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AIDS ALERT

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Optimism is growing as researchers move toward an AIDS vaccine

There are plenty of candidates in the pipeline

Researchers are exploring a variety of novel ways to create a vaccine that will prevent HIV-1 infection and offer some therapeutic help to the millions who already are infected.

"Now I think we're at the most optimistic point we've ever been in," says **Margaret I. Johnston**, PhD, assistant director for AIDS Vaccines at the National Institutes of Allergy and Infectious Diseases (NIAID) in Bethesda, MD.

"That's not to say we have the answer in hand, but it's to say that for the first time we have an extremely healthy pipeline of product and more and more encouraging results from animal studies, along with enthusiasm for moving ahead to clinical trials," Johnston explains.

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The AIDS vaccine story

In this issue, *AIDS Alert* takes a look at the latest progress made in developing an AIDS vaccine by talking to some of the world's experts in the field and through coverage of the AIDS Vaccine 2001 conference held in September in Philadelphia. Included in this special coverage is a close-up look at the Phase III clinical trials of AIDSVAX as discussed in a question-and-answer session with renowned AIDS scientist Donald P. Francis, MD, DSc. ■

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The vaccine pipeline has grown from a trickle to more than two dozen candidates, notes **Ashley Haase**, MD, regents' professor and head of the Department of Microbiology at the University of Minnesota in Minneapolis.

"From a pragmatic standpoint, pharmaceutical people have seen increasing hope and promise that something is going to work at least partially," Haase adds.

Researchers are exploring a variety of ways to enhance immune response through vaccines, and the studies are showing promise, says **Larry O. Arthur**, PhD, director of the AIDS Vaccine Program at the Scientific Applications International Corp. (SAIC), which does work for the National Cancer Institute - Frederick Cancer Research and Development Center of Frederick, MD.

"Two years ago, I would have felt there was little or no chance of developing an AIDS vaccine," Arthur says. "Now I think we're developing additional information about ways to get around CD4 cell help."

What's the value of a vaccine?

Some of the biggest obstacles to bringing an effective AIDS vaccine to market are the social and financial barriers, which hamper most efforts to develop a new vaccine, researchers say.

"An AIDS vaccine has an incredible social value for me and you and for the taxes and health insurance we pay, but no one puts that into perspective, because if they did we'd be showered with money from all directions," says **Donald P. Francis**, MD, DSc, president and co-founder of VaxGen Inc. of Brisbane, CA. VaxGen has developed the only HIV vaccine that currently has made it to Phase III clinical trials. **(See Q&A interview with Francis, p. 141.)**

Even when the first vaccine is licensed, it may be decades before it's used and available to everyone who is at risk for HIV infection, says **David Gold**, JD, vice president of policy and public sector support at the International AIDS Vaccine Initiative (IAVI) in New York City.

"Experience with the hepatitis B vaccine shows us that there is still an average 20-year delay before vaccines licensed in industrialized countries are first introduced in developing countries," says Gold. He spoke about the need for a quick and decisive global response to developing an AIDS vaccine at the AIDS Vaccine 2001 Conference, held Sept. 5-8, 2001, in Philadelphia.

IAVI recently announced plans to work with the Uganda Virus Research Institute to develop and test three AIDS vaccines based on HIV subtype A, which is the most common HIV strain in East Africa.

Another example is the smallpox vaccine, which finally did the trick of eliminating smallpox 140 years after its discovery, Francis notes.

"Unless there's something very shocking with HIV, we should be able to eliminate it," Francis says. "Unless I'm wrong, the issue is not going to be science; it's going to be social commitment to make it and ultimately deliver it."

Gold says the international effort to develop and implement an AIDS vaccine requires these kinds of support:

- major governmental financial investment;
- support for tiered pricing that allows developing countries to receive lower vaccine purchase prices;
- incentives for accelerated vaccine research and development;
- regulatory reform to ensure AIDS vaccine trials are not delayed unnecessarily;
- cooperation with private industry to ensure sufficient manufacturing capacity for production of AIDS vaccines.

Although the Bethesda, MD-based National Institutes of Health (NIH) has greatly increased vaccine research funding in recent years, with a projected budget of more than $350 million for fiscal year 2002, there has been very little government support for AIDSVAX, the front-running vaccine candidate, Francis says.

"We have a great collaboration, but it's not like everyone is anxious to put money into an AIDS vaccine," Francis says. "I don't see it."

Part of the problem is that there are so many different approaches to creating an AIDS vaccine that it's difficult for the NIH to choose which research to support, says **Barney S. Graham**, MD, PhD, chief of the Clinical Trials Core and Viral Pathogenesis Laboratory in The Vaccine Research Center of NIAID.

"I think there's a huge commitment, in particular from NIAID and NIH, to see a successful vaccine development process occur, so I don't know so much that the level of funding is restricting what needs to be done," Graham says. "I think the agonizing part is choosing what's the best thing to do rather than there being insufficient funds right now to get done what needs to be done."

One of the most important issues in AIDS vaccine development is safety, because licensed vaccines either contain whole killed versions of the

disease-causing agent or have attenuated virus, Johnston says.

"For HIV, we don't want to make a vaccine that comes from HIV or causes AIDS because it's uniformly deadly," Johnston says.

That means AIDS vaccine research has explored ways to stimulate human immune responses against HIV without directly infecting cells with whole HIV, dead or alive.

All of the vaccines currently being evaluated are safe, so that is the good news about where the world is in developing an AIDS vaccine, Graham says.

"The problem is not safety, but it's immunogenicity and consensus-building about what type of immunogenicity it has and how much of it is needed to have any confidence that your vaccine might work," Graham adds.

Some of the most convincing data in recent years suggest that a vaccine that elicits a strong cytotoxic T-lymphocyte (CTL) response in HIV-negative recipients may provide a good chance of preventing infection and, in some cases, controlling infection, Graham says.

This strategy is being enthusiastically explored by investigators who are working with DNA-type vaccines, such as those based on recombinant DNA type and those that use vectors to deliver vaccine antigen, he adds.

