IAVI REPORT

A Newsletter on International AIDS Vaccine Research

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INTERNATIONAL AIDS VACCINE INITIATIVE

Live-attenuated AIDS Vaccines: New Safety Findings Reported

A pilot study released in January may ease concerns that a live-attenuated vaccine is a danger to newborn monkeys. The study, reported in *Nature Medicine* (January 1997), found that only monkeys given extremely high doses of the vaccine showed signs of disease. All monkeys given the lower doses remained disease-free.

In the study, researchers led by Ronald Desrosiers of the New England Regional Primate Research Center (USA) gave a live-attenuated simian immune deficiency virus (SIV) vaccine to 18 monkeys. The two newborn monkeys who developed signs of immune deficiency both received an extremely high dose of the vaccine, about 300 times the amount needed to orally infect an adult monkey. The live-attenuated (or weakened) vaccine was genetically created by deleting three key genes from a strain of SIV.

An earlier study, by researchers at the Dana-Farber Institute (USA) had found that newborn monkeys given the same high doses of the vaccine developed immune deficiency.

SIV infection in monkeys is considered by many to be the best animal model for HIV disease. The viruses are structurally similar; both target immune cells and result in high viral load, CD4 cell loss and death.

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IAVI Launches Scientific Program

With its scientific program gearing up, the International AIDS Vaccine Initiative (IAVI) announced the primary scientific areas that it will fund in its initial stage of development. The plan, developed by IAVI's scientific director and scientific advisory committee, and endorsed by the board of directors, focuses on two key scientific areas: development of HIV-DNA vaccines and expanded safety studies of live-attenuated HIV vaccines.

The announcement comes on the heels of rapid progress made in developing IAVI's scientific program. The program began with the selection of Margaret (Peggy) Johnston, Ph.D., formerly of the National Institute of Allergy and Infectious Diseases, NIH (USA) as scientific director. Johnston then oversaw the formation of a scientific advisory committee comprised of 13 of the world's leading scientists in HIV and vaccine research from nine different countries (see box). The committee, which has met twice so far, also endorsed the core scientific strategies set for IAVI.

IAVI's emphasis will be on scientific areas that have not received adequate attention. According to Johnston, "the Initiative seeks to fill gaps in existing scientific efforts and especially to accelerate applied research and development."

Development of HIV-DNA Vaccines

While DNA vaccines are being studied for a number of indications, only a few companies have active programs in the area of HIV, and these programs focus almost exclusively on HIV subtypes found in North America and Europe. In addition, only one HIV-DNA vaccine has progressed to

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Impressive Protection

In 1992, Desrosiers and co-workers demonstrated that a live-attenuated SIV vaccine can provide impressive protection in monkeys. After receiving the vaccine, monkeys become infected with very low levels of virus but without any signs of immune deficiency. Even after challenge with large doses of virulent SIV, the animals have remained healthy and disease-free for more than four years. Control animals who were given the same challenge, on the other hand, all developed an AIDS-like illness and died.

With these results replicated and extended by teams in the United Kingdom and France, and the failure of other vaccine approaches (including subunits or recombinant proteins, inactivated or pseudovirions particles, virus vectors or prime boost) to consistently provide high levels of protection in monkeys, the live-attenuated SIV vaccine has become the "gold standard" of protection in this animal model. Indeed, many researchers have called for a directed, systematic research effort to determine why these animals were protected.

Even after challenge with large doses of virulent SIV, the vaccinated monkeys have remained healthy for more than four years.

Concerns Over Safety

Despite the optimism that greeted the original findings, concerns regarding the safety of live-attenuated HIV vaccines began to grow when the Dana-Farber team reported that high doses of the triple-deleted live SIV vaccine caused disease in newborn monkeys (*Science*, 24 March 1995). The vaccine, which was orally administered to the newborns, caused increased levels of SIV and immune deficiency. The research team, led by Ruth Ruprecht, concluded that live-attenuated HIV vaccines raised serious safety concerns.

New Data Reported

In the new study, designed to address these concerns, nine newborn monkeys were given three different doses of the live-attenuated SIV vaccine. Two of the three monkeys given the highest dose (283 nanograms) developed signs of disease. Yet none of those given the two lower doses (50 and 5 nanograms) showed any sign of disease during the 11-month period of observation, now extended an additional five months.

The research team then examined what would happen when pregnant monkeys were vaccinated with the highest dose during the second trimester. While all four mothers developed the expected vaccine response (low levels of virus, no sign of disease), none of the newborns became infected. These newborns were then given the same high dose of vaccine directly and none developed any sign of disease. Desrosiers suggests that the passive transfer of immunity *in utero* may have protected these newborns.

Two other newborn monkeys received the highest dose of a vaccine with four genes deleted. While none of these monkeys showed signs of disease, Desrosiers told the *IAVI Report* that the quadruple-deleted vaccine may not be as immunogenic and protective as the more widely tested triple-deleted vaccine.

Unanswered Questions

Overall, Desrosiers notes that in studies of more than 40 adult and juvenile monkeys given the triple-deleted live-attenuated SIV vaccine, no sign of disease has ever emerged. Even when monkeys were injected with a vaccine dose 10,000 times greater than the amount needed to cause infection, no disease has been seen. Yet researchers cannot fully explain why the newborns, unlike the adult and juvenile monkeys, develop disease when given high doses of the vaccine.

Moreover, Ruprecht believes that the 16-month follow-up is too short a time-period to reach conclusions. "It is premature to make safety determinations from this data," she suggests. The retrovirus infection caused by low doses of the live-attenuated vaccine, the Dana-Farber researcher believes, "can potentially create long term problems."

But Mickey Murphy-Corb of the Tulane Regional Primate Center (USA) notes that the live-attenuated SIV vaccine "is the only one to provide 'working vaccine' level protection." She believes that safety concerns should not prevent further research into the live-attenuated vaccine. "After all these years of effort," she notes, "no other vaccine has provided any real protection in animal models."

Desrosiers suggests that human studies of his vaccine may be appropriate in populations at high risk for HIV infection. "No live-attenuated vaccine, including the widely used live polio vaccine, is absolutely 100 percent safe. Yet in all vaccines we make a risk/benefit analysis and consider the likelihood of adverse events versus the potential to protect against disease." ◆

Live-attenuated AIDS Vaccines

The live-attenuated vaccine that first protected monkeys from SIV was developed by genetically deleting the nef gene from live SIV. After developing the nef-deleted vaccine, a research team led by Ron Desrosiers, then attempted to delete as many SIV genes as possible, while still preserving the vaccine's immunogenecity. Consequently, the triple-gene deleted vaccine was developed. This vaccine has also demonstrated broad protection against large doses of virulent SIV.

Development rights to the gene-deleted vaccines developed by Desrosiers are held by Therion, a U.S.-based biotechnology company. At present, the company is seeking additional funds to pursue development of these vaccines.

