, is mainly concerned with avoiding a statistical pitfall called "selection bias," which could interfere with interpretation of VEp results. In the case of AIDS vaccines, the bias has to do with unforeseen interactions affecting efficacy and the ways in which these interactions could skew data analysis. For example, if a vaccine worked only in people with strong immune systems, then vaccinees who became infected in an efficacy trial would represent mostly individuals with weaker immune systems; in contrast, infections in the unvaccinated group would include individuals with weak *and* strong immunity.

In this scenario, when statisticians analyzed VEp data from all infected volunteers, they would be comparing individuals with varying immune strength (from the unvaccinated group) with a pool of people having weaker immune systems. And if infected vaccinees appeared to progress more rapidly, or to have higher viral load setpoints than the infected controls, this could be wrongly attributed to the vaccine, rather than to bias introduced by fact that vaccine protection failed only in people with weak immunity overall.

Another example involves strain virulence: a trial could end up comparing a group of infected vaccinees infected mostly with highly virulent HIV strains to controls infected with HIV strains of varying pathogenicity.

So far, the HVTN team has developed a framework for estimating how big a trial would need to be to avoid errors in interpretation of VEp data. This depends, to a large extent, on the vaccine's VEs: the better a vaccine is at preventing infection, the fewer individuals this leaves for the VEp analysis. For example, in a 2000 person trial of a vaccine which prevents infection 50% of the time (VEs = 0.5), there would have to be 45 infections in the control arm, and 23 in the experimental arm to say with certainty that a 0.5 log drop in viral load among infected vaccinees was due to the vaccine. If VEs is increased to 80%, cohort size would have to be increased by about 50% to measure the same effect on VEp. Knowing the HIV incidence in a cohort, the estimated VEs of the vaccine and the minimal level of VEp the trial aims to detect, planners can begin to get a sense of how to design efficacy trials that yield conclusive data on vaccine effects.

The HVTN work is one piece of the puzzle. At Emory University, Ira Longini and colleagues have done a series of studies that look at other, related trial design aspects, such as how to gather information about vaccine effect on infectiousness (they suggest recruiting sexual partners of trial participants) and building studies that look at heterogeneity in type and frequency of HIV exposure among participants, thereby reducing the risk of erroneous assumptions about vaccine efficacy.

Forecasting A Bumpy Ride

The models presented in Barcelona leave open as many questions as they answer. "We're only just beginning to look at whether we need to design different strata [of trial data analyses], by gender and clade of circulating virus, to get independent looks at vaccine effects in different settings," says the HVTN's Steve Self, who lists genetic background, age and HLA type as other potential variables that could affect responses to vaccines.

It may also be difficult to use existing natural history data to set viral load goals for vaccine trials, since there is wide variability in viral kinetics over time—a factor that could complicate decisions about VEp goals. And eventually, the approval of low-to-moderate efficacy AIDS vaccines could have a dramatic effect on the design (and size) of subsequent vaccine trials, since these products may replace the placebo arm of the trial—and raise the bar for the level of efficacy new candidates will need to achieve.

It won't only be clinical researchers who must come to terms with these issues, but also the policy makers and advocates who will plan vaccine deployment strategies. Some efforts are already underway to begin forecasting the demand for vaccines with partial efficacy, issues that were discussed in a presentation on a qualitative study co-sponsored by the WHO, UNAIDS and IAVI (WeOrD1297) (to be covered in the Oct-Nov 2002 issue of the *IAVI Report*).

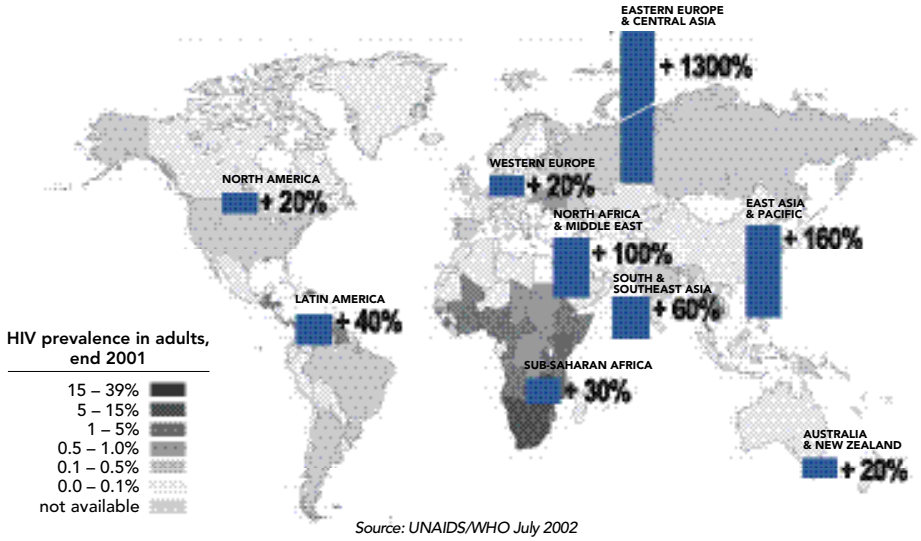
Ultimately, these mathematical tools will be only partial guides—ones that may help the AIDS vaccine field steer clear of a Kilombero-like trial, but which can still not ensure perfect clarity. "A math model is a blunt tool," warned Jorge Beloqui, a mathematician and AIDS vaccine advocate who co-chaired a bridging session where models were discussed. Yet despite these limitations, the simulations presented at Barcelona gave a sense of the work that needs to be done—and, perhaps, a preview of Bangkok, 2004. ◆

Snapshots of an Epidemic:

Recent trends in HIV infection, 1996-2001

"The last two decades have taught us a great deal about failure and how it is measured: new HIV infections and AIDS deaths are the grim gold standard. A lack of decent medical care and effective prevention strategies, including a vaccine and women-controlled prevention options, are others."