Using canarypox as a vector

For example, some of the new research presented at the recent vaccine conference involved using canarypox, which is lethal to birds, as a nonreplicating vector for delivering an AIDS vaccine. Investigators are focusing on using canarypox as a nonreplicating vector because it is safe, causes no disease in humans, and can accommodate large amounts of foreign DNA.

"The canarypox is engineered to deliver HIV proteins into the cell, and that's all it does," Johnston explains. "The human cell doesn't have the necessary components to make a fully infectious canarypox particle."

One abstract presented data about use of a live genetically engineered recombinant canarypox vector, which expresses HIV subtype E env and B Gag / Pro. Made by Aventis Pasteur of Lyon, France, the canarypox vector (ALVAC-vCP1521) induces CTL activity against HIV Env and Gag vaccine antigens. The CTL activity occurs as early as after the second injection, prior to a protein boost, and researchers concluded that vCP1521 might be a potential phase III vaccine candidate.[1]

Another study of the use of canarypox as a vector found that ALVAC HIV-1 vectors produce anti-env and anti-gag CTL activity after multiple dose administration to normal participants.[2]

Graham says some other interesting research presented at the vaccine conference includes a study of immunization using an SIV replication-incompetent adenovirus vector that elicited a potent T-cell response in a trial involving rhesus macaques.[3]

Investigators at Merck Research Laboratories of West Point, PA, were involved with several other studies of immunization using DNA, DNA-adjuvant, and replication-defective adenovirus vectors. The Merck investigators concluded that the adenoviral vaccine provided the greatest degree of protection against the pathogenic SHIV89.6P virus, suggesting a direction for new vaccine candidates in human clinical trials.[4]

"The diversity of HIV is one of our greatest challenges," Johnston says. "The strategy is to design a vaccine that enables the immune response to recognize the parts of the virus that are the same."

SAIC vaccine research is focusing on developing an inactivated virus vaccine by manipulating the virus until it no longer is infectious, Arthur says.

"It became clear to us that all targets for activation were internal to the virus, so we had the opportunity to inactivate the virus yet preserve the structural integrity and functional activity of the surface proteins," Arthur says.

Using purified, inactivated virus, SAIC investigators are studying the effect of immunization on primates, Arthur adds.

"We've immunized primates and challenged them with SIV, and in the first experiment we showed protection from the challenge," Arthur says. "Then we moved to the second experiment with a more rigorous challenge, and that's ongoing."

The inactivated virus also has potential as a therapeutic vaccine, so SAIC researchers are looking at the monkey model to learn whether they can decrease the amount of SIV in the animals by treating with antiviral drugs and with the inactivated virus vaccine, Arthur says.

Another obstacle to developing an AIDS vaccine that will work in a majority of humans is related to how the virus can take advantage of its host's pre-existing health problems.

It's taken five years for researchers to prove

experimentally that HIV must make use of the cells it finds in order to continue infection, Haase explains. "In the first week of infection, in the resting T-cells, HIV replicates poorly in those cells, but keeps the embers glowing until it gets into the activated T-cells," Haase says. Haase spoke at the AIDS Vaccine 2001 Conference about how lessons from acute infection are relevant to vaccine development.

It's been shown in primate studies that primates with pre-existing inflammatory conditions are rapidly infected when challenged with the virus, Haase says.

"It's my belief that in areas of the world like Thailand, where you have a high rate of heterosexual infection and underlying inflammatory condition, there won't be any vaccine that will work," Haase says. "We need to deal with a virus that can very quickly establish infection when there's a pre-existing inflammatory condition."

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AIDSVAX is safe, but efficacy question remains

VaxGen founder discusses quest for AIDS vaccine

(Editor's note: AIDS Alert *asked* ***Donald P. Francis****, MD, DSc, president and co-founder of VaxGen of Brisbane, CA, to answer questions about his company's phase III clinical trials of AIDSVAX, the AIDS vaccine that is furthest along in development. In the interview below, Francis describes the current status of AIDSVAX and the obstacles that still must be overcome before a successful AIDS vaccine is brought to market. Francis previously has worked as an infectious disease investigator with the Centers for Disease Control and Prevention in Atlanta, and was instrumental in the elimination of smallpox and in the development of a highly efficacious hepatitis B vaccine that is now used worldwide.)*

AIDS Alert: In the AIDSVAX Phase III efficacy trial in North America and The Netherlands, what are the chief results?

Francis: There are no results yet on efficacy because the study is blinded. But there were many hurdles that we had to overcome to get where we are, and many people said it wasn't possible to accomplish a phase III trial. The hurdles were the issues of getting regulatory approval, getting ethical approval, finding recruiting sites that were interested in doing this study, and finding HIV-negative volunteers — by and large gay men and at-risk heterosexual women. Another concern was retention. If you did get them in the study, would they stay in for three years? Oh, and there were a couple of other pieces that were important from an ethical standpoint, and that related to whether people coming into the study, despite counseling, would assume they were protected by the vaccine and increase their risk behavior, ultimately becoming harmed by joining the study. That was a potential infection harm.

The other potential harm that was at least discussed was social harm; the fear, for instance, that volunteers would falsely test positive in an HIV test for insurance purposes. We also knew from phase II studies that a couple of volunteers told the wrong people that they were participating in the trials and their bosses found out. Since this is a highly publicized trial, if you're a male, you're likely to be identified as a gay man. For some people, that could create a problem with their employer and others, so there were potential social harms and concerns.

Then there is always the potential issue of medical harm. We had already given the vaccine to about 1,000 people, and there were no adverse effects. But now we were moving up to a 5,000-person trial, with two-thirds of them getting vaccine. So far, everything had gone remarkably well, though it was arduous getting all of the approvals: IRB approvals, regulatory approval . . . The FDA actually was very positive. All that was done with significant effort, but certainly it was accomplished.

By the time we stopped recruiting, people were volunteering at a rate that could have filled the whole trial in about two months — that many people were coming in. We only wanted 5,000 people, though, because 10,000 would increase expenses and statistically wouldn't be worth it. The volunteer retention has been terrific. We have 95% of the people who joined the study still in it.

