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IAVI REPORT

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Next Front in HIV Vaccines: Gearing Up for Large-Scale Clinical Trials

by Patricia Kahn and Donald Burke

On 30-31 May 2000, IAVI held a workshop in New York to discuss prospects for establishing large-scale HIV vaccine trial sites in developing countries. Participants were drawn from various government agencies and from African nations not already committed to specific vaccine projects or partnerships but potentially interested in becoming involved.

A working assumption of the meeting was that at least several Phase III sites will be needed, so that a variety of vaccine designs can be tested against the real-life challenges they will have to meet: HIV strains that vary around the world; different routes of transmission, and populations with different genetic, nutritional and health status.

The past year has already brought more international activity into HIV vaccine trials. Thailand and the U.S. became the first (and so far only) countries to launch Phase III trials, while Uganda hosted Africa's first HIV vaccine trial, a Phase I study of a canarypox-based vaccine. Kenya and South Africa are expected to follow suit, beginning soon with Phase I tests of the first vaccines specifically targetted to African strains of HIV. And this month, three Latin American countries will start a multi-site Phase II canarypox study.

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NIAID Announces U.S. Sites for HIV Vaccine Trials Network

by Jim Thomas

On 25 May 2000, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) took another step in fleshing out the new HIV Vaccine Trials Network (HVTN) with the announcement of funding for nine U.S. sites. Further information on up to eight international sites is expected at the upcoming International AIDS Conference in Durban, South Africa.

The HVTN is the successor to the AIDS Vaccine Evaluation Group (AVEG) and the HIV Network for Prevention Trials (HIVNET). Under that arrangement, AVEG was a purely U.S. network responsible for early clinical testing of candidate HIV vaccines (Phases I and II), while HIVNET, which included sites both within and outside the U.S., was charged with Phase III trials and testing of other prevention strategies. The HVTN will now handle all three phases of HIV vaccine clinical testing; trials of other prevention strategies have been spun off to a separate entity, the HIV Prevention Trials Network.

Another change is that HVTN investigators will now have a stronger role in developing and carrying out their own scientific program, whereas previously NIAID played a key role in setting the agenda. The HVTN will be funded at US$29 million during its first year under a five year renewable grant.

In addition to the nine U.S. sites (which include all 6 former AVEG sites and 2 HIVNET sites), three others will carry out centralized functions. A Core Operations Center, headed by Lawrence Corey at the Fred Hutchinson Cancer Research Center in Seattle, will coordinate the network and its administration. Data management and statistical analysis will also be centered at the Hutchinson, under Steve Self, while

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Other developing nations, including India and China, are establishing national AIDS vaccine programs that include building capacity for conducting efficacy trials.

Yet even moving from small Phase I and II trials into Phase III – let alone starting from scratch – is an enormous undertaking, as shown by Thailand's experience building its infrastructure over ten years, eight Phase I and II HIV vaccine trials and tens of millions of dollars. That's because the scale-up usually means moving from hospital or clinic-based work with small numbers of low-risk volunteers to community-based studies involving thousands of high-risk participants. And it means establishing everything from laboratories for handling and testing tens of thousands of blood samples to building trust between trial sponsors and host country governments, media, clinical scientists and communities.

In considering the future of Phase III trials, the workshop focused on several questions: Where is the epidemic going? What is needed to establish a Phase III trial site? What capacity exists, or can be built upon existing projects? This report will briefly summarize the first two and describe in more detail the discussions on capacity and on the participating African sites. [Upcoming issues of the *IAVI Report* will focus on other cohorts in different parts of the world.] A full report of the meeting is available on the IAVI website (www.iavi.org).

Where is the epidemic going?

Since vaccine cohorts should ideally reflect the population to be protected, it is crucial to follow the epidemic's geographic and demographic trends – information that also provides key baseline data for vaccine trial sites. Karen Stanecki of the U.S. Census Bureau presented selected data from the agency's latest compilation, which show that sub-Saharan Africa is still the most severely affected region in the world, with high prevalence rates especially among teenage women and males in their early 20's. Uninfected spouses of HIV-positive people are also at high risk. She also pointed out that there are few overall incidence studies in most parts of the world, so that estimates of infection rates are usually based on seroprevalence in pregnant women who visit antenatal clinics, or extrapolated from very limited data sets; studies in rural populations are especially rare.

Another important trend for vaccine scientists to follow is the genotypic movement of the epidemic: which HIV subtypes predominate where, and how this is changing. Here, the key trend appears to be the continued generation and/or spread of recombinants wherever two widely different strains overlap in geographic space. Prominent recent examples are the A/B recombinant strains in Russia, the B/C recombinants in China and the A/C recombinant in Tanzania. Given this rapidly shifting picture, it is all the more important to resolve whether vaccines can work across the full range of HIV-1 subtypes.

What is needed for Phase III vaccine trial sites?

Participants agreed that strong political commitment to AIDS control is key to the success of HIV vaccine trials. So is local commitment to the trial's goals; as Merlin Robb of the Walter Reed Army Institute of Research said, "Are there local people who identify with getting the trial done?" Another absolute requirement is access to sufficiently large cohorts (at-risk or with a high baseline prevalence) that are interested and willing to participate.

Other factors were identified as being important, but could be built up during the trial preparedness phase. These include having clear procedures for approval of clinical trials and reviews of ethics; a core of trained personnel for HIV testing and other laboratory work, informed consent and prevention counselling; and an infrastructure that provides basic transportation, communication and utilities. Laboratories must be able to handle, store and ship blood samples, and ideally also carry out other HIV diagnostic and research assays, and to work under the standards of good clinical practices (GCP). Experience with other vaccine trials or international collaborations was also seen as a major advantage.

Current vaccine trial efforts in developing countries

Only two developing countries (Thailand and Uganda) have carried out HIV vaccine trials within the framework of a national plan that commits the country to combatting HIV. (Three others conducted trials without this framework – China and Brazil, both participants in a Phase I trial in 1994, and Cuba, which has an ongoing Phase I trial.)

Several other developing countries are now beginning to build Phase III cohorts. Preparations are underway for Phase I/II trials in Haiti, Trinidad and Brazil sponsored by the U.S. National Institutes of Health (NIH), and cohorts in these countries are being evaluated for possible inclusion in Phase III studies within two years. Salim Abdool Karim's unit of the Medical Research Council in Durban, South Africa has been building capacity as a U.S. HIVNet site since 1997, with the community of Hlabisa (300 km north of Durban) as a potential Phase III cohort. Numerous other high HIV-incidence countries throughout the Americas, Asia, and Africa have the potential to establish cohorts for HIV vaccine efficacy trials, based on building up their ongoing work.

Several presentations were devoted to the activities of four sub-Saharan countries with the potential to become future Phase III trial sites: Botswana, Ethiopia, Côte d'Ivoire and Tanzania.

Botswana

Moketsi "Joseph" Makema of the Princess Marina Hospital in Gaborone discussed the explosive HIV epidemic in Botswana, a nation of only 1.6 million people but now one of the most severely affected countries in the world. HIV prevalences at antenatal clinics in Francistown rose from less than 10% in 1991 to 45% in 1997 and are stabilized near 50% (virtually all subtype C). These statistics have now brought about a strong commitment to HIV control from the highest levels of government, which has seen its formerly stable

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Viewpoint

Vaccine Access Issues Need Attention Now

by Chris Collins

Even before activist protests made headlines last summer, the debate over international access to AIDS drugs had become deeply polarized. Health advocates argued that people in developing countries could not afford to buy AIDS drugs at full, industrial-market prices. Pharmaceutical companies countered by defending the importance of patent rights and claiming that the health care infrastructure in many countries could not deliver drugs even if they were provided free.