Paul Farmer , *(Partners in Health, Haiti),* Introducing ARVs in Resource Poor Settings: Expected and unexpected challenges and consequences, *Plenary speech, 11 July 2002*



Source: UNAIDS/WHO July 2002

"Every year that we delay a comprehensive response to HIV/AIDS, costs 5 million more lives."

Bernhard Schwartländer , *(WHO, Switzerland)* The HIV Epidemic: What is it doing? Where is it going? *Plenary Speech, 8 July 2002*

"There remains an illusion that drug users are somehow separate and isolated and that illness and death among them has no impact on the fabric of society...Those of us who work on HIV in this region have spent over ten years … advocating action. Now, in 2002, we no longer speak of what may be: HIV and AIDS have arrived and as everywhere else, are causing devastation."

Kasia Malinowska-Sempruch , *(Open Society Institute, USA)* From Concern to Action–Addressing HIV and Drug Use, *first-ever plenary speech on Eastern Europe and the former Soviet Union, 9 July 2002*

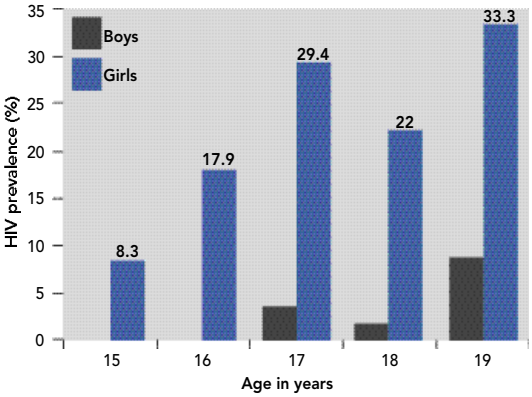
In a 2001 Centers for Disease Control Study, new HIV infections among men who have sex with men (MSM) in the United States were higher than in any other recent studies–and comparable to levels seen in studies of MSM in the mid-1980s…the same CDC study showed that young African-American MSM are particularly hard-hit, with rates of new HIV infections in some cities as high as those now seen in South Africa.

Source: CDC, No Turning Back: Addressing the AIDS Crisis in MSM (November, 2001)

HIV prevalence among teenagers in Kisumu, Kenya, by age and sex

"On average, young women are becoming infected ten years earlier than men due to early marriages, rape, and being compelled into prostitution by economic necessity."

Suniti Solomon , *(YRG Care Clinic, India)* Empowerment of Women in HIV Prevention, *Plenary speech 9 July, 2002*



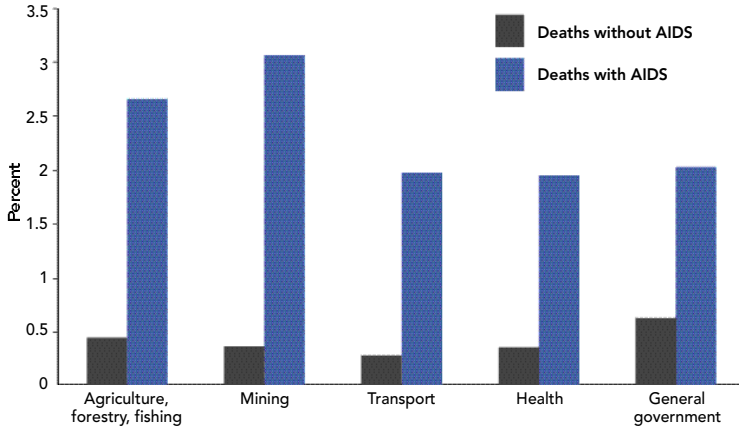
Source: National AIDS Programme, Kenya, and Population Council, 1999 (unpublished)

"After so many years, I am still shocked at how fast the epidemic is growing among young girls having sex with only one partner."

Lieve Fransen , *(European Commission, Belgium),* The European Union Policies to Confront the AIDS Pandemic, *Senior Lecture, 10 July, 2002*

Views and Voices from Barcelona

Projected death rates in workers in different sectors without and with AIDS, South Africa, 2015



Source: Adapted from ING Barings, The Economic Impact of AIDS in South Africa, *2000*

By 2010, primary school enrollment will shrink by 24% in Zimbabwe, 14% in Kenya and 12% in Uganda, as AIDS orphans must leave school to help care and provide for their families … and AIDS kills about 2.1% of teachers in Zimbabwe, 1.7% in Zambia and 1.4% in Kenya each year.