In Australia, researchers led by John Mills of the MacFarlane Burnet Centre for Medical Research in Victoria, are closely following a cluster of HIV-infected individuals who received blood from a single donor over ten years ago and remain healthy with no sign of disease or immune suppression. These individuals all have deletions in the nef gene of HIV. Mills and his team are now attempting to use the information from this cohort to gain a greater understanding of live-attenuated HIV vaccines. ◆

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human trials. According to Johnston, "increased testing of HIV-DNA vaccines in one or more developing countries would assure their accelerated evaluation against a range of HIV genetic subtypes."

Johnston reports that IAVI is now working to identify partners to conduct preclinical research leading to the testing of HIV-DNA vaccines in Phase I trials in developing countries. The Initiative is also considering partnerships to study an HIV-DNA vaccine with a suitable booster immunization to induce stronger humoral immune responses.

Safety Studies of Live-Attenuated HIV Vaccines

IAVI's second area of emphasis will be on safety studies of live-attenuated HIV vaccines. In macaque monkeys, live-attenuated vaccines have provided impressive protection against simian immunodeficiency virus (SIV), a virus similar to HIV that causes an AIDS-like illness. In addition, humans who received apparently-attenuated HIV through transfusion or transplant have remained healthy with no signs of disease for more than 15 years. Despite these promising findings, few comprehensive efforts have been made to address the safety issues relating to live-attenuated HIV vaccines. Additional research is needed on both naturally acquired live-attenuated HIV in humans and monkeys infected with live-attenuated SIV.

IAVI will seek partners to address the safety of live-attenuated HIV in suitable animal models. The Initiative will also continue to work with others, particularly colleagues from developing countries, to evaluate the possible risks and benefits of pursuing human trials.

First Awards Slated for Spring

Research will not be done by the Initiative itself, but rather by companies or research institutes worldwide that are best qualified to do so. In the coming year, IAVI expects to invest approximately $2 to 4 million in four or more projects. According to Johnston, the first grantees will be identified by this spring. As its funding stream increases, IAVI plans to expand its focus to other gaps in HIV vaccine development.

IAVI Scientific Advisory Committee Members

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The scientific advisory committee, which is headed by Jaap Goudsmit, M.D., University of Amsterdam (the Netherlands), will advise Johnston in guiding IAVI's targeted vaccine development effort. The panel is committed not only to providing IAVI with scientific expertise but also to advising the Initiative in its efforts to advocate for effective HIV vaccine research and development worldwide.

At its most recent meeting, the committee also reviewed development of candidate HIV vaccines based on live viral vectors, learned about the plans for HIV vaccine development at the National Institutes of Health (USA), and examined the state of research on correlates of protection and immunological significance of HIV genetic subtypes.

According to Johnston, "much of the committee's discussions were broader than IAVI. Members are very interested in the overall status of HIV vaccine research and in helping IAVI address broad scientific issues relating to HIV vaccine development."

A key focus of IAVI is its emphasis on applied research to determine whether vaccines will protect against HIV and to increase general understanding of human immune responses to candidate vaccines. According to Goudsmit, "Vaccine development has traditionally been a partially empirical process. Successful vaccines have been developed without knowledge of the correlates of protection or a perfect animal model." IAVI, he adds, "can move development and testing of promising approaches forward on a global level."

Overall Core Strategies

The key scientific areas of emphasis are consistent with IAVI's core strategies: 1) development and testing vaccines based on HIV subtypes found in the developing world, where the vast majority of new infections are occurring; 2) research with complex vaccine designs based on multiple HIV proteins or combinations; and 3) collaboration with developing country researchers, national programs and international agencies.

All told, Johnston is pleased with the progress made so far on IAVI's scientific program and advocacy efforts. "In a very short time, we have come a long way. Nevertheless, our challenge remains urgent." ◆

Studying AIDS Vaccines in Thailand: An Interview with Natth Bhamarapravati

Natth Bhamarapravati, M.D., D.Sc., is a member of the National AIDS Commission of Thailand and chairman of its Subcommittee on HIV Vaccine Trials. He is also a member of IAVI's Scientific Advisory Committee and of the UNAIDS Steering Committee for AIDS Vaccine Development.

Dr. Natth's main area of research is dengue hemorrhagic fever, for which he has developed a live-attenuated vaccine. Transmitted by mosquitoes, the dengue virus is common in southeast Asia and Latin America. The vaccine will enter Phase III trials shortly. Dr. Natth has also served as president of Mahidol University.

IAVI REPORT: Where is the AIDS epidemic at this point in Thailand?

NATTH: The epidemic started in commercial sex workers and intravenous drug users. Then heterosexual transmissions began spreading, particularly in northern Thailand. Now, between 500,000 to 800,000 Thais are infected with HIV.

The rate of increase for new infections was very high until about three years ago, but has now stabilized. For example, the rate of HIV infection in soldiers recruited at age 18 was 1.5 percent, then climbed to 2.5 percent. Now it has come down to 1 percent, thanks to the youth condom distribution program.

IAVI REPORT: And what about the epidemic in the rest of southeast Asia?

NATTH: Many of our neighboring countries are in the phase that Thailand was about seven years ago. The governments close their eyes, their ears and their mouths like the three monkeys.

IAVI REPORT: What type of HIV vaccine trials are being planned in Thailand?

NATTH: Phase I trials of the recombinant gp120 vaccines produced by Genentech and Chiron have been completed and Phase II trials are about to be completed. A trial of Chiron's gp120 vaccine made from HIV subtype E, which predominates in Thailand, will begin shortly.

IAVI REPORT: Are there plans for a trial of a bivalent vaccine based on both subtypes E and B?

NATTH: We've proposed to initially test Chiron's bivalent vaccine in the intravenous drug user population and then in the North. It will also be combined with another vaccine, Pasteur-Merieux-Connaught's canary pox (ALVAC) vaccine. The ALVAC vaccine is designed to generate cytotoxic lymphocytes (CTL), the immune response believed to be important in clearing HIV infection. The gp120 vaccines generate neutralizing antibodies, so we hope the combination of the gp120 plus the ALVAC vaccine will induce both types of immune response.

IAVI REPORT: Are any trials of the ALVAC vaccine underway?

NATTH: No, they are in the planning stage. There will probably be preliminary (Phase I and II) studies and then, hopefully, a Phase III efficacy trial which could have three arms: placebo, gp120 based on a combined E and B subtype, and the ALVAC/gp120 arm.

IAVI REPORT: How are these vaccine trials being viewed by the Thai people?

NATTH: At first people thought we were being guinea pigs for the Westerners. But we have tried to educate and involve the medical community, the scientific community, the politicians and, most importantly, the mass media.

Once these four groups understood what we were doing, we could move ahead. The National AIDS Commission has decided that Thailand should initiate trials of HIV vaccines that are safe from a scientific standpoint.

We hope the trials will be done in the context of an overall plan to increase the capacity of Thailand to manage clinical trials. Once we get through a couple of trials, we should be competent to do many different clinical studies.

If we wait until all the pieces of knowledge are in place like a jigsaw puzzle, I don't know when we will get an HIV vaccine.

