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IAVI REPORT

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Cent Gardes Meeting

Researchers Increasingly Optimistic About Prospects for AIDS Vaccine

But will vaccines that lower viral setpoint and delay disease be enough?

By David Gold

According to data presented at a key scientific meeting, the development of vaccines capable of providing at least some protection against HIV is becoming not only possible, but increasingly likely. How fast this can happen and how much benefit such vaccines will actually provide still remain to be seen.

The meeting, the invitation-only Cent Gardes Symposium, attracted the top tier of AIDS researchers to Marnes-la-Coquette, France on 25-27 October 1999. This was the twelfth and last such meeting to be held at the facilities where Napoleon housed his "hundred guards" ("Cent Gardes" in French). Future meetings are likely to be held at the Annecy facilities of the Mérieux Foundation, a sponsor of the symposium.

The meeting made clear, from studies in the SIV/monkey model, that a number of vaccines, given alone or in combination, may provide some degree of protection. When challenged, some immunized monkeys are showing lower levels of viral replication, and, at times, delayed disease progression and death. Others show detectable virus only briefly post-challenge.

In the view of most researchers,

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South African Initiative Makes First Vaccine Awards

By Michelle Rotchford Galloway

The South African AIDS Vaccine Initiative (SAAVI), launched last year as a key component of the government's increased efforts to combat HIV/AIDS, announced its first funding allocations on 9 November 1999. Altogether R7 million (US$1.1 million) was awarded to four projects: two for developing specific candidate vaccines suitable for sub-Saharan Africa; one for vaccine advocacy and education, and one for work on ethical issues in conducting HIV vaccine clinical trials. The four projects, which were selected from ten proposals after review by an international panel, will be assessed annually over the three year grant period to determine continued funding. Depending on progress and available funds, further applications will be invited in the future in specific research areas.

Following is a brief description of the selected projects.

BCG and particle-based vaccines

This effort will focus on developing and comparing four types of candidate vaccines, all containing *env* and *gag-pol* gene inserts derived from a local HIV-1 clade C isolate. One candidate will be based on the bacteria BCG and another on virus-like particles (VLPs) produced in plants - inexpensive technologies that are already established in South Africa and could therefore lead to affordable

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vaccines that can prevent HIV infection (sterilizing immunity) still appear to be a long way off. The "protection" seen so far has been in small monkey studies lacking standardized immunization and challenge procedures, making comparisons among them difficult. Animals are often challenged with SIV or SHIV at the time of peak immune responses, and it is still not certain that vaccine-induced reductions in "viral setpoint" (the level at which HIV eventually plateaus after infection) will translate into significantly lower rates of disease and death in humans.

This point was emphasized by University of Amsterdam researcher Jaap Goudsmit, who, in his concluding remarks, cautioned that vaccines which simply reduce viral setpoints may not dramatically alter the overall global epidemic. Goudsmit, who also chairs IAVI's Scientific Advisory Committee, discussed data from cohort studies in Amsterdam indicating that HIV-infected individuals with a lower viral setpoint still eventually progress to AIDS.

Taken together, though, the data presented at Cent Gardes suggest the very real possibility that vaccines capable of limiting HIV replication and disease may be on the horizon. And the increasing interest in testing some of these new immunogens as therapeutic vaccines given with anti-retroviral therapy indicate that vaccine developers might see another potential market for these products.

Many researchers cited a lack of available monkeys for testing candidate vaccines as a critical barrier.

At Cent-Gardes, the meeting began with Jean-Jacques Bertrand of Pasteur-Mérieux-Connaught reaffirming his company's commitment to AIDS vaccine research. "It is the right thing to do," he stated. Michel Kazatchkine of France's Agence Nationale de Recherche sur le SIDA (ANRS) then announced that an annual meeting on AIDS vaccine research, the first of which was held at NIH in May 1999, will now alternate between the U.S. and Europe, with the next gathering to take place in Paris in May 2000.

Increased Interest in Tat

Robert Gallo of the Institute for Human Virology (IHV) in Baltimore led a session on the Tat protein that included presentations from a number of researchers. Tat, which is produced early in HIV replication, plays a critical role in HIV replication. According to Gallo, Tat also suppresses T-cell proliferation, induces immune suppression and can be a toxin for uninfected cells.

Barbara Ensoli of the Istituto Superiore di Sanita in Rome then presented data on two different Tat-based approaches: an SIV Tat protein and an SIV *tat* DNA construct. Since the Tat protein results were previously published (*Nature Medicine*, June 1999, pp. 643-650), Ensoli primarily discussed the *tat* DNA vaccine data. She compared *tat* DNA delivered intramuscularly (IM) or intradermally (ID), and found that the ID method generated more antibodies but lower CTL responses.

After challenge with the pathogenic SHIV 89.6P, four IM-immunized monkeys had no detectable viremia and normal CD4 levels. In comparison, the ID-immunized and the control monkeys all had high levels of SIV. (It was unclear from the presentation how much disease the control animals developed.) Ensoli suggested that CD8+ CTL response seemed to be the correlate of immunity in this study.

Daniel Zagury of the Université Pierre et Marie Curie in Paris presented data on a chemically inactivated Tat protein. The Tat toxoid is being studied as an immune therapy in HIV-infected individuals in Phase II trials by Alessandro Gringeri of the Maggiore Hospital in Milan. The study, according to Zagury, suggests that Tat toxoid is safe, well-tolerated and capable of stimulating antibodies to Tat.

Data from a monkey study of Zagury's Tat toxoid immunogen was presented by David Pauza of the University of Wisconsin. Pauza immunized monkeys with: 1) Tat toxoid ID; 2) Tat toxoid plus gp160 IM; and 3) native Tat protein ID and IM. He then challenged the monkeys with a pathogenic SHIV 89.6PD strain. Animals immunized with Tat toxoid plus gp160 or Tat protein seemed to do better in terms of viral setpoint, alpha interferon and beta chemokine levels. Although lymphoproliferative response to Tat seemed to correlate with more protection against disease, these differences did not reach statistical significance.

Albert Osterhaus of Erasmus University in Rotterdam presented data about a prime boost combination of vectors - Semliki forest virus (SFV) vector and modified virus Ankara (MVA) - both expressing the *rev* and *tat* genes. Osterhaus presented his rationale for using *tat*: HIV-infected long-term non-progressors have significantly greater CTLs to Rev and Tat, and in lab studies, Tat and Rev-specific CTLs inhibit SIV replication.

The Dutch research team immunized two monkeys with SFV and MVA, both expressing *rev* and *tat*. Two control monkeys were immunized with blank vectors. After challenge with a pathogenic SIV strain, both control monkeys developed high levels of virus and were sacrificed at 30 weeks. In contrast, the vaccinated monkeys had a transient "blip" in viral load, which then became undetectable. Osterhaus is now conducting a larger study of 18 monkeys immunized with SFV and MVA expressing: 1) *rev* and *tat*; 2) *tat* alone; and 3) *rev* alone.

The session also included a presentation on a potential anti-Tat therapy. Erwann Loret of CNRS in Marseilles presented data on TDS1, a molecule that binds to the Tat protein and may be useful as an anti-HIV therapy. TDS1 appears to inhibit Tat-induced activation of HIV.

MVA, DNA Vaccines Show Promise in Monkeys

Norman Letvin of Harvard Medical Center (see interview, page 7) presented a series of monkey studies evaluating a number of different vectors and DNA plasmids.

An ALVAC canarypox vector (produced by PMC and expressing SIV *gag* and *pol*) generated an overall CD8+ T-cell response that was "measurable but fairly low" in monkeys, according to Letvin. These responses, he suggested, could possibly be boosted by a DNA or lipopeptide construct.

Letvin then presented data on an MVA SIV *gag/pol* construct. His team immunized 4 monkeys intradermally. CTL response in

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"AIDS in Africa" Meeting Spotlights Epidemic's Continuing Devastation

by Patricia Kahn

The XIth International Conference on AIDS and STD's in Africa, held in Lusaka, Zambia from 12-16 September 1999, drew over 5,000 participants from dozens of countries. Entitled "Looking Into the Future: Setting Priorities for HIV/AIDS in Africa," the meeting was both a stock-taking of AIDS and its devastating impact in Africa, and an attempt to identify concrete, achievable steps to help turn the tide. For the thousands of African health workers, policy makers, scientists, community representatives and PWAs who attended, it was also an important opportunity to compare notes on what does and doesn't work in practice and to forge ties across nations.

Many of the plenary talks documented the impact of AIDS on sub-Saharan Africa, home to two-thirds of all people now living with HIV/AIDS (but to only 10% of the world's population). Speaker after speaker spoke of the misery endured by infected people without access to effective medical care, many living in poverty; the millions of AIDS orphans; and the erosion of national health care systems, life expectancies and economies. "AIDS now poses the foremost threat to development in Africa," said Callisto Madavo, World Bank vice president for the Africa region. And many speakers, including some high-ranking African politicians, addressed the failure of African governments and international agencies to acknowledge the scale of the devastation and the response it demands. "Nowhere is the effort strong enough to turn the epidemic back," said Madavo. "We simply must do more or we shall forfeit our future."

Governments, international agencies and AIDS policy

Madavo announced that the World Bank will intensify its own efforts to combat AIDS, but that strong national government commitment will be a pre-requisite for increased Bank support. New Bank strategies will include more funding (with 80-85% as grants rather than loans for most countries), mainlining AIDS in every Bank program, and placing greater emphasis on building national infrastructure and capacity.

Several African politicians discussed their countries' difficulties in responding to the epidemic, with both the Prime Minister of Mozambique and the Vice President of Malawi attributing past failures partly to treating HIV/AIDS purely as a health issue rather than one requiring action from every government sector.

Pierre Mpele, president of the Society on AIDS in Africa, described the key role political commitment played in Africa's only two countries that have made real headway in fighting the epidemic: Senegal, which has a seroincidence below 2%, and Uganda, which has succeeded in lowering the rates of new infection in some groups by 50%. The clear lesson, he said, is that governments can achieve a lot even without large sums of money.

UNAIDS Executive Director Peter Piot echoed many of these themes and emphasized the paltry amount of money spent on AIDS in Africa (US$15 million from African countries and $150 million from abroad in 1998). But he also said he sees "a tinge of hope" that change is on the horizon. For example, one day earlier, ten African nations declared HIV/AIDS a national disaster requiring emergency responses, and they pledged more political leadership in moving from talk to action. "The heavy artillery is beginning to arrive," Piot said.

Other plenary speakers were harsher in criticizing African leaders and the world-at-large for their neglect. Several pointed out – to long, loud applause – that African governments pour far more money into supporting armies and waging wars than into fighting AIDS. (Military spending by African governments in 1998 was about US$6 billion, according to the Stockholm International Peace Research Institute.)

With funds for AIDS so scarce, one session focused on Africa's massive foreign debt and the Zambian government's "debt swap" idea. Speaking before a packed audience, Zambia's Minister of Finance and Economic Development, Godfrey Simasiku, presented his government's proposal to exchange at least part of its debt for money that would go into HIV/AIDS programs. Many African countries spend as much or more servicing their debt as on health, education and welfare combined; Zambia's debt of US$6.5 billion amounts to $650 per capita, more than twice the annual per capita GDP, Simasiku said. The proposal also includes provisions to ensure that funds would genuinely go to HIV/AIDS, not to general government coffers. Jonathan Simon of Harvard presented an analysis of four African countries showing that bilateral debt swaps could release several times their present HIV expenditures, generating more money (on a per capita basis) than the cost for Uganda's entire HIV/AIDS reduction effort.