Source: UNAIDS, Barcelona Fact Sheet: The Impact of HIV/AIDS, *2002*

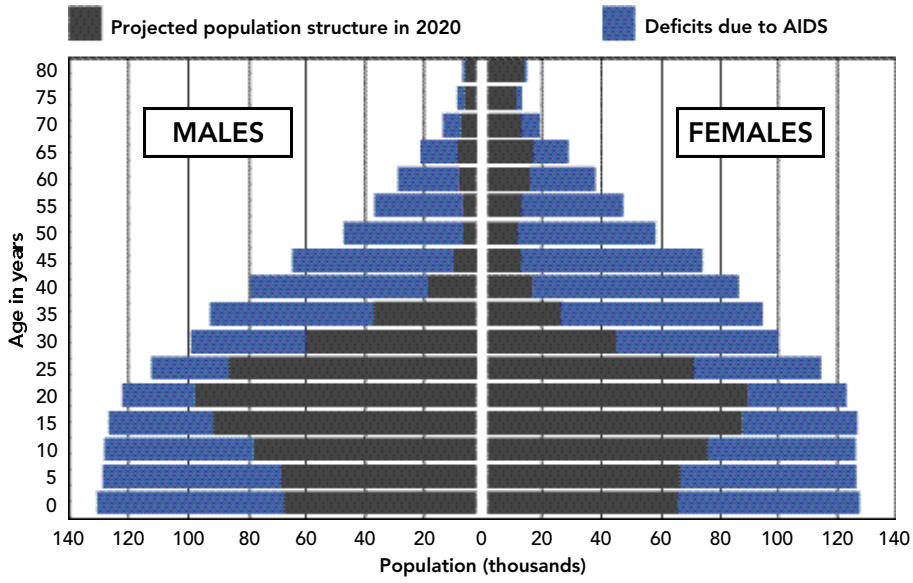
"I have been asked repeatedly at this conference about cost effectiveness. Let me tell you a fairy tale. I was driving across Uganda with an economist. We came upon a horrendous traffic accident. A school bus had collided with a truck. Children were lying all over the road. Some were dead. Some were dying. Others were seriously injured. I said, 'Hurry, hurry let us call for ambulances and get these children to hospital quickly. Many of them may be saved.' The economist said, 'No! Let us drive on to Kampala, to discuss seatbelt legislation with the government. It's more cost effective.' The Global Fund will not be calling on that economist."

Richard Feachem *, (Executive Director of the Global Fund to Fight AIDS, Tuberculosis and Malaria),* Domestic Responses, Global Solutions, *Senior Lecture, 9 July, 2002*

A lost generation: projected population structure, Botswana, 2020

"The population structure is being turned around by HIV/AIDS. The classic pyramid is turning into a narrow chimney."

Bernhard Schwartländer *, (WHO, Switzerland)* The HIV Epidemic: What is it doing? Where is it going? *Plenary Speech, 8 July 2002*



Source: US Census Bureau, World Population Profile, 2000

A Community Advocate on the Global Stage

AN INTERVIEW WITH Shaun Mellors

"How many silences have you broken since Durban? How many more still need to be broken?"

These questions greeted participants in the opening pages of the Barcelona Programme, posed by Shaun Mellors, Chair of the Interventions, Programme Implementation, Advocacy and Policy Committee for Barcelona. Between this position and his work as Community Programme Coordinator for the Durban 2000 meeting, Mellors has intense, first-hand knowledge of the expectations, opportunities, and potential outcomes of the world's largest AIDS meetings. A native South African and longtime AIDS activist, Mellors has spent nearly two decades blending treatment and vaccine advocacy and working to include developing world perspectives in global discussions—first as coordinator of the Global Network of People Living with HIV and AIDS and then as HIV Vaccine Lobbyist for South Africa's Medical Research Council. In September, Mellors took on a new role, as vaccine policy coordinator at the International Coalition of AIDS Service Organizations (ICASO)* [Editor's Note: Mellors' position is funded by an IAVI grant]. ***Recently, Mellors spoke with Emily Bass, Senior Writer at IAVI Report, ***to share his thoughts on Barcelona, his new job, and the global challenges and unbroken silences that lie ahead.***

What was most striking to you about the Barcelona meeting?

Two important aspects stood out to me. The first was a change in how people think about and see the epidemic. In the presentations and corridor discussions, there was a sense of urgency returning. We know what we need to do to combat this epidemic. So we need to get on and do it.

The other interesting aspect for me was the elevation of the link between prevention and care. Although the conference did introduce a separate prevention track, the link between prevention and care was strengthened and reinforced in several presentations and plenary sessions—that you cannot have effective prevention programs without effective care programs; that it's pointless to pit the two against each other, but that we have to concentrate on them at the same time.

Do you think the prevention versus treatment debate has ended?

I'm not convinced it's over. I suppose the debate has happened on the international, theoretical level, where we all acknowledge the link between prevention and treatment and care. But although we can talk about it on the global level, the challenge is always what do we do on the country level.

I have to say that I left the Barcelona conference with very mixed feelings. Although we had a framework that tried to integrate science and community in a meaningful manner, I don't think at the end of the day that we were very successful. The theme of the conference was "Knowledge and Commitment for Action." I'm not convinced that sufficient action came out of the conference. It's certainly difficult after five days of conferencing to justify spending 40 million euros when clear actions did not emerge.

What role can the International AIDS Conference play in the future?

Although these conferences try to be different every time, they're still being organized in isolation. And they aren't really linked with what's happening in the regions. What has happened up to now is that, if there's been—for want of a better word—a weakness in a conference, then the organizers have tried to solve the problem by organizing another one. For example, the International AIDS Society now has the HIV and Pathogenesis conference, because the science in these international AIDS conferences wasn't as strong. We have the International Conference on Home and Community Care for Persons Living with HIV/AIDS because that was not well-covered.

All of us have a responsibility to look at the purpose of this international AIDS conference. What are we trying to achieve? Is a successful AIDS conference determined by the number of people who actually attend or by the actions that come out of the conference, and how they are integrated and implemented? How do we hold ourselves and each other accountable?

What kind of actions were you hoping for? What opportunities do you think were missed?

Without a doubt, there certainly was opportunity [to act] on the issue of access to treatment. At the Durban conference, this was a big issue.

Everybody acknowledges now that access to treatment is, and should be, and can be a reality. Barcelona would have been an ideal opportunity to talk about how we are going to start implementing that. In Barcelona we had a number of promises that, by the time of the Bangkok conference [in 2004], at least three million more people will have access to antiretrovirals. But there was absolutely no discussion about how that is going to happen. What are the implications of that? How

are we going to make it a reality?