Regarding the other questions of harm and social harm: We monitor behavior and now know that individuals are not increasing their risk behavior during the trial, especially in Thailand, where there essentially is a decrease overall. And the social harms have been minimal.

I volunteered for the phase I study, and I was surprised at my family's reaction. It's traditional for a vaccinologist to volunteer for the study, but I can't say there was a wonderful reception from all my family members. So it is interesting who you tell and the reaction of people.

Finally, the Data and Safety Monitoring Board [DSMB] has met five times to review data from the combined Thai and North American / European group specifically to look at safety. They ask very specific questions about harm: Do people who get vaccinated then get infected? Do they have a worsening of their disease? Is their viral load a little higher? Are there any other side effects? Is there something else that you didn't expect?

With a placebo-controlled trial, you get wonderful answers. What is the incidence of cancer, heart attacks, or whatever it might be, in the vaccine group compared to the placebo group? You get a very good estimate of the potential side effects. Frankly, we can tell there is nothing. So few serious things have happened to people — there's no cluster. So the safety reviews have been excellent.

All of those things are huge accomplishments. I guess, parenthetically, the question is, can you raise money to do it all?

I always say, in general, vaccines are given very low social value in society, and I think vaccines are terribly undervalued in the AIDS community. Prevention with a vaccine is the only way you're going to prevent HIV infection. You can try to prevent risk behavior, fine, but we know the limits of that.

I think only recently . . . now that an estimated 30% of the people in Botswana, for instance, are infected with HIV . . . do you hear people say a vaccine is important. If you're going to stimulate a business, you have to have a profit and motive, and frankly, in our society, you get a lot more kudos and money to make therapeutic drugs or heart and lung transplants then you do to prevent smoking, for example.

AIDS Alert: Your study about AIDSVAX presented at the recent vaccine conference says there has been no acceleration of disease associated with vaccine receipt in those infected post-vaccination. What percentage of volunteers have been infected post-vaccination, and do you have any data yet comparing the infection rate of the control group with the AIDSVAX group?

Francis: We specifically asked the DSMB to examine the data for any potential indication, however unlikely, that the vaccine conferred some sort of advantage to the virus. In each of the DSMB's five safety reviews, the answer was "no."

In answer to your questions, the first time the DSMB will look at the study data to evaluate the number of infections in the placebo group, compared to the number of infections in the vaccinated group, is when they conduct their interim efficacy analysis later this year. So we don't know the answers yet.

The study was designed to detect efficacy based on an estimated annual infection rate of 1.5%. What we do know from the DSMB is that the infection rate of the study population is at least that high, so we're certain that we'll have conclusive results regarding efficacy by the end of the study, either later this year or next year.

AIDS Alert: Where does this Phase III trial head next?

Francis: It's a full three-year study; everyone is to be in for three years. The North American / European study is scheduled to conclude at the end of 2002, and we will have an interim analysis one year before, so it is coming up at the end of this year. We have analyses by the DSMB every six months, but that's just for safety.

The FDA has set a very high hurdle to stop the interim analysis. If it's highly efficacious, we'll stop; otherwise it will be continued for the full time. If you have an observed number, like a poll for intervention for terrorists, and the poll says 80% of the people support intervention, plus or minus 5%, those are the confidence limits — plus or minus 5%. In this study, the FDA said if the minus part of that plus or minus, if that lower bound of efficacy at the P = .03 level — which means 97% confidence — exceeds 30%, then they will stop the trial. It will mean the observed levels will have to be well in excess of 60% efficacy

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Giving away HIV drugs is not as easy as it seems

Drug company runs into snags

When officials with a German pharmaceutical firm announced in July 2000 that the company would make its HIV antiretroviral drug nevirapine (Viramune) available to any pregnant women in sub-Saharan Africa who need it for the prevention of mother-to-child transmission (MTCT) of HIV, they thought their biggest problem would be to meet the flood of demand.

They were wrong.

"When we began, we thought our supply chain would be overwhelmed by the number of requests," says **John Wecker**, PhD, an HIV specialist and coordinator of HIV activities in the developing world for Boehringer Ingelheim of Ingelheim, Germany.

"What happened was that in the end it turned out we've given away very little drug to date, although it is increasing," Wecker says. "The major obstacle has been the lack of quality health care capacity within most of these developing countries."

Boehringer Ingelheim's experiences can serve as both a model for and a lesson to other drug manufacturers who plan to make HIV medications available at no or very low cost to the developing nations hit hardest by the pandemic.

"Preventing mother-to-child transmission is not just having the drugs available; it's much more," says **Dirk Buyse**, MD, international program officer for the Elizabeth Glaser Pediatric AIDS Foundation in Washington, DC.

"The essential components are, first, to have voluntary testing and counseling on HIV and MTCT," Buyse says. "When you look at an MTCT program, the cost of the drug component is less than 5% of the total budget of the MTCT program."

Programs that seek to prevent MTCT also could serve as models and leaders for future HIV antiretroviral therapy treatment in the developing world, says **Connie Osborne**, MB.Ch.B, the MTCT voluntary counseling and testing focal point for UNAIDS in Geneva, Switzerland. **(See story on prevention of MTCT in sub-Saharan Africa, p. 144.)**

"Initially, we were overly enthusiastic and we thought countries would just jump at it, but MTCT programs in developing countries are relatively new," Osborne says.

Now as more pregnant women are being reached through the programs that will distribute free nevirapine, perhaps the next step will be to provide follow-up care to these women so they might also receive antiretroviral therapy, Osborne says.

UNAIDS is promoting such an extension of MTCT prevention programs through its new MTC Plus initiative, which advocates drugs for the treatment of mothers who are living with HIV. This may also help slow the sub-Saharan region's tremendous growth in orphans.

But none of these programs are cheap or easy, as Boehringer Ingelheim has learned.