Unfortunately, there is enough wrong with the international drug and vaccine delivery systems for both sides to be right. In the long run the private sector needs some intellectual property (IP) protection if it is to invest resources, yet respect for IP agreements is ultimately not sustainable unless credible plans for access to life enhancing drugs are put in place.

A credible plan to purchase and deliver AIDS vaccines affects critical decisions being made today.

The reasons for limited access to AIDS drugs in developing countries are many and complex, and the raging debate on this issue foreshadows similar controversy on access to AIDS vaccines. History provides ample reason for concern that when an AIDS vaccine is finally available, it will sooner protect people in rich countries than those in the poor areas of the world where the epidemic is spiraling out of control. Hepatitis B, for example, kills approximately one million people annually, yet the Hep B vaccine, first licensed in the early 1980s, was not purchased by international aid agencies until more than a decade later. Even today, Hep B vaccine is not delivered in many poor countries. Another example is the Haemophilus influenzae type b (Hib) vaccine, which could potentially save half a million children each year – yet it remains unavailable in many countries of the developing world 13 years after being licensed.

Purchase of future vaccines may be even more challenging. With current vaccine research employing expensive new technologies, initial prices of new vaccines against AIDS or any other disease may be significantly higher than those for Hep B and Hib.

But why address the thorny issue of access now, when a licensed AIDS vaccine is still years away? The answer is that a credible plan to purchase and deliver an AIDS vaccine affects critical decisions being made today. Absent a clear plan for purchase of AIDS vaccines for the world's poorer countries, there is little incentive for industry to invest in developing vaccines appropriate for these populations or to build manufacturing plants that can produce them fast enough to meet the anticipated demand. Likewise, other access-related issues also require years of pre-planning if they are to be resolved by the time an effective vaccine is ready.

If the story with AIDS vaccines is to be any different than that of Hep B or Hib, public and private sector leaders must begin working now to design a comprehensive system - from the patent office to the rural health clinic - that can improve vaccine delivery. Many ideas for assuring access to AIDS vaccines have been proposed, and they address multiple stages of the product development and delivery pipeline. These include:

- **Delivering existing vaccines:** A first step in being able to deliver AIDS vaccines is to do a better job of delivering vaccines that are already available, such as those for Hib, Hep B, and yellow fever. One effort along these lines is the Global Alliance for Vaccines and Immunization (GAVI), which is working to improve immunization systems in developing countries. If it succeeds, GAVI will provide immediate health benefits for the developing world and demonstrate to vaccine makers that the international community is able to effectively purchase and deliver pharmaceutical products.

- **New purchasing mechanisms:** Novel financing schemes that guarantee a paying market for AIDS vaccines would expedite purchase of these products and therefore provide an incentive for industry to accelerate research on vaccines appropriate for the developing world. There are several worthy proposals that urgently need political support. However, it is important to realize that none of them would, by themselves, secure rapid purchasing of AIDS vaccines for *all* lower and middle-income populations, and that a range of purchasing mechanisms will therefore be needed.

One of the most promising proposals involves creation of a new low interest loan program through the World Bank's International Development Agency (IDA), to help the poorest countries strengthen their health care delivery systems. Loans would also be available to purchase vaccines for AIDS and other diseases. Adoption of this program would be a big step, although other purchasing mechanisms would still be needed, particularly since not all developing countries are eligible for IDA loans.

Another approach is now being widely discussed in U.S. government arenas. One proposal was made by U.S. President Bill Clinton who, in his final State of the Union address, called for a tax credit on the sale of vaccines for malaria, TB, and AIDS. Administration officials hope such a credit would entice more industry research on these products and help promote the sale of vaccines for the developing world. Legislation now pending in the U.S Congress would provide an even broader range of research and access incentives. *The Vaccines for the New Millennium Act*, introduced by Senator John Kerry and Representative Nancy Pelosi, would create a purchase fund in

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the U.S. Department of Treasury for vaccines against AIDS, TB, and malaria, and would direct the President to negotiate for creation of a multi-lateral vaccine purchase fund. (See *IAVI Report*, April-June 2000.) The bill also includes Clinton's vaccine tax credit.

Yet another idea comes from Harvard economics professors Jeffrey Sachs and Michael Kremer, who proposed a system of purchase pre-commitments for HIV, TB and malaria vaccines. Countries would pledge to fund purchase of these vaccines when they become available, and an international body would enter into negotiations on vaccine purchase and pricing. The Sachs/Kremer proposal calls for funding of individual country accounts that would give developing countries a role in deciding whether or not to purchase vaccines for their populations.

Each of these purchasing proposals raises the question of credibility. Will industrial-world governments keep their pledges to purchase vaccines for lower income countries once a product is available? Will developing world government leaders take advantage of low interest loans or specially created accounts to buy AIDS vaccines? Perhaps legally binding commitments can strengthen government commitments. Ultimately, sustained political pressure from health leaders, advocates, and the public will be needed if such new purchase mechanisms are to be effective.

- **Market based (or tiered) pricing:** Differential pricing is a common practice in many industries, from airlines to vaccines. Vaccine buyers in industrialized nations are generally charged a "market" price that factors in R&D costs and profit, while purchasers in middle income countries and buyers for the poorest countries are offered much lower rates. Yet, although market-based pricing will be essential if AIDS vaccines are to reach poor countries, some vaccine makers have concerns about this approach. Some politicians in the U.S. have questioned why their constituents pay what they see as a premium price for drugs. With the pharmaceutical industry under growing scrutiny in the US, simultaneous multi-tiering of prices for an AIDS vaccine may be politically difficult.

> *"One price for the world would be disastrous."*
>
> – Amie Batson, World Bank Health Specialist

But according to Amie Batson, Health Specialist at the World Bank, "One price for the world would be disastrous." International public health leaders, consumer groups, and industry will need to convince political leaders of the validity of differential pricing for AIDS vaccines.

- **Intellectual property agreements:** Agreements between funders, researchers and vaccine manufacturers early in the vaccine development process can accelerate access to a licensed vaccine. For example, in its vaccine development partnerships, IAVI has secured commitments from biotechnology companies that will help a successful vaccine be distributed in lower income countries at a reasonable price. Should a company decline to produce the vaccine for lower income countries in reasonable quantity at a reasonable price, IAVI has certain rights to contract with other manufacturers to make the vaccine available in those countries.

- **Manufacturing plants:** The production capacity of vaccine manufacturers dictates how many people receive a vaccine, and how soon. Difficult decisions about plant size need to be made relatively early in the research process, even before vaccines have been licensed for use. Private sector vaccine makers typically design a plant to meet the immediate need in industrialized markets; only years later, when that initial demand is met and companies have recouped their investment and made a profit in industrial country markets, is the vaccine produced for the developing world and sold at much lower ("marginal") cost. The public and non-profit sector could promote expanded vaccine production capacity by guaranteeing to purchase vaccines at an attractive price, or by helping to finance construction of manufacturing facilities, in exchange for promises of early bulk sales of vaccine at very low prices.

Another approach is to encourage technology transfer between vaccine makers in industrialized countries and their counterparts in developing world. But, while tech transfer holds long-term promise, it also raises issues of intellectual property negotiation, quality control, and ability to rapidly manufacture large quantities of vaccine.

- **In-country demand and infrastructure:** In a 1999 report, the U.S. General Accounting Office identified factors limiting availability of vaccines to children in developing countries, including inadequate health care infrastructure and insufficient information about disease burden and the cost-effectiveness of vaccines. With respect to AIDS vaccines, such issues must be addressed quickly if these products are to be made widely available immediately after licensure. Concerns about health care infrastructure are especially complex given that AIDS vaccines will initially need to be provided outside of the existing childhood immunization system, and to target the sexually active teenagers and adults most urgently in need of protection from HIV.

