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PEPFAR funds not being used efficiently to prevent HIV epidemic, say critics

Money has too many political stipulations

The, United States has spent hundreds of millions of dollars on HIV prevention around the world, but the rules surrounding the money have made the prevention efforts far less efficient than desirable, critics say.

The US President's Emergency Plan for AIDS Relief (PEPFAR), which was first authorized in 2004, is due to be reauthorized by Congress this year. But before it is, many changes should be made, says **Serra Sippel**, acting executive director of the Center for Health and Gender Equities (CHANGE) in Tacoma Park, MD.

First, Congress should eliminate the abstinence earmark in the bill, Sippel says.

"Congress imposed a requirement that one-third of prevention funding has to go to abstinence, and that earmark should be eliminated in the new law," Sippel says.

"The earmark doesn't mean that no US money can ever be used for distributing condoms, but what Congress did was say that one-third of prevention funding has to be for abstinence until marriage programs," Sippel explains.

Such funding stipulations are rhetoric, not truth about the epidemic, says the **Rev. William G. Sinkford**, president of the Unitarian Universalist Association of Congregations in the United States. Sinkford spoke at a World AIDS Day event media conference about PEPFAR.

"The truth is that HIV/AIDS is most often spread through sexual contact, and because sex is involved, we have been unwilling to share life-saving information, truthful information about effective prevention," Sinkford says.

"According to UNAIDS, prevention efforts are reaching fewer than 20 percent of the people in dire need," Sinkford says.

"The highest rates of infection are found among young people between the ages of 15 and 24 and married women in their 20s and 30s," he adds. "If we truly want to save lives, we must get serious

about delivering effective prevention."

One way to do this is to expand access to HIV prevention programs and reproductive health services, Sinkford suggests.

Congress needs to ensure that PEPFAR funds will be used to integrate family planning and reproductive health in HIV prevention programs, Sippel says.

"How it works now is PEPFAR funding cannot be used for family planning, which hinders the whole integration component of this," Sippel explains. "It causes confusion on the ground about what the money is being used for."

A gag rule, instituted on President George W. Bush's first day of office, prohibits any US funds from going to overseas programs that provide counseling or information about abortion, she notes.

"That is not supposed to apply to PEPFAR funding, but in the field, it causes confusion," Sippel says.

A third needed change is the elimination of the requirement that organizations taking US money sign a pledge that they object to prostitution, she adds.

From a public health perspective, this means that non-government organizations (NGOs) that do outreach work with sex workers have difficulty developing trust with the very population they are targeting for prevention work, Sippel says.

Also, some NGOs have effective programs that use sex workers as peer counselors, and their work is jeopardized by this requirement.

Global HIV prevention experts say that PEPFAR misses the mark in its aim to stop the HIV epidemic because of these political stipulations and requirements.

"The United States government has, unfortunately, put ideologies before evidence-based best medical practices at the expense of lives of young people," says **Krystie Corpuz** of the International Youth Leadership Council, Advocates for Youth. Corpuz spoke at a World AIDS Day event media conference about PEPFAR funding.

The abstinence until marriage programs are harmful to youths, Corpuz says.

"Not giving youths access to information about the full range of HIV prevention tools at their disposal — such as abstinence, being faithful, and correct and consistent condom usage — means that the very lives programs like PEPFAR are trying to protect are being lost unnecessarily because of ideologically-based public policy," Corpuz says.

The abstinence until marriage programs do not work for African women, says **Bernice Heloo**, president of the Society for Women and AIDS in Africa in Ghana. Heloo also spoke at a World AIDS Day event media conference on PEPFAR.

"We as African women are concerned about the fact that for a very long time HIV prevention and management have been seen from very nar-

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row perspectives, devoid of the context in which we live and also in which the pandemic thrives in Africa," Heloo says. "It is this parochial approach that has resulted in the apparent narrow focus and emphasis on abstinence until marriage and faithfulness."

What's needed are fully-funded programs that are comprehensive, holistic, nonprescriptive, and provide access to female condoms, Heloo says.

One such program would target women in violent and other difficult situations, she says.