In the case of providing nevirapine, an economic analysis by Boehringer Ingelheim and the German government showed that to prevent MTCT in Uganda, Kenya, and Tanzania, the value of the drug represented only 1.2% of the total investment needed to establish MTCT programs, Wecker says.

The other expenses come from identifying, hiring, and training counselors; making physical/medical services available; providing necessary transportation and information to bring pregnant women into the health care system; providing women with antenatal care; providing nevirapine therapy; and providing quality postnatal care, Wecker says.

Then there's the issue of infant feeding: Is it safer for women to nurse their babies, even when there's the potential for transmitting HIV, or do women have clean water available with which to mix infant formula?

However, as Boehringer Ingelheim officials learned, the key is to take what little infrastructure is available and work with it.

The German pharmaceutical company has begun to work with nongovernmental organizations (NGOs), physicians, charitable organizations, and others who directly provide health care services to the poor in developing nations. Also, the company hired Axios International of Dublin, Ireland, to organize the distribution of nevirapine to sub-Saharan Africa.

"When we went to the NGO level, we heard that the number of applications for the drug will begin to increase dramatically," Wecker says. "And so that's one thing Axios will do for us: Help us manage the sheer load of applications we're hoping to get."

Axios will ensure that the requests for nevirapine match the organization's ability to distribute the drug, says **Joseph Saba**, MD, chief executive officer of Axios.

"We basically open the dialogue in programs, discuss ethical issues, and make sure we're comfortable that these programs have established an infrastructure and will be able to implement what they say they can implement," Saba explains.

"Many of these programs have a good idea and are well thought through," Saba adds. "But some of them are coming from people who have their hearts in the right place and want to do something, but they don't have experience in calculating doses correctly."

There have been examples of programs in a country where the HIV prevalence rate is 6% that made a forecast of needing 20,000 doses of nevirapine. Then when the situation was further explored, it was discovered that the program really could only handle 800 doses at the start, Saba says.

"We don't want drugs expiring on the shelves," Saba adds.

The logistics of distributing even a simple therapy of nevirapine can be difficult. The therapy to prevent MTCT of HIV involves giving the pregnant woman one 200 mg tablet during labor, followed by a less than one milliliter of suspension drug given to the infant within 72 hours after birth, Wecker says.

But here is where such simple therapy for an affluent nation becomes complicated for a poor country: The pregnant woman may see a physician at some point before her due date, but there is little guarantee that the woman will return to the same clinic when she is in labor, Saba says.

Further complications involve the fact that only an estimated 5% to 10% of pregnant women in sub-Saharan Africa and other parts of the developing world know whether they are HIV-positive, and their clinicians have no fast way to discover their serostatus as the women go into labor. This means that for a drug giveaway program to prevent MTCT successfully, it would need to include testing and counseling facilities for pregnant women.

"They would need to hire counselors and very simply have a private room where the counselor can sit down with the women and discuss HIV and testing, and then, with HIV-positive women, explain to them what it means to be HIV-positive and how they can get help," Saba says.

Now, more than a year since beginning the program, Boehringer Ingelheim is making progress in distributing the drug to pregnant women. So far there are 19 projects in 12 countries that are part of the Viramune Donation Program for the prevention of MTCT, and these projects have ordered enough drug to treat 49,800 mother-child pairs. The countries involved include Congo Brazzaville, Ghana, Guyana, Kenya, Namibia, Nigeria, Rwanda, Senegal, Sierra Leone, Uganda, Zambia, and Zimbabwe.

Wecker's advice to other pharmaceutical companies offering free or deeply discounted antiretroviral drugs to poor nations is to anticipate these types of infrastructure problems before starting the program.

"You can't underestimate the lack of health care capacity," Wecker says. "Whenever you set your goals, you have to take into consideration the realism and the reality of what's there and what's not there." ■

MTCT programs work in a variety of ways

UNAIDS, others working to help pregnant women

While mother-to-child transmission (MTCT) of HIV has been reduced to very small numbers in the United States and Europe, more than 1,600 children still become infected with HIV each day, mostly in sub-Saharan Africa, where an estimated 46% of pregnant women are infected with HIV.

Besides free drug programs to prevent MTCT, there have been efforts made by UNAIDS of Geneva, Switzerland, the Elizabeth Glaser Pediatric AIDS Foundation in Washington, DC, and others to combat this problem.

Here are brief looks at how some of the programs work:

• **Call to Action project:** Initiated by the Elizabeth Glaser Pediatric AIDS Foundation in September of 1999 to reduce MTCT of HIV in the developing world, this project allows international health care sites to apply for funding that is used to start MTCT prevention programs.

The project supports prevention programs that use proven antiretroviral regimens to reduce MTCT, including zidovudine (AZT) alone, zidovudine and 3TC (Combivir), and nevirapine (Viramune).

As of June 2001, 350 health care workers were trained as part of the Call to Action project, and 18,000 women had been reached with counseling. Of these women, 14,000 agreed to be tested and 2,100 were found to be HIV-positive. A total of 1,248 or 58% received nevirapine to reduce MTCT.

The project's future goals include providing all mothers with access to voluntary counseling and offering access to care to HIV-infected mothers so they may protect their own health, as well as the health of their families.

"Care and support for the HIV-infected mothers and for infants who are infected despite intervention is extremely important," says **Dirk Buyse**, MD, international program officer for the Elizabeth Glaser Pediatric AIDS Foundation.

Entry points for comprehensive care

"I think, and this is something that we have been advocating, that these MTCT programs might be entry points for more comprehensive care and treatment programs later on," Buyse says. "These are a whole group of people who know their HIV status and will need care and support, and that's very important when you look at the issue of orphans."

• **Accelerating Access Initiative:** UNAIDS has encouraged competition between pharmaceutical companies to provide antiretroviral drugs at a reduced cost to poor nations.

At present, less than 10% of the HIV-infected people in developing countries have access to antiretroviral therapy. Of the estimated 25 million people infected with HIV in Africa, only 10,000 to 25,000 receive antiretroviral therapy. UNAIDS has been working to change this dire situation through its Accelerating Access Initiative, which has helped bring down some prices.