But vaccine access is not a problem that rich countries can unilaterally solve for the developing world. Political will in developing countries is a critical factor, requiring leaders in these countries to make improved healthcare infrastructure and control of diseases such as AIDS a top priority. Without that commitment, purchase funds and loan programs will have only limited impact.

Each of these proposals raises questions that need attention. How will an AIDS vaccine purchase and delivery system work if a series of different vaccines are licensed over several years? With nearly six million new HIV infections annually, how will public health agencies decide whether to purchase a vaccine that is 30% effective if they believe that a vaccine with 60% efficacy is two years down the road? What standards will be

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Canadian AIDS Meeting Highlights Vaccine Development

by Ian Grubb and Craig McClure

Over 700 researchers, health care providers, policy-makers and community representatives attended the 9th annual Canadian Conference on HIV/AIDS Research (CAHR), held in Montreal from 27-30 April.

For the first time in the conference's history, AIDS vaccine development was included as a major theme, alongside coverage of basic, clinical, epidemiological, and socio-behavioral studies. This new emphasis was reflected in a half-day symposium highlighting state-of-the-art vaccine research and applications, and in the final plenary panels and presentations on vaccines.

Several presentations revolved around the Canadian government's increasing attention on vaccine development, in particular its recent announcement of funding for a new Canadian Centre of Excellence in Vaccines and Immunotherapeutics for Cancer, Hepatitis C and HIV (CANVAC). CANVAC will receive C$4.75 million over 4 years, along with additional support from the vaccine industry.

Rafick-Pierre Sékaly, chair of the CAHR conference and director of CANVAC, praised the decision to fund the CANVAC initiative. The University of Montreal immunologist described CANVAC as "the first major funding initiative in Canada towards the development of an effective AIDS vaccine, bringing together scientists from over 30 academic institutions in Canada." Sékaly said CANVAC would aggressively pursue public/private partnerships aimed at fast-tracking laboratory findings to the clinic. "The promotion of knowledge and technology transfer between all partners will help CANVAC become the leading Canadian discoverer of vaccines and immunotherapies," he said.

Kelly MacDonald, leader of CANVAC's HIV component, discussed other key elements of the initiative. CANVAC will focus its research on several areas, including novel co-stimulatory molecules that might enhance immunogenicity of candidate vaccines, emerging technologies to deliver vaccines, development of markers for mucosal and systemic immune responses, and several vector-based vaccine designs. CANVAC will also support a socio-epidemiological sub-study examining the impact of participation in the VaxGen trial at the three Canadian sites (Vancouver, Toronto and Montreal).

Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases, gave the keynote address at the conference. The talk focused on strategies aimed at stimulating HIV-specific immunity in HIV-infected and uninfected individuals.

Mark Wainberg, president of the International AIDS Society and an immunologist at McGill University in Montreal, presented a passionate overview of the international dimensions of the AIDS crisis, calling on all researchers to unite in a collaborative effort to end the epidemic. His provocative comments urging action to curb misinformation from AIDS dissident theorists were widely reported in the Canadian media. Wainberg warned that by lending credence to such misinformation, politicians and the media damage efforts to control the pandemic.

Several speakers in the final plenary sessions discussed efforts to reduce HIV transmission rates in developing countries. Frank Plummer of the University of Manitoba presented long-term data on reductions in HIV incidence by treatment of sexually transmitted diseases in Kenyan sex workers. Michel Alary of Laval University showed encouraging data on results of targeted peer prevention campaigns in Benin, while Bill Cameron of the University of Ottawa used mathematical modeling to demonstrate the potential positive impact of HIV treatment and health care on the spread of HIV infection. Carol Vlassoff presented the Canadian International Development Agency's (CIDA) draft framework for re-structuring the agency's HIV/AIDS program. A consultative process is currently underway with Canada's domestic AIDS and development communities, and with international partners. The draft framework includes a recommendation to incorporate funding for vaccine research and development into the country's AIDS and development policy.

> *"Within 5 to 10 years, we should have an AIDS vaccine which looks like it will really work."*
>
> — Neal Nathanson, U.S. Office of AIDS Research

Sékaly and Aventis Pasteur's Michel Klein chaired a vaccine symposium held on the final afternoon of the conference. Neal Nathanson of the U.S. Office of AIDS Research, Seth Berkley of IAVI, David Ho of the Aaron Diamond AIDS Research Center, David Montefiori of Duke University, and Genoveffa Franchini of the U.S. National Cancer Institute were among the presenters.

In his talk, Nathanson predicted that researchers will develop an AIDS vaccine that is at least partially effective within five to 10 years. "By that time, we should have something which looks like it's really going to work," he said. "It may not be licensed, but it would be on its way."

Although several AIDS vaccine candidates have conferred some level of protection in monkeys, few vaccines have reached human trials. The complexity of HIV has made creating a vaccine a particularly daunting task, Nathanson said, adding that there is no single measure that can gauge the efficacy of potential HIV vaccines. In addition, HIV is hard to neutralize because there are very few areas on its outside structure where an antibody can attach.

Ho presented mathematical modeling that describes the

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viral kinetics of acute HIV infection and its possible implications for vaccine development. He suggested that the dynamics of HIV replication immediately following infection may be relatively faster (approximate doubling time 0.5 days) than the dynamics observed upon withdrawal of therapy in chronic infection (approximate doubling time 2.4 days).

According to Ho, current vaccine research may be unnecessarily ambitious in terms of the immune response required for protection. He suggested that using high doses of highly pathogenic strains of SIV or SHIV as challenges in animal experiments may be "raising the bar too high." He theorized that the stimulation of partial, varied immune responses may be sufficient to confer significant protection against the HIV strains now in circulation. Therapeutic vaccines might require even less potency, due to the decreased doubling time of HIV in chronic infection when maximal virologically-suppressive therapy is stopped. Ho stressed that these views are based on theoretical models, and that only carefully designed animal and human studies will confirm or refute them.

The session was a fitting conclusion to the first CAHR conference that recognized HIV vaccine research as an essential component of HIV research and of development funding in Canada.

Ian Grubb and Craig McClure are partners in Health Hounds, Inc., a Toronto-based consultancy group focused on HIV policy, education and community issues.

Canada Announces C$5 Million Grant to IAVI as Part of Larger Plan to Fight AIDS in Developing Countries

by Ian Grubb and Craig McClure

Canada has become the third government to provide major financial support to IAVI, after the Dutch and British governments, with the announcement on 1 June of a C$5 million (US$3.5 million) grant from the Canadian International Development Agency (CIDA). The grant to IAVI forms part of an ambitious three-year, C$120 million program to fight HIV/AIDS in developing countries, announced at a conference in Toronto by Minister for International Cooperation, Maria Minna, who described the HIV epidemic as "a devastating issue that demands action now." The package of initiatives under CIDA's new HIV/AIDS Action Plan represents a threefold increase in Canada's spending on HIV/AIDS in the developing world, from C$22 million in the 2000-2001 fiscal year to C$62 million in 2002-2003.

The program aims to focus CIDA's investment on countries which have demonstrated a political, social and economic commitment to HIV/AIDS, and includes C$13 million over five years for HIV prevention in Malawi. It also awards C$3.8 million to UNICEF for research in sub-Saharan Africa on the prevention of mother-to-child transmission using the antiretroviral drug nevirapine (Viramune™).

In announcing the grant to IAVI, Minister Minna emphasized the importance of working to find HIV vaccines that are tailored to the specific types of HIV prevalent in endemic regions. "The clock is ticking," she said. "We need breakthroughs, in treatments and hopefully vaccines... In Durban I will continue to lobby and urge my counterparts to join me in doing more to attack and confront this global pandemic".