Vaccines for Africa

Lack of political leadership and commitment also featured in several overview talks on vaccines, a low-profile topic on the meeting's agenda but one that attracted wide coverage in African media. Harvard's Max Essex, IAVI president Seth Berkley and UNAIDS vaccine head Jose Esparza collectively provided an overview of progress and obstacles, emphasizing the low priority given so far to HIV vaccine development, especially those aimed at the subtypes circulating in Africa. Peter Young, CEO of AlphaVax (a North Carolina-based biotechnology company developing a subtype C-based vaccine, with funds from IAVI and others), discussed the private sector's lack of interest in AIDS vaccine development and some of the marketing and intellectual property concerns behind it.

Despite the many obstacles, Essex stated that he is increasingly optimistic about the scientific feasibility of an AIDS vaccine. "Up until two years ago I was much more pessimistic...Most of my colleagues now sincerely believe a vaccine is possible," he said.

Other speakers described the few ongoing vaccine efforts that have reached, or are approaching, clinical trials in Africa.

Uganda's canarypox trial

A. Kebba of Kampala's Joint Clinical Research Center reported on the only HIV vaccine trial in Africa so far, a Phase I study of Pasteur-Mérieux-Connaught's vCP205 canarypox (subtype B-based) vector (supported by NIAID). Kebba described how the trial, started in February, 1999, was the culmination of a long process that began a decade ago with studies on HIV seroincidence, subtypes and potential cohorts, work made possible by the Ugandan government's pro-active response to HIV/AIDS. That support was also key to staying the course over the four difficult years it took to get the trial approved, when "the government sought the consensus of the whole nation," said communi-

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ty representative Sophia Monico, director of The AIDS Service Organisation (TASO) in Uganda. The trial will test whether this vaccine (now in Phase II in the U.S.) induces the same immune responses in Ugandans as in North Americans and Europeans, and if so, whether these responses extend to the non-B subtypes circulating in Uganda.

Kebba reported that enrollment of 40 low-risk volunteers took eight months, far longer than expected, but had just been completed. The delay was not due to lack of volunteers - on the contrary, willingness to participate was high - but to the many people excluded because of high-risk behavior, STD infection, or other medical conditions. Another (unexpected) hurdle was the lack of appropriate reference values for "normal" white blood cell and platelet counts: Ugandans tend to have lower counts than Caucasians, which led to the exclusion of many otherwise eligible volunteers.

Monico elaborated on the long, difficult approval process for the trial and on lessons learned: the need to involve communities much earlier, particularly in countries with widely-held misconceptions about HIV and vaccines; and the enormous effort and time needed to build local capacity for scientific and ethical review and for conducting trials.

Subtype A DNA/MVA vaccine for Kenya

Omu Anzala of the University of Nairobi and IAVI's Berkley described a subtype A-based DNA/MVA vaccine that should come into Phase I trials next year (as an IAVI-sponsored "vaccine development partnership" between the groups of Andrew McMichael at Oxford University and Job Bwayo at the University of Nairobi). The DNA and MVA constructs each contain a string of 44 individual HIV epitopes derived from an HIV-subtype A strain isolated in Kenya, where A is the main circulating subtype.

Anzala described the genesis of the vaccine in studies dating back to the mid-1980s, when researchers identified some highly exposed but seronegative women in a Nairobi cohort of commercial sex workers. Intensive studies of their immune systems showed high levels of HIV-specific CTL's but no antibodies, and led to the idea of designing a vaccine aimed at eliciting this same CTL response.

Pilot production of both vaccine components has begun and a Phase I trial is slated to start in Britain early next year, followed by a Phase I trial in Kenya.

Vaccines and African Communities

Another interesting vaccine session took place at a community meeting organized jointly by IAVI and AfriCASO (the African Council of AIDS Service Organizations, Africa's largest consortium of AIDS-related community groups). Approximately three hundred people, including community advocates, health workers and PWAs, turned out to hear about vaccine development and clinical trials and to discuss their implications for African communities.

The session began with Berkley and Anzala speaking on vaccine development and the upcoming Kenyan trial, and continued with a talk by Abdel Kader Bacha – a physician in Senegal and manager of the community health program at the development agency ENDA Tiers-Monde. Bacha spoke passionately about the need for African communities to get active in supporting vaccine development and preparing for clinical trials. "The community movement is convinced that vaccines are necessary and urgent....We commit ourselves to helping people around the world make an AIDS vaccine."

Bacha also outlined concrete activities that community representatives could undertake: providing information to help prepare communities and decision makers for trials; assuring an inclusive process that involves communities early on, "not just as guinea pigs at the end;" and helping to stimulate informed debate about the ethics and science of trials. As examples of issues to resolve, he mentioned the scarcity of centers for carrying out HIV testing and guaranteeing confidentiality, and - within the context of health care systems that provide little for HIV-positive people - the question of what to offer people who learn they are infected after volunteering for trials. "We cannot just toss them out when they're not useful," he said.

During the discussion, a major theme was the need to ensure that Africans get immediate access to any effective vaccine, unlike the situation with anti-HIV medications. "We must stress access. With drugs, we weren't prepared for this issue," said one participant. Others pointed out that the lack of care is a powerful incentive for Africans to support vaccines. "I assure you, the community will be ready [for vaccines]," said another participant. "When we go to the clinic and ask for medicine, all we get is panadol, panadol, panadol" [an over-the-counter pain medication].

The meeting concluded with remarks by Moustapha Gueye, head of AfriCASO, who called vaccines "the best long-term hope" and stressed the need to build capacity within community organizations to advocate for an inclusive development process.

Molecular epidemiology

Several speakers presented data on the distribution and spread of HIV subtypes in Africa, information which is crucial for vaccine design. Africa has all known HIV subtypes in circulation, yet their distribution remains highly uneven. Anne Buvé reported new data from a four-city comparison (part of a larger study described in the following section), based on typing a fragment of the envelope protein (see table). Recombinants also showed a heterogeneous distribution,

UNEVEN DISTRIBUTION OF HIV-1 SUBTYPES ACROSS FOUR AFRICAN CITIES (1997–1998)

	# of samples	% HIV+	% of samples				
			subtype A	C	D	G	other
Ndola, Zambia	114	28.4	—	100	—	—	—
Kisumu, Kenya	100	25.9	71	6	20	2	1
Yaoundé, Cameroon	104	5.9	86*	—	4	5	5
Cotonou, Benin	57	3.4	83**	—	2	16	—

* 9 of 32 tested more closely proved to be A/G recombinants
** 7 of 12 tested were A/G recombinants

Source: Study Group on Heterogeneity of HIV Epidemics in African Cities / UNAIDS

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Commonwealth Leaders Urge Greater Support for AIDS Vaccines

Blair announces UK£14 million grant to IAVI

By Victor Zonana

Leaders at the biannual Commonwealth Heads of Government Meeting in Durban on 12 November 1999 declared that the HIV/AIDS pandemic constitutes a "Global Emergency" and urged governments, international agencies and the private sector to give greater priority to developing a preventive vaccine. The leaders also "pledged personally to lead the fight against HIV/AIDS within their countries and internationally," according to the summit's official communiqué.

Giving force to those words, British Prime Minister Tony Blair announced a UK£22.7 million funding package to combat AIDS from the Department for International Development – including £14 million to IAVI.

Blair, saying he was "horrified" by the toll of AIDS in sub-Saharan Africa, said he will try to enlist leaders from other countries – most prominently, the U.S. and France – to join the UK in confronting the epidemic.

"HIV/AIDS is a death sentence for poor and marginalized people," said Clare Short, UK Secretary of State for International Development. "It lays a crippling burden on societies and is sharply reducing life expectancy in many countries. The development of a safe, effective and affordable vaccine is the best long-term hope of ending the HIV/AIDS epidemic. Only international funding from governments will ensure that we get a vaccine that is effective, safe and accessible to the poorest people in the world," she added.

The UK grant to IAVI was the first major government support for the global initiative. "We salute the United Kingdom for its vision and leadership. Vaccine development is beginning to assume its proper place in the world's overall HIV/AIDS prevention agenda," said Seth Berkley, IAVI's president. "This grant will serve as a powerful catalyst to our efforts to develop a globally accessible AIDS vaccine and will help enlist other governments in this cause."

Berkley said other promising signs of political leadership in the Commonwealth include the recent creation of the South African AIDS Vaccine Initiative (see article, page 1) and the declaration by Indian Prime Minister Atal Behari Vajpayee of the need for a "mission-like" program to develop an AIDS vaccine. "Without political leadership and adequate resources, a vaccine against AIDS will continue to elude us," he added.

Another Commonwealth leader, Ugandan President Yoweri Museveni, urged African heads of state to confront the epidemic forthrightly . "In our villages, when there's danger, you make alarm," he said at the Summit. "So when you see a lion coming and you don't make alarm you're not helping the village." Uganda is the first African country to take part in clinical trials to develop an AIDS vaccine.

Since its inception in 1996, IAVI has raised nearly US$75 million toward the $350- $500 million budget outlined in the organization's Scientific Blueprint for AIDS Vaccine Development, a global scientific strategy to accelerate AIDS vaccine development. The British grant represents the cornerstone of IAVI's new campaign to raise $100 million by the end of 2001.

IAVI's research focuses on vaccines that would be most useful in developing countries. Such vaccines would be inexpensive to manufacture, easy to transport and administer, stable under field conditions and require few inoculations. IAVI has negotiated agreements with its industry partners to ensure that vaccines will be made available in developing countries at just above the cost of manufacture. "Dealing with the access issue at the start of the process represents a wholly new approach to vaccine development that will ultimately benefit both industrialized and developing countries," Berkley said.

"We are scouring the globe for the most promising vaccine approaches to fast track," said Wayne Koff, IAVI's vice president for research and development. "While the scientific challenges to successful AIDS vaccine development remain considerable, we believe that the simultaneous testing of a wide variety of different vaccine approaches will yield the fastest path to safe and effective AIDS vaccines." He said IAVI will shortly announcing a series of new scientific initiatives. ◆

EU to Fund HIV Vaccine Development

by Julian Meldrum

As the *IAVI Report* went to press, the European Commission's DG XII was expected to announce decisions on a round of scientific grants that includes support for AIDS vaccine research. A budget line of 300 million euros (US$318 million) is available for "control of infectious diseases" under the Fifth Framework Programme, which runs until 2002. While HIV vaccine development is a priority under this heading, the funding category also covers work on other vaccines and on strengthening European Union scientific responses to a range of other diseases, both animal and human.

One likely beneficiary of this funding round is a three-year, US$9.2 million multicenter project known as EuroVac. EuroVac will set out to create a number of HIV vaccine candidates and take them into Phase I clinical trials. The project is co-chaired by Jaap Goudsmit at the University of Amsterdam and Marc Girard at the Pasteur Institute in Paris, neither of whom was able to comment in advance of an agreement on funding.

The project proposes to compare MVA and NYVAC, two weakened strains of vaccinia virus, as vectors for a range of HIV proteins from isolates belonging to subtype B and a subtype C from China. These live recombinant vaccines would be evaluated with or without an envelope-based subunit boost, with the aim of assessing their ability to generate immune responses that act against isolates of different subtypes.

The funding awards are also expected to include up to US$5.3 million for other AIDS vaccine-related research. ◆

Julian Meldrum is the editor of "Body Positive," a London-based newsletter for people living with HIV/AIDS.

Industry Insider

Merck to Start Human Trial of AIDS Vaccine
Pharmaceutical giant Merck & Co. appears to be on the verge of starting its first human trial of a candidate HIV vaccine. According to a number of sources, the company has filed plans with the U.S. Food and Drug Administration to launch a Phase I study of one of its "human codon-optimized" HIV DNA vaccines. Merck will reportedly test a number of different doses of the vaccine in HIV-negative volunteers. The company is looking at an eventual prime boost combination of an HIV DNA vaccine (based on a licensing agreement with Vical, a San Diego-based biotechnology company) and a viral vector, most likely based on adenovirus.