Another issue which fell off the agenda has to do with vaccines and microbicides. At the Durban conference, vaccines and microbicides were highlighted in the conference program and in the plenaries. In Barcelona they only had three oral sessions, two symposia and a prevention-related plenary. Questions about community involvement around vaccines and microbicides weren't on the platform at all—questions like, how do we ensure that the pertinent issues on the global vaccine and microbicide agendas come together? How do we implement them to the benefit of the communities and, of course, for scientific research? How far have we come since the Durban conference? What lessons have we learnt?

You've been a vocal advocate for allowing local communities to define the standard of care and other issues in a context-specific way. How can communities support one another's agendas and develop shared agenda issues?

Up to now it has largely been either global players or global organizations that have tried to define partnerships with developing countries and talk about their issues and concerns. Part of the challenge will be to ensure that community voices are actually brought to the global advocacy agenda, as opposed to the global advocacy agenda coming to the community.

The US has been involved in vaccine trials for a number of years already, grappling with advocacy issues within their own environment, with their own obstacles and challenges. So what has happened by default is that the American advocacy agenda is becoming the standard for developing countries, which then automatically places them at a disadvantage because their discourse or community mobilization or sense of activism is certainly not the same as it is in the US at the moment.

So I certainly think that what AVAC [the AIDS Vaccine Advocacy Coalition] and, to a certain degree, ICASO and IAVI have to do is not only to form partnerships with each other on the global level, but to create the mechanisms for the country and regional community voices to be brought to the global agenda. It's going to require a fair amount of transparency and hard work to overcome some of the challenges facing communities, particularly in developing countries. But I think if the global players commit to ensuring that those voices are heard—immaterial of whether they are different from American or Canadian voices—they have an opportunity to portray the issues from their own perspective.

It seems like there is sometimes a false dichotomy in discussions about vaccine trials, or community-based research in general, which says that community involvement comes at the expense of speed in moving forward. How do you respond?

It's very true that this comes up frequently. I think part of the reason is that in a country like South Africa, for example, or even Zimbabwe or Kenya, we haven't yet been able to define exactly what we mean by community mobilization or preparedness for clinical research.

Also, policymakers and politicians have a big impact on communities. And in a country like South Africa, there have been high-profile political leaders behind the vaccine agenda. They have been pushing the vaccine agenda and emphasizing prevention, but not making the link to care and treatment. So communities are now saying, 'What is it that I have to do around the issue of vaccines if we have all these politicians and opinion leaders talking about this, but not about treatment or care or support?'

But if we can get the communities to see that it's a matter of equal attention, and that they can actually take advantage of the fact that politicians are talking about vaccines and microbicides—that they can use this commitment to further the treatment agenda—then I think communities will become more mobilized in terms of advocacy.

What did you do in your job as vaccine advocacy and lobbying manager for the Medical Research Council?

I was with the Medical Research Council [MRC] for 15 months, and then I had to concentrate on the Barcelona conference. Part of my MRC portfolio was to interact with the media around issues of vaccines, because obviously if you have an informed media, you are going to have an informed public. So I held briefing sessions and training workshops for journalists and media. The job also involved trying to prepare for the time when the first person would be vaccinated.

What gaps did you see in the public understanding of vaccines?

Part of the difficulty for the media is that vaccine trials planned for South Africa have constantly been postponed. So obviously the media are skeptical. Why is it being postponed all the time? There wasn't a very effective, comprehensive strategy for interacting with the media on this issue.

Did you work at all in Hlabisa [an HVTN site preparing for vaccine trials]?

I did work in Hlabisa with the community advisory board. I suppose Hlabisa is a prime example of preparing a community for something that's supposed to take place but never happened.

To what extent did the microbicide trials in the region—and now, plans for a microbicide trial in Hlabisa—change that sense of just waiting?

Part of the reason I left the Medical Research Council was because trial organizers' understanding of community mobilization and preparedness is very different from what communities them-

continued on 12 ▶

◀**MELLORS INTERVIEW** *continued from 11*

selves would see as mobilization and preparedness. The microbicides trials which took place in a number of sites in a dedicated area—I'm just bracketing them under one umbrella, perhaps not rightly so—concentrated on community preparedness only in terms of the people who participated in the trial. It doesn't address that those individuals belong to their community and go back to their community.

I think we have to go further to avoid disappointment in the community. Hlabisa is now a potential site for a Phase III microbicide trial. But yet again, only those participants who have made it through the pre-screening protocol are seen as community and concentrated on. All those who went through other surveys and participated in other ways are excluded.

> *"We haven't been able to define what we mean by community mobilization."*

What will you do in your new position as vaccine advocacy coordinator at ICASO?
ICASO has had a vaccine portfolio for the past two to four years, but not too much has come out of that. One of my challenges is to add credibility to the portfolio and ensure that partners and stakeholders who have lost faith, or who are uncertain, come back to ICASO as a player with lots of potential.

I think it's important that the ICASO portfolio adds value to what is already being done by groups like AVAC and the HVTN education group and IAVI and KANCO [Kenya AIDS NGO Consortium]. ICASO has the credibility to ensure that community voices are brought to the global advocacy agenda. At the same time, ICASO can take those global advocacy issues and, through their partners and regional networks, present them to communities on the country level. We can say, 'These are the global advocacy issues. How do they pertain to your country's issues, and what from your country or region is important to take to the global level?'