For instance, African women often suffer from gender-based violence, including rape and abuse, which can cause the HIV epidemic to spread, Heloo says.

"Additionally, funds are required to rescue women from harmful social, cultural, and religious practices that predispose them to HIV infection," Heloo says.

"We add our voice to demand the removal of the one-third abstinence earmark and also ask for a track out of the anti-prostitution pledge, which is really discriminatory," Heloo adds.

PEPFAR makes the HIV prevention message a moral one, which is harmful to the goal of eliminating the spread of the virus, says the **Rev. J. P. Heath**, co-founder and director of the International Programs at the African Network of Religious Leaders Living With or Affected by HIV and AIDS (ANERELA) in South Africa. Heath also spoke at the recent PEPFAR media conference.

"The common strategy that we all know, in terms of HIV prevention is ABC: abstain, be faithful, use a condom," Heath says. "The challenge with this is that the only thing we're talking about is sex."

Once an epidemic's prevention focus turns to sex, it makes the disease a moral issue, Heath explains.

"HIV is a virus — it's not a moral condition," Heath says. "And the way in which we deal with HIV has to reflect that."

Heath offers this example of how destructive the focus on morality can be from a public health perspective: "Yesterday, I was speaking at a gathering in a northwest province of South Africa, and Dr. Kizito from Uganda was there and he related to us a story of a young girl who found out, in Uganda, that one of her previous boyfriends had died of AIDS-related illnesses," he says.

"So what she did was she went out and solicited 10 young men and slept with them and then committed suicide," Heath explains. "She had posted their names on her door and said, 'These people are dying with me.'"

But a post-mortem exam found that the woman was not infected with HIV, he adds.

"Because of the focus on sex, her knowledge that she had a sexual relationship with this man who had died clouded her mind," Heath says. "She didn't know she had to go for a test, and she didn't know that not every time you have unprotected sex the virus is transmitted."

This provides a tragic illustration of why the PEPFAR funding should go toward programs that focus on HIV prevention through the best strategies available, rather than be used as a tool to promote a certain type of morality, he adds.

"You cannot stress enough the need for people to know their HIV status," Heath says. "We have to move to a place that not 10 percent, but 100 percent of humanity knows their HIV status." ■

Brief Internet prevention intervention can have effect

Even 15-minute message matters

New, unpublished research supports the idea that HIV prevention programs on the Internet could have a positive impact on behavioral change.

"We now are finishing up a study with young adults, and we've employed stronger, more rigorous methodology, and we have shown a very moderate effect of the intervention on condom use among adults with the use of a one-time, 15-minute intervention," says **Sheana S. Bull**, PhD, MPH, an associate professor in the department of family medicine at the Colorado Health Outcomes Program, the University of Colorado, and the Denver Health Sciences Center in Denver, CO.

"It's encouraging because now we know how to do these interventions on line and how to evaluate them appropriately so people will participate," Bull says. "But the effect is so moderate that we would have to ensure exposure and reach many more people than typically are enrolled in a study to have an impact and show a population-level impact."

Investigators are enthusiastic about the intervention's possibilities, she notes.

"We're excited by the possibility that you

could get a very brief intervention, expose a lot of people to it, and show population-level effects," Bull says. "Typically, a behavioral-level intervention requires more exposure and greater intensity before you show an effect, and the effect of the intervention wears off very quickly without multiple visits."

Bull's research involving the Internet has included on-line surveys and collecting surveillance data.

"We learned that people will respond to sensitive questions in the Internet environment, and they will come to your site," Bull says. "So that led us to consider ways we could use the Internet and computers for standardized, tailored kinds of HIV prevention interventions."

The initial Internet intervention was designed to increase HIV/STD testing and increase condom use, she says.

"For that study, we weren't able to show any effect, primarily because our methodology was limited," Bull says. "We erred in that study by trying to protect people's anonymity over anything else."

What happened was that researchers had only email addresses for participants, and this resulted in a large loss of participants to follow-up, she explains.

"So we couldn't determine whether the intervention had any effect," Bull says. "Since then, we've made the methodology more vigorous: we make sure people are who they say they are, and we have the necessary follow-up."