IAVI REPORT: Do we need vaccines based on the HIV subtypes found in the population?

NATTH: I don't have the answer to this. With dengue, there are four types of virus. So we use a vaccine with all four types mixed in because we don't know whether one type would be effective or not.

One reason we've tried to push ahead with gp120 trials is that the vaccines are made from the E and B HIV subtypes. It would be very bad if we wasted three or four years not knowing whether vaccines based on different subtypes generate different immune responses in our population. That's why we decided to go ahead with the bivalent vaccine. And Chiron deserves credit for producing the vaccine based on different subtypes.

IAVI REPORT: What are the biggest roadblocks to developing a safe and effective vaccine?

NATTH: We don't know the correlates of protection, that is, what immune responses provide protective immunity. That's the biggest gap. But in the history of vaccine development many effective vaccines have been developed without knowing this. They have been developed through what might be called empiricism, starting from the first smallpox vaccine made by Jenner who did not even know that smallpox was caused by virus.

If we wait until all the pieces of knowledge are in place like a jigsaw puzzle, I don't know when we will get a vaccine. That's why

Thailand was the first developing country to be involved with vaccines trials. We are really frustrated and want to facilitate vaccine development as much as possible because HIV is a real threat to our country.

IAVI REPORT: Where do you see IAVI's role in the overall effort?

NATTH: I believe that IAVI has an important role to play. It will be funding promising areas of research not being pursued adequately due to bureaucratic reasons, government policy, politics or corporate decisions. As an international, non-governmental agency, IAVI can also play a vital role in bringing together governments, industry, researchers, and national organizations to ensure development of HIV vaccines for use throughout the world.

IAVI REPORT: Can companies make a reasonable return from an AIDS vaccine?

NATTH: I can only tell you about the experience with the hepatitis B vaccine which was developed 20 years ago.

In the first couple of years the price of the vaccine was as high as $25.00 to $40.00 a dose, with three doses needed. So companies aimed for the upper end of the market and the market stalled. The price could not go too high despite the global need for the vaccine. In China alone, with 1.2 billion people, the hepatitis B carrier rate is 10 percent, so there are 120 million Chinese walking around with chronic hepatitis B. In Thailand, the carrier rate is also 10 percent. Yet many countries were practically out of the purchasing market.

When the recombinant hepatitis B vaccine was developed the price decreased a little. Now the price has come down to probably $1.00 per dose. And four years ago, Thailand put the hepatitis B vaccine on the general program of immunization. So all babies in our country now receive the vaccine.

Companies must realize that the potential market for an HIV vaccine in the developing world is tremendous, but it can only be captured by using two or three price tiers. The high price would be for industrialized countries, while developing countries would have another price. Figuring how to work this out is a very important challenge for government, business, scientists and international organizations. Companies must profit from their investment. And developing countries must be able to afford the vaccine. To bring the price down, the gap between the high and low end will have to be met by private foundations, government assistance and other sources. It's a real challenge but if you are successful in this, we can boost the development of many vaccines.

IAVI REPORT: Are there any plans for HIV-DNA vaccine studies in Thailand?

NATTH: Many people consider DNA vaccines to be a promising approach, but these vaccines need to be tested. We would like to initiate DNA vaccine trials in Thailand and while doing so encourage collaboration between Western and local scientists.

Many of these vaccines can be produced in our laboratory in which has produced the dengue vaccine. We can begin safety tests and animal tests. If the vaccine appears safe, we can start human trials. And if it works, and there can be an agreement that the intellectual property would be shared, then a lot of things can happen.

The best vaccine is one that could be used for both industrial and developing countries because that would assure us that the development would go on.

IAVI REPORT: What are your thoughts on testing live-attenuated HIV vaccines?

NATTH: The live-attenuated vaccine is the best vaccine in the world. We developed a live dengue vaccine based on this concept. But the safety issue is tremendous. People ask what happens if the attenuated virus gets situated into the genome. Or about the possibility of malignancy and autoimmune disease in fifteen years. This is the main roadblock to testing live-attenuated HIV vaccines at the present.

IAVI REPORT: Are the HIV protease inhibitors drugs being widely used in Thailand?

NATTH: Only for the very few who can afford them. AZT is more widely available, but the drug is not too useful alone. I believe it is an ethical crime that so many people cannot get the drugs they need.

IAVI REPORT: When planning AIDS vaccine trials in developing countries, will it be necessary to initiate parallel trials of the same vaccine in industrialized countries?

NATTH: People talk a lot about an HIV vaccine for developing countries. But the best vaccine is one that could be used for both industrial and developing countries because that would assure us that the development would go on. If a vaccine is earmarked for developing countries alone, it may be dropped for lack of support, financing or other reasons. Initiating parallel trials in industrial countries would be a great assurance to other countries. Thailand has already gone through the stage of doubting. We have passed through the guinea pig syndrome. But other countries still will have to go through that.

IAVI REPORT: What have you learned about those who participated in the HIV vaccine studies so far?

NATTH: The profile of our participants is extremely interesting. We expected that our volunteers would be relatively uneducated people who received some incentive, financial or otherwise. But so far the profile is much different. Three-fourths of them are university educated. Some are doctors and nurses. When asked why they volunteered, more than 65 percent said that they wanted to help advance development of an AIDS vaccine. They think it's important and want to contribute. Only about five percent of the people said they expected the vaccine to protect them from high risk behavior. That's contrary to what we expected. We have learned that people are interested in participating in AIDS vaccine trials because it can help end this horrible epidemic. ◆

ALVAC Trial Moves Forward in Uganda

Editors note: This article is based on a report by Helen Epstein of the Panos Institute and Lillian Nsubuga of The East African *as well as interviews conducted by the* IAVI Report. *Panos is a London-based nonprofit organization that distributes information worldwide.*

A four-day meeting held in Kampala has apparently set the stage for a Ugandan trial of Pasteur-Merieux-Connaught's ALVAC vc205 HIV vaccine. The meeting, held in September 1996 and sponsored by the Joint United Nations Programme on AIDS (UNAIDS), brought together Ugandan and international experts to discuss the proposed trial.

Known as a live-vector vaccine, ALVACvc205 consists of HIV genes inserted into a live canary pox virus. The canary pox virus, which is harmless to humans, is intended to increase the immune response to the HIV genes (*see* IAVI Report, *vol. 1, no. 1*). The vaccine has already been tested in more than 300 volunteers in France and the United States, with no harmful side effects seen.

An effective vaccine is urgently needed to stem the epidemic in Uganda, where approximately 1.9 million people have already been infected with HIV and rates of infection range from 40 percent of adults in some rural communities to 18 to 25 percent in urban areas. To date, more than one million Ugandan children have become orphans due to the epidemic.

Recent advances in HIV treatment, which include use of the new protease inhibitor drugs, can cost more than US$15,000 a year per person, plus expensive monitoring tests, and are unlikely to be available in developing countries. Despite the desperate need for an HIV vaccine, only a small percentage of all international AIDS spending is devoted to vaccine research.