Sharon Baxter, executive director of the Canadian AIDS Society, which represents over 100 community-based AIDS service organizations, commended CIDA for showing vision in expanding its HIV/AIDS programming. She described the C$5 million contribution to IAVI as "a great display of leadership by the Canadian government. Canada should play such a role in contributing to the global challenge." On the domestic front, Baxter expressed hope that the details of the CIDA Action Plan would continue to be fleshed out, and that ways could be found to enhance the capacity of Canadian AIDS service organizations to provide "real, useful assistance" in the developing world. "We have much to offer – and much to receive – from cooperation and partnership," she said.

Mark Wainberg, president of the International AIDS Society and a prominent vaccine researcher in Canada, praised CIDA for expanding its programming into the area of HIV vaccine development. "IAVI has demonstrated a commitment to collaborative vaccine research, putting the critical issue of developing world access upfront in its research partnerships with industry. I welcome CIDA's funding announcement as a major first step towards building a strong relationship between the Canadian government and IAVI. I encourage other industrialized countries to step up to the plate."

African Health Ministers Discuss Strategies to Fight AIDS, Boost Vaccine Efforts

by Nicholas Gouédé

Health ministers from member states of the Organization of African Unity (OAU) met in Ouagadougou, Burkina Faso, on 7-9 May 2000, to discuss joint responses to the HIV epidemic. Many of the ministers described the impact of the epidemic and how it has now become the single biggest drain on socio-economic development in their countries.

The meeting, the first of its kind in the history of the OAU, was designed to identify approaches that allow Africa to combat the pandemic within its own means. By the time it was over, delegates had drafted and adopted a plan of action (released two weeks later) that includes a call to "develop South-South cooperation in technology transfer for health care and the fight against HIV/AIDS and [to] develop partnerships between North-South researchers to create national programs for AIDS vaccine development."

"This is a time of great opportunity," UNAIDS Executive Director Peter Piot told the ministers. "National governments and the international community are finally waking up to the impact of the epidemic, and are now deeply serious about reversing the damage of the last decade."

Delegates adopted a plan that includes a call for North-South partnerships to create national AIDS vaccine programs.

The meeting also provided an opportunity to lay groundwork for political support from the OAU for AIDS vaccine development in Africa. This writer, as IAVI's representative at the meeting, briefed many of the participants about the organization's activities in different parts of the world. Alain Ludovic Tou, Minister of Health from Burkina Faso welcomed IAVI's mission and expressed interest in being actively involved in IAVI work on the continent. Meetings also took place between IAVI and Amina Ndalolo, Minister of State for Health in Nigeria, as well as ministers of health from Mali, Togo, Seychelles, Benin, Tanzania, Lesotho, South Africa, and Côte d'Ivoire.

The OAU appears to be interested in playing a greater role in ensuring that AIDS vaccine development efforts progress more rapidly. Mahamat Habib Doutoum, the Assistant Secretary-General of the OAU, made clear that OAU Secretary General Salim Ahmed Salim was enthusiastic about HIV vaccine development as the best long-term hope to stop the AIDS epidemic. OAU officials reported that they would attempt to implement a comprehensive advocacy and communication strategy in collaboration with IAVI to secure a real political commitment from the pan-African political body.

Several upcoming meetings will provide new opportunities for African health leaders to support AIDS vaccine development efforts. These include the XIII International AIDS Conference in Durban, South Africa, on 9-14 July 2000; a meeting on AIDS Vaccine Trials in Africa, organized by the National Institute for Pharmaceutical Research and Development (NIPRD), in Abuja, Nigeria, on 25-27 October 2000; and the 12th International Conference on AIDS and STDs in Africa (CISMA), scheduled for 9-13 December 2001, in Ouagadougou.

Moustapha Gueye, president of the Africa Council of AIDS Service Organizations (AfriCASO), circulated a position paper at the meeting on the role of African communities in HIV vaccine development. He noted that "our governments must fully understand potential new developments, successes, challenges and gaps that vaccine development trials and deployment pose for Africa. Efforts must be undertaken to ensure that our communities understand the development and impact of vaccines and are mobilized and prepared to debate emerging ethical issues during trials. Any potential vaccine must be both affordable and accessible.It is important that we do not end up with a vaccine program that only industry, science and public health understands and only affordable by northern countries."

The three-day meeting was attended by about 53 delegations from the OAU member states and representatives from UNAIDS, UNICEF, UNDP, UNFPA, as well as delegates from the World Bank, the Economic Commission for Africa (ECA), NGOs, parliamentarian and community groups. It was sponsored by UNAIDS and seven other U.N. agencies, including the African Development Bank. Burkina Faso, which hosted the meeting, is West Africa's second most severely -affected country after Côte d'Ivoire.

Nicholas Gouédé is a communications specialist at IAVI and represented the organization at this meeting.

HIV Vaccine and Prevention Research at NIAID: An Interview with Peggy Johnston

Margaret (Peggy) Johnston oversees extramural research programs on HIV vaccines, microbicides and other biomedical prevention at the U.S. National Institute of Allergy and Infectious Diseases (NIAID). As NIAID's Assistant Director for HIV Vaccines and Associate Director for Vaccine and Prevention Research at the Institute's Division of AIDS (DAIDS), Johnston has responsibility for a significant part of the HIV vaccine program at the National Institutes of Health. Johnston began her career in AIDS research at NIAID in 1987 and from 1993-96 served as Deputy Director of DAIDS. In 1996, she joined IAVI as its first scientific director, and two years later returned to NIH, where she serves in her current role. We spoke with Johnston at her office in Bethesda.

IAVI Report: Where do you see AIDS vaccine research today?
Peggy Johnston: We've clearly made some progress. But we're still quite a way from having an effective vaccine that will be accessible to those who need it in the world.

You've been back at the NIH for a little more than 18 months. How's it going?
It's going well. My first priority was to look at the organization and reorganize things. We're now well under way to filling vacancies with top-notch people. You have two types of resources – financial and people power. We need both.

What are your overall goals?
One of my key goals was to bring more attention to international needs. And I think that's been accomplished. There's now strong recognition that our mission is global and not simply focused on high-risk populations in the U.S.

Another goal was to focus on the pipeline and to move more strategies towards clinical testing and efficacy studies. The "Baltimore" [NIH AIDS Vaccine Advisory] Committee has focused on the earliest part of the pipeline. And Neal Nathanson (OAR Director) has taken on animal models. So my focus has been complementary to what was already here.

You had once called the AIDS vaccine pipeline a "pipette". Is that still true?
That originally came from Bill Heyward [of the U.S. Centers for Disease Control and Prevention]. But I do believe the pipeline has broadened, particularly at the earlier stages. There are now a number of products in pre-clinical development that weren't there three ago. It's not where I'd like it to be, but it's heading in that direction.

Can you tell us about NIAID's vaccine design and development teams?
The "Teams" began to be formulated prior to my return – about the same time that IAVI was developing its team concept, so I am told. I was able to tweak the program and put more of an international focus and implement it. We expect to announce three or four awards totaling between US$55-70 million sometime in July.

Do you want to tell us who will be getting an award?
No. But there will be a strong presence by the private sector in these awards. We consider that an important part of moving ideas into the clinic.

Is there significant private sector investment in HIV vaccine development right now?
It's hard to judge how much companies are investing their own money. The numbers are difficult to get and companies are reluctant to give out their numbers, in part, because so much of the costs cut across different programs.

I know with our program, we can add the numbers in different ways; how you define vaccine-related research is very subjective. So within a company if you're talking about research on a certain platform – say a viral vector – how much goes toward an AIDS vaccine versus a hepatitis or flu vaccine? It's subject to interpretation.

In the past, NIAID has not done much direct funding of private sector development activities. But we have started to do more than the more traditional role of funding animal model and clinical evaluation of products. And NIAID funding of basic research continues to increase the knowledge base on which to design vaccines.

What are the biggest obstacles to developing a vaccine?
To me, one of the biggest challenges is the time factor. Everything just seems to take so bloody long – from pre-clinical development to protocol development to clinical trials.