Part of my task will be to identify potential partners on the country, regional and international levels and to do a needs analysis in terms of where ICASO can actually add value. What other products are needed, what other services? I also want to broaden the scope of the portfolio to include both vaccines and microbicides.

Do you have your first projects in mind?
At the moment, I'm still trying to get over to Toronto [home to ICASO headquarters]. I was supposed to start on the 1st of August. But there has been a bit of a delay in terms of my medical examination, because Canada introduced a new law on the 28th of June requiring HIV testing [for immigrants seeking working permits].

Often, communities that are most at risk or in need of mobilizing—for instance, MSMs and commercial sex workers—are among the most traditionally disenfranchised. But to convey their input to a global level, these communities need a national voice. How do you do that?
There has slowly been a greater recognition of the so-called minor epidemics. In a country like South Africa, the homosexual epidemic is now a kind of minor epidemic, or forgotten epidemic. But it's all a process. In South Africa, there are now organizations and groups that have managed to get involved in community advisory boards; to go to international conferences and start vocalizing issues of the MSM epidemic. It is happening, and it is a responsibility of ICASO, AfriCASO and ApCASO to ensure that the communities without voices actually have the means and the ability to reclaim them.

In terms of the IV drug-using epidemic—another minority epidemic—ICASO put out a call for submissions by NGOs in Eastern Europe and Russia to host the EuroCASO secretariat. So they've identified this as a need and a gap.

You're very forthright in situations where some people are less comfortable stating what they think or what they're frustrated with. Yet you work very effectively within established organizations. That's a rare skill. How do you do it?
Oh, goodness, I'm not quite sure. I think there is a sense of mutual respect for all the stakeholders and funders I interact with. Although I'm always prepared to speak my mind or voice my concerns or preferences, I'm also prepared to listen, learn and try to understand. I suppose that strengths gained from being involved in the gay and lesbian and, to a certain degree, the apartheid struggle, have also helped me. It's this combination—and, at the end of the day, always delivering on what you say you are going to deliver. ◆

THERAPEUTIC VACCINE SHOWS ENCOURAGING FIRST RESULTS IN CHRONICALLY INFECTED MONKEYS

BY PATRICIA KAHN

On the final afternoon of the meeting, Julianna Lisziewicz of the Research Institute for Genetic and Human Therapy (Washington, DC) presented encouraging preliminary data on a therapeutic vaccine used together with structured treatment interruption in chronically infected monkeys—among the first hints of success in immune treatment of chronic infection (ThPp2128).

DermaVir is a DNA vaccine designed to target dendritic cells (antigen-presenting cells which are key players in the immune response). The monkey version contains nearly a full genome (*env* from SHIV89.6P plus the remainder of SIVmac251 genome) except for the integrase gene, so virus can neither replicate nor integrate into host cells—yet it presents the immune system with a nearly full spectrum of HIV antigens expressed under their natural promoter. The DNA is formulated into particles through the addition of PEI (polyethylenimine)—a polymer known to gene therapy aficionados as an enhancer of DNA uptake and expression—with sugar (mannose) molecules tacked on, giving the particles some resemblance to bacterial pathogens.

Immunization is done simply by exfoliating the skin lightly and applying the vaccine topically. Lisziewicz believes that particles enter the local Langerhans cells (immature dendritic cells), which then migrate to the lymph nodes, since the researchers can detect viral RNA and protein expression a day later in the lymph node dendritic cells. This pathway, she says, does not activate pre-existing immunological memory but stimulates naïve T-cells—a difference to most other therapeutic vaccines.

Lisziewicz presented two separate studies in chronically infected monkeys. The first, a small pilot study, involved 7 animals infected 14 months earlier with SIVmac251, all with late-stage AIDS. Three began receiving continuous HAART treatment, while 4 were put on an STI regime (3 weeks on HAART, 3 weeks off) for six cycles. STI led to rapid suppression of virus during treatment, resulting in prolonged survival of 3 monkeys (the fourth one died). But it failed to lower viral loads during the "off" period—that is, virus quickly rebounded to roughly the same level each time. At that point, one dose of DermaVir was added to the HAART treatment just prior to interruption, and this modified STI regime continued for three more cycles.

The effect of DermaVir was dramatic:: Median viral load dropped by 3 logs (1000-fold) during each subsequent interruption and was undetectable after the third round, when all treatment was discontinued. Virus eventually rebounded in two of the three animals, with one surviving for another 6 months, another for 12 months, and the third at 18 months (shortly after the Barcelona meeting). Immune monitoring showed that, in each cycle, the numbers of HIV-specific CD8-positive cells increased (measured by intracellular cytokine staining for interferon-gamma, with whole-inactivated SIV virions as the test antigen).

Lisziewicz then reported on a larger, randomized study of 26 monkeys infected with SIVmac251 six months before the trial's start. The study had four arms: control (no treatment), STI-plus DermaVir, STI-only and DermaVir-only, all treated for 33 weeks (encompassing 6 cycles of STI and concluding shortly before Barcelona).

Once again, three rounds of STI plus DermaVir brought viral loads down to undetectable levels, and ICC analysis at 33 weeks showed increased levels of HIV-specific CD4- and CD8 cells. DermaVir alone somewhat blunted viral load but was much less effective than the combination with STI. Drug treatment without DermaVir was ineffective at long-term control of virus replication in 5 of 7 monkeys but showed short-term suppression of viremia in one, while the seventh animal is still controlling viral load (and remains virus-negative) at 8 weeks post-treatment (including post-Barcelona follow-up time).

Also since the Barcelona talk, virus has rebounded in several of the DermaVir + STI animals, Some animals remain virus-negative at about 8 weeks of follow-up.