With Internet prevention programs there is a trade-off between obtaining the necessary follow-up numbers and obtaining the best available intervention effect.

"We're showing that one 15 to 20 minute intervention can have a notable effect," Bull says. "We can increase the size of the effect by having multiple interventions, but you lose the guarantee that people will come back."

In an Internet environment, an intervention competes with different Web sites and different objectives, so while people might want information about HIV, attracting people who are at highest risk for infection is a challenge, she says.

Researchers are experimenting with strategies like embedding HIV prevention information in social networking sites, so people don't have to navigate away from their favorite site to view the information.

"We're targeting young adults particularly because we want to start doing an intervention for some of the highest risk groups, including African-American youth," Bull says. "If we're going to develop HIV intervention preventions, then we need to go where the [high-risk people] are and put our content on existing sites they visit."

A final evolution in thinking about using the Internet and technology to reach high-risk groups involves the philosophical reality that the Internet may not be the best technology for reaching target audiences.

"When we're trying to reach lots of people, there might be other technologies out there that are more ubiquitous and popular with the highest-risk groups," Bull says. "These include mobile phone technology, so we're starting to look at how we can use text messaging for HIV prevention intervention."

This stage is down the road because of infrastructure limitations, she says.

But a similar strategy has been piloted in studies involving young girls and nutrition work in Colorado, she notes.

"We're exploring how to get a sense of opportune moments to send prevention messages," Bull says. "We're sending HIV prevention messages to people on their phones to increase their awareness."

The key is to find the type of messages that will be the most resilient and resonant for the target audience.

"We'll use social theory to guide those messages," Bull explains. "We may take an opportune time like Friday night and send out a text message about being careful and carrying a condom with them, or a message about decision-making if they're out partying."

Then on Monday morning, the prevention message could be sent to get tested for HIV or STDs if they've done something over the weekend that put them at risk, she says.

"We need to time messages to cue action and also raise their awareness and get them to practice carrying condoms with them," Bull adds.

This intervention project is in its infancy, she says.

And even if these new technology approaches succeed, they shouldn't replace other interventions, Bull says.

"I see it much more as one tool among many interventions," Bull says. "I think we can use the technology to shape norms and attitudes very effectively, and it also may increase access to services so that people can get prevention messages and better understand where to go and how to access services." ■

Latinos and HIV epidemic

[Editor's note: This is the second in a two-part series that examines the HIV/AIDS epidemic among Latinos in the United States. In this issue, there is the following story about an HIV intervention that spreads HIV education and condoms to Latino men in the rural, Southeastern United States. In the December 2007 issue of AIDS Alert*, there were stories about the extent of the problem and about an effective intervention that is aimed at reducing HIV transmission among Latino youths.]*

Intervention reaches Latino men at soccer games

Finding target audience is the challenge

One of the challenges in targeting Latinos in the United States for HIV prevention messages has been the diversity of this ethnic group, both culturally and geographically.

Investigators at Wake Forest University in Winston-Salem, NC, have found that designing HIV interventions for Latinos requires some creativity and time spent on getting to know the target audience in any specific town or area.

"We contend the Hispanic population we're working with in the Southeast is very different from Hispanics in California," says **Scott D. Rhodes**, PhD, MPH, an associate professor at Wake Forest University, division of public health sciences/social sciences and health policy in the school of medicine.

It's difficult identifying a prevention approach that will work, as well as to identify ways to find the target audience, Rhodes says.

"We tried to find out what was going on for these men and what would be their outlets," he says.

While HIV prevention services often conduct outreach in community churches, this might not be the best way to reach the Latino men who are most at risk, he notes.

"People are always pushing the importance of a church and say a church is the way to reach people," Rhodes says. "What we've learned is that if you go to a church, you probably have a family there with you, and if you don't go to a church, then you might be a single man who is most at risk."

Also, there's sort of a brothel system in the Southeast and in rural communities, which adds to the risk of transmitting HIV, he says.

Latino men say there are advantages to living in the Southeast, including cheaper housing, but on the negative side, the health care infrastructure is not as strong, Rhodes says.