Drugs are 'cheaper than they used to be'

"The drugs now are very expensive for the majority of people, but they are much cheaper than they used to be," says **Connie Osborne**, MB.Ch.B, the MTCT voluntary counseling and testing focal point for UNAIDS.

"In Africa, they have about 13 countries that are in the Accelerating Access Initiative," Osborne says. "Because the prices are coming down, there are other people who are getting on board with the program."

• **MTC Plus:** MTC Plus is a new program that UNAIDS would like to begin as a pilot project in 10 low-income countries that have not yet been selected but probably will include nations in Africa, the Caribbean, and Asia. UNAIDS has begun the program as an extension of MTCT prevention therapy. Rather than stopping treatment with the single dose given to mothers during labor, MTCT programs could extend treatment to mothers after they give birth.

This continuation of treatment could help prevent MTCT during breast-feeding and keep the mothers alive, Osborne says. ■

Special Report: Caribbean HIV Epidemic

Caribbean plays catch-up in HIV prevention efforts

Efforts focus on education, cultural issues

(Editor's note: This is the second part of an occasional series about the AIDS epidemic in the Caribbean. The May 2001 issue of AIDS Alert *featured a story about the new Pan-Caribbean Partnership and a story about the factors driving the HIV epidemic in this region of the world.)*

HIV prevalence remains high in many Caribbean nations as testimony to early mistakes made by governments that did not fully appreciate and respond to the threat the epidemic posed.

The Caribbean has one of the highest rates of

new AIDS cases among women in the Western hemisphere, which is partially a result of Caribbean women having little power to negotiate safe-sex practices. High rates of sexually transmitted diseases (STDs) also help fuel the epidemic. Meanwhile, many Caribbean governments and religious leaders have made it difficult for HIV prevention efforts to provide honest, useful information about how youths, women, and others can avoid HIV infection.

Under the guidance of a new partnership in the region, the Pan-Caribbean Partnership, officials with UNAIDS and other nongovernmental organizations hope the region's nations will devote more time and money to preventing HIV infection, particularly among youths.

'In-country action' emphasized

"What we want to see happen has to be translated into in-country action," says **Ruben F. del Prado**, MD, MPH, acting team leader for the Caribbean and UNAIDS Intercountry Programme Advisor & Technical Network Development for the Caribbean in Trinidad and Tobago, West Indies.

"Prime ministers go and sign all sorts of agreements, but it's what they do when they go back to their country that matters, and ministers of finance are extremely important because funding is needed," del Prado says.

The strategies of UNAIDS in the Caribbean are driven by priorities set in the "Regional Strategic Plan on HIV / AIDS (2000-2005)," prepared by the Caribbean Task Force on HIV / AIDS. The plan's strategies cover these areas: political commitment and action; greater involvement of people living with HIV / AIDS; national strategic planning for HIV / AIDS; resource mobilization and addressing vulnerable populations, including youths; government capacity building; prevention of mother-to-child transmission of HIV; and access to treatment.

"Good public health is stifled in most of the Caribbean by a lack of resources, and not in the least by rampant hypocrisy when it comes to human sexuality," del Prado says. "The age of initiation of sexual intercourse is declining significantly and is initiated in the majority of cases by the same older men and women who oppose honest and open discussion on sexuality in schools."

Other problems fueling the epidemic are the rising sex tourism trade, the taboo on masturbation, and the fact that male-to-male sexuality is a criminal offense.

Nonetheless, international organizations and Caribbean governments are putting more resources into prevention programs. Here's a brief look at some of the prevention efforts and plans in the Caribbean:

Youths learn about HIV

- **Health and family life education:** The Health and Family Life Education initiative is a partnership of more than 10 organizations. It provides a proactive approach to the epidemic through prevention education directed at young people. Educators teach students skills, values, attitudes, and knowledge about HIV, sexual health, substance abuse, environmental health, safety, and nutrition. Role-playing is one of the classroom techniques designed to promote behavior change.
- **Training health care workers:** The University of the West Indies, which has campuses in Jamaica, Trinidad, and Barbados, has plans to implement a long-term effort to expand the skills base of health care workers. The university's medical school has a new program that offers post-graduate research and training in the medical aspects of HIV / AIDS, prevention approaches, public health relations, and economics.

  The medical school will design new modules at medical undergraduate and postgraduate level in HIV / AIDS / STD diagnosis and management for nurses and physicians, and the university's department of psychology will develop a course on behavioral modification for risk reduction.

  Also, the university will support a special course for journalists on HIV / AIDS.
- **Suriname:** A former Dutch territory, Suriname has integrated sexual education into its school system. The country is different from most of its Caribbean neighbors in that it has fewer taboos surrounding sexuality, and homosexuality is not criminalized, del Prado says.

  "The overall stigma surrounding HIV / AIDS is much less than in most of the rest of the Caribbean," del Prado says.

  However, the country has suffered severe setbacks in its national HIV / AIDS prevention and control efforts because of a reduction in financial support to the National AIDS Programme in the late 1990's, del Prado says.

  With limited resources, the program has maintained and improved a level of general HIV / AIDS awareness nationwide, he says. ■

(Continued from page 142)

before we stop. And I mean solid efficacy.

This is very common. I did the phase III study of the hepatitis B vaccine. We had two interim analyses and were told in both of them to "carry on," meaning that we had not yet eliminated the statistical fog. That vaccine was later proven to be very highly efficacious. We always conduct these interim analyses, because if it's a 100% efficacious vaccine, there's no reason to carry on with the trial. But if the confidence levels are too broad, then what is the true efficacy? Suppose I tell you the vaccine is 40% efficacious, plus or minus 40%. You don't know whether it's zero or 80%. With time, that may change to 40% plus or minus 10%, and then you can say it really is 40%. It's a matter of confidence of your measurement that the DSMB statisticians will rely on. Nobody wants to have a vaccine with a gray endpoint. You want to know what it is, and if it needs another year of follow-up, it's sure worth it.

AIDS Alert: What are you seeing so far from the Thailand trial, and are there any striking differences between this trial and the North American / Netherlands trial?