"DermaVir is a therapy, not a cure," says Mark Lewis (Southern Research Institute, Frederick), whose group did the primate work. "But so far it seems to have some benefit. There's definitely something there. It's an evolving story, though," he adds, noting that future studies will shift to combining DermaVir with continuous (rather than interrupted) HAART, to improve reconstitution of the immune system and avoid the potential emergence of drug resistance. Another challenge, he says, will be to tease apart the effects of DermaVir from those of HAART.

Plans are now underway to test DermaVir in humans through the US AIDS Clinical Trials Group (ACTG), as Lisziewicz reported in concluding her Barcelona talk. (Toxicity studies in swine revealed no safety issues, other than transient irritation at the vaccination site.) A Phase I trial, which she hopes will start in early 2003, will look at safety and immunogenicity of DermaVir at three doses in 24 HIV-infected volunteers on HAART, who have CD4 counts above 350/mm^3 and viral loads below 50 copies/ml for at least 6 months. Participants will remain on continuous HAART treatment. ◆

◀**VACCINE SATELLITE** *continued from 2*

nity mobilization, concerns about HIV testing and stigma, clinical trials infrastructure, financing and regulatory structures, and—in the industrialized world—overcoming complacency. To succeed, he said, "we need principled leadership….and angry activism."

Illustrating an advocacy movement built from these links, Jorge Beloqui of Brazil (Grupo de Incentivo à Vida, Sao Paulo) described how Brazil's AIDS NGOs and community groups became involved with vaccines early on, and how advocates and general AIDS outreach programs are incorporating vaccine issues into their ongoing work.

Communities: Moving Towards Fuller Partnerships

With more vaccine trials on the horizon, several speakers emphasized that outreach efforts should focus not only on potential trial volunteers but on engaging the broader community.

This need was underscored by Emmanuel Mugisha of the Ugandan Virus Research Institute (and community development coordinator for the IAVI/Ugandan vaccine partnership), who described recent studies on local knowledge and perceptions of AIDS vaccines. Despite many years of public awareness campaigns around HIV/AIDS, the studies detected many stigmatizing attitudes. For example, focus groups with students, religious groups, police and workers in hospitals and industry revealed beliefs that vaccines would make people more promiscuous, and that trial participants are somehow "not normal."

Others addressed the role of Community Advisory Boards (CABs) in expanding outreach. Winnie Serobe, nurse and vaccine CAB member at the Perinatal HIV Research Unit in Soweto, South Africa, pointed out that this CAB was started by the "Gogos" (elderly people), who will not be trial participants. Steve Wakefield of the HIV Vaccine Trials Network (HVTN) emphasized that supporting CABs as they build capacity, and intensifying community preparedness overall, is an iterative process. "This is an intense learning experience, and in most cases the answers to the problems and challenges are being discovered as the work develops," he said.

There was also broad agreement with advocates' call to engage people already involved in AIDS work, as well as HIV-positive communities. "Not many people have done vaccine trials, but many have AIDS experience," said Chris Beyrer of Johns Hopkins University and the HVTN. Paisan Tan-Ud, former chair of the Thai Network of People Living with HIV/AIDS, drove home this point, saying that even in a country as deeply involved with vaccines as Thailand, the effort is poorly connected to AIDS NGO's and HIV-positive groups. He also pointed out the glaring discrepancy in Thailand's successful prevention efforts to reduce sexual transmission, and the paucity of programs geared towards injecting drug users—not only in Thailand but throughout Asia and Central Europe—and called on the vaccine community to help close this gap.

The Big Science Questions

Alongside overviews of candidates and research programs, the meeting highlighted some key issues in vaccine R&D. In the near-term, these include:

- optimizing designs for T-cell based vaccines;
- resolving hurdles to making vaccines that elicit broad neutralizing antibodies;
- standardizing immune assays so that results from different studies can be more readily compared;
- determining whether any candidates now in the pipeline offer any protection;
- choosing the best trial endpoints and establishing what will be licensable.

Looking more broadly, the field is continuing to search for immune correlates of protection, and to understand the role of mucosal immunity and the importance of clades.

In a concluding panel discussion, Jaap Goudsmit (Crucell N.V.) criticized the proliferation of "me-too" candidates in the pipeline, while *Science* magazine correspondent Jon Cohen questioned whether the field is doing all the right things, or needs to expand (not only speed up) its activities—which is what would happen "if 20% of the US population were infected," he said.

Gearing Up for Efficacy Trials

Besides issues of trial endpoints(see also article on p.5), several other speakers addressed the challenges of building capacity for Phase III trials. Tim Mastro (CDC, Atlanta) and Glenda Gray (PRHU, Soweto) each described how rapid changes in HIV incidence complicates the task of establishing large cohorts—a process that usually takes years. Gray also raised the sensitive issue of including adolescents in trials—a move that makes sense in terms of their high risk but raises other issues, such as obtaining informed consent while maintaining confidentiality.

Getting Access and Manufacturing Issues On the Table

IAVI president Seth Berkley discussed the challenge of convincing people that manufacturing issues need to be tackled now. "It's been said that if you create a pot of gold, this will take care of itself," he said. "This is clearly not true." Berkley called for more work on scaling up key new vaccine technologies, to avoid delays once a vaccine is found.