In November, Vical announced receipt of a US$2 million payment from Merck in accordance with a 1997 license agreement. The payment extends Merck's exclusive worldwide rights to use Vical's DNA technology to develop and market HIV and hepatitis B (HBV) therapeutic vaccines. Merck had previously licensed the technology to develop preventive vaccines for HIV and HBV and for a therapeutic vaccine against human papilloma virus.

VaxGen Gets Paul Allen, CDC Funds
Microsoft Corp. co-founder Paul Allen has invested an additional US$25 million in VaxGen, increasing his stake in the California-based biotechnology company to 22% from 8%. In October, VaxGen disclosed that Vulcan Ventures, Allen's investment company, bought 2.17 million shares of VaxGen at US$11.50 each. The investment came as VaxGen completed enrollment in the first-ever Phase III clinical trial of a preventive HIV vaccine (AIDSVAX). More than 5,400 volunteers have been immunized at 56 clinics in the U.S., Puerto Rico and the Netherlands. VaxGen also announced that Ruth B. Kunath, director of Vulcan Ventures biotechnology portfolio, has joined its board of directors.

VaxGen is also conducting a Phase III trial of a different formulation of the AIDSVAX bivalent gp120 vaccine that will enroll 2,500 volunteers in Thailand. The company said that the new financing will enable it to create AIDSVAX versions targeted at subtypes common in other parts of the world, particularly Africa.

In addition, the U.S. Centers for Disease Control and Prevention (CDC) will provide approximately $2 million annually to VaxGen's trial sites over the next four years. CDC will help assess the impact of the trial on attitudes and risk behaviors of trial participants and affected communities

SmithKline Beecham Strengthening Program
One of the world's largest vaccine manufacturers, SmithKline Beecham Biologics, appears to be taking steps to strengthen its HIV vaccine development effort. To date, the company's program has focused primarily on developing gp120 constructs used with its own adjuvants. However, SmithKline recently moved its vaccine work on tuberculosis, malaria and HIV into one program and is now evaluating a number of HIV protein vaccines with its proprietary adjuvants in monkey studies. Company researchers are also working on a malaria vaccine that is now in human testing in The Gambia. Data released at a recent scientific meeting indicates that infection rates among the 300 vaccinees dropped 66 percent, but that this protection only seemed to last four months.

Chiron R&D Cuts May Not Impact AIDS Vaccines
In early November, a number of press reports indicated that Chiron, a leading biotechnology firm and one of the few with an active HIV vaccine program, is cutting overall research and development spending. The company's chief executive, Sean Lance, is reportedly trying to focus company researchers on programs most likely to lead to development of "blockbuster" products. However, Chiron insiders indicate that R&D spending will remain level, but overall development costs will take up a bigger share of expenses. Novartis AG, the Swiss pharmaceutical giant owns 44% of the company.

Margaret Liu, head of Chiron's vaccine research program, hopes to move candidate HIV vaccines into human trials by 2001.

Glaxo Interested in HIV Vaccines
Glaxo Wellcome, the world's largest pharmaceutical company and a leading developer of HIV therapies, appears to be taking a closer look at HIV vaccines. The initial focus of the company's efforts will be to test a vaccine construct as an immunotherapy in HIV-infected individuals, possibly in the next two years.

In 1998, Glaxo announced that it will collaborate with Powderject Pharmaceuticals, a U.K-based biotechnology company, to develop a technology that administers vaccines and therapeutics to patients by delivering microscopic DNA-coated gold particles into the skin, without intramuscular injections. Glaxo invested US$20 million in Powderject and paid the company $4 million to license a hepatitis B DNA vaccine that is now in Phase I studies in the U.S. Powderject is also working with researchers from Oxford University and the University of Nairobi on an HIV DNA and MVA prime boost combination. IAVI is providing funds for the project.

Therion Gets NIAID Contract
NIAID has awarded three contracts totaling $1.5 million to Therion Biologics Corporation in Cambridge, Massachusetts for the development and manufacture of novel AIDS vaccines and related research reagents. Two agreements cover the production of MVA vectors for Phase I and II trials. The third contract relates to the production of reagents for evaluating specific cell-mediated immune responses in individuals infected with HIV or immunized with candidate HIV vaccines

An Interview with Norman Letvin

Norman Letvin is widely considered to be among the most influential AIDS researchers in the field. An internist by training, he heads the Viral Pathogenesis Laboratory at Harvard Medical Center's Beth Israel Hospital in Boston. Focusing primarily on cellular immune responses to HIV and SIV, Letvin's lab has built strong relationships with many key companies and institutions. He is a member of IAVI's Scientific Advisory Committee and NIH's AIDS Vaccine Research Committee, and also advises NIH's Vaccine Research Center and the French ANRS.

IAVI Report: Where do you think we are in AIDS vaccine research?

Norman Letvin: I think we may be at a turning point. When we started years ago, we didn't really understand what immune responses were going to be important for containing viral replication. So we focused on how vaccines have worked in the past.

But now we have a much more profound understanding of how HIV is contained in infected individuals, and are in a position, for the first time, to harness that for making a vaccine.

There are now very compelling data suggesting that HIV replication can be well contained by two types of immune responses: the virus-specific cytotoxic T cell (CTLs) and neutralizing antibodies. And for the first time, we have a good sense how to elicit some of those immune responses. Today, a number of approaches, including poxvirus and adenovirus vectors and plasmid DNA, appear to elicit potent, durable HIV-specific CTLs. And they appear to be safe in humans. So we are in a good position to move these technologies rapidly into human trials and I have every confidence that some of these will at least be able to dampen viral replication, if not fully contain it.

The issue of neutralizing antibodies has been a major problem since we first tried to make an HIV vaccine. The original focus was on making envelope-specific antibodies, but that turned out to be a difficult target. While we don't have an approach for eliciting antibodies that neutralize primary HIV isolates, we do have a conceptual framework for approaching the problem.

What is that?

We know that the neutralizing determinants of gp120 appear to be very genetically diverse. Therefore, approaching gp120 as a primary target will be difficult. But the gp41 protein is very well conserved – there is greater than 90% genetic conservation from one strain to another. And neutralizing antibodies that recognize at least a component of gp41 can neutralize primary isolates.

Peter Kim's work at the Massachusetts Institute of Technology shows how membrane fusion is likely to occur. And that model suggests potential targets on gp41. So, in terms of both CTLs and neutralizing antibodies, we're substantially further along.

Do HIV clades matter in vaccine development?

The more genetic similarity between the vaccine immunogen and the virus you're trying to protect against, the more likely you are to generate CTLs with specificity for that virus, and neutralizing antibodies. Whether clades, per se, matter or not, is up in the air.

So will vaccine manufacturers have to produce twenty different vaccines for the world?

The answer will come from human studies. But, conceptually, that is not necessarily the case. We know that CTLs from some of the structural proteins of the virus can be well conserved across clades, and if the target for neutralization turns out to be gp41 rather than gp120, there would be no need to make clade-specific vaccine.

You recently presented data at the Cent Gardes meeting (see article, page 1) **about a number of vaccine approaches. What is the overall message from that data?**

The message is that we have in hand right now is that a number of diverse and possibly complementary technologies appear to elicit very potent, reasonably durable CTL responses in monkeys.

And I feel very confident that we can do much better, by using better delivery vehicles, adjuvants, and antigens in different combinations. We have preliminary data suggesting that newer approaches will further augment these responses.

Some people are frustrated because your data only includes CTL responses, and nothing about other responses such as lymphoproliferative responses, chemokines or neutralizing antibodies. How do you answer them?

The answer is that our laboratory tries, as much as possible, to focus the question we're asking, and to design experiments that will very directly answer those focused questions.

The tetramer technology we're using for measuring CTL responses is a huge advance. It allows us, for the first time, to measure in a highly quantitative, reproducible way, vaccine-elicited T-cell response.

Our ability to measure some of these other responses you're referring to is improving dramatically. We're working very actively on tetramer technologies that measure CD4-positive T-cell responses. Some of the other kinds of responses you mention have not been quantitative enough to prove useful for our studies.

But are we focusing too much on CTL response as a correlate of protection?

There is compelling data from many laboratories, without question, that in primary and chronic SIV/HIV infection, CD8 -positive CTL response is absolutely required for containing viral replication. In its absence, virus replication is not contained.

What about CD4 T-cell response?

Clearly, one needs CD4 helper cells. If one didn't, there's a reasonable chance that HIV infection would not cause immunodeficiency. We need helper CD4 T-cells to maintain a CTL response, to generate and maintain antibodies, and perhaps for other functions.

How far are we from the CD4 tetramer assay?

A number of laboratories are working on this and there is every reason to believe that the technology will be readily developed. It will be a very, very useful tool in both human and monkey studies.

This technology tells us, in a very quantitative way, the number of cells in any lymphocyte population that bind to a specific peptide fragment of the AIDS virus, in association with the MHC molecule. And that number is of orders of magnitude more useful than simple proliferative assays.

But a CTL response alone will not be sufficient to generate sterilizing immunity against the virus. There is every reason to suppose that both an antibody and a CTL response will be needed.

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the MVA-immunized monkeys was "measurable and boostable." Interestingly, Letvin found significant differences in CTL levels in the blood and lymph tissue. The SIV DNA vaccine (described below) generated similar levels of CTLs in both compartments.

The monkeys were then challenged intravenously with a highly pathogenic SIV strain (E660). Two control monkeys died, compared to none of the immunized animals. Viral setpoint differences did not reach statistical significance, although there was clearly a trend towards lower viral load in immunized animals.

Letvin then presented data on a codon-optimized plasmid DNA (expressing SIV *gag*) developed by Merck. Four monkeys were immunized intradermally with SIV DNA and 4 with a blank DNA plasmid. A "quite robust" Gag-specific CTL response was seen in 3 of 4 immunized monkeys. After IV challenge with SIV E660, 3 of 4 vaccinated monkeys had undetectable levels of SIV and there was a statistically significant difference in viral setpoint compared with controls.

Looking to further improve the DNA construct, Letvin's team added Interleukin-2 (IL-2) linked to IgG to increase the half-life of the vaccine. Monkeys were vaccinated with: 1) SIV DNA plus IL-2 protein; 2) SIV DNA containing IL-2 in the plasmid; 3) SIV DNA alone; and 4) blank DNA. The DNA containing IL-2 generated the best immune responses, and the DNA and IL-2 protein combination was second best.

Updates on Viral, Bacterial Vectors (VEE, MVA and BCG)

Bernie Moss of the National Institute of Allergy and Infectious Diseases (NIAID) also presented data on the use of MVA as a vector. The NIAID team immunized monkeys with: MVA (expressing SIV *gag, pol*, and *env*); MVA plus gp140; or blank MVA as a control. After IV challenge with non-pathogenic SHIV 89.6, all three control animals had measurable virus, while 2 of 5 monkeys in both the MVA and the MVA-plus-gp140 arms had undetectable virus. Moss concludes that at this stage, the MVA alone and MVA plus gp140 appear to offer similar levels of protection in monkeys.

Nancy Davis of the University of North Carolina reviewed data on a Venezuelan Equine Encephalitis (VEE) replicon being developed by AlphaVax (with support from IAVI, NIAID and the Walter Reed Army Institute of Research). In the first study of a VEE replicon, monkeys were challenged IV with a pathogenic SIV E660. Peak viral load levels were 100-fold lower in immunized monkeys. Davis reported that a new study will evaluate VEE replicons expressing parts of *gag, pol* and *env* with monkeys challenged either IV or rectally.