Francis: The Thai trial is a test of injection drug users, so there are differences in reported things that happen to volunteers. The primary serious adverse event in Thailand is drug overdose. Interestingly, though, the DSMB reports that we're not seeing the usual rate of infection in this group, although we expect there will be enough infections in the placebo group to determine efficacy. When we ask people why they volunteer in North America and why they volunteer in Thailand, in both countries it's altruism for most of them. They say it's to get a solution to the AIDS epidemic.

The retention of volunteers in Thailand has been at least as good — if not better — among IV drug users as compared to gay men in the U.S. They're eight months behind and are running 2% higher right now in follow-up rates compared to the North American / European trial. So in eight more months, they'll probably be about the same. But I'm really impressed; the clinics and volunteers there are just as committed.

AIDS Alert: How optimistic should HIV clinicians and others be about AIDSVAX accomplishing its primary purpose of preventing HIV infection? Could you predict when a vaccine might be brought to market, either here or overseas?

Francis: It's a good question. No one knows what the efficacy of the vaccine is. This vaccine was 100% efficacious in preventing chimpanzees from getting HIV infection, and that's good because that was a huge viral dose. It was truly preventing HIV-1 in chimps, and those were 100% infectious doses. Most people who get infected through sexual exposure or even IV drug sharing have a risk of one in 1,000 per exposure of getting infected; those chimps had a risk of 100%, because we saw to it they got that amount of virus. So I'm very optimistic the vaccine will work.

What you do then is you have to balance what the chimpanzee results mean. We only challenged with two viruses that were available for a chimp challenge, and then we did the challenge a few weeks after their last dose of vaccine. And although it was 100% effective in preventing chimp infection, how broadly and how long will it prevent infection in the world? I don't know.

There are so many different subtypes and strains of HIV that strain variation is what worries me most. HIV has a variability that may outsmart a vaccine tested against two strains. But to think we understand this virus is the ultimate arrogance. It's not until you go out there and really do a vaccine trial that you find out if it will work or not. And that's the reality of research — you have to let nature tell you how good you are, and nature can be harsh.

If we had success early on, we still don't think we could get large-scale production out there until early 2004. If we have a successful vaccine, I think we'll have all the forces of humankind and money to get it done. ■

North Carolina clinic employs holistic approach

Care includes nutritionist, psych assessment

HIV physicians have stayed busy in the last decade just keeping up with the latest treatment and pharmaceutical advances that will keep their patients alive. But when clinicians focus entirely on HIV patients' medical treatment, they might be missing the big picture, according to one long-time HIV physician.

"Having treated HIV patients for well over 15

years, I recognize that certain aspects of care were glossed over," says **Joseph G. Jemsek**, MD, of the Jemsek Clinic in Huntersville, NC. "And when these aspects are glossed over long enough, they become very important in terms of the patient's well-being and satisfaction with care."

Jemsek refers to aspects of care involving social issues, nutritional counseling, physical therapy needs, and psychological assessment.

Before Jemsek opened his own clinic for the holistic treatment of HIV patients, he relied on other clinicians to take care of his patients' ancillary needs, although he was never satisfied that this patchwork of services was in his clients' best interest.

"Since HIV is such a complex illness with multiple systems involved and very heavy psychosocial issues, I felt the only way to do a satisfactory job was to coordinate all these elements of care under one roof," Jemsek says.

The clinic, which is close to a year and a half old, now has more than 400 patients, with a growth rate of eight to 15 new patients per month.

Here are some of the disciplines and services provided by the clinic in the interest of treating the patient holistically:

• **Nutritionist:** Jemsek Clinic has a registered dietitian who discusses nutritional and dietary supplement information with HIV patients. The dietitian stays up to date on herbal compound research.

"We're open to what herbal compounds people are taking, but we want to make sure there's no harm in them," Jemsek says.

The clinic also has bought a Dexa machine, manufactured by GE Medical Systems of Milwaukee, which can analyze segments of a patient's body and give measurements of fat and body cell mass.

"It's an expensive investment, but with the possibility of lipodystrophy and lipoatrophy, this procedure is proving very helpful in terms of designing therapies for our patients," Jemsek says.

With the machine's data, Jemsek and the nutritionist can determine which nutritional and anabolic therapies would be best for a particular patient.

• **Neurological testing:** Working with a physiatrist, the clinic can offer patients neurological testing when the patient has insurance that will cover the service. The clinic occasionally will provide the testing at no charge to Medicare or Medicaid patients who are not covered for the service.

"This will allow us to give objective measurements of a predominantly sensor distal neuropathy associated with HIV itself and with more commonly used potent nucleosides: DDI and D4T and DDC," Jemsek says.

"I've treated some patients in the past with drugs, and their neuropathies have improved because we've improved their disease," he notes. "Other patients have had early, dramatic, and painful neuropathy after a couple of weeks on the drugs."

The physiatrist will analyze a patient's neurological tests, which are conducted by a technician.

• **Clinical research nurse:** The clinic's nursing staff includes a dedicated clinical research nurse. This position is in addition to several other nurses and two physician assistants.

Tracking developments in HIV medicine

Because scientific advances related to HIV and AIDS have been rapid and often crucial to providing the best quality of care to patients, the research position is essential and probably will be expanded to include a part-time research nurse, Jemsek says.

"I think HIV medicine is generating more information and changing faster than any other field in medicine," Jemsek says. "It's fascinating and captivates the imagination, and if you don't stay involved with it from week to week, you do lose ground."

• **Counselor:** The clinic used to have an ordained minister provide once-a-week counseling services for patients. The minister, who was HIV-positive, was a real asset to the group, Jemsek says. Now that the minister is no longer available, Jemsek is looking to replace him with a person who has similar counseling experience and background.

In order to ensure the position will remain permanent, the clinic is establishing a tax-exempt foundation with the goal of raising enough money to cover the counselor's part-time salary. Jemsek says he hopes to hire a counselor who will work in the clinic three times a week, which will allow the counselor to see more patients than the previous counselor did.