"Their access to health services is lower here, and we don't have a history of providing bilingual services," Rhodes adds.

California has a long history of providing bilingual services, and Hispanics in California can be more easily reached for HIV interventions, he adds.

Given these differences, it does not make sense to use in cookie cutter style any HIV prevention intervention that was designed for a Latino community in California.

"So we wanted to explore sexual priorities and health among Latino men," Rhodes says. "And we wanted to see what is the best way to recruit and work with Latino men in the Southeast."

The answer turned out to be soccer leagues.

"We found that soccer leagues were a community asset that allowed us to partner with Latino men," Rhodes says. "So we use a lay health provider approach where we train men from a soccer team on basic HIV and sexually transmitted disease (STD) information."

One of the important findings in the prevention research was that Latino participants helped investigators understand their social networks.

"Our participants said, 'We help each other get driver's licenses, buy cars, find housing, and we use family and friendship networks,'" Rhodes recalls. "We knew we should be using these networks to help prevent infection and disease."

For example, as the network helps newcomers obtain the essentials of living in the United States, they could also provide men with free condoms and show them how to receive health care and get tested for HIV, he says.

In exchange, the peer leaders received a monthly stipend of $50 as payment for their data collection.

"They had to give us low literacy activity logs so we could figure out who they were talking to," Rhodes explains. "Half of their work as lay advisers went beyond the soccer league."

Researchers taught these leaders how to access health services in their local community; they

trained them to be opinion leaders, and they gave them condoms to use.

"We used a penis model to show people whether they're using the condoms correctly," Rhodes notes. "The men were very eager to learn these things and help their community, and they wanted to participate and be part of the project."

Investigators found that sexual health is a priority among the Latino men they targeted.

"We collected information monthly on how to access care and changing cultural norms," Rhodes says. "We didn't give condoms to women or talk about sexual health with women."

Researchers trained Latino community leaders to teach their peers that it is okay to seek help when they need it.

"We trained Latino advisors to teach teammates that it's okay for men to go to the health department to obtain information about STDs," Rhodes says. "This approach seems to be effective."

Investigators still are analyzing the outcomes data, Rhodes says.

The project began with focus groups.

"We were doing qualitative data collection, using focus groups, and we wanted to do it with Latino men," Rhodes says. "We worked with the director of a soccer group to get men in."

What they found was that the soccer league is a very important community asset among Latinos in the Southeast, he says.

This was an important find for researchers because it's very difficult to market HIV prevention services to a little-known group.

"We don't know what they're eligible for and where they'd get access to services if they were eligible," Rhodes says. "Many of these men are undocumented, and they don't want to seek assistance."

Their reluctance to seek health care services has the effect of understating their presence in the community, and this leads to health care institutions understaffing with bilingual staff.

"We have a very complicated health care system that's different from the community these folks come from," Rhodes explains. "So understanding how to access services is tough, and having only an occasional interpreter makes it very difficult."

Plus, there are huge racial tensions in the Carolinas, particularly about immigration, he adds.

"These tensions are felt by the Latino community," Rhodes says. ■

New microbicide for HIV prevention now in trials

By Rebecca Bowers
This article originally appeared in the October 2007 issue of Contraceptive Technology Update.

Researchers have launched a clinical safety trial of VivaGel (SPL7013), a topical vaginal microbicide, for potential use in preventing the sexual transmission of HIV. The trial is being conducted in two sites, the University of South Florida in Tampa and the University of Puerto Rico in San Juan, and it is supported by funding from the Division of AIDS at the National Institute of Allergy and Infectious Diseases and the National Institute of Child Health and Human Development.

Starpharma Pty. Ltd., of Melbourne, Australia, is looking at VivaGel as a candidate microbicide for the prevention of HIV/AIDS and genital herpes. The gel's active ingredient belongs to a class of compounds known as dendrimers, large molecular structures that incorporate multiple units of an active component on their surfaces. Each dendrimer in VivaGel incorporates 32 copies of the active component. Researchers believe the gel's unique molecular structure may hamper the ability of HIV to attach to and infect healthy cells.