Nathalie Winter of the Pasteur Institute in Paris discussed using BCG (bacillus Calmette-Guerin) as a bacterial vector. BCG is a live attenuated strain of *Mycobacterium bovis* that is currently used as a vaccine against tuberculosis and leprosy in parts of the world. It persists and replicates within antigen-presenting cells and is suitable for mucosal delivery.

Winter's team immunized mice with a cocktail of three BCG strains expressing SIV *nef, gag* and *env*. The vaccines were administered via oral, nasal, rectal and aerosol routes, with intrarectal immunization generating the highest levels of CTLs in the mucosal system.

DNA Prime, Poxvirus or Protein Boost

Harriet Robinson of the Emory University Vaccine Center in Atlanta reviewed her already-published data on a DNA and fowlpox prime boost combination that provided some protection

AIDS Vaccines Highlight Gallo Meeting

Vaccines were a central topic at this year's meeting of the Institute for Human Virology (IHV). The IHV meeting, widely referred to as the "Gallo Meeting" (after IHV's director, researcher Robert Gallo) attracts scientists from around the world to discuss HIV and cancer biology. This year's meeting, held on 28 August–2 September 1999 in Baltimore, included more than 1,000 researchers from 20 countries.

Many speakers at the IHV meeting updated their data at Cent Gardes two months later, so their presentations are covered only in the article on that meeting (see page 1). Here we describe some of the Gallo meeting's noteworthy vaccine-related reports not discussed at Cent Gardes.

Ruprecht Gives Overview on HIV Vaccines

Ruth Ruprecht presented an overview of progress in AIDS vaccine research. Ruprecht said it was too early to discard the live attenuated HIV vaccine approach. However, instead of just searching for ways to reduce HIV's replication capacity, she suggested focusing on genetic regions that may cause disease. In sooty mangabey monkeys, Ruprecht noted, SIV replicates at high levels but still doesn't cause disease. The mechanism which protects these animals from disease is not known.

Ruprecht described 1999 as the year of "the comeback of the antibody" and called for rapid movement of candidate vaccines into parallel animal studies and Phase III human trials. Even if the vaccines are not fully protective, she noted, the trials will help researchers determine correlates of protection and the usefulness of particular animal models.

Allo-immunization as a Vaccine Approach

Allo-immunization may hold promise as a potential HIV vaccine approach, according to data presented by Thomas Lehner of Guy's Hospital in London. Lehner noted that in monkey studies years ago, protection generated by whole-inactivated SIV turned out to be based not on SIV antigens but on human antigens present in the SIV challenge (since the challenge strain was grown in human cells), causing the monkeys to develop protective anti-human cell antibodies.

Lehner's team found that women who were allo-immunized with their partner's white blood cells to prevent spontaneous abortion generated significantly increased levels

against SIV challenge in monkeys. Robinson recently initiated a new study evaluating a DNA prime plus MVA boost combination and reports that she is already "seeing strong CTL responses" in immunized monkeys.

Marc Girard of the CERVI, Mérieux Foundation presented data on a DNA prime, envelope protein boost combination. Girard's team immunized monkeys with DNA (expressing SIV *gag, nef, env, rev*, and IL12) and an oligomeric envelope protein (ogp140). After 5 immunizations (3 DNA, 2 protein boosts), monkeys were challenged rectally with a non-pathogenic SHIV 89.6 strain. Of 6 immunized monkeys, 4 had no measurable virus. These animals were then re-challenged with pathogenic SHIV 89.6P, as were 4 naïve control monkeys. Two of four "protected" monkeys still had no measurable virus; overall these monkeys had a 3 to 4 log lower level of virus. Girard is planning a new study of the DNA/protein prime boost where the monkeys will be challenged directly with SHIV 89.6P.

Live Attenuated and Herpes Vector Vaccines

Ronald Desrosiers of the New England Primate Center provided data on a number of approaches, including live attenuated SIV vaccines, herpes vectors and deglycosylated constructs. In an attempt to create "highly-exposed but seronegative" monkeys, Desrosiers's team administered an extremely attenuated SIV strain via low but increasing rectal doses. These monkeys, unlike the IM-immunized monkeys, did not develop measurable virus or SIV antibodies, but did show SIV-specific lymphoproliferative responses. Using a very sensitive test, Desrosiers found evidence of SIV antibodies. He plans to challenge these animals shortly. Desrosiers also wants to test exposed but uninfected humans with this new, super-sensitive antibody test.

The US researcher then presented data on recombinant herpes viral vectors. In tests of first generation constructs in monkeys, 5 of 7 of immunized animals showed some protection against non-pathogenic challenge. Desrosiers is now preparing new constructs (expressing *gag pol* and *env* in a different herpes vector) that he believes will be more immunogenic. He also briefly discussed live attenuated SIV strains his lab has created by deleting glycosylation sites and parts of the V1 and V2 loop on the envelope. These constructs appear to generate significantly higher immune responses than wild-type virus.

HIV Lipopeptide Vaccines

The conference included two presentations on PMC's lipopeptide candidate vaccines. Dominique Salmon-Ceron of Hôpital Cochin in Paris reported data from human trials of the different lipopeptide candidate vaccines. To date, lipopeptide vaccines have been studied in six trials, 4 as a single vaccine, 2 as part of prime boost. A Phase I trial will evaluate lipopeptide immunizations plus an ALVAC canarypox vCP1452 boost. The ANRS is also testing a lipopeptide vaccine with highly active anti-retroviral therapy (HAART) in newly and chronically HIV-infected individuals.

Whole Inactivated SIV Confers Some Protection

Larry Arthur of the Frederick Center at the US National Cancer Institute (NCI) presented data on whole SIV virions inactivated by aldithiol-2, a chemical which irreversibly binds to the "zinc finger" motif in the nucleocapsid protein but preserves the viral envelope.

To test for safety, Arthur's group immunized a total of 6 monkeys with very high doses of inactivated SIV. No infectious virus was detected in any animal. He then immunized four other monkeys with the inactivated SIV. Significant proliferative responses were seen. The monkeys were then challenged with

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of CD8 suppressor factor activity (against HIV) and beta chemokines, and lower levels of chemokine receptors. In addition, CD4 cells taken from immunized women were more resistant to HIV infection in test tube studies. The degree of resistance correlated with the dose of allo-immunization. Lehner is hoping that NIH will support a large monkey trial of allo-immunization.

Heat Inactivation Maintains HIV Envelope

Inactivating HIV with heat may not eliminate its immunogenicity, according to data presented by Katherine Grov-Ferbas of the University of California at Los Angeles (UCLA). A number of different mechanisms have traditionally been used to inactivate viruses, including heat, irradiation and chemical inactivation. The UCLA researchers heated HIV at 62^{O} C, which dramatically reduced viral infectivity. But recently-developed crystallographic methods show that the envelope glycoproteins are maintained. Grov-Ferbas is working with Irwin Chen, another UCLA researcher, and Bert Dorman of Acrogen, a California based biotechnology company.

Gordon Douglas on Challenges to Vaccine Development

Gordon Douglas, former president of Merck Vaccines (and a member of IAVI's Board of Directors) discussed key challenges in HIV vaccine development. "The downstream challenges of distributing an AIDS vaccine," he said, "may be just as difficult as developing one."

Much of the world still does not have access to currently approved vaccines, including the recombinant hepatitis B vaccine (HBV), according to Douglas. The reasons: lack of funds, less familiarity with the seriousness of certain diseases, an emphasis on treatment rather than prevention and fears about vaccines, mostly unfounded. Douglas noted that French health officials have suspended routine vaccination with HBV, contrary to the recommendation of public health experts. But recent initiatives by the Gates Foundation and others have boosted efforts in vaccine research and availability.

Gallo on Vaccines

In a wide-ranging talk, Robert Gallo called on researchers "not to settle for vaccines that simply lower virus levels. There is a risk," he suggested, "that some people will prematurely conclude that we have succeeded. Sterilizing immunity must still be the ultimate goal." Gallo called Lehner's studies of allo-immunization "very interesting" and suggested that *tat* would be an important component of any vaccine. The IHV is planning larger studies of a Tat toxoid as part of a therapeutic and preventive vaccine. ◆

In this and the following article, the IAVI Report *profiles two openly HIV-positive individuals whose work has contributed enormously to raising awareness of HIV vaccines and making community participation in their development a reality in parts of the world.*

Major Rubaramira Ruranga

by Mark Schoofs

As a young man in rural Uganda, Major Rubaramira Ruranga hunted hippos and elephants with only a spear. When he went to the bush to fight Idi Amin and successor dictatorships, he served as a spy, infiltrating enemy camps. And when he went public 10 years ago as a person with HIV, his son suffered the inevitable schoolyard taunts but came up with the perfect retort: "All your fathers have AIDS too, but they're cowards."

This personal courage has helped "Major," as everyone calls Rubaramira, emerge as one of Africa's most vocal, charismatic AIDS advocates, both for people living with HIV and for an AIDS vaccine. "His decision to come out openly soon after the freedom fighters took power is to be applauded, because he sacrificed prestige and risked professional and social discrimination," says Roy Mugerwa, who heads the first and only vaccine trial in Africa, launched early this year in Uganda.

"A visionary and an articulate spokesman for an AIDS vaccine" is how IAVI president Seth Berkley describes Rubaramira. "He had the foresight to think about his children, his children's children and the people of Africa at a time when vaccines were on very few peoples' agendas."

Yet the Major's views can be unorthodox and controversial, such as his criticism of Uganda's vaccine trial as too modest and timid. "He has been a source of inspiration and sometimes a challenge to health care providers and researchers," says Mugerwa.

Rubaramira, now 51, discovered he was positive because of an argument. When he was fighting in the bush, he and his comrades "thought AIDS was just more imperial propaganda to tarnish our name." But after the war, his friend Viola Mukasa was working for a community AIDS organization and one night they quarreled about the disease. Exasperated, she thrust a fistful of pamphlets at him and said, "Just go and read this."

After poring over it, he called her to say he thought he was HIV-positive. "Being in the bush was really like incarceration," he explains. "You don't meet people, and all the time you're under fear. Then you come back and everyone loves you." So he had had "a couple of relationships" in which he didn't use condoms.

Despite expecting to test positive, when the nurse actually told him he was infected, "My mouth went dry," he recalls. "I was very, very scared." A doctor told him he had 2 or 3 years to live. That was in 1989.

At the end of that grace period, in 1992, he was in Amsterdam for the World AIDS Conference and saw an ACT UP contingent. "I said, 'Ow, what kind of people are these?' I followed them and asked them why they were demonstrating, and they told me they had HIV. I asked for how long, and some said 10 years or even longer." A military man, Rubaramira is not comfortable with ACT UP-style activism, but, he says, meeting those activists with HIV "was a real turning around – maybe even being born again, because I had already decided to die."

Today, Rubaramira is a well-known AIDS advocate and the founder of the wholly volunteer National Guidance and Empowerment Network of People Living with HIV/AIDS in Uganda (NGEN+). That network encourages people with AIDS – many of whom live in Uganda's poorest districts – to live positively, disseminate AIDS prevention information, and lobby for better treatment.

In recognition of his AIDS work, the Ugandan Ministry of Defense pays for Rubaramira's triple-combination antiretroviral therapy. But, he says, "I know many people will never have these drugs – and that's were a vaccine comes in. At least you know those without the virus won't get it."