An intense public debate has surrounded the ALVAC trial in Uganda. The September meeting brought together more than 200 representatives of the medical and religious communities, legal experts, counselors, policy experts and the media. The meeting helped allay concerns voiced in the Ugandan media that Ugandans were being used as guinea pigs to test a vaccine from which they may never benefit.

The meeting appears to have been successful in satisfying the skeptics. "We were very concerned at the beginning of this process, but now we are assured that the vaccine is safe," says Samuel Tindifa of the Faculty of Law at Makerere University in Kampala.

The main reason for public acceptance of the trial seems to be the apparently high ethical standards being applied to the trials by the organizers. The Joint Clinical Research Centre of Uganda (JCRC), in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) in the United States, has spent almost five years preparing a cohort of young male soldiers to participate in an HIV vaccine trial. The forty participants will be chosen from these ranks. Using soldiers in Africa makes sense because they are a mobile, sexually active group and have a high risk of HIV infection.

One of the biggest concerns was whether trial participation would really be voluntary. All participants must give their "informed consent" under the rules of the Helsinki Declaration on Human Rights. Concern was particularly strong because the volunteers chosen for testing were soldiers from the Ugandan army, who are used to following orders.

In response to claims that soldiers would be pressured by their superiors to enroll in the trial, Major Rubamira Ruranga, an AIDS counselor for the JCRC, states that volunteers are lining up for the vaccine. "They want to be part of the struggle," says Ruranga, who is HIV-positive himself and is also founder of the National Network of People Living with HIV/AIDS in Uganda. Nevertheless, trial organizers did adopt the workshop's recommendation that trial counselors not themselves be in the military.

Concern over the trial has also focused on how the vaccine, if it is shown to be effective, will be affordable in Uganda. Annual per capita health care expenditures in the country are US$5. UNAIDS acknowledges this is a problem. "It is very difficult at this stage to ensure availability of a vaccine. We must get the companies to agree to the next stage of trials first. It is hard to negotiate for a product you don't know even works," says Jose Esparza of UNAIDS. Negotiations about pricing are expected if large scale efficacy studies begin.

Some are also worried as to whether the vaccine will be appropriate for use in Uganda. There are a number of subtypes of HIV that circulate in different parts of the world. An ideal vaccine would protect against all of these. However, almost all vaccines currently being developed, including the ALVAC vaccine being tested in Uganda, are based on subtype B which predominates in North America and Europe. In Uganda, subtypes A and D predominate. Some workshop participants questioned the wisdom and motivation behind testing a subtype B vaccine in Uganda. Yet preliminary data presented at the workshop suggested that at least some of those vaccinated with a subtype B ALVAC vaccine could have immune responses against subtypes A and

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ALVAC HIV Vaccines

ALVAC vaccines consist of HIV genes inserted into a live canary pox virus (which is harmless to humans). Three classes of ALVAC vaccines are currently in clinical trials. ALVAC vCP125 contains gp160 spliced into the canary pox vector. vCP205, the vaccine to be tested in Uganda, contains gp160 and the HIV genes, gag and protease. The third ALVAC product, vCP300, contains additional HIV genes including *nef*, to elicit an even broader immune response.

In the United States, ALVAC vaccines are being tested in combination with a booster shot of a gp120 vaccine manufactured by Chiron Corp., a U.S.-based biotechnology company. Preliminary studies suggest that the combination is safe and can induce some cellular and antibody responses. Stanley Plotkin, scientific director of Pesteur-Merieux-Connaught (PMC), reports that up to 60 percent of participants in some ALVAC trials have developed new cellular immune responses to HIV.

A Phase II study of ALVACvCP205, enrolling 420 volunteers, should begin in the United States in April 1997. The study will compare ALVAC plus gp120 versus ALVAC alone versus placebo. If sufficient immune responses are seen, a Phase III efficacy trial, conducted jointly by PMC and the U.S. National Institute of Allergy and Infectious Diseases (NIAID), could begin in 1998.

IAVI Issues Report on Intellectual Property Rights

When Jonas Salk was asked in 1955 who held the patent rights to his polio vaccine, he replied to a surprised television reporter, "The people. To patent the vaccine," he suggested, "would be like patenting the sun."

Today, intellectual property issues have a far greater impact on vaccine development. As vaccine research and manufacturing become ever more complex, every stage of the process is now likely to be patented. The recently developed recombinant hepatitis B vaccine — the world's first genetically manufactured vaccine — requires 14 different patents to produce. Royalty payments for these rights add significantly to the vaccine's ultimate price, thus reducing its availability around the world.

In an attempt to examine the role of intellectual property rights in its research and development efforts, the International AIDS Vaccine Initiative (IAVI) organized a consultation in August 1996 in New York City. The consultation explored intellectual property strategies that could be used by IAVI to further its overall mission of ensuring development of HIV vaccines appropriate for use throughout the world, as well as specific mechanisms that could be utilized to implement such strategies. A comprehensive report which summarizes the consultation has just been issued by IAVI.

The consultation brought together many of the world's leading authorities on intellectual property issues and vaccine development. Fourteen individuals, with backgrounds in law, private industry, public health and research institutions, discussed a range of traditional and innovative intellectual property rights strategies that could be used by IAVI to further its mission, as well as mechanisms by which these strategies could be implemented.

"Intellectual property rights," according to Seth Berkley, president of IAVI, "have become a critically important issue in international vaccine development and deployment. Our efforts represent an attempt to initiate comprehensive intellectual property discussions early in IAVI's research and development efforts.

"IAVI," Berkley added, "is committed to working closely with industry, international organizations, national governments and the research community to ensure that intellectual property issues are not a barrier to development and deployment of HIV vaccines throughout the world."

> ***Participants at the consultation concluded that an effective HIV vaccine is likely to be based on a combination of different patents.***

Participants at the consultation concluded that an effective HIV vaccine is likely to be based on a combination of different patents. For this reason, they recommended that, when funding research and development, IAVI should work to protect the intellectual property generated from such research. By protecting these rights, access to other patents will be facilitated. Even more importantly, IAVI and its partners will be in a stronger position to ensure that HIV vaccines are made available for use throughout the world.

One of the most challenging issues addressed at the meeting, according to Lita Nelson, director of the Technology Licensing Office at the Massachusetts Institute of Technology (MIT), was "how the Initiative can use intellectual property rights to provide incentives for industry to work with IAVI in the development and distribution of an HIV vaccine."

Participants agreed that IAVI's intellectual property strategies will be shaped by a number of different factors including the stage of research being funded, the vaccine being developed and the parties involved. Broader issues such as international agreements (including GATT), intellectual property laws in individual countries, and current vaccine pricing practices will also influence these strategies.

A number of implementing strategies, principles and actions were recommended. Peggy Johnston, IAVI's scientific director, noted that "we are grateful to have had the assistance of this impressive group of international experts." Johnston is especially pleased that Nelson has agreed to be a formal adviser to IAVI on intellectual property issues, and that MIT has donated a significant percentage of her time to assist IAVI in all its negotiations. According to Nelson, "IAVI's mission is so critically important on a global level that we have decided to make this commitment to the Initiative."