It's a long process and while we can make it more efficient, it's difficult to shave off a lot of time. And the clade issue remains an important scientific question that could be an obstacle. Whether and to what extent clades will be relevant to vaccine development remains an enormous area of controversy.

We probably won't have the answer until we have a vaccine that works. Then we'll see how it works in different populations. And we still don't know what immune responses are needed to protect. We can say CTLs are broadly reactive, but if CTLs aren't the final answer, then what do we really know? So we have to remain open to being surprised, because I think we will be surprised in the end.

So you're not sold on CTLs being the correlate?
I would like to see both antibodies and CTLs. I think there are enough experiments in animals to suggest that both are better than either one alone.

Is there much out there in terms of generating potent antibodies?
There's actually a lot out there - although most designs are still at the very early lab stages. Certainly several newer vectors for inducing CTLs are further along in preclinical development.

They've been in primates and many of them should move into human trials in the next year or two.

A lot of folks are working on trying to induce broadly neutralizing antibodies. And there are ideas about how one might approach that. Very preliminary data looks like some of the newer constructs will have broader immunogenicity. Will it be broad or potent enough? I don't think we're there yet. But I definitely see some improvements in the pipeline in terms of generating antibodies.

Like what?
There's the V2-deleted envelope and a construct developed at the Institute of Human Virology – both of which look intriguing. And then there's the deglycosylation and the fusion complex approaches.

What about the trimers that Sodrowski and Moore are working on?
That's one of the approaches I also put in the category of "Gee, it's a very nice antigen, let's see what it's going to do in a real animal."

Preliminary findings show that Jack Nunberg's fusion complex immunogen does not seem to be working in monkeys as it did in mice. Is this a major setback?
I don't think so. Sometimes the seminal studies that stimulate people to go in a certain direction prove to not be completely reproducible. But the fact that those results stimulated people to believe something was possible and got them working on it was, in itself, an accomplishment worthy of note.

Look at the early studies of vaccine development. Many people didn't believe a vaccine against AIDS was possible until monkeys immunized with whole-killed SIV were protected. Well, that turned out to be a response to the human antigens in the vaccine and in the challenge virus. While the approach wasn't great, it did stimulate the whole field.

In fact, there's a proposal for NIH to fund a study of this phenomenom. Is that going to be happening?
I don't think so because the data has still not been convincingly presented. But I do think Jack's study will prove to be an important milestone whether it's reproducible or not. People are now looking at envelope-CD4 fusion proteins and complexes and co-expressing molecules.

Do you think the findings by U.S. researcher Peter Kim will be useful in making a vaccine?
Those studies are very interesting. The question becomes: How do you translate that into a good immunogen?

So are there any approaches that you are especially excited about and think should be fast-tracked?
I was instrumental in helping bring in IAVI's first partnerships, so that speaks for itself. I continue to find the DNA priming followed by a vector boost to be intriguing. DNA could be especially important because it may be less expensive, which would be useful in developing countries.

I am also hopeful about the prime/subunit boost combination. NIAID's AIDS Vaccine Evaluation Groups have shown that you can get both antibody and CTL responses with this strategy and people were not sure this could happen. And I really would love to see and fast-track a new envelope presentation.

Is there going to be a Phase III trial of canary pox vector?
It's certainly part of the plan. But we don't have nearly enough data on the current vector (vCP1452). So we're doing a Phase II trial to monitor safety and immunogenicity. If it does hold out, then we'll move ahead.

Why not make some reasonable assumptions from other canarypox studies that vCP1452 is going to be reasonably safe and move ahead with a Phase III study now? Then you could find out as soon as possible whether measurable CTL responses protect and you wouldn't need to wait another year.
I agree with you in part about the immunogenecity data, but not about safety. This is a new product, so I would be very hesitant to go into ten thousand people based on safety data in a few dozen. It would be a hard case to make to the U.S. Food and Drug Administration.

One of the biggest challenges is the time factor. Everything just seems to take so bloody long – from pre-clinical development to protocol development to clinical trials.

And there are additional dosing and scheduling questions that need to be answered before moving into a large trial. We want to use the best dosing schedule that we can. In smaller prime boost trials, we got a better antibody response by priming first with a vector and then boosting with a protein. Another small trial found that with a prime and protein boost together, you get earlier antibodies that may not come up to the same level. But we don't even know if these are significant results because the trials have been so small.

There are still some people who suggest that canarypox isn't ready for Phase III trials yet.
There's always something that looks more promising in the pipeline and it's usually the one with the least data. But if I were investing in an AIDS vaccine, I would want to know if CTLs were protective, even partially. What will stimulate this field more than any other single thing will be finding some protection in an efficacy trial.

So if we can do that, at least we'll know we're on the right track. I would rather accomplish this than wait and wait for what may or may not prove to be a better product. Those who say that the number of volunteers is limited don't have a global perspective. Remember 15,000 people are infected every day.

There seems to be a growing realization that governments have a responsibility to invest more in vaccines.
It's enlightened self-interest. There's a realization that AIDS is having an impact on economic growth in developing countries and that infectious diseases of sufficient magnitude may

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contribute to government destabilization.

One of your challenges will be to coordinate efforts with other parts of the NIH, including the Vaccine Research Center (VRC), the National Cancer Institute, the Office of AIDS Research and the intramural research programs. How do you do that?
Don't forget the programs outside the NIH as well: CDC, USAID and other governments. The list is endless. And part of my job is to help coordinate the intramural and extramural programs at NIH. But we are making progress: for example, we will now be more closely coordinating our program with the U.S. Army's Walter Reed Army Institute of Research.

Is there any level of competition among the different programs?
I'd be naïve if I said no. And that's not a bad thing. There's nothing like a little competition to spur people to work their best and hardest. One of the things we struggle with is how to prevent unnecessary duplication, but at the same time have enough duplication so that there's a competitive edge driving things. And that's always a hard thing to try to mix.

One of NIAID's intramural programs has developed a fairly promising MVA vector, but it has taken a long time to get the construct into clinical trials. Who is responsible for pushing that approach forward?
We are responsible for making sure promising designs move forward. But we don't have the desire or authority to take away a project away from anyone. And in the long run, keeping the investigators involved and providing support is the most productive approach, since they have the "know how" to make the product. So with MVA, NIAID researchers are working with Therion Biologics to produce vectors for clinical trials. Therion will also help support VRC Director Gary Nabel's work in looking at different MVA constructs and ways to arrange genes to increase immunogenicity.

There's always something that looks more promising in the pipeline, and it's usually the one with the least data.

You also oversee NIAID's Prevention Program. Where do vaccines fit in the overall prevention agenda?
There are real opportunities to look at multiple prevention strategies. We've intend to start trials in Uganda that will give newborns the anti-HIV drug nevaripine and a vaccine to prevent mother-to-child transmission. Because even if a newborn is born uninfected, breastfeeding in populations without practical alternatives brings risk of HIV infection.

I'd also be interested in eventually comparing a vaccine, a microbicide and a vaccine plus microbicide. And all our vaccine trials compare a vaccine plus behavior intervention with behavior intervention alone. We don't do vaccine trials without doing a behavioral intervention.

Will it be acceptable to do efficacy trials in developing countries without offering anti-HIV drugs to participants infected while in the trial?
UNAIDS released its guidelines and this was controversial. Their recommendation was essentially that everything possible should be done. The minimum would be what is "commonly available" but with pressure to do more.

I think it's going to be case-by-case negotiations with the country. There's a flip side of it too. From an ethical perspective, you want to avoid coercing people into participating. If your trial population wouldn't otherwise have access to anti-HIV drugs, participants may enroll just to get access to drugs if they get infected.