What about behavior change? After all, Uganda has a world-renowned AIDS education campaign, one that has been credited with reducing the prevalence of HIV in urban communities. For example, in Kampala's Nysambya hospital, infection rates among pregnant women dropped from 29.5% in 1992 to 13.4% last year, according to Uganda's Ministry of Health. But as Rubaramira points out, that's still a huge pool of HIV-positive people. Driving through Uganda's rural north, where civil unrest has undermined AIDS education efforts, he gestures out the window and says, "Here, more people are getting infected."

Lack of information isn't the only culprit. "Poverty is the main cause of the virus continuing to spread," he says. Indeed, many Ugandans struggle to get enough to eat, which pushes many women into commercial sex or sugar-daddy relationships. And men migrate to cities in search of a better living – but away from their families, they acquire the virus. Without enough money to afford an HIV test, they never know they are bringing HIV back to their wives.

Rubaramira insists that people living with the virus understand the epidemic better than anyone, so he maintains there's nothing unusual in an HIV-positive person pushing for a preventive vaccine. "We have children and relatives, and if they get infected, they become a burden to us. That's especially true in Africa, where the culture dictates that any

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Bill Snow

by Patricia Kahn

Nine years ago, when Bill Snow first began talking to his fellow AIDS activists about vaccines, it was hard to get their attention. The battle was for survival of already-infected people and finding effective drugs as fast as possible; few activists viewed vaccines as a priority, and some even feared that they would weaken support for treatment research. An activist from the time recalls a meeting where Snow stood up and talked about vaccines, and "nobody was interested. Nobody even listened. But Bill kept saying, we should get involved in this, this is important."

Today, few would argue with the colleagues who call Snow "the father of vaccine advocacy in this country....the central thread around which the community fabric in HIV vaccines has been woven." "Bill has an enormous impact on the whole field," says Susan Buchbinder, principal investigator at the San Francisco vaccine trial site where Snow sits on the community advisory board (CAB). "His contributions range from big picture conceptual ideas and national policy to nitty gritty trial implementation issues." And David Baltimore, the Nobel laureate who heads NIH's blue-ribbon AIDS Vaccine Research Committee (which Snow belongs to) calls him "a very dedicated and insightful contributor....who knows the field of AIDS vaccine research in great detail."

That's not the most obvious vocation for someone who studied English literature in college and ran a business developing computer and management training programs for the likes of IBM and Levi Strauss. But that background served him well in honing the skills he now brings to the vaccine task: pragmatism and the persistence to solve problems, eliminate or circumvent obstacles and make the next steps happen.

Snow's career as an activist began shortly after he discovered he was HIV-positive, back in 1989. Given how little the medical establishment had to offer, he set out to learn all he could about AIDS and experimental treatments, ending up at ACT UP New York, around the corner from his apartment. A loosely organized group of AIDS activists, ACT UP was working to push the government into higher gear on AIDS, partly through their flamboyant protests at locations such as NIH, the Federal Drug Administration and the New York Stock Exchange. Although Snow was impressed with their 'in your face' style, he says, it wasn't really his own; instead, he gravitated to the Treatment and Data Committee, which was accumulating considerable expertise on experimental AIDS treatments and drug development.

It was a turbulent time in AIDS research. Activists, spurred on by anger at what they considered the U.S. government's plodding, regulation-choked approach to testing new drugs while so many people were dying, wanted to participate in designing trials and making decisions. At first it was a tough fight: "Researchers were used to doing things behind closed doors, and most were very resistant to meaningful community involvement," says Snow. But within a few years, community representatives had gained full voting membership on the most important research and policy committees, and CAB's were established at all sites within the NIH-run AIDS Clinical Trials Group (ACTG) - steps that would soon lead to profound changes, such as wider access to clinical trials and experimental drugs for HIV-positive people, and streamlined procedures for approving trials and licensing new drugs.

Snow first encountered HIV vaccines during this time, as he searched for a treatment to start while he was still healthy. Jonas Salk, developer of the original polio vaccine and a "childhood hero" to Snow, was championing the idea of boosting the immune system in infected people, and in 1991 Snow enrolled in the ACTG's first therapeutic vaccine trial (of Microgenesis' gp160-based product). That, in turn, introduced him to preventive vaccines, an area he quickly concluded was being unjustly ignored by researchers and activists alike. Undaunted by his fellow activists' lack of interest, he and a few like-minded spirits set out to penetrate the research establishment, just as the treatment activists had done. And this time around, said Snow, with the ground already broken, it proved surprisingly easy.

From the beginning, he realized that vaccine advocates faced a very different task than did treatment activists: making sure trials happen at all, given how few people were fighting for the cause. "Everybody needs a vaccine for AIDS, but "everybody" isn't a constituency," he told researchers in 1991 at the second NIH-funded annual vaccine meeting attended by community representatives. Establishing that constituency would mean engaging the high-risk communities which stood to benefit most from a vaccine.

That goal stayed central to Snow's advocacy, even as he gradually started working at the national level. By late 1994, HIV vaccine preparedness efforts had begun in earnest in the U.S. and Snow became deeply involved with the San Francisco trial site (now part of NIH's HIVNet vaccine trial network) and its cohort of gay men, which has run preparedness and Phase II studies and is now part of the VaxGen Phase III trial. From his CAB seat he has helped with everything from conceiving and designing trials to devising informed consent forms and recruitment strategies, says Buchbinder. And he has become a strong presence on national HIV vaccine policy boards, from the 1996 "Levine Committee" that reviewed NIH's entire AIDS research effort and recommended major changes to its vaccine program (which Snow now sees as "the beginning of the elevation of AIDS vaccines") to the advisory panel of the Office of AIDS Research and the AIDS Vaccine Research Committee (AVRC), which advises NIH.

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breadwinner supports not only his immediate family, but also members of the extended family who are down on their luck. So, he says, "people with HIV support a vaccine."

Nevertheless, getting approval for Uganda's current Phase I vaccine trial (HIVNET 007) was nothing short of excrutiating, with researchers forced to run a three-and-a-half year obstacle course filled with scientific and political hurdles. According to Mugerwa, the protocol had to pass five scientific and ethics committees and gain the blessing of cabinet and Parliament, even though the candidate vaccine (ALVAC vCP205, a recombinant canarypox vector with the HIV *env, gag,* and *pol* genes) had already been through several Phase I and Phase II trials in the U.S. and France.

As the trial began to recruit volunteers, Rubaramira worked in the HIV counseling department of the host institute, the Joint Clinical Research Centre. His job, as he describes it, was "getting people to understand that they have a responsibility to help develop a vaccine." But, he maintains, "we had more problems with doctors than with ordinary people. AIDS is really hurting ordinary people, so once the vaccine is explained to them, they are very happy to participate." On the other hand, "intellectuals have those intellectual problems; they look for ideal situations."

Rubaramira wishes the trial had skipped Phase I and plunged directly into Phase II. In his typically outspoken fashion, he argues that "Africa's historical backwardness in science" and its "dependency" on European and American research is one reason for the cautious start. Mugerwa and others respond that it would be premature to launch larger trials without laboratory evidence that the ALVAC construct, made from a clade B virus, provokes cross-clade immunity; such experiments are a major element of the Phase I test. But the fact that this research wasn't carried out long ago by African scientists, says Rubaramira, demonstrates his point that African science lags behind.

But the main reason researchers favor Phase I is safety. The ALVAC vCP205 construct has been tested so far only in North America and Europe, and Ugandan researchers say that differences between Ugandans and these Caucasian populations – including genetic variation, nutritional status and the presence of other infections – could theoretically influence safety.

Given the political explosiveness of HIV – many Africans believe the virus was concocted by white scientists to wipe out blacks and homosexuals – any glitch in safety could have disastrous consequences. Rubaramira concedes this, but insists that waiting also has consequences. "While we're doing Phase I, how many will get infected and die?"

What researchers and Rubaramira agree on is that, as the Major puts it, "With this trial, we will overcome the inhibitions [to conducting HIV vaccine trials]. We have set a precedent. You have to start somewhere." ◆

Mark Schoofs writes for the Village Voice *in New York. In 1998, he was awarded the Science Journalism Award of the American Association for the Advancement of Science, and he recently completed a six-part series on AIDS in Africa (available at: www.villagevoice.com)*

BILL SNOW
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Along the way, Snow, Garance Franke-Ruta and David Gold (editor of the *IAVI Report*) decided that vaccine advocacy, still a stepchild of AIDS activism, was in danger of languishing and needed a separate effort. That led them to found the AIDS Vaccine Advocacy Coalition (AVAC), now a small, independent group based in Washington, D.C. that follows progress, identifies obstacles and advocates to remove them. Snow sits on its Board of Directors and remains a guiding spirit as AVAC has carved out an identity combining activist and watchdog activities. Its first report in 1996 was an in-depth analysis of obstacles to industry involvement in AIDS vaccine development, and its annual publication (issued on the anniversary of President Clinton's 1997 call for an AIDS vaccine within a decade) evaluates the year's progress and makes detailed recommendations. This year's list included calls for more funds, better coordination among government agencies and greater accountability for results - steps aimed at raising the sense of urgency among key players, without which, says Snow, there is little chance of meeting Clinton's ten-year goal.

The accountability issue is one he has also taken on personally. In an open letter to top NIH officials that accompanied this year's report, AVAC reiterated its recommendation that NIH progress should be evaluated by clear, measurable milestones, such as increasing the numbers of candidate vaccines moving through the development pipeline, attracting more industry partners and establishing more trial sites, and Snow is pressing this controversial issue in the national committees. In their response to AVAC, NIH officials expressed agreement with the underlying goals but questioned AVAC's assumption that setting specific targets for research outcomes was the best way to achieve them, given the unpredictable nature of research. Yet some scientists, including AVRC head David Baltimore, welcome the discussion. "[Bill's] recent emphasis on establishing milestones is especially important because it highlights the need to use new criteria to judge the program," Baltimore told the *IAVI Report*.

It's an issue that illuminates the balancing act Snow constantly walks between his roles as an activist pushing for results and an insider to policy-making. But it's one he seems to relish. "This role suits me," he says. "I'm a gadfly. I'm impatient with things that don't make sense."

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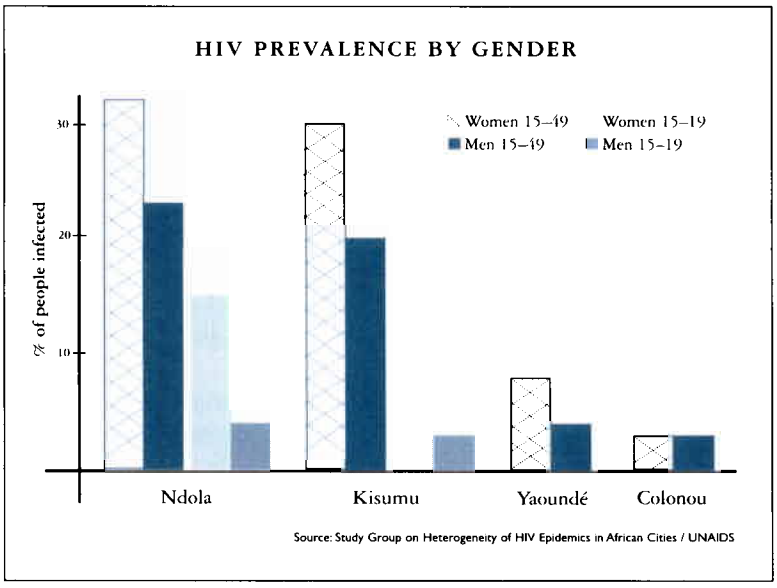
comprising 11 out of 50 samples tested in Kisumu, 6/43 in Yaoundé, 1/18 in Cotonou and none in Ndola.