Intellectual property strategies, Johnston believes, "can help IAVI stimulate new HIV vaccine research and help ensure that vaccines that are developed can be made available throughout the world. By beginning to examine these issues systematically," she adds, "the Initiative can help others involved in AIDS vaccine development negotiate partnerships that benefit all parties."

To obtain a copy of the report on intellectual property rights, send a written request to IAVI Interim Secretariat, c/o The Rockefeller Foundation, 420 Fifth Avenue, New York, NY 10018, USA. ◆

Report on Industry Investment

In January, the AIDS Vaccine Advocacy Coalition (AVAC), a U.S.-based policy group, issued a report on private sector investment in HIV vaccine research. The report, based on in-depth surveys of researchers from 23 companies in the United States, Canada and Europe, includes a series of recommendations, survey results and a review of current HIV vaccine research programs at pharmaceutical and biotechnology companies. To order a copy of the report, send US$10 to: AVAC, 2215 Market St, #501, San Francisco, CA, 94114 USA. ◆

Developing HIV-DNA Vaccines: An Interview with Vince Zurawski

Vince Zurawski, Ph.D., is the chief executive officer of Apollon, Inc., a U.S.-based biotechnology company that develops gene-based products and vaccines. Apollon is the only company to have initiated human studies of an HIV-DNA vaccine. Zurawski studied immunology at Harvard Medical School prior to becoming a co-founder of Centocor, another U.S.-based biotechnology company. In 1992, he founded Apollon.

IAVI REPORT: Can you tell us where Apollon is with its HIV-DNA program?

ZURAWSKI: We've initiated two therapeutic trials of a HIV-DNA vaccine, one at the University of Pennsylvania (USA) and the other at the University of Zurich in Switzerland. The vaccine we've used is our "envelope-directed" vaccine which is based on the HIV envelope proteins gp120, gp41, as well as rev. And in spring 1996, we began a preventive trial of this vaccine in HIV-negative individuals at the National Institutes of Health (NIH). We have also developed a "core-directed" HIV-DNA vaccine (consisting of HIV genes, gag and pol) and have applied for Food and Drug Administration (FDA) approval to begin therapeutic and preventive trials of this vaccine. In addition, we are planning a preventive trial using both the envelope and core directed HIV-DNA vaccines together.

IAVI REPORT: What have you seen from the therapeutic trial?

ZURAWSKI: We've seen new immune responses to gp120 and several peptides. But we have yet to see any real decreases in viral load. Obviously, we can augment the immune response directed against the virus. But it's not clear that we're having a clinical effect, yet.

IAVI REPORT: Did you see any unexpected side effects?

ZURAWSKI: None at all. CD4 counts were stable. We didn't see any kind of unusual laboratory or immunologic outcomes. We had a few minor, local reactions of short duration, a little redness at the site of injection. But that's no different than you would see with any intramuscular vaccine.

IAVI REPORT: What about the preventive trial of the HIV-DNA vaccine?

ZURAWSKI: So far 10 HIV-negative people have received the vaccine. The trial, which is ongoing at the NIH, will enroll 16 people. We also expect to start additional preventive trials in the United States, in all likelihood, in the first half of this year.

DNA Vaccines

DNA vaccines, also known as "naked DNA vaccines" or "genetic immunization", are being studied for many diseases including HIV, influenza, hepatitis, malaria and tuberculosis. The vaccines are created by inserting one or more of genes from a pathogen on to another piece of DNA which acts as a vector. The genetic material — or fragments of DNA — is then injected directly into the muscle tissue. Once in the cells, it encodes information, enabling the individuals' own cells to create an antigen, which causes the immune system to generate a response.

The scientific appeal of DNA vaccines is that they attempt to create the immune reaction of a live vaccine without using a live virus. Recent animal studies suggest that DNA vaccines can generate powerful immune responses, particularly those known as cytotoxic lymphocyte immune responses, which researchers believe may be necessary to protect against HIV. DNA vaccines are also more heat stable than most vaccines and relatively inexpensive to produce. Consequently, they are one of the few HIV vaccine approaches that have the potential to be distributed throughout the world at a reasonable cost.

IAVI REPORT: What have the tests of your HIV-DNA vaccines in chimpanzees shown?

ZURAWSKI: To the extent that we can evaluate these studies, we believe that we've protected them against challenge. Those animals were first challenged in November 1995. Thus far, we have no evidence of any virus replication or infection. In contrast, the control animals showed obvious signs of infection and circulating virus.

IAVI REPORT: Have you tested different routes of administering the HIV-DNA vaccines?

ZURAWSKI: We've examined intramuscular, intravenous, intranasal, oral and vaginal routes of administration in animals. And we've seen immune responses in every case. So, the question is, what's the best route going to be? For any sexually transmitted disease you have to worry about mucosal immunity. And we've paid a lot of attention to the mucosal immunity aspects of this, as we've moved ahead.

IAVI REPORT: What was your experience in getting FDA approval for human studies of the HIV-DNA vaccine?

ZURAWSKI: We had a long series of meetings prior to getting FDA approval. The first approval was for the therapeutic study. In spring 1995, we got approval to begin the first HIV-DNA study in HIV-negative volunteers. That was very important from a regulatory point of view and it took quite an enormous effort in terms of the studies we determined were needed to prove the potential safety of the vaccine. Obviously, our feeling, after doing a lot of investigation, is that these vaccines are quite safe.

I made it a criterion that we would not start any clinical trials, either in HIV-infected or in non-infected volunteers, until all our people were convinced that they would be willing to take the vaccines personally. And that made it a lot easier with the FDA, because we really believed in what we were talking about.

IAVI REPORT: Some have raised the possibility that antibodies to the DNA may increase the likelihood of an autoimmune reaction.

ZURAWSKI: We have yet to see, in our clinical trials, any evidence where the immune response is directed against the DNA. But we will continue to evaluate everything.

Secondly, it seems that DNA often leads to immune responses against itself, when it is combined with other materials. Because of that, we've taken great pains in purifying the DNA and have very stable, highly purified preparations. It is important that the product be of very high quality. We have an extremely sensitive assay that can detect integration. And we've seen nothing yet. We're quite encouraged by that.

I have no doubt that if we get an effective HIV vaccine there will be a very substantial market for it.

IAVI REPORT: What are your plans for international trials of the preventive HIV-DNA vaccine?

ZURAWSKI: We are in active discussions with a number of parties about international trials. We're already developing prototype vaccines with different HIV subtypes. We've done work with subtypes E and A. So, we've clearly made the commitment to move ahead.

IAVI REPORT: How far are we from efficacy studies of HIV-DNA vaccines?

ZURAWSKI: It's always extremely tough to predict the future. We hope to be doing some true Phase II trials this year. And we continue trying to develop the best formulation, route of administration and dosing interval to move ahead with. But this is difficult work that requires attention to detail. Fortunately, we've received a lot of support from NIH, and the FDA has looked favorably on our applications and allowed us to begin clinical studies.