Starpharma recently announced trial results that showed VivaGel was well tolerated and safe for continued development following topical penile application in men, says **Jackie Farley**, MBA, the company's chief executive officer. Acceptability was a secondary end point in this study, and interviews indicated that VivaGel would be acceptable to participants if shown to be protective against sexually transmitted infections, she notes.[1] Findings from an earlier, unpublished Phase I study of VivaGel in sexually abstinent women ages 18-43 indicate no safety concerns. Women were randomly assigned to receive different doses of the gel and closely examined during a seven-day inpatient stay in a clinical research unit.

Two sites eye drug

Screening of potential candidates for the trial began in July 2007. The trial, which will include 40 women ages 18 to 24, who are sexually active and HIV-negative, is designed as a randomized, placebo-controlled Phase I safety and acceptabili-

ty trial with two treatment arms. Participants will be randomly assigned to one of two study groups, with one group applying VivaGel twice a day for two weeks, and participants in the other group using a placebo gel. All women in the study will be given condoms for use during each sexual interaction. Participation in the study is scheduled for three weeks, which will include the two-week period that gels are used.

If trial results prove satisfactory in terms of the safety profile and the acceptability, then the next step likely will be an extended safety study, where the study group may include a larger group of women who will use the product for a longer period of time, typically six months, says **Ian McGowan**, MD, PhD, visiting professor of medicine at the University of Pittsburgh School of Medicine and Magee-Womens Research Institute. McGowan is co-principal investigator of the Microbicide Trials Network and protocol chair for the current study of VivaGel.

The VivaGel study is the first of three trials expected to be launched this year by the Microbicide Trials Network (MTN). MTN is an HIV/AIDS clinical trials network established in 2006 by the Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health.

The active ingredient in VivaGel, SPL7013, is a fourth-generation polylysine dendrimer. Thirty-two naphthalene disulfonate moieties, attached by amide linkages, are found on the molecule's surface. The structure prevents HIV infections by binding to the gp120 glycoprotein receptors on the virus's surface, an interaction which in turn stops HIV from attaching to receptors on T cells in the body.[2] Given VivaGel's potential for infection prevention, Starpharma is looking at use of the product as a coating for condoms.

"The potential for VivaGel to be used as a condom coating reflects some of the growing momentum building to bring an effective preventative measure for HIV and STIs to market," notes Farley. "Starpharma has already signed an agreement with a leading manufacturer of condoms, which will include a program of evaluation and development and also commercialization rights covering condoms with VivaGel costing within a specific geographical region."

Preclinical animal studies on VivaGel have provided early evidence that VivaGel may serve as an effective contraceptive, says Farley. Further studies on the contraceptive ability of VivaGel are already under way, she notes.

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Condom conundrum: What spells program success?

By Rebecca Bowers
This article originally appeared in the December 2007 issue of Contraceptive Technology Update.

Officials at the District of Columbia Department of Health (DOH) are retooling the city's condom distribution program after meeting public resistance to its customized condoms.

The city launched its own private-label condoms, DC Condoms, in February 2007, as part of its "One Million Ways to Stop HIV" condom program. The condoms, packaged in a purple and mustard-yellow package, carried the message, "Coming together to stop HIV in DC."

In its work order for the private-label condoms, the DOH specified that FDA and American Society for Testing and Materials standards must be met in order to offer reliable protection.

To kick off the condom campaign, the DOH partnered with a variety of community providers to distribute an initial 250,000 DC-branded condoms. However, sites that signed up for the distribution program began to see a drop-off in interest in the free condoms as months progressed. Complaints were raised that packets were ripping in purses or bursting open in pockets. As a result, many recipients said they had little confidence that the condoms would offer protection.[1]

As of September 2007, the DOH said 650,000 condoms had been distributed through 50 community organizations across the city, including DOH clinics, health care and community groups, street outreach projects, youth-serving organizations, as well as at nontraditional locations, including dance clubs, bars, barber shops, beauty salons, and Laundromats.[2] The private-label condoms were purchased from Boston-based Global Protection Corp. Some of the condoms were

manufactured in China, while others were produced in Malaysia.[3]

Health officials met with community organization representatives in mid-September. Following that meeting, the public health department has worked with community partners to collect condoms still in storage for return to the manufacturer, says **Leila Abrar**, MPH, department spokeswoman. Condoms in storage at DOH also are being returned, she reports. The manufacturer is replacing all remaining supplies with brand-name condoms usually found on drugstore shelves.[4]

What steps are public health officials taking to bolster the condom distribution program? According to Abrar, plans for specific packaging of a DC condom are on hold, based on feedback received from community stakeholders during a Sept. 13 meeting.