It's interesting because we don't require anti-HIV drugs be provided to people who are infected while in other prevention approaches, such as microbicides.
That's why it needs to be a case-by-case decision and the important thing is that participants must be given a full and proper informed consent process. Clinical studies aren't for everyone. People have to make an individual decisions based on what they perceive the benefits and risks.

What do you see as the major barriers to doing vaccine trials in developing countries?
Many of them relate to infrastructure and training. If trials are going to done be in full partnership, developing country scientists have share in the leadership roles. That means being trained and having expertise in all aspects of conducting a vaccine trial, including: counseling, recruitment, informed consent, data management, specimen handling, monitoring adverse events, and more.

I was amazed when I first visited several developing countries and saw the enormous effort required to provide appropriately controlled climates for the computers and back up generators for the freezers and temperature monitors and so forth.

There are also political obstacles. And in populations where they barely understand the germ theory of disease, it's hard to bring people up to a knowledge base where they understand what a vaccine is, let alone what vaccine research is.

What do you think of some South African government leaders questioning whether HIV causes AIDS?
With respect to this controversy, I recognize that it is causing a great deal of consternation amongst our scientific colleagues in South Africa. I think that the South Africa government has every right to ask the questions they're asking. But it would be a problem if these questions are allowed to drag on for a long period of time, because there's certainly enough data to answer the question of whether HIV causes AIDS.

If you had US$100 million more for your vaccine program, could it be spent well?
The short answer is yes, although I wouldn't want to see it all come in one year. I have seen the effects of putting too much money into one single area too quickly. Funding programs are then viewed as entitlement programs and it is very difficult to change direction because investigators feel they're entitled to money.

Frankly, I don't mind wasting some dollars. As Neal Nathanson says, when you're in an emergency situation you have to take greater risks. And that means that some of the money, when viewed in retrospect, will appear to have been wasted. But there are a lot of excellent scientific opportunities that we can fund.

Speaking of Neal Nathanson, do you agree with him that there is a crisis with access to animal models?
I think the crisis is that we don't know to what extent there is a crisis. Some vocal investigators say that there is a shortage of monkeys. And I have to believe that for them there is a shortage. But how universal is it? We need a comprehensive survey to understand what is needed.

What will stimulate this field more than any other single thing will be finding some degree of protection in an efficacy trial.

In some ways, it's got to be challenging to try to move quickly within a large government agency.
Oh absolutely. I believe that the most productive organizations are those that have a certain amount of what I call "box", which is structure, mechanisms and regulations, as well as a certain amount of "chaos", which is creative energy and thinking outside the box.

The government has a lot of box. And we are looking for people who are willing to work outside the box with a little more chaos. One factor that attracted me back to NIH was that I enjoy being the person putting chaos into a box. And with a growing budget there are lots of opportunities to think outside the box.

How do you create greater accountability for these government programs?
Accountability is important. We are paid by the public, so we should answer to the public. And in the case of HIV, that's many "publics", including the scientific community, politicians and affected communities. But the same scrutiny needs to be applied to everyone, including other governmental agencies and organizations that are publicly and not-so-publicly funded.

I have to ask why you left IAVI.
That was probably the most difficult career decision I ever made. But you know, having two wonderful choices is something that everyone should be blessed with at some point in their lives. I can't say that my decision was based on any one thing. As I mentioned, for me, it's more fun putting chaos into the box than trying to put the box or form around the chaos.

And with NIH's budget and commitment to vaccines growing, there were clear opportunities to make an impact on the direction of that growth. But I still have a big interest in IAVI's success. I put two and a half years of my life into it, so I feel like part of me is still there.

Are you reasonably optimistic that there's going to be an AIDS vaccine?
I'm convinced there's going to be an AIDS vaccine.

IAVI's updated website debuts for the Durban conference

Visit www.iavi.org to subscribe to the IAVI Report.

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Duke University's Kent Weinhold is director of a central laboratory that will perform all immunological evaluations and serve as a repository for specimens and blood samples.

Internationally, negotiations are in progress with institutions in the following countries: Brazil, China, Haiti, India, Peru, South Africa, Thailand, and Trinidad and Tobago, according to Peggy Johnston, NIAID's assistant director for AIDS vaccines (see interview, page 8). Several of the sites under consideration were previously part of HIVNET.

According to network coordinator Larry Corey, it is expected that the international roster of sites will grow as more HIV vaccine candidates move towards clinical trials. "By year four there could be three times [the present number]," he said. "You can't look at this as a fixed pot. We have in place what the field needs at this moment, but [the network] was designed to grow when the field demands it."

NIAID is working on bringing several new HIV vaccine designs into Phase I research in the HVTN, but the network's biggest initial challenge could be to conduct the first U.S. government funded Phase III trial (HVTN Protocol 501). The vaccine under consideration is a prime-boost combination of a canarypox-HIV construct (manufactured by Aventis Pasteur), which stimulates cellular immune responses, together with a bivalent gp120 candidate (manufactured by VaxGen). (See *IAVI Report,* April-June 2000.) The gp120 product is designed to stimulate antibodies to HIV. A decision on whether to go ahead is expected sometime next year, after completion of a just-launched Phase II trial. To further inform this decision, the HVTN is undertaking a series of consultations with external researchers, community advocates and other interested parties. This process has already led to revisions in the proposed study design.

Jim Thomas is founding chair of the community advisory board (CAB) for the AIDS Vaccine Evaluation Site at Saint Louis University and chairs the national CAB of the HVTN. He is also a board member of the AIDS Vaccine Advocacy Coalition.

HVTN Sites with Centralized Functions

- *Core Operations Center*
  Fred Hutchinson Cancer Research Center
  Seattle, Washington
  Lawrence Corey, Principal Investigator (PI)
- *Statistical and Data Management Center*
  Fred Hutchinson Cancer Research Center
  Seattle, Washington
  Steve Self, PI
- *Central Laboratory*
  Duke University
  Durham, North Carolina
  Kent Weinhold, PI

HVTN U.S. Trial Sites

- Saint Louis University
  St. Louis, Missouri
  Robert Belshe, PI
- Johns Hopkins University
  Baltimore, Maryland
  Donald Burke, PI
- Vanderbilt University
  Nashville, Tennessee
  Barney Graham, PI
- University of Rochester
  Rochester, New York
  Michael Keefer, PI
- Fred Hutchinson Cancer Research Center and University of Washington-Seattle
  Julie McElrath, PI
- University of Alabama at Birmingham
  Mark Mulligan, PI
- University of Maryland, Baltimore
  William Blattner, PI
- San Francisco Health Department
  San Francisco, California
  Susan Buchbinder, PI
- Harvard University
  Boston, Massachusetts
  Raphael Dolin, PI

Other NIAID Initiatives

In addition to the HIV Vaccine Trials Network (HVTN), NIAID is about to launch several other programs to boost the pace of clinical AIDS vaccine research. The largest will support three or four HIV "Design and Development Teams," in which several partners – usually representing both academia and industry – collaborate to move a specific vaccine concept forward. Funding for the program will be in the US$55-70 million range, with the solicitation of teams to be announced before the Durban conference.

A new program to support international efforts in vaccine development is due to be under way, following a proposal made on 16 June by the Division of AIDS to the NIAID Council and AIDS Research Committee. Dubbed the Comprehensive International Program for Research on AIDS (CIPRA), the program is designed "to support a broad range of basic, preclinical and early clinical HIV research and capacity [and] infrastructure building in developing countries, with developing country leadership," according to Peggy Johnston, NIAID's assistant director for vaccines. Funding has been approved up to US$15 million per year, which Johnston says should cover four to six full projects, grants and possibly some planning grants.