If we see some reasonable success in immune responses over the next 18 months it's not totally unrealistic to imagine starting efficacy studies at or near the turn of the millennium. And with a little luck, it could happen before that.

IAVI REPORT: What would you consider a successful endpoint in the Phase I and II studies?

ZURAWSKI: Success is going to be defined as we go along. But, certainly, we'll be looking at immune responses. That's number one. Of course, no one knows exactly what the correlates of protection are going to be. There was one thing that we found very interesting in the chimpanzee experiments. In one protected animal, we had a very strong cytotoxic T-lymphocyte response and a not-so-strong antibody response. In another animal that was protected, we had much higher neutralizing antibodies and a more modest cytotoxic T-lymphocyte response. This suggests to me that there's more than one way for the immune system to create a protective immune response.

IAVI REPORT: Are there any plans to test your DNA vaccine with a gp120 vaccine boost?

ZURAWSKI: Our company is focused on DNA-based vaccines. I have every reason to believe, based on the animal studies we've done, that these vaccines, by themselves, have the potential to be effective. If we believe we can get better outcomes by combining with a recombinant protein vaccine, we will consider moving in that direction. However, our immediate plans are to hopefully prove that our DNA-based vaccines, by themselves, give us effective immune responses.

IAVI REPORT: Has it been difficult to raise funds for your HIV-DNA program?

ZURAWSKI: As a privately-held biotechnology company, we are still impacted by the ups and downs of the public market for biotechnology stocks. Nevertheless, over the last four years, we have successfully raised more than $25 million in equity financing, in addition to our agreement with Wyeth Lederle. But to be very frank, if our only program had been an HIV vaccine, it would have been very difficult for us to raise money in the equity markets.

IAVI REPORT: Why is that?

ZURAWSKI: In terms of candidate HIV vaccines, there have been a lot of well publicized failures. The investment community sees that for ten years some very good people have been struggling without success. Why is it that some new company or new technology coming along is going to have a better chance of success? So, many potential investors have adopted a wait-and-see attitude regarding HIV vaccines. People recognize that there may be a big market and upside. But looking at what has happened thus far, investors have become concerned.

IAVI REPORT: What about fears of liability issues in HIV vaccine developed?

ZURAWSKI: The whole vaccine field is a potential minefield for liability issues. And we have always paid close attention to this, in developing our programs. But I don't see any reason why HIV is a greater concern, except to the extent that people scrutinize AIDS more carefully.

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HIV-DNA Vaccine Research at Other Companies

Although Apollon is the only company to initiate human studies of an HIV-DNA vaccine, pre-clinical research is ongoing at a number of companies and research institutes. Merck, the U.S-based pharmaceutical giant, has an extensive DNA vaccine program. The company is testing HIV-DNA vaccines in a broad range of animals, including primates and is currently focused on improving antibody responses in these animals. Auragen, a U.S.-based biotechnology company, has developed a "gene-gun" delivery system in which small amounts of HIV DNA are placed in gold "beads" and injected into the skin. The company has conducted animal studies of its gene gun HIV-DNA vaccine, alone, and in combination with other products such as a gp120 vaccine. The French pharmaceutical company, Pasteur-Merieux-Connaught recently acquired the rights to DNA vaccine technology, including HIV-DNA vaccines, being developed by Harriet Robinson, a researcher at the University of Massachusetts (USA). Chiron, the U.S.-based biotechnology company, also has an HIV-DNA program. In addition to these companies, a number of researchers and research institutions are also studying HIV-DNA vaccines. These include: Stephen Johnston of Southwestern Medical Center (USA), Britta Wahren of the Karolinska Institute (Sweden) and the National Cancer Institute (USA).

Baltimore to Head NIH AIDS Vaccine Panel

With growing attention focused on the need to develop a safe and effective AIDS vaccine, William Paul, head of AIDS research at the National Institutes of Health (NIH), announced in December 1996 that Nobel laureate David Baltimore will lead a new AIDS vaccine committee to oversee NIH's efforts in the area.

Baltimore, who is co-discoverer of reverse transcriptase, an enzyme that is essential for retroviruses such as HIV to replicate, will serve as a consultant to the NIH. Administratively, he will work out of the offices of the National Institute of Allergy and Infectious Diseases (NIAID), the division which manages virtually all of the NIH's AIDS vaccine efforts.

The appointment comes on the heels of growing concern about the U.S. government's commitment to AIDS vaccine development. A review of AIDS research at the NIH conducted by a panel of outside researchers noted last year that "vaccine research historically has received less funding and attention than other areas of research. Although this may have been justifiable in the past, the continued spread of the HIV epidemic and recent advances in our knowledge dictate a reassessment of priorities and a restructuring of the NIH vaccine effort."

Known as the Levine Report (for the panel's chair, Arnold Levine, a Princeton University researcher), the review concluded that "only with a reinforced effort and commitment will a vaccine against HIV be attainable," and recommended creation of a restructured, trans-NIH vaccine program with centralized leadership to mobilize and focus the necessary resources.

Paul announced the appointment at a meeting of the advisory committee to NIH director Harold Varmus. He also announced that the NIH would increase the amount it spends on AIDS vaccine research from $109 million to $129 million. The NIH spends a total of approximately $1.5 billion on AIDS-related research. Varmus and members of the advisory committee expressed strong support for the appointment.

In a talk with *IAVI Report*, Baltimore noted that he will devote at least twenty percent of his time on the appointment while keeping his research position at the Massachusetts Institute of Technology. He also reported that before accepting the appointment he undertook a review of the science to make sure he was convinced an HIV vaccine was scientifically possible.

Baltimore expressed a willingness to use his position to vocally support AIDS vaccine research. "I think it is important to be a spokesperson for the NIH program," he said. His leading priority is to "move the science forward. NIH has got to show the way by providing attractive and exciting possibilities."

When asked about the need for directed research in AIDS vaccine development Baltimore said, "at the right moment there is a need for directed research. I am not going to wait until we dot every 'i' and cross every 't' before supporting clinical trials of AIDS vaccines."

Baltimore reported that he has already been in touch with "major international players, such as the leaders of UNAIDS and IAVI." and looks forward to working closely with these and other international partners. ◆

UGANDA TRIAL continued from page 6

D. In addition, representatives from Pasteur-Merieux-Connaught (PMC) report that the company is developing ALVAC vaccines based on HIV subtypes A and E.

Of the 40 participants ultimately enrolled, half will receive the vaccine. The 20 receiving placebos will either get the canary pox vector (without the HIV genes) or a saline solution. In this way researchers can compare the impact of the vaccine with that of the vector.

One of the endpoints of the study is the development of new cellular immune responses to HIV in participants. As part of the trial, NIAID and PMC are setting up a lab for Ugandan researchers to test the immune reactions seen in participants. Blood samples will also be sent to the United States for testing by NIAID researchers. Principal investigators for the trial are Roy Mugerwa of Makerere University in Kampala and Jerold Ellner of Case Western Reserve University in the United States.