• **Psychological assessment:** Depression is a normal consequence of HIV disease, and clinicians need to assess for this and help patients adjust to these changes in their lives.

Jemsek and staff advise patients not to allow themselves to be overwhelmed by HIV facts. They recommend that patients call local AIDS service organizations or a counselor or close friend to discuss their feelings and fears.

"You'll find some people will reject you, and others will embrace you more," Jemsek says. "You only need a few friends, and you don't need the whole world to understand your situation."

Jemsek typically asks patients two or three times during a visit if there is anything else they would like to discuss, something from their own agenda. This lets patients know Jemsek is open to hearing about their thoughts and feelings.

Although AIDS no longer carries a relatively quick death sentence, there still are emotional and psychological issues that HIV / AIDS patients must address. "We don't have quite the depths of depression and hysteria we've had in past years," Jemsek notes. "Nonetheless, it's a lifetime illness, and people go through a series of steps with this."

• **Cultural sensitivity:** As the epidemic evolves, clinicians need to be more sensitive to issues that relate to women and minorities with HIV or AIDS.

"I started noticing two to three years ago that, without exception, the heterosexual, non-drug-user women who came into see us had no idea that they were at risk for HIV," Jemsek says. "They were not sexually promiscuous, with generally no more than two or three partners."

Now women account for 30% of the Jemsek Clinic's patient census. With this change in demographics, Jemsek and staff have had to learn how to counsel women to take greater charge of their lives by saying "No" when they are uncomfortable and how to stop feeling ashamed of their illness.

"They say they feel dirty and feel ashamed, and they need to know that in a great sense they are blameless," Jemsek says. "They haven't done anything knowingly to put themselves into this situation, and they haven't done anything for which they should be criticized by society."

Jemsek admits that he had to undergo a personal cultural change in attitude during the early years of AIDS, when most of his patients were white homosexuals.

"I was a heterosexual Midwestern homophobic whose curiosity and commitment to medicine overcame that when I became involved with my new clientele in the early 1980s," Jemsek says. "What working with HIV patients has taught me is compassion, and I learned how to be a better doctor because I became more involved with my patients."

Likewise, the clinic's staff have been taught to be sensitive to issues that relate to minority patients. For example, some of the clinic's African-American patients believe that the AIDS epidemic was caused by U.S. government actions. While staff are willing to listen to patients' concerns, they insist that the patients focus on the present and what can be done to help them cope with their disease.

"If someone wants to come see us, it's time to get real with what's going on," Jemsek says. "Otherwise, it's a waste of time." ■

Mathematical model offers clues to Africa epidemic

European bubonic plague could be a clue

It's been known for some time that certain people of European descent have a mutation on their CCR5 coreceptor molecule, and people who have two copies of this mutation appear to be completely protected against HIV infection.

About 1% of people of European or Caucasian descent have both copies of the mutation, while about 19% have one copy of the mutation, which typically results in a slower progression to AIDS among those who are HIV-infected.

However, people of African or Asian descent have neither of these mutations, which has led researchers to theorize that the mutation is the result of some long-ago viral epidemic that never made its way to Asia or Africa. That has resulted in the theory that the mutation in some way is related to the bubonic plague, which appeared some 600 years ago in Europe.

Michigan researchers have designed a mathematical model that may provide one explanation for why HIV has spread so much more rapidly among heterosexuals in Africa than it has in the United States or Europe.

"We wondered if we could explain the severity of the epidemic in Africa," says **Denise Kirschner**, PhD, an associate professor in microbiology and immunology at the University of Michigan Medical School in Ann Arbor, MI.

Economic factors, inadequate or missing health infrastructures, high levels of sexually transmitted diseases, and too few prevention efforts are all thought to be contributing factors to Africa's AIDS pandemic. But even when considering these economic and social differences, sub-Saharan Africa's estimated 20% HIV infection rate is incredibly high.[1]

"A lot of people come up with different explanations about why the epidemic is so bad in Africa," Kirschner adds. "We wondered if something more uniformly distributed throughout the population would affect it, and our model showed that it could."

The model, which mimicked a heterosexual epidemic, compared the rate of HIV transmission in two populations. One population had no mutations on the CCR5 gene, and the second group had mostly normal plus some heterozygous and homozygous CCR5 mutations.

With data provided by UNAIDS of Geneva, Switzerland, the model used demographic data and initial values for infection from surveys conducted in Botswana, Zimbabwe, and Malawi. The model showed how HIV might have spread if the sub-Saharan population contained mutations of the CCR5 gene, Kirschner says.

"We'd see much lower prevalence incidences in Africa if they did have the mutation," says Kirschner.

It's possible that if the mutations were present in sub-Saharan Africa, it might have lowered HIV prevalence there by as much as one-third, she adds.

The study indicates that the overall model predictions are consistent for a wide range of transmission and progression rates. Investigators assumed that lower viral loads correlate with reduced infectivity, which would mean that a population's proportion of heterozygotes, who are assumed to have reduced viral load, would have a major influence on disease spread.

Investigators considered two possible scenarios of how the presence of heterozygotes of the CCR5 mutation might affect the spread of HIV. In one scenario, the single mutation might exacerbate the epidemic because individuals with it would spend more time in the sexually active population, spreading the virus to others; in the other scenario, the single mutation might lower the viral loads of those who are infected with HIV and therefore decrease the probability of infection. The study's results suggest that the heterozygote mutation reduces transmission of the epidemic due to reduced viral loads.

"In the end, we could ask the question of how long would it take to select for this protective CCR5 allele in Africa, given we introduced it 50 years ago, and it would take 1,200 years in our model," Kirschner says. "That means HIV likely is a very recently introduced virus into the African population."

In other words, it would take the population of Africa about 1,200 years of battling HIV infection to reach a level of 1% of the population having two of the CCR5 mutations and 19% of the population having one of the CCR5 mutations.