Determinants of HIV spread: a multi-site study

HIV prevalence also shows wide variation across Africa: for example, infection rates in pregnant women are less than 10% in most of West Africa but exceed 30% in some central and eastern countries. Several researchers presented results from a UNAIDS/WHO-sponsored consortium (the Study Group on Heterogeneity of HIV Epidemics in African Cities) designed to explore the reasons for these differences and to identify the key determinants of rapid spread. The study compared populations in two high-prevalence cities (Kisumu and Ndola) with those in two lower-prevalence ones (Cotonou and Yaoundé) in terms of sexual behaviors and biological factors thought to influence HIV spread. Each site surveyed approximately 1,000 men and 1,000 women, ages 15-49, plus 300 commercial sex workers.

Overall, women showed much higher rates of infection than men, except in Cotonou (see figure). The most pronounced differences were in the 15-19 year age group, where girls in the two high-prevalence cities were 4-6 times more likely than boys to be infected - meaning, according to Rosemary Musonda of the Tropical Diseases Research Center, Zambia, that these teenage girls are being infected not by boys their own age but by older men. These relationships are often driven by the girls' economic need and are a key factor driving the epidemic in these cities, she said.



Other conclusions of the study were:

– Besides sex with an older man, early age of sexual initiation for girls (often before age 15 in high-incidence cities) was correlated with a higher risk of HIV infection, as was early marriage, due to the high risk of pre-maritally acquired HIV.

– Male circumcision correlated with a lower risk of infection: nearly all men are circumcised in the lower-incidence cities, compared to only 30% and 10% in Kisumu and Ndola, respectively. Past or current infection with an ulcerative STD also increased the risk of HIV infection, as already known from other studies.

– Behavioral factors did not correlate with high or low prevalence. Condom use was similarly low in all four sites, with just under 25% of men saying they used condoms regularly or frequently with partners other than their spouse. Nor were there correlations between HIV prevalence and either the number of different sexual partners (which was highest in the lower-incidence city of Yaoundé) or of contacts with sex workers.

– HIV subtype did not appear to play a role, since subtype A predominates in the lower-incidence cities and in high-incidence Kisumu.

Mother-to-child transmission during breastfeeding

Despite much effort to deploy drugs that prevent HIV transmission during birth (such as AZT and the newer, much cheaper regimen involving nevirapine), relatively few studies have focused on transmission via breast milk. Yet cultural traditions and the lack of clean water for preparing formula milk reduce the prospects for safe bottle feeding in Africa, so that HIV-negative babies born to HIV-positive mothers (with or without drugs) are still at risk from breastfeeding.

There was therefore strong interest in new data from the Kenyan Breastfeeding Study, designed to estimate the risk of transmission and determine its correlates. The project was carried out in Nairobi, where there is reasonable access to clean water and sanitation so that breast-fed and bottle-fed babies could be compared.

According to the University of Nairobi's Ruth Nduati, the study enrolled 425 HIV-positive pregnant women, treated any STD's at 32 weeks of pregnancy and randomly assigned the women to breast- or bottle-feeding groups. Blood samples were then taken from their infants at birth, 6 weeks, 3 months and every 3 months thereafter up to two years, and the children monitored for seroconversion and death. By comparing the two groups at two years, the study estimated the risk of transmission via breastfeeding as at least 16% (probably more, due to some unreported breastfeeding by mothers in the bottle-feeding group), with a higher risk in the months immediately after birth.

Grace John at the University of Washington described the study's analysis of the correlates of transmission in 279 mother-infant pairs (including 92 infected babies). Early transmission was associated with mothers having higher viral loads, CD4 T-cell counts below 200 or prior STD's, especially ulcerative STD's (even when these were treated). Later transmission correlated with mastitis (breast infections) in the mothers and possibly with subtype C infection. ◆

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vaccines. These candidates will then be compared to modified vaccinia Ankara (MVA) and DNA vaccines, both singly and in prime-boost combinations.

Anna-Lise Williamson of the University of Cape Town will serve as project coordinator, and her team will collaborate with those of Carolyn Williamson, Ed Rybicki and Bernhard Ryffel of the University of Cape Town and of Lynn Morris at the National Institute for Virology.

A novel recombinant fungal system

This project will be led by Estrelita Janse van Rensburg of the Department of Medical Virology at the University of Stellenbosch, which is well-known in the field of fungal biotechnology, and involves collaborators from several other departments and universities.

The plan is to exploit fungi as a system for expressing HIV proteins, which in turn will be incorporated into a subunit vaccine. In all likelihood it will be based on *Aspergillus* (a well-studied fungus already used to produce other pharmaceutical proteins) containing the HIV *gag* and *env* genes from isolates of circulating clade C HIV strains. Future constructs may include other HIV genes.

Outside of SAAVI, the group is also collaborating with the Chiron Corporation in California to develop a clade C vaccine using several viral vector-based designs. "We feel that we can contribute towards the development of a vaccine for South Africa by exploring more than one avenue in vaccine design," says van Rensburg.

Community mobilization and advocacy

An essential part of SAAVI's activities involves garnering community support for HIV/AIDS vaccine development and future clinical trials. To that end, the third SAAVI award will fund a human rights and community mobilization effort with five components: broad-based advocacy; education and community mobilization; public health, legal and human rights; communication and media; and a supporting information system and knowledge network.

Participating groups are the Medical Research Council (MRC), the National AIDS Convention of South Africa (NACOSA), the AIDS Legal Network, the Centre for the Study of AIDS at the University of Pretoria and the National Association for People With AIDS (NAPWA), with overall coordination by Koos Louw, MRC group executive for informatics and communication, and Ashraf Grimwood, chair of NACOSA. The consortium will also link up with existing community-based structures, non-governmental organizations and international advocacy initiatives, and will work through district health systems and ongoing educational programs.

Activities will be geared to potential trial participants, their communities and the broader civil society and government. The aim is to promote understanding of the complex issues around HIV vaccine development and clinical trials, which should help in making informed decisions about participation. Other efforts will focus on developing novel communication strategies and stimulating increased media coverage of vaccines.

The researchers hope their work can also benefit other countries. "The models developed by this program potentially have wide application on the African continent and in other developing country contexts, and will hopefully add to the global knowledge base for HIV vaccine programs," says Louw.

Ethical issues

The fourth project will tackle the legal and ethical issues arising from the conduct of HIV vaccine trials, with the aim of resolving them before any trials begin in South Africa. Among the specific issues are: informed consent; fair treatment of volunteers; confidentiality; developing a contract between researchers and research participants; fair selection of communities and individuals for research; legal and ethical obligations of researchers towards participants; and future access to any products developed through the trial. Existing international ethical guidelines, including those specifically developed for AIDS vaccine research, will be reviewed and modified to fit the specific needs of the South African population and the limitations of our health care system. This will be accomplished by three types of activities: 1) discussions and debates culminating in the development of trial guidelines; 2) empirical research into the relevant issues; and 3) training of research staff involved in vaccine trials.

The principal investigator of this project is Graham Lindegger of the University of Natal, with collaborators from the University of Natal (Schools of Psychology and Law; Unilever Centre for Ethics), Lawyers for Human Rights and the MRC's Centre for Epidemiological Research.

Ongoing SAAVI projects

In addition to these four new projects, SAAVI already supports work on the development of trial sites and of infrastructure for manufacturing pilot lots of candidate vaccines for trials. Plans also include a program for evaluating experimental vaccines produced in South Africa and elsewhere, so that promising approaches can be assessed quickly and, where feasible, adapted for use in South Africa. Another important part of SAAVI's portfolio is a collaborative project to develop and test a candidate vaccine made with a consensus sequence from clade C HIV (isolated in Durban) and inserted into a vector made from the Venezuelan Equine Encephalitis (VEE) virus. Partners for this work include South African scientists from the MRC's Centre for Epidemiological Research, the University of Cape Town and the National Institute for Virology, and American scientists from AlphaVax, a small biotechnology company, and the University of North Carolina, who developed the VEE system. This project, funded by IAVI, aims to begin Phase I trials simultaneously in South Africa and the United States towards the end of 2000.

SAAVI: working for an HIV vaccine by 2005

SAAVI was launched in 1999 to pursue the goal of a safe, effective, affordable and accessible vaccine for South Africa and the Southern African Development Community by 2005. This date is two years earlier than the 2007 goal set by U.S. President Clinton in 1997 and was chosen, says SAAVI research coordinator Walter Prozesky, because the catastrophic nature of the epidemic in the sub-Saharan region makes speed absolutely vital.

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pathogenic SIVMne. While both control animals had high levels of SIV, only one of four vaccinated animals had detectable (but transient) levels of SIV. Arthur's team has produced new inactivated, deglycosylated SIV strains. Animals are now being immunized with these constructs and will be challenged mucosally. The team is also looking at different adjuvants, including CpG motifs, to further enhance immunogenicity.

NYVAC as a Therapeutic Vaccine

Genoveffa Franchini of the NCI discussed using vaccines as immune therapy in SIV-infected monkeys. Franchini examined whether HAART plus NYVAC, an attenuated vaccinia construct expressing SIV *gag, pol*, and *env*, could reconstitute SIV immune responses and control virus once therapy was halted. Twenty-four monkeys newly infected with pathogenic SIV were divided into three groups: 1) HAART alone (ddI, d4T and PMPA); 2) HAART plus SIV NYVAC (3 IM immunizations); and 3) NYVAC with no SIV antigen (blank vaccine).

After 28 weeks, HAART was stopped in all monkeys. While every monkey experienced a viral rebound, 5 of 6 (and later 6 of 6) HAART plus NYVAC-treated animals eventually controlled virus (defined as less than 1,000 copies of RNA per ml.). These monkeys also had an increased CD4 helper response.

But the differences in viral load did not reach statistical significance. Franchini believes this is due to the small number of animals used. She describes this as a proof-of-concept study that provides the rationale for studying therapeutic vaccines. The NIH's Office of AIDS Research (OAR) is now helping to fund such a study.

More Native Envelope Vaccines

Joseph Sodroski of the Dana-Farber Cancer Institute in Boston presented data on several HIV envelope glycoprotein "trimers" his lab has created. These soluble trimers, Sodroski hopes, will generate more potent antibodies that can neutralize primary isolates of HIV. Because trimers are not very stable, Sodroski's lab has modified the envelope protein by replacing certain sequences through genetic engineering.

It is hoped that the new trimers will maintain antigenic properties of the native glycoprotein and thus show enhanced immunogenicity. Sodroski hopes to test these trimers in monkeys but will not do so until he has evaluated data from ongoing studies in mice.

Monoclonals Provide Sterilizing Immunity

Ruth Ruprecht of the Dana-Farber Institute presented data on a combination of three monoclonal antibodies that appear to generate sterilizing immunity in monkeys. Ruprecht's team immunized four pregnant monkeys with the monoclonal combination five days before caesarian delivery and again right before birth. The pregnant monkeys were then challenged IV with non-pathogenic SHIV. Six months after delivery, none of the animals had seroconverted (or showed other evidence of virus), while all five control animals became infected.

The newborn infants also received the monoclonals one hour after delivery. Ten hours later they were challenged with SIV and then given another dose of monoclonals. At 6 months, all immunized newborns were uninfected while all control monkeys became infected. Ruprecht concludes that neutralizing antibodies with well-defined specificity can generate sterilizing immunity in adult and newborn monkeys. She hopes that this approach can be used to prevent mother-to-infant transmission of HIV and as a post-exposure prophylaxis (PEP) regimen.

Discussion on Barriers to AIDS Vaccine Development

In a wide-ranging discussion on the barriers to HIV vaccine development, former ANRS head Jean-Paul Levy noted that while a number of approaches are generating good cellular immune responses and decreasing viral load in challenged animals, inducing sterilizing immunity is still a long way off. Levy urged researchers "to plan for the fact that we may fail in the next three years."