Geeta Rao Gupta, president of the International Center for Research on Women (Washington, DC) raised another issue in facilitating rapid access to vaccines: the need for community-based research on factors that will influence its acceptability. In the case of drugs that reduce mother-to-child transmission, she said, researchers failed to consider stigma and womens' fear of testing positive, which have led to low uptake in some regions of the world. ◆ **—PK**

New Vaccines in the Pipeline

The growing number of candidates in pre-clinical development featured heavily in the vaccine presentations at Barcelona, along with updates on products already in clinical trials. Many of these have been covered in recent *IAVI Report* articles (for example, see Merck's DNA/adenovirus studies and Oxford/Nairobi/IAVI's DNA/MVA candidates, Mar-Apr 2002, p.1; Harriet Robinson's DNA/MVA strategy, Oct-Dec 2001, p.13). Here, we focus on a few candidates that have received less coverage.

Envelope—CD4 complexes

The lack of success in developing vaccines that can neutralize a broad range of HIV subtypes—a property thought to offer the best hope of preventing initial infection—has been one of the field's most frustrating impasses. But an antibody-inducing candidate developed by Tim Fouts and Anthony DeVico at the Institute of Human Virology (IHV, Baltimore) has now shown some early promise in the monkey model, as reported in a presentation by IHV director Robert Gallo. (This work was published shortly after the Barcelona meeting in *PNAS* 99:11842;2002.)

The IHV immunogen contains gp120 (or gp140) cross-linked to CD4, the T-cell surface molecule that binds HIV—causing a shape change in gp120 that reveals epitopes normally hidden from the immune system—and, in turn, initiating viral entry into the cell. When the gp120-CD4 complex was used to immunize monkeys, Gallo reported that it generated antibodies which neutralized primary strains from HIV subtypes A through E, regardless of their co-receptor use, but worked poorly against laboratory isolates. The researchers are now testing ways to enhance this response (for example, through use of a cholera toxin fragment that shows strong adjuvant activity) and, in collaboration with Merck, are evaluating the vaccine's ability to protect monkeys against a SHIV challenge.

However, the vaccine they move into clinical development may look somewhat different, Gallo told the *IAVI Report*. To avoid possible safety and regulatory concerns over the use of CD4 in a vaccine, the IHV team has sought a replacement for the CD4 component. Through modeling studies, they have now found a promising substitute: an attenuated version of scorpion toxin, a molecule with a similar 3D structure to CD4 that seems to induce the same shape change in gp120. Although the gp120-toxin complex is still at an early stage, it is the most likely immunogen for further development as a vaccine.

GlaxoSmithKline's protein vaccine

This candidate contains gp120 along with a Nef-Tat "fusion protein." According to GSK's Gerald Voss, speaking at the vaccine satellite meeting, the vaccine is formulated with a new adjuvant called AS02A, an oil-water emulsion containing the immunostimulants QS21 and 3D-MPL. ASO2A appears to stimulates both antibody and cell-mediated immune responses and showed a good safety record in GSK's 1,300-person malaria vaccine trial. It is now being used in studies of several other (non-HIV) vaccine candidates.

Following a Phase I study of gp120 by itself, the complete vaccine entered clinical testing in February 2002 at 10 centers of the US-based HIV Vaccine Trials Network (HVTN). The 84-person trial will test the Nef-Tat protein alone and in combination with increasing doses of gp120, all in AS02A. Final results are expected in mid-2003. GSK also plans to study the vaccine as a therapeutic in HIV-positive volunteers.

Prior to launching the trial, the vaccine was found to protect rhesus macaques against challenge with a partially heterologous virus (SHIV89.6P, which differed from the vaccine strain by 20% in gp120 and 10% in Tat). Voss reported that these animals remain healthy three years after challenge.

Semliki Forest Virus (SFV)-based vaccines

New to the roster of viruses used to develop vaccine vectors, SFV is an alphavirus that is pathogenic in rodents but only rarely infects humans (so pre-existing immunity to the vector is seldom seen), and at most produces mild, flu-like symptoms. Peter Liljestrom (Karolinska Institute, Stockholm) described his team's work on designing vectors from an attenuated SFV in which the viral structural genes are replaced by foreign antigens, rendering the vector non-infectious. To maximize safety, they are engineered to persist only transiently—yet they induce potent immune responses in mice and monkeys.

Liljestrom also presented data from challenge studies in a small number of monkeys. Four animals immunized with SFV-*env* (containing the SIV-PBj14 *env* gene) and then challenged with homologous SFV were protected from illness and death, and suppressed viral replication. (In the control group, one of four animals survived.) Protection was also seen in 2 of the 4 monkeys vaccinated with 6 SIV-J5 genes (*env, gag, pol, nef, rev* and *tat*)—first as naked DNA, followed by MVA-SIV 12 weeks later and finally by SFV-SIV—and then challenged with SIV-J5. The SFV boost appeared to be required for protection, since neither MVA-SIV alone (three immunizations) or DNA plus 2 MVA boosts, protected against a J5 challenge.

Efforts are underway (through a partnership with IAVI and Bioption, a Stockholm-based biotechnology company) to produce SFV vectors carrying HIV subtype C antigens, for testing and use in India. ◆ —PK

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IAVI is a scientific organization founded in 1996 whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI focuses on four key areas: accelerating scientific progress; education and advocacy; ensuring vaccine access and creating a more supportive environment for industrial involvement in HIV vaccine development.

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vaccine BRIEFS

GRO HARLEM BRUNDTLAND STEPS DOWN FROM WHO

Gro Harlem Brundtland, Director-General of the World Health Organization since 1998, announced on 24 August that she will step down at the end of her term in July 2003. Under Brundtland's leadership, the WHO developed guidelines for use of antiretroviral therapy in the developing world and created an expanded essential drug list. A new Director-General, who will serve until mid-2008, will be nominated by WHO's Executive Board in January 2003 and elected at the May 2003 World Health Assembly.