Lastly, NIAID is launching a public information campaign through a National HIV Vaccine Communication Working Group, intended to "stimulate and enhance the national dialogue concerning HIV preventive vaccines," according to NIAID's 25 May announcement. The group will be composed of vaccine advocates and communications specialists working with the HVTN to help foster a supportive environment for vaccine trials. This initiative comes on the heels of NIAID's hiring the Washington, DC-based Matthews Media Group to develop a communications and education strategy around HIV vaccine development and testing.

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economy devastated by the epidemic.

Botswana has already built some of the infrastructure needed for HIV vaccine trials. The government funds surveillance work and a health system providing "reasonably good" access to care, according to Makema, and several international collaborations have added capacity on HIV. Most important is a strong working relationship with the Harvard AIDS Institute, which has helped build up a laboratory and train personnel to carry out many HIV research and diagnostic assays. Botswana is also about to launch a UNICEF-sponsored pilot study on reducing breastmilk transmission from mother to child, a three-arm trial that will compare formula-fed babies of HIV-positive mothers to breastfed infants treated with either AZT alone or AZT plus nevirapine. The country also has experience in tracking and treating people, gained through a TB control program with the U.S. Centers for Disease Control and Prevention (CDC).

Makema says that there is substantial interest in HIV vaccine trials in Botswana. There are no established cohorts for this purpose yet, but several prospects: A cohort of diamond miners is now being set up, both to study incidence and provide triple-drug therapy for infected people, and the possibility of a military-based cohort is also under discussion.

Ethiopia

Ethiopia is similarly hard hit by the epidemic, and as a highly populous country is home to more HIV-infected people (3 million) than any nation in the world except India and South Africa. HIV prevalences are now a staggering 50-75% in commercial sex workers and 10-20% at urban antenatal clinics, according to Arnaud Fontanet of the Ethiopia-Netherlands AIDS Research Project (ENARP), the focal point of the country's HIV/AIDS research efforts.

Fontanet described the beginnings of ENARP in 1994 as a bilateral collaboration between Ethiopia and The Netherlands. Since then it has built a substantial scientific program that carries out HIV surveillance, cohort studies on the progression of HIV infection, and studies on the interaction of HIV and TB, the most common opportunistic infection. It also runs a training program for graduate students, who rotate through collaborating labs at the University of Amsterdam and then return to set up new techniques, as well as for technical and computing staff. The laboratory at the Ethiopian Health and Nutrition Institute, built up with US$10 million over the past 5 years, can now carry out procedures ranging from standard viral load, T-cell subset determination and antibody testing to more sophisticated analyses, such as HIV gene sequencing and T-cell proliferation assays. Funding at this level of US$2 million annually is committed from the Dutch government through at least 2002.

In 1997, ENARP established two cohorts of factory workers, a population chosen because the high desirability of secure factory employment makes it a highly stable group. These two cohorts of approximately 1,200 people each have been followed closely, and HIV incidences measured at 1 and 0.5 per 100 person-years. Follow-up rate was over 90%, after an initial drop of 15% shortly after enrollment. The project has generated a solid infrastructure for informed consent, HIV testing and counselling, collection and storage of blood samples, and providing medical treatment. A workshop on HIV vaccines in Ethiopia was held in Addis Ababa this past March, as a first step to building a national consensus around vaccine development and evaluation in the country.

Participants emphasized that strong political commitment is key to the success of HIV vaccine trials.

Côte d'Ivoire

Madeleine Sassan-Morokro, head of the surveillance, vaccine and clinical section at Projet Retro-CI at the Côte d'Ivoire/CDC site in Abidjan, presented the research program at her unit. Côte d'Ivoire is now the most severely affected country in West Africa and among the 15 most severely affected countries in the world, according to the latest UNAIDS statistics. Surveillance among pregnant women shows that 8-14% are HIV-infected, with higher prevalences in the southeastern regions of the country. Among TB patients, 50% are also HIV-infected, most with HIV-1 but 2-3% with HIV-2. Among the HIV-1 strains prevalent in Côte d'Ivoire, 75% are circulating recombinant forms A/G (CRF-02A/G), commonly called the IbNg strain. This subtype appears to predominate throughout West Africa.

To date the project has not conducted vaccine studies, but Sassan-Morokro reported that follow-up rates in clinical studies are very high, around 90% for one year. The laboratory in Abidjan is well-supported financially and technically by the CDC and can carry out basic HIV tests as well as more sophisticated T-cell assays (including ELISPOT, flow cytometry and cytokine intracellular stain assays). It is also a UNAIDS drug access pilot study site. No cohorts have been established yet, but Sassan-Morokro said that there would probably be a very positive response to suggestions of HIV vaccine trials in Côte d'Ivoire.

Alan Greenberg, chief of the CDC's AIDS epidemiology branch, also indicated his agency's interest in pursuing cohort development and further buildup of this site. They are collaborating on development of a subtype A/G DNA vaccine made by Harriet Robinson (Emory University and Yerkes Primate Research Center, Atlanta).

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Tanzania

Michael Hoelscher of the University of Munich reviewed the HIV epidemic in Tanzania, focusing on the Mbeya AIDS control program, a joint cooperation of regional and national health authorities, Germany's Gesellschaft für Technische Zusammenarbeit (GTZ), and the University of Munich. The project began 12 years ago and is now one of the largest intervention programs in Africa, conducting surveillance, molecular epidemiology, and behavioral intervention studies. During this period HIV prevalences at antenatal clinics throughout the region have increased from less than 10% to 15-30%.

Pilot studies in Tanzania suggest an unexpectedly high proportion of doubly-infected people.

Because Tanzania is at the interface of the east African A and D subtypes and the southern African C subtypes, all three types are present in appreciable proportions. Detailed studies in collaboration with the Henry M. Jackson Foundation (including 9 full-length sequences) have detected an extraordinary number of A/C and C/D recombinants: around 50%, says Hoelscher. And most of them are different from one another, suggesting that they have independently developed and implying that an unexpectedly high proportion of people in this region have dual infections. To look closer at this question, the project (a partnership called the HIV Superinfection Study, or HISIS) is now putting together a cohort study of 600 female bar workers, who will be followed over 3 years to establish the prevalence of dual infections, determine when they happened and look for immune correlates. In a pilot study with 104 women, the HIV prevalence was 56% and 10% of the women had dual infections. The study, which is funded by the European Commission's International Cooperations, Developing Countries division (INCO), plans to start recruiting in about two months. Other cohorts have also been well characterized in Kagera, Mwanza, Ifakara, and Dar-es Salaam, and Hoelscher said that acceptance of the studies among the local communities is high when they are done in the context of an intervention program such as the Mbeya AIDS control project. There is also a good laboratory for handling cells and blood samples in Mbeya, and the Muhimbili Medical Center in Dar-es-Salaam is establishing facilities for carrying out various cellular immunity assays.

This talk led to a discussion of the need for more full-length sequencing of HIV from regions like Tanzania and Uganda that have several circulating subtypes. Hoelscher said that little full-length data has been available (since it is arduous to generate), but the more it is, the more frequent recombinants are turning out to be. Merlin Robb said that the Henry M. Jackson Foundation and Walter Reed Army Institute of Research (WRAIR) are working on techniques to detect recombinants more easily by taking a quick sampling across the whole HIV genome.

Current capacity: sponsoring agencies and their programs

Increasing capacity for large-scale HIV trials in developing countries is happening largely through the targetted efforts of national and multi-lateral agencies, some of which presented their current programs and future plans at the workshop. Peter Wright of Vanderbilt University reported on NIH's new HIV Vaccine Trial Network (HVTN), a restructured program based on the former AVEG and HIVNET projects (see article, page 1), with the goal of conducting Phase I, II and III trials at nine domestic sites and some international ones. (The number, locations and funding levels of the international sites had not yet been announced as the *IAVI Report* went to press.) The revamped NIH program also includes an HIV Prevention Trials Network that will conduct trials of non-vaccine preventions such as microbicides, nevirapine, STD control and behavioral measures. Sten Vermund of the University of Alabama at Birmingham, a member of the PTN leadership group, said that the cohorts at some sites are also highly suitable for vaccine studies and could offer additional capacity.