According to Mark Grabowsky of NIAID, "the meeting brought together a cross section of Ugandan society in an open forum to discuss the trial. Most importantly," he says, "it helped build trust between all the parties and support for HIV vaccine trials in the country."

Other observers were also impressed. Steve Wakefield, a U.S. activist with the Night Ministry in Chicago, says, "the meeting was successful because it was a collective, collaborative effort." Wakefield added that he thought the trials would "most definitely move forward because in Uganda there is a commitment from the top down that a vaccine is the only answer to the AIDS epidemic."

Ugandan authorities are now in the process of establishing their own review committee to oversee all future medical research in the country. The high ethical standards apparently being applied to the trial together with open public debate surrounding it should, according to Esparza, be "held up as a model for other countries." ◆

ZURAWSKI INTERVIEW... continued from page 9

IAVI REPORT: Do you think there's a sizable market for an HIV vaccine?

ZURAWSKI: I don't have any doubt that if we get an effective vaccine there will be a very substantial market for it. How fast a vaccine would be adopted and in which patient groups is hard to say. An interesting comparison is the hepatitis B vaccine. People thought the vaccine would not take off the way it has. When it was first developed, people felt it would be used by health care workers, not as a routine vaccine. And now it's recommended by the American Academy of Pediatrics.

IAVI REPORT: How do you try to get the best vaccine, while not waiting too long for human studies?

ZURAWSKI: We are pressing ahead on a first-generation approach, and evaluating whether that approach is leading to the outcomes we want to see. Simultaneously, we are evaluating and developing other approaches that can be injected into the program. That's one of the huge advantages of DNA-based vaccines. The manufacturing is relatively standard, we're not looking at a vastly different process for core-directed versus envelope-directed vaccine. They're both basically DNA and we manufacture them by essentially the same process.

I became involved in gene therapy and DNA-based vaccines because they are extraordinarily exciting areas that could lead to real effective products, in a real time frame. And from the outset it was my opinion that if any vaccine methodology was going to succeed in leading to an effective vaccine for HIV, this was the one. ◆

Leading International Organizations Fund IAVI

IAVI continues to attract growing support and funding from key organizations and institutions around the world. Lead funders at this point are the Rockefeller Foundation and the Alfred P. Sloan Foundation. Other significant backers include the World Bank, UNAIDS, Until There's a Cure Foundation, Chubb Insurance, and the Merieux Foundation.

The Rockefeller Foundation, which has long been committed to international health care, played a central role in launching IAVI, lending its worldwide expertise and prestige to the effort. Peter Goldmark, the Foundation's president, notes that "AIDS is a lethal, persistent, contagious disease that ties together the North and South scientifically, epidemiologically, and emotionally." After Foundation officials closely examined AIDS vaccine development, "we learned of the failure of market mechanisms to trigger private sector investment and of national governments which long ago should have made AIDS vaccines a high priority. This required us to step in, prime the pump and ring the warning bell." Goldmark strongly believes that "to create an AIDS vaccine for the world, all sectors, including foundations, will need to work together."

In 1994, Ralph Gomory, president of the Alfred P. Sloan Foundation, was alerted to the fact that a number of promising AIDS vaccine approaches were not being aggressively pursued. Surprised, Gomory decided to take a closer look at the situation despite the fact that the Sloan Foundation had not previously focused on either medical or international issues.

"We learned from companies and scientists involved in AIDS vaccine development that it was indeed very difficult to raise funds," recalls Gomory. After discovering that the Rockefeller Foundation had already laid the groundwork for an international initiative focused on HIV vaccine development, Gomory decided to work together.

While the Sloan Foundation traditionally focuses on areas related to science and technology, on occasion it will address selected issues of overriding importance. According to Ted Greenwood, program officer for the Foundation, "even though AIDS vaccines didn't fit into our traditional programs, we felt it was important for the world that we play a role in this effort."

Overall, Gomory sees the issue in very clear terms. "If we can play some role in helping to advance efforts to develop an AIDS vaccine, how could we not participate?"

One of the most significant partners in IAVI's efforts has been the World Bank. Over the last decade the organization has become a major lender in the area of international public health. In responding to the global AIDS epidemic, the World Bank has already committed more than US$700 million in loans to over 50 countries.

In doing so, according to Dr. Richard Feachem, chair, Health, Nutrition, and Population Sector Board of the World Bank, "it became apparent that current efforts are not sufficient to end the epidemic. We are losing the global war against AIDS."

The World Bank became involved with IAVI after concluding that "international AIDS vaccine efforts needed to be refocused to accelerate progress and ensure that when a vaccine is developed it will be appropriate for use and widely available throughout the world," says Feachem, who is a member of IAVI's board of directors. "Because of this, we strongly support the goals and objectives of IAVI and are pleased to have helped launch the Initiative," he adds.

An early partner in the founding of IAVI, Until There's a Cure Foundation is a U.S.-based organization that raises funds for AIDS vaccine development, care services and education. The Foundation was formed three years ago by Dana Cappiello and Kathy Scutchfield. According to Cappiello, Until There's a Cure became involved with IAVI because "it seemed that little was being done in the area of AIDS vaccine research." Until There's a Cure, which has sold over 175,000 AIDS bracelets as a tool to raise funds and increase awareness, is now expanding globally.

Another of IAVI's early backers is the Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS has committed financial resources to the Initiative and its executive director, Peter Piot, sits on IAVI's board of directors. According to Piot, IAVI has "brought renewed attention to the urgent need to develop an HIV/AIDS vaccine. In our partnership with IAVI, UNAIDS looks forward to working together in moving the most promising vaccine concepts to field trials," he adds.

In addition to these initial donors, IAVI has begun discussions with a number of other leading international institutions and foundations, national government agencies, and key AIDS and vaccine organizations around the world about collaborating with the Initiative. "We are excited about the broad range of international and national organizations that may work with IAVI to advance HIV vaccine development," says Seth Berkley, president of the Initiative.