US GLOBAL AIDS FUNDING: A STATUS REPORT

The US Senate unanimously passed the "US Leadership Against HIV/ AIDS, TB and Malaria Act of 2002," sponsored by Sens. Kerry, Frist and Kennedy, authorizing US$5 billion in spending for global AIDS. Several steps remain before these funds materialize: First, a joint House-Senate subcommittee will meet to harmonize the Senate bill with a similar one already approved by the House of Representatives. Next, the legislation will be subject to final approval by the two chambers and then signature by the President. Finally, Congressional spending committees must act to appropriate the monies, since authorization bills do not specify funding sources.

In August, President Bush vetoed a $5 billion package—including $200 million for global AIDS—that was part of the post-9/11 supplemental budget for fiscal year 2002. Presidential aides say that the $200 million may be restored in the FY 2003 budget, but have not said whether it would be an addition to, or part of, the FY 2003 budget line.

NEW ROLES FOR SOUTH AFRICA AIDS LEADERS

After four years as president of the Medical Research Council, Malegapuru William Makgoba is stepping down. Makgoba, a champion of the South African AIDS Vaccine Initiative (SAAVI), will assume a new role as Vice-Chancellor at the University of Natal. William Pick, head of the Community Health Department at the University of the Witwaters-rand, will be the interim MRC head.

Ashraf Grimwood is the new head of the South African HIV Vaccine Action Campaign, SAAVI's advocacy and education wing. Grimwood has served as chairperson of the National AIDS Convention of South Africa and Director of Scientific Affairs for the Bristol-Myers Squibb "Secure the Future" program.

EXPANDED FUNDING FOR PRE-FILLED VACCINE SYRINGES

A new UNICEF-sponsored program to increase vaccine coverage against maternal and neonatal tetanus will use a pre-filled injection device called Uniject to reach 118,000 women of childbearing age. Uniject has several advantages over traditional syringes: It cannot be reused; does not release toxic fumes when incinerated (as some syringes do); and can be used by non-medical professionals, including midwives, traditional birth attendants and school teachers, facilitating immunizations in remote areas. Indonesia's Ministry of Health has begun using the device to expand neonatal hepatitis B vaccinations. The Seattle-based Programs for Appropriate Technology in Health (PATH), is preparing a cost-effectiveness report on Uniject.

APPOINTMENTS AT US-NIH, CDC

At the end of May, Jack Whitescarver assumed the directorship of the NIH Office of AIDS Research (OAR). Previously, Whitescarver was a liaison between the National Institute of Allergy and Infectious Diseases and disease-oriented community organizations, and has served as acting director of the OAR since 2000. Julie Gerberding, an infectious disease expert specializing in AIDS and anthrax, is the new head of the Centers for Disease Control and Prevention. Gerberding spent many years at San Francisco General Hospital, one of the epicenters of the early US AIDS epidemic. She is the first woman to head this agency.

AVAC APPOINTS FIRST EDUCATION DIRECTOR

In July, Edd Lee became the first director of Education and Outreach for the AIDS Vaccine Advocacy Coalition (AVAC). Previously, Lee was associate director of prevention services at the Asian & Pacific Islander Wellness Center in San Francisco, where he coordinated outreach to gay men, commercial sex workers and other groups; and community co-chair of San Francisco's HIV Prevention Planning Council. Lee hopes to strengthen links between vaccine advocates and community-level prevention groups. "We need to tie into the service community, including mental health and substance abuse networks, so that they can take ownership of the vaccine agenda," says Lee.

VACCINE GROUP INCLUDED IN HHS INQUIRY

Twelve members of the US Congress have asked the Department of Health and Human Services (HHS) to launch an inquiry into federal funding given to 11 US groups, including the AIDS Vaccine Advocacy Coalition, Gay Men's Health Crisis, and African Services Committee. These groups signed a flier demanding a "more rational" US response to global AIDS and participated in a demonstration at US Secretary of Health Tommy Thompson's speech in Barcelona. The letter sent to HHS criticized the demonstrators for drowning out Thompson's speech and expressed concern about the lack of representation from faith-based groups at the meeting. It also requested information on federal funds spent to bring US participants to Barcelona.

US AIDS service organizations, many of which receive some federal support, say that this is the first time the possibility of "retaliatory" actions has emerged in response to protests. "AVAC does not receive federal funding," says executive director Chris Collins. "But that's not the main issue. Our main concern is harassment of AIDS organizations exercising their legal right to critique domestic policy."

NEW HEAD, NEW NAME FOR AVRC

On 4-5 September 2002, the AIDS Vaccine Research Committee (AVRC) of the National Institutes of Health reconvened with a new name—the AIDS Vaccine Working Group—and a new chair, Barton Haynes. Haynes heads the Department of Medicine at Duke University and is developing a peptide vaccine in partnership with Wyeth Lederle.

Founded in 1997, the AVRC was originally envisioned as a board of directors-style group for NIH's vaccine program and was known unofficially as the "Baltimore Committee," after its chair, Nobel laureate David Baltimore. In addition to Baltimore, three members—Barry Bloom (Harvard School of Public Health), Harold Varmus (Memorial Sloan Kettering Cancer Center) and Dan Littman (New York University School of Medicine)—are rotating off. Four new members have joined the group: Bette Korber (Los Alamos National Laboratory), John Moore (Weill Cornell Medical College), Dennis Kasper (Harvard Medical School) and Gordon Douglas (former Vice President, Merck & Co.; former President, Merck Vaccines). The group's new name was selected to better reflect its governance structure—including standing membership selected by the Chair—which does not fall within the rules governing official NIH committees.