WRAIR's Merlin Robb summarized the Army's small but tightly-focused HIV vaccine development program, which has already developed and tested subtype E vaccines in Thailand. WRAIR is building up cohorts and doing baseline studies of HIV and subtype prevalences in the Rakai region of Uganda where further clinical trials are planned. Cohort development and molecular epidemiological studies are also being conducted in Keya and Tanzania.

Several agencies are contributing to vaccine trial preparedness in other ways. UNAIDS, which recently merged its HIV vaccine program with WHO, now supports a range of capacity-building activities that includes help in preparing national AIDS control plans, monitoring epidemiological trends and fostering consensus on ethical issues, according to Saladin Osmanov. David Stanton of the U.S. Agency for International Development (USAID) reported that the agency has already spent US$1.2 billion in AIDS prevention worldwide over the past 13 years. The result is a well-established infrastructure for STD control and condom distribution along with trained, community-based HIV counsellors, in many nations of Africa and elsewhere, that might assist in providing prevention services to HIV vaccine cohorts. The CDC is now carrying out research on selected behavioral, social and virological aspects of the ongoing Phase III trial in the U.S. and is working in supoort of the Thai government in the Phase III trial in Thailand. They are also supporting the Abidjan site, as described above. Alan Greenberg (CDC AIDS epidemiology branch) also reported that Tim Mastro, who has directed CDC's research station in Thailand, will return to head the agency's HIV vaccine unit formerly run by Bill Heyward, and could expand CDC's involvement in AIDS vaccine trials.

Lastly, Michael Sweat of Johns Hopkins University and the CDC described efforts to track and analyze cohort data through the Prevention Research Synthesis Project, which has established a database of international behavioral research projects worldwide, both published and unpublished.

Future needs

Overall, participants concluded that several cohorts with relatively high HIV incidence and good follow-up rates do exist, but none has a large enough study population to support HIV efficacy studies. To conduct Phase III trials in developing country settings therefore means either expanding existing cohorts, studying new ones, or merging multiple cohorts from one region into a single trial population (as in VaxGen's Phase III North American study, which involves over 60 separate trial sites).

The workshop finished with a recommendation that IAVI continue to explore potential Phase III trial sites, with the goal of identifying several that collectively encompass diversity in populations, HIV strains and routes of transmission. ◆

Donald Burke, who organized and chaired this workshop, is Director of the Johns Hopkins Center for Immunization Research, Scientific Advisor to IAVI, and principal investigator of an HVTN site at Hopkins.

VIEWPOINT

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used to set prices of an AIDS vaccine, knowing that a high price could drain precious resources but a very low one could slow vaccine production and dampen research and development on improved vaccines? How can advance promises to purchase AIDS vaccines be made credible to vaccine manufacturers?

At this stage in AIDS vaccine research, access may seem like a distant problem. Yet if the international community does not quickly and comprehensively address access issues, the result will be an AIDS vaccine that benefits a lucky few but fails to bring the international epidemic under control. The complexity of the issues, and the immediate positive effects that credible vaccine purchase and delivery plans would bring, mean that tackling the access challenge should be a top priority today. ◆

Chris Collins is president of the board of directors of the AIDS Vaccine Advocacy Coalition. He was formerly on the staff of Rep. Nancy Pelosi in Washington, DC, where he helped develop the Kerry/Pelosi legislation. He is now a health policy consultant with Progressive Health Partners.

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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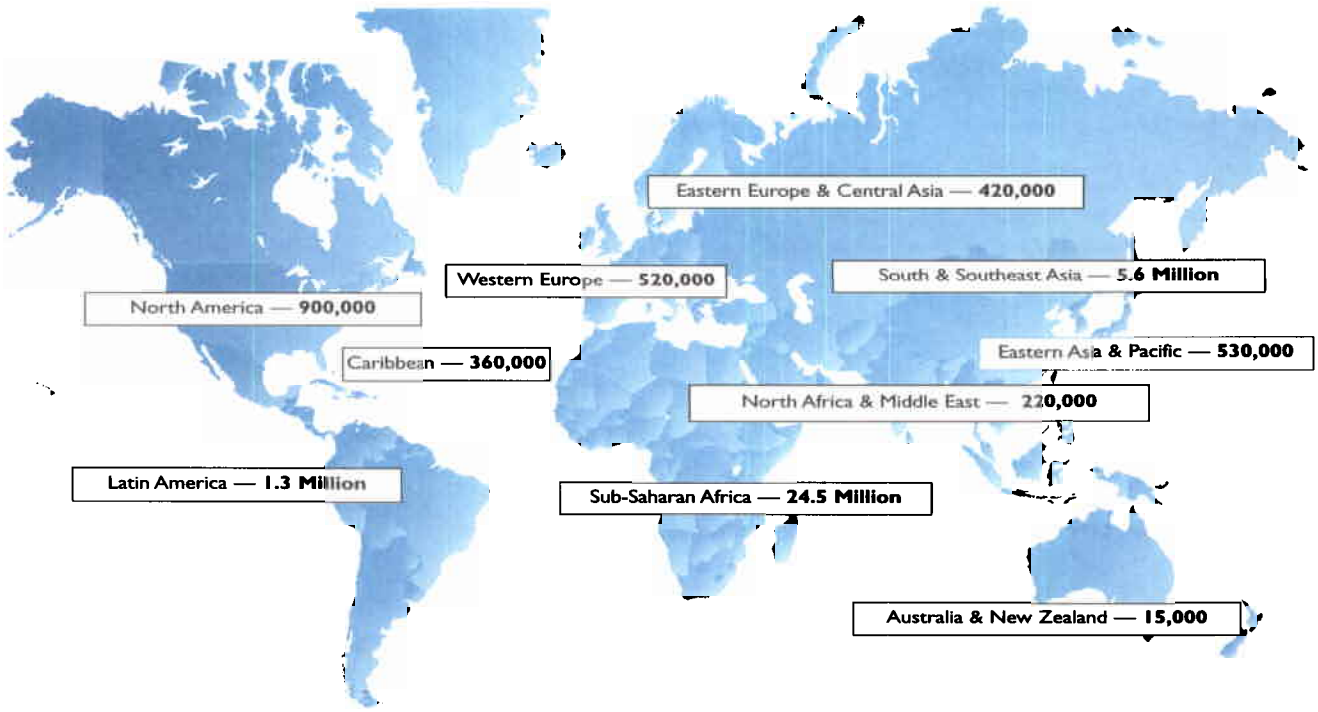
AIDS at the New Millennium: A Grim Picture

According to the most recent estimates by the Joint United Nations Programme on AIDS (UNAIDS), HIV continues to spread rapidly in many parts of the world. Updated estimates of the number of people living with HIV are listed below. (Figures are as of December 1999.)



Adults and Children Living with HIV/AIDS — 34.3 million

People Newly Infected with HIV in 1999	**Total**	**5.4 million**
	Adults	4.7 million
	Women	2.3 million
	Children	620,000
Number of People Living with HIV	**Total**	**34.3 million**
	Adults	33.0 million
	Women	15.7 million
	Children	1.3 million
AIDS Deaths in 1999	**Total**	**2.8 million**
	Adults	2.3 million
	Women	1.2 million
	Children	500,000
Total Number of AIDS Deaths Since Beginning of Epidemic	**Total**	**18.8 million**
	Adults	15.0 million
	Women	7.7 million
	Children	3.8 million
Total Number of AIDS Orphans Since Beginning of Epidemic	**13.2 million children**	

Source: UNAIDS "Report on the Global HIV-AIDS Epidemic," June 2000