Gary Nabel, director of the NIH's AIDS Vaccine Research Center, presented an update on the new center's progress and on his laboratory's activities. One key goal, he said, was for researchers to learn how to generate good antibodies to the gp41 protein. Nabel said that he was "a bit disheartened to learn here that it was so easy [for HIV] to develop resistance to peptides that target this region" with the experimental AIDS drug T-20.

In the discussion period, Robert Gallo called the lack of available monkeys for vaccine studies "one of the critical barriers." OAR head Neal Nathanson agreed, noting that "in the US, we have a crisis – a shortage of monkeys and a shortage of facilities for monkey research."

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From the start, SAAVI was endorsed by the South African Cabinet and designated an MRC lead project, meaning that it has the highest national priority and must have clearly established objectives and outcomes. SAAVI's current budget of R60 million (US$9.5 million) comes from both government and non-governmental sources, including the South African Departments of Health and of Arts, Culture, Science and Technology; Eskom (the national electricity supplier); and IAVI. SAAVI hopes to attract additional local and international funding, particularly from the private sector and international agencies. Its activities are overseen by a steering committee with representation from the Department of Health, funders, the MRC and other stakeholders; a scientific advisory committee of high-profile local and international scientists responsible for scientific decisions; and an ethics committee. ◆

Michelle Rotchford Galloway is at the MRC in Cape Town, South Africa. She is Managing Editor of "AIDS Bulletin," a periodical that covers the HIV epidemic and AIDS research in Africa.

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NIAID's AIDS Vaccine Program

Peggy Johnston discussed NIAID's AIDS vaccine program. Reviewing different vaccine approaches, Johnston observed that "some progress has been made. Good immunogenicity has been seen with a number of candidates, and there is now greater support for moving products into human trials." She described the newest part of NIAID vaccine program – the HIV vaccine design and development teams – and said that grants for selected teams will be awarded by mid-2000.

PMC's AIDS Vaccine Program

Michel Klein of PMC reviewed his company's AIDS vaccine program. Klein reported that PMC's HIV oligomer envelope protein (ogp140) is generating low levels of neutralizing antibodies against primary isolates. "They are not high levels," he said, "but they are positive." PMC plans to test the ogp140 in Thailand.

Prime boost combinations of the canarypox vector ALVAC vCP205 and gp120, Klein noted, have generated measurable CTLs in 30% of volunteers at any one time and 60% cumulatively. A Phase I study is comparing vCP205, vCP1433 and vCP1452, and a Phase I/II trial of vCP1452 plus gp120 will begin shortly in Brazil, Trinidad and Haiti. A much larger Phase II study could start later in 2000. PMC is also developing DNA vaccines, lipopeptide vaccines and alphavirus vectors (SFV). "Today there is a reason for optimism," he suggested, "but even if we had an AIDS vaccine, without concerted action, it could take 10 years to get it on the market to the entire world."

Klein also reported that PMC has a substantial therapeutic HIV vaccine program and that trials of poxvirus vectors with lipopeptide are about to be initiated in HIV-infected individuals.

IAVI's Scientific Agenda

Wayne Koff, IAVI's vice president for research and development, reviewed the Initiative's overall scientific plans, which will focus on approaches that can be used in the developing world. "If a vaccine is going to need eight shots, can it really be used in much of the world?" he asked. An ideal vaccine "would be administered by oral or intranasal immunization," he said.

Koff sees "no rationale to exclude any genes." He described IAVI's two current vaccine development partnerships, which include a collaboration with researchers at Oxford University and the University of Nairobi to develop a DNA and MVA combination, and a U.S.-South African effort to develop a VEE replicon vaccine.

IAVI is also looking closely at adeno-associated virus (AAV) vectors, which are currently being studied in gene therapy trials. In monkeys, AAV vectors generate "robust immune responses – like attenuated SIV." In a pilot study, a single immunization of AAV (expressing SIV gp160) generated CTLs that were still measurable more than 14 months later. IAVI is examining the regulatory and safety issues involved with using AAV.

Koff also discussed the potential advantages of putting DNA in a bacterial vector: less DNA is needed and there is better mucosal expression. The construct might also be inserted into an alphavirus vector. Koff concluded by noting that even when a vaccine appears to "blunt disease" or reduce viral setpoint, the virus still might rebound. He also stated that "the urgency of moving into Phase III trials cannot be underestimated."

A Drug-Induced Attenuated Vaccine?

In an all-too-brief presentation on the last day, Jeff Lifson of the NCI's Frederick Center presented data on using potent AIDS drugs as post-exposure prophylaxis (PEP) to prevent SIV infection in monkeys. Lifson's team had already shown that monkeys treated with the drug PMPA within 24 hours of exposure to pathogenic SIV (E660) did not seroconvert and had no evidence of virus. Yet these animals did have a measurable proliferative response to SIV, similar to that seen in highly exposed seronegative humans.

Lifson then challenged two PEP-treated monkeys with homologous virus and found that both were protected against new infection. He calls the PEP treatment a "pharmacologically attenuated SIV vaccine." Viral infections, Lifson noted, "must be considered a race between the host and the virus. With HIV, the virus gets a head start by shooting the host immune defenses, but under the right conditions (a vaccine or drug), most individuals appear capable of containing infection." For early virus control, he believes a vaccine must generate persistent antigen expression or elicit extremely rapid immune responses.

Immune Activation in Highly-Exposed, HIV-Negative Women

Mario Clerici of the University of Naples presented data on exposed seronegative (ESN) individuals. Clerici's team compared: 1) ESN women whose sexual partners are HIV-infected; 2) HIV-positive women; and 3) low-risk HIV-negative women. The ESNs, like the HIV-negative low risk women, had no trace of virus in either their mucosal surfaces or blood. Yet, like the HIV-positive women, they had increased levels of cytokines (IL-6, IL-10, IFN alpha, TNF). According to Clerici, this immune activation diminished when the ESNs reduced their exposure to HIV through regular condom use.

Lessons from FIV

Oswald Jarrett of the University of Glasgow reviewed studies of feline immunodeficiency virus (FIV) and discussed what these studies may suggest for HIV vaccine development. None of the FIV recombinant protein or peptide vaccines studied to date have demonstrated clear protection; in fact, envelope-based subunit vaccines (made with recombinant p27 or gp120 constructs in mammalian cells) have actually enhanced disease. Jarrett said he was unsure of the reason for this. But as with HIV, a strong FIV-CTL response seems to correlate with long-term protection. Among the most promising vaccines, according to Jarrett, is an FIV DNA construct expressing interferon gamma.

Immune Responses in HIV-Infected Individuals

Bruce Walker of the Harvard Medical Center in Boston discussed HIV-specific immune responses in individuals newly infected with HIV. During primary infection, HIV levels skyrocket – the average viral load is 14 million copies per ml., and Walker's team saw loads as high as 95 million copies. Of 21 persons treated at this very early stage, all but 2 developed HIV Gag-specific CD4 helper responses (both of these had drug-resistant virus). This CD4 helper response is similar to that seen in long-term nonprogressors. (Chronically-infected patients show less of a CD4 helper response when started on

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Is there any reason to believe that competing immune responses may drive the immune system to one or the other?
There is discussion in the literature from about ten years ago that a vaccine eliciting a CTL response may be counterproductive in terms of generating antibodies. But there's no hard, believable data in humans. Now it's unlikely that a single vaccine will elicit both neutralizing antibodies and a potent CTLs, so the ultimate vaccine may require two, or even more components.

So vaccines capable of limiting disease might be available in X number of years, and then further down the road will be a vaccine that provides sterilizing immunity?
I totally agree. In fact, monkey data suggest we have a number of vaccine modalities that ought to delay disease for quite some time following HIV infection. That data is not unequivocal, but there is so much suggestive data in this direction that I'm quite confident of it. That vaccine may not be what people are looking for in industrialized nations. But such a vaccine would be of enormous benefit in developing countries where HIV infection is at very high levels.

How do we know that a reduced viral setpoint will translate into clinical benefits and extended survival?
We know that in humans, HIV setpoint levels closely correlates with clinical course and survival. In SIV-infected monkeys, lower viral setpoint also predicts both of these. What we don't know is whether vaccine-induced decreases in SIV setpoint also correlate with lower disease and extended survival. But the studies are underway. When the data is available I would surprised if there is not a significant correlation.

"The approaches that generate the most potent and durable CTL responses should move into government-supported efficacy trials."

If regulatory people came to you and asked, how much delay of disease would you need to approve an AIDS vaccine, what would you say?
The answer is: "where?" In the United States, a vaccine that delays progression of disease may not be that useful, because most HIV-infected people have access to AIDS drugs.

But in Africa and certain areas of Southeast Asia, where individuals infected with HIV will never have the opportunity to receive drug therapy, a vaccine that substantially delays disease will have enormous benefits.

In 1994, many well-known researchers opposed U.S. government funding of a Phase III gp120 study, but you were one of the few who would go on the record with your opinions. Now some people are beginning to quietly question whether a Phase III study of a canarypox/gp120 study is the best use of NIH funds. What is your opinion?
There is no question that the pox viruses represent potentially useful vaccine immunogens. But before we launch a major, long-term study that will require a huge investment of personnel, financial resources and human volunteers, I think it's very important that we pick the best vector.

Whether the best vector turns out to be canarypox, fowlpox, MVA, or vaccinia itself, and whether that it is given alone, in combination with some other vaccine, can now be determined very quickly. And the approach that most efficiently elicits potent and durable CTL responses should be moved into government-supported Phase III trials.

It's been a tough struggle getting these comparative studies underway in monkeys. Why?
Only recently have we had the ability to accurately compare immune responses and to measure viral loads after challenge, using PCR technology. Now it becomes incumbent to prioritize what should go into more in-depth studies.

When will these comparative monkey studies begin?
The trial should start in two months, with challenges occurring within a year and viral set-point levels available 60-100 days after challenge. This will hopefully be the first of many such studies.

What do you think of including *tat* as a vaccine antigen?
The data generated to date are provocative, but the studies have been pretty limited. It will be very interesting, in the next few months, to see what data looks like from other laboratories.

It was interesting that your MVA constructs generated different levels of CTLs in the lymph system and the blood, whereas with DNA they seemed similar.
That observation was made in very small numbers, but it was quite surprising. It may be that different vaccines elicit CTLs with different homing characteristics. And that may be very important in choosing a vaccine. While the data is preliminary, it suggests that something other than CTL levels in the blood may be very important.

Can current vaccines generate long-lasting CTLs?
In any effective vaccine, the vaccine-elicited immune response has never been of a magnitude sufficient to generate protection. What is important is generating sufficient memory B- or T-cells that can then contain infection.

In your monkey challenge studies, how quickly after the last immunization do you challenge?
Challenges have been as early as one month and as late as two to three months after the last immunization.

Do you expect any dramatic differences if you challenge monkeys after a year, rather than one or two months?
We haven't done those experiments. It's an empirical question that needs to be answered with experimentation.

What do you think about using these CTL-generating vaccines as potential immune therapies?
HIV-infected individuals whose viral load is controlled by therapy and CD4 counts are preserved, can clearly mount immune responses against vaccines. The question is whether these vaccine-elicited CTLs can contain virus when therapy is stopped. Hopefully this will be answered over the next year.

I have to ask you about VaxGen's Phase III gp120 study.
My thoughts about using a recombinant gp120 vaccine alone are well known. There has been compelling data, for some time, that a recombinant envelope glycoprotein will not elicit a CTL or broadly neutralizing antibody response.