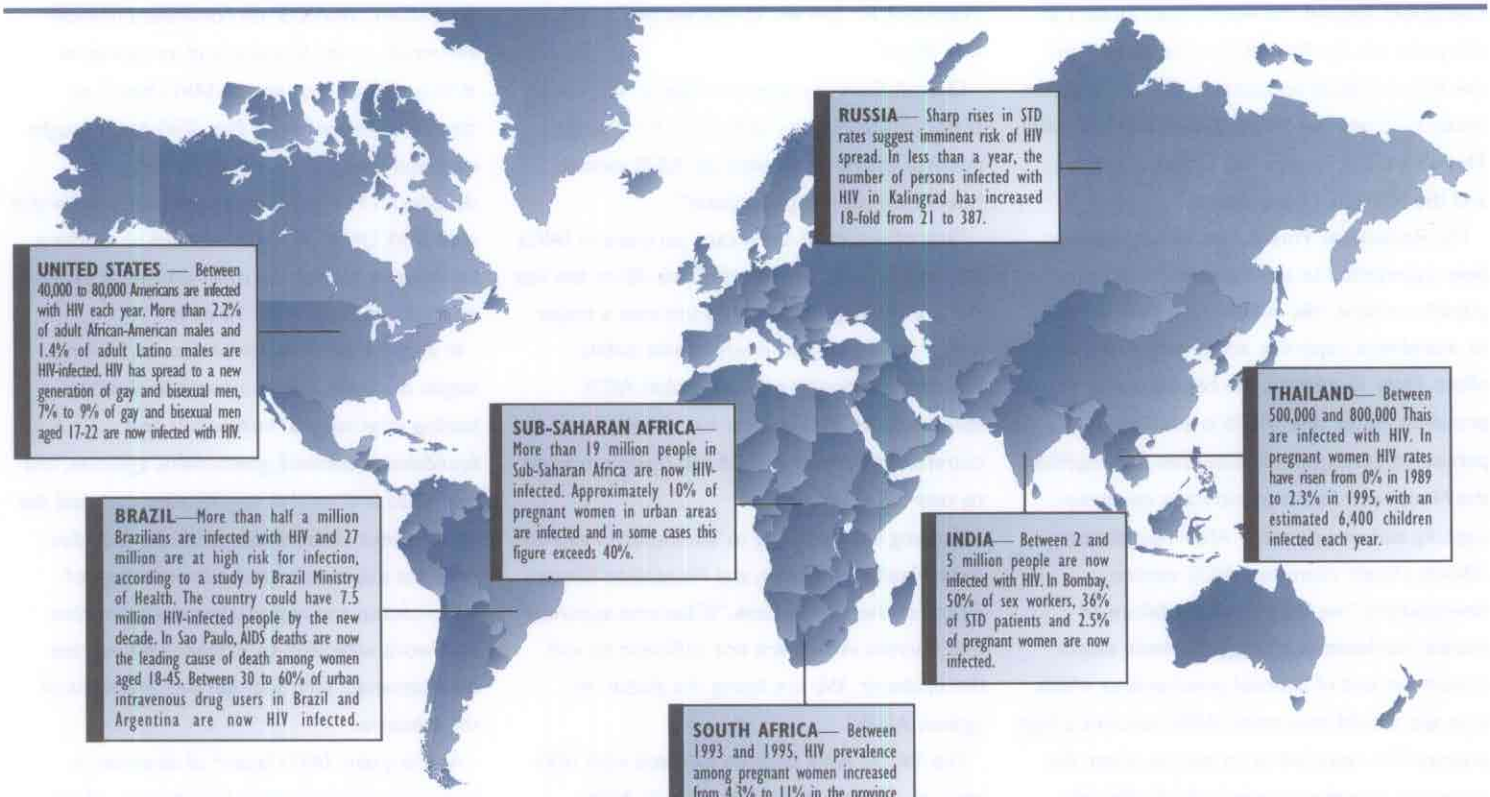
At this point, IAVI's board of directors is evaluating an international fundraising plan for the Initiative. Berkley makes it clear that the Initiative's goal is to obtain new funds for its research and development efforts and "not cannibalize existing sources of AIDS funding." ◆

Princess Diana Urges Support for IAVI

In a World AIDS Day 1996 message, Diana, Princess of Wales, noted that "there is renewed global collaboration to find a long-term solution to HIV in the shape of the International AIDS Vaccine Initiative." In an earlier message, in June 1996, the Princess observed that recent treatment advances were "beyond the reach of many people, particularly in the developing countries. I therefore fully endorse the objectives of the International AIDS Vaccine Initiative to provide more speedily a vaccine that can assist in controlling this epidemic and which one day may eliminate the risks of HIV for all of us."

The Global AIDS Epidemic: No Place on Earth Untouched

HIV has now reached every country on earth. In many parts of the world, the epidemic is spreading explosively. High rates of infection in commercial sex workers, truck drivers, injection drug users and patients at sexually transmitted disease (STD) clinics often presage widespread epidemics in a particular country.



RUSSIA— Sharp rises in STD rates suggest imminent risk of HIV spread. In less than a year, the number of persons infected with HIV in Kalingrad has increased 18-fold from 21 to 387.

UNITED STATES — Between 40,000 to 80,000 Americans are infected with HIV each year. More than 2.2% of adult African-American males and 1.4% of adult Latino males are HIV-infected. HIV has spread to a new generation of gay and bisexual men, 7% to 9% of gay and bisexual men aged 17-22 are now infected with HIV.

SUB-SAHARAN AFRICA— More than 19 million people in Sub-Saharan Africa are now HIV-infected. Approximately 10% of pregnant women in urban areas are infected and in some cases this figure exceeds 40%.

THAILAND— Between 500,000 and 800,000 Thais are infected with HIV. In pregnant women HIV rates have risen from 0% in 1989 to 2.3% in 1995, with an estimated 6,400 children infected each year.

BRAZIL—More than half a million Brazilians are infected with HIV and 27 million are at high risk for infection, according to a study by Brazil Ministry of Health. The country could have 7.5 million HIV-infected people by the new decade. In Sao Paulo, AIDS deaths are now the leading cause of death among women aged 18-45. Between 30 to 60% of urban intravenous drug users in Brazil and Argentina are now HIV infected.

INDIA— Between 2 and 5 million people are now infected with HIV. In Bombay, 50% of sex workers, 36% of STD patients and 2.5% of pregnant women are now infected.

SOUTH AFRICA— Between 1993 and 1995, HIV prevalence among pregnant women increased from 4.3% to 11% in the province of Free State and from 9.6% to 18% in Kwazulu/Natal.

WORLDWIDE

Global Total	24.1 million
Cumulative number of all HIV infections	29.4 million
New Infections in 1996	3.1 million

Sources:
Joint United Nations Programme on HIV/AIDS (UNAIDS); Centers for Disease Control and Prevention (USA); National Program for Transmissible Diseases/AIDS (Brazil)

VIETNAM AND MALAYSIA— HIV rates in sex workers climbed from 9% to 38% in four years in Vietnam, and from 0.3% to 10% in Malaysia.

CAMBODIA—Five years ago, Cambodia had no cases of AIDS. Today 10% of blood donors and 2.5% of pregnant women in Phnom Penh are infected with HIV.

CHINA—The number of HIV-infected people grew tenfold from 10,000 people in 1993 to 100,000 in 1995.

UKRAINE—HIV rates among injecting drug users in city of Nikolayev exploded from 1.7% in January 1995 to 56.5% just 11 months later.

HAITI—More than 5% of adults in rural areas and 10% in urban areas are believed to be HIV-infected.

KENYA—In Kenya, rates of infection among sex workers are as high as 80% in Nairobi.

UGANDA—HIV rates range from 40% of adults in some rural areas to 18-25% in urban areas. More than one million Ugandan children have become orphans due to the epidemic.

To obtain future issues of the *IAVI Report*, send your name and address by fax: 212/852-8279; by mail: IAVI, c/o The Rockefeller Foundation, 420 Fifth Avenue, New York, NY 10018, USA; or by e-mail: 103423.355@compuserve.com

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