Reference

1. Sullivan AD, Wigginton J, Kirschner D. The coreceptor mutation CCR5 32 influences the dynamics of HIV epidemics and is selected for by HIV. *Proc Nat Acad Sci* 2001; 98:10214-10219. ■

Antibody-based drug could hinder progression

Research points to potential of this approach

No matter how far-reaching a viral epidemic is, some people don't become infected when exposed to the virus, and this may be due to their innate immunity. Researchers who are studying how and why this happens are paving the way for creation of an antibody-based medication that will prevent or slow the progression of HIV to AIDS.

"The idea is that there are certain species-specific innate characteristics of immunologic system materials which allow for a spontaneous control of infectious diseases," says **Toby C. Rodman**, PhD, professor emeritus at Cornell University Medical Center and an HIV researcher in New York City. Rodman's research into innate immunity and HIV infection receives grant funding from The Institute for Human Genetics and Biochemistry of Geneva, Switzerland.

Rodman and colleagues, who published their results in the August issue of *Experimental Hematology*, have used human umbilical cord blood to obtain monoclonal antibody secreting cells. They've identified these cells as innate human immune system factors with specific disease-resistant characteristics.

"One idea is there must be antibodies that are reactive with certain infectious agents, certain proteins, or infectious agents, and those antibodies are capable of exerting a certain amount of protection," Rodman says.

Specifically, the investigators found evidence that IgM antibodies that are specifically reactive with the HIV Tat protein are innate human immune factors, and these are capable of restricting certain mechanisms of HIV pathogenicity attributed to the Tat protein.

"I looked at a series of specimens taken from HIV-positive people and found those antibodies that maintained constant titer in [HIV-negative] people declined after infection of HIV," Rodman says.

Then investigators showed that the same IgM antibodies inhibited a well-defined pathogenic activity of the Tat protein, which kills many different kinds of cells, but particularly CD4 T-cells.

"We showed in vitro that these antibodies that were in circulating blood of HIV-negative people could inhibit the decline of CD4 T-cells in HIV-positive people," Rodman says. "Finally, we showed that the cells that make these antibodies are present in cord blood, so they're definitely innate antibodies."

Since the study was published, there has been a great deal of interest in the potential commercial use of the findings, Rodman says.

For example, scientists might be able to develop a way to use human umbilical cord blood to isolate cells for the production of human monoclonal antibodies that would be used therapeutically.

Rodman says the model has a strong potential for efficacy, with little obvious potential for side effects. ■

FDA notifications

In vitro drug resistance genotype assays

(Editor's note: Beginning in this issue, AIDS Alert *will print HIV drug notices and other information issued by the Food and Drug Administration.)*

In September 2001, the Food and Drug Administration (FDA) released a notice of draft guidance for industry with pre-market notifications for in vitro HIV drug resistance genotype assays.

The guidance is available on the Internet at this address: www.fda.gov/OHRMS/DOCKETS/98fr/010286gd.pdf.

An HIV Drug Resistance Genotype Assay is an in vitro diagnostic device intended for clinical laboratories to use in detecting HIV genomic mutations that confer resistance to specific antiretroviral drugs, as an aid in monitoring and treating HIV infection.

The FDA Center for Biologics Evaluation and Research (CBER) has issued this draft guidance to help manufacturers and sponsors of HIV Drug Resistance Assays comply with the requirement of special controls for class II devices, if the HIV Drug Resistance Assay devices are reclassified from Class III.

Devices must comply with guidance

Designation of this guidance document as a special control would mean that sponsors and manufacturers must establish that their device complies with either the specific recommendations of this guidance or some alternative control that provides equivalent assurances of safety and effectiveness [§513(f) (21 U.S.C 360c(f)]. The guidance is intended to help ensure the production of standardized, reliable, and reproducible tests for detecting HIV mutations known to be associated with HIV drug resistance.

This draft document is being distributed for comment only, and is not intended for implementation at this time.

Interested people may submit written comments on the document to: Dockets Management Branch (HFA-305) Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Comments may also be submitted electronically to www.fda.gov/dockets/ecomments.

Submit written or electronic comments by Oct. 29, 2001, to ensure consideration in preparation of the final document. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments should be identified with docket number 01D-0286. For further information, contact: Nathaniel L. Geary, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. Telephone: (301) 827-6210.

FDA/CBER guidance documents are on the web at www.fda.gov/cber/guidelines.htm. ■

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After reading this issue of *AIDS Alert*, CE participants should be able to:

- identify the particular clinical, legal, or scientific issues related to AIDS patient care;
- describe how those issues affect nurses, physicians, hospitals, clinics, or the health care industry in general;
- cite practical solutions to the problems associated with those issues, based on overall expert guidelines from the Centers for Disease Control and Prevention or other authorities and/or based on independent recommendations from specific clinicians at individual institutions. ■

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Dear Readers:

We at *AIDS Alert* would like to take the time to thank you for your support in the last year. We, along with our excellent editorial advisory board, strive to bring you the best, most useful newsletter each month that we possibly can.

Over the last year, here are some of the special features included in *AIDS Alert*:

- Comprehensive coverage of the Conference on Retroviruses and Opportunistic Infections
- Insights into the international struggle to control HIV and AIDS
- Practical, plain-English information in our "Common Sense About AIDS," which you can copy and provide directly to patients
- Coverage of the ongoing effort to develop an effective vaccine
- The latest clinical developments

As we approach 2002, you can look forward to 12 more issues of incisive, up-to-date coverage of developments in the fight against HIV/AIDS. We will continue to add "extras" that make your newsletter subscription an even greater value. And, especially for 2002, look for the introduction of an *AIDS Alert* web site exclusive to newsletter subscribers.

Our most important tool in keeping *AIDS Alert* relevant to your needs, as always, is the feedback that you give to us. Thank you to all who filled out and returned to us a reader survey or CME survey. This helps us a great deal. We'd like to hear about the issues that are important to you so that we can provide the most relevant information to help you, as a clinician, do a better job. Please direct your comments to Glen Harris, Editorial Group Head, at glen.harris@ahcpub.com, or call him directly at (404) 262-5461.

Thank you again for your support.

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