I believe these are the crucial components needed to contain

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VACCINE BRIEFS

Fondation Marcel Mérieux's Betty Dodet
Most issues of the *IAVI Report* are available in French due to the generosity and hard work of Betty Dodet, scientific director of the Fondation Marcel Mérieux in Lyon, France. Since 1997, Dodet has carefully and painstakingly assured the translation of the *IAVI Report* and other key IAVI documents into French, enabling us to expand our readership in the francophone world. These French-language issues can be found at: www.iavi.org. (The *IAVI Report* is considering production of selected issues in a number of other key languages.) We are grateful to the Foundation, a founding partner organization of IAVI, and Betty Dodet for their support and look forward to continuing our work together.

Leaving Washington
A number of key figures in U.S. vaccine advocacy are leaving their positions in Washington, D.C. for opportunities in other locations. In November, Sam Avrett, AVAC's first executive director resigned his position to return to New York. Avrett, who helped establish AVAC as a credible U.S. organization advocating for AIDS vaccine research in the U.S., will continue to be involved in AIDS issues as a consultant for IAVI and other groups. In December, Chris Collins will be leaving his post as Rep. Nancy Pelosi's chief aide on healthcare issues, including HIV vaccines. The influential Collins helped craft the "Pelosi Bill" which would provide tax credits for investments in vaccine development. He will be returning to San Francisco, but will also remain active in AIDS vaccine issues as a board member of AVAC and in other positions. Finally, Scott Carroll, AVAC's administrative coordinator, and a well-known vaccine activist, is leaving the organization to work on AIDS vaccine issues in Latin America.

CENT GARDES MEETING
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HAART.) A total of 7 patients treated during primary infection had a planned therapy interruption after one year of HAART. The treatment interruptions produced a viral rebound in all patients, but also the first measurable signs of CTL response in some individuals. (Potent CTLs only occur in a minority of patients treated during acute infection. CD4 helper response also increased, and was broader and more directed towards the envelope.)

Walker believes that the immune system may be able to be manipulated by exposure to a person's own virus. This has also been suggested by data from Doug Nixon at the Aaron Diamond AIDS Research Center in New York (two patients self-immunized by treatment interruptions) and by Franco Lori of Georgetown University (treatment interruption in monkeys and humans). Walker also discussed possible benefits of therapeutic vaccination given with HAART.

INTERVIEW WITH NORMAN LETVIN
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HIV infection, so there is no compelling reason to carry out very expensive tests of that vaccine. I wouldn't invest my money, but I would be very happy to be proven wrong. And the tests are being done, so we'll find out.

Have things gotten better in terms of the NIH's AIDS vaccine program?
There is a new commitment and focus by the NIH to make an HIV vaccine. And the ANRS in France is making a substantial commitment, as is the European Community. And for the first time, there is a sense that the investment will not be futile. So our efforts must be maintained and even increased.

You are a member of the NIH's AIDS Vaccine Research Committee, also called the "Baltimore Committee." How is the committee's work progressing?
The AVRC has made substantial contributions. Some of them are easily visible – the innovation grants, and the emphasis on discovery to drive vaccine development. Some may not be apparent, because you don't know the decision-making that would have occurred without the AVRC.

The meetings at times seem to be a like science club, without a concrete connection to programmatic change.
Many of the most crucial decisions are not made during open session. And much of the input doesn't necessarily come from formal committee meetings, but rather in discussions that occur between people in decision-making capacity at the NIH and committee members.

At the last meeting, public concerns were expressed about the Vaccine Trials Network (VTN). What do you think?
The VTN is an ambitious, necessary, and, in the end, very difficult operation. One needs an operation that is an egalitarian, collegial group of investigators where decisions are made by consensus. On the other hand, the most rapid progress could be made with a more hierarchical decision-making apparatus. So there is a tension, but with proper leadership, there is every reason to hope that the VTN will be leaner, meaner, and more efficient.

But the best trial network in the world cannot make a bad vaccine look good. The problems have been with the immunogens. Hopefully the next group of immunogens will make the trial network leaders look like heroes.

How do you establish a sense of accountability in NIH-funded programs like this?
It is very difficult. A group of academicians can only be led by consensus, but a group of employees of a large pharmaceutical company can be led by dictate. And one has to accept the fact that academicians, working together, may be less efficient. That does not mean, however, that they will reach the finish line second.

Many labs are planning to test DNA and poxvirus combinations. Are we putting too many resources into these two approaches?
I think not. Although it seems that we're looking at only poxviruses and a little DNA, over the next few years, a number of other technologies will move into human trials. These include some approaches IAVI is supporting such as VEE, gene therapy vectors like AAV and bacterial vectors.

You've been a member of IAVI's Scientific Advisory Committee since it was formed. Where should IAVI be going?
IAVI can do something no other organization can really do – leapfrog technologies, very rapidly, into extensive clinical trials in the developing world. That must remain its focus and mission. Like everyone else, IAVI needs to be very selective as to what technologies it supports, then support them to the hilt, both with financial resources and expertise and drive those technologies quickly into clinical trials.

Your opinions about live attenuated HIV vaccines are well known. Any change?
With live attenuated vaccines, the data overwhelmingly suggest that you need higher levels of viral replication to get better protection. But this generally means a higher risk of pathogenicity. Today, a number of very safe technologies that elicit good immune responses haven't even gone into human testing yet. So we are many years away from having to consider the use of a potentially lethal vaccine modality in humans.

What about the other traditional way of producing vaccines — whole-inactivated virus?
There is little question in my mind that one can safely inactivate the virus. But will an inactivated virus vaccine generate the best CTL and neutralizing antibody responses? The answer is likely no. So, I'm not sure where an inactivated virus vaccine falls. But, again, people will work on this, data will be generated, and I would be happy to be swayed by the data.

With 15,000 new HIV infections per day, what can be done to move vaccine research faster?
IAVI can do things that no one else can do. Other organizations in the world have constraints that require moving more slowly. A number of very good vaccine technologies that exist today need to go into extensive testing. So the gauntlet has been thrown down, and IAVI should grab it. Take some of these new, exciting vectors and DNA constructs and get them into extensive trials in a focused, aggressive way.

What about Merck's program?
Substantial resources and personnel have been put into Merck's program. The first vaccines to be tested represent early generation approaches. There is every reason to suppose that their more advanced constructs will also see testing. It will be exciting to see the immunogenicity of these vaccines. This first step into humans is part of a very well-thought-out and carefully considered program. We don't know what will happen in humans, but this is a company that has done their work without putting its hand out and asking for anyone to assist it.

Well, in all fairness, your lab's work for them has been supported by NIH.
This has been very helpful, but in the big picture it's a minor amount. And hopefully what the scientific community learns from all these new trials will help generate new-generation platforms for vaccines against HIV and other diseases as well.

So you're feeling pretty excited about where we are now?
I'm very upbeat, right now. I really and truly think that the next few years are going to be very exciting years in this field. ◆

IAVI REPORT

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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. Lean in structure and catalytic in nature, IAVI focuses on three key areas: accelerating scientific progress; education and advocacy and creating a more supportive environment for industrial involvement in HIV vaccine development.

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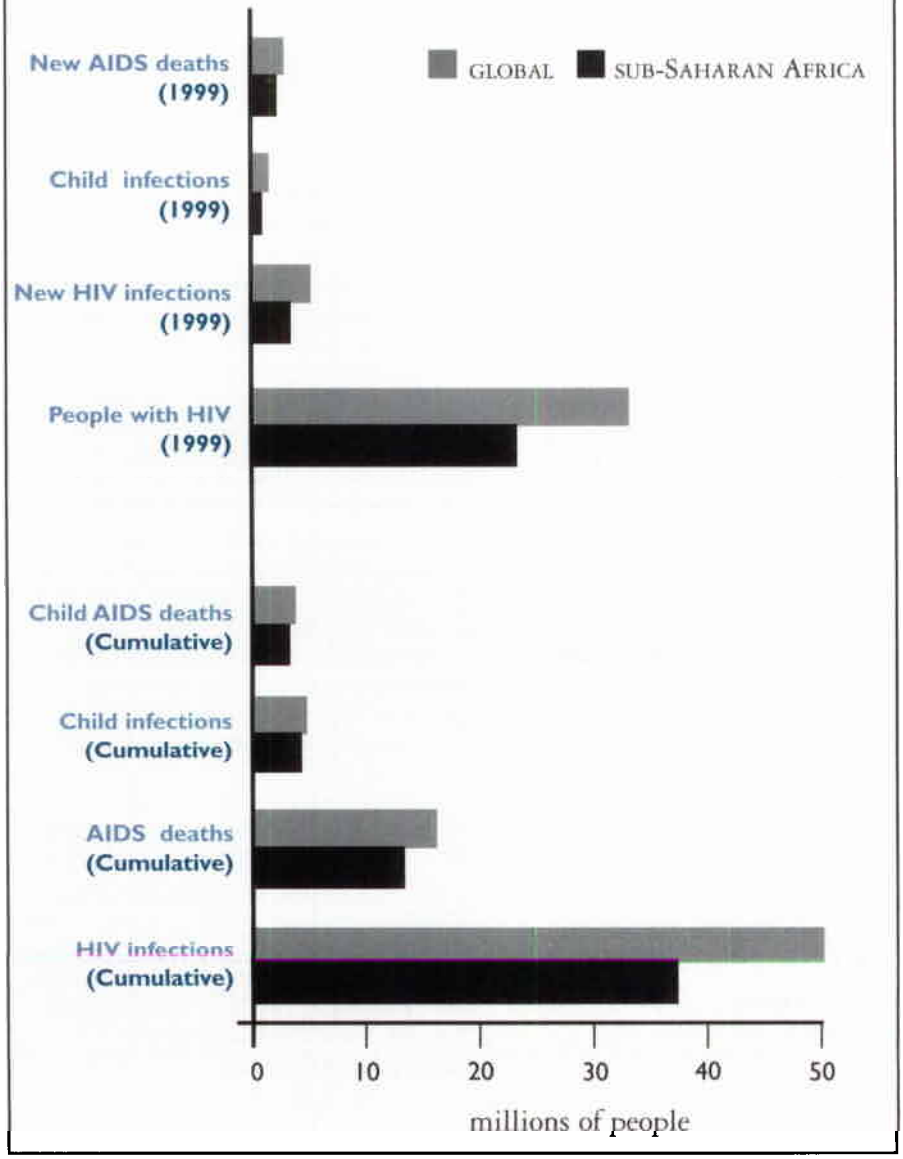
At A Glance: HIV IN AFRICA

- The 21 countries with the world's highest rates of HIV are all in Africa.
- In 13 African countries, more than 10% of adults are HIV positive.
- There is a 60% chance that a 15 year-old in Zambia today will die of AIDS.
- 13 million Sub-Saharan children will have lost one or both parents to AIDS by 2000.
- In some southern and eastern African countries, life expectancy will soon be up to 15 years shorter because of AIDS.
- Between 12 and 13 African women are infected for every 10 African men.
- 90% of HIV+ people in sub-Saharan Africa are unaware of their status.

AFRICA'S DISPROPORTIONATE AIDS BURDEN



"No sensible person can deny that an HIV vaccine is the solution. Africa is on fire."

MAJOR RUBARAMIRA RURANGA,
UGANDAN AIDS
VACCINE ADVOCATE

• • •

"HIV is rapidly becoming a significant and growing threat to peace and stability in the world."

CAROL BELLAMY,
EXECUTIVE DIRECTOR,
UNICEF

• • •

"To the governments of Africa: have you ever heard our cry? Where are you spending our money? Now is the time to make AIDS our number one priority."

EMMA TUAHEPA,
PWA AND YOUTH EDUCATOR,
TO A TUMULTUOUS
STANDING OVATION IN LUSAKA.

Sources: UNAIDS, UNICEF, World Bank