"Community partners stressed their preference for brand-name condoms that are clearly identifiable as having been produced by a leading manufacturer," states Abrar. "DOH will continue to seek out recommendations from community partners on retooling the DC condom distribution program to obtain more brand-name condoms; identify more accessible, nontraditional locations; and improve overall public awareness and education on the importance of condom use."

Public health officials also will continue to seek recommendations from its community partners relating to consumer feedback and how to improve the condom distribution program, she states.

What spells success?

The Washington, DC, condom distribution program was designed to complement the health department's goals to encourage residents to be screened for HIV, institute routine screening in all health care settings, educate and equip residents to prevent HIV, and provide care and treatment to people with HIV/AIDS. Public health officials are facing an uphill battle: In 2005, the District of Columbia had the highest rate of AIDS cases — 128.4 cases per 100,000 people — among all jurisdictions in the country conducting AIDS surveillance.[2]

What aids in implementing a successful condom program? Developing a reliable distribution program is an important factor, says **Thomas Farley**, MD, MPH, professor and department chair of community health sciences at Tulane University School of Public Health and Tropical Medicine, New Orleans. Farley was involved with the first statewide condom social marketing intervention in the United States. The program, "Operation Protect," was implemented in Louisiana in the mid-1990s.[5]

"Since they [condoms] are not paid for by users, you can't distribute them through regular business channels," he says. "In a good program, condoms will be distributed by the millions, so any agency involved has to have a robust system to deliver them and make sure the highest-priority sites — eg, gay bars — have them displayed consistently and prominently."

Program staff and partners alike need to understand that condoms are extremely inexpensive and should be distributed in abundance, says Farley. Staff members often want to distribute condoms very stingily and express vague fears that people will "waste" them, he notes. "Condoms are like clean water in a refugee camp: the more the better," Farley states. ■

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Researchers halt HIV vaccine trial — What's the next step?

By Rebecca Bower
This article originally appeared in the December 2007 issue of Contraceptive Technology Update.

Progress toward an effective HIV vaccine has encountered a major roadblock with the cessation of a HIV vaccine clinical trial sponsored by Merck & Co. Meanwhile, the need for an effective vaccine continues to grow: The number of new infections in 2006 rose to 4.3 million around the globe, 400,000 more than in 2004.[1]

"While we are very disappointed that this vaccine candidate did not demonstrate protection, the data from this trial will provide critical insights into this disease and future vaccine development," says **Lawrence Corey**, MD, principal investigator of the HIV Vaccine Trials Network (HVTN), which co-sponsored the Merck trial.

The study had enrolled 3,000 participants at sites in Australia, Brazil, Canada, the Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, and the United States since its initiation in late 2004. US study sites included Boston; Birmingham, AL; Chicago; Decatur, GA; Denver; Houston; Los Angeles; Miami; New York City; Newark, NJ; Philadelphia; Rochester, NY; St. Louis; San Francisco; and Seattle. Study volunteers all were HIV-negative, between 18 and 45 years of age, and at high risk of HIV infection. Enrollment for the study was closed in March 2007.

The trial was designed to test Merck's candidate HIV vaccine, the MRKAd5 trivalent vaccine. Made with a weakened version of adenovirus Type 5, which was used as a delivery vector, the vaccine included three synthetically produced HIV genes, gag, pol, and nef. Its design was aimed to stimulate production of immune system T cells to kill HIV-infected cells. During a scheduled interim efficacy analysis of the study, an independent monitoring group reviewed safety data from some 1,500 volunteers who were expected to have the best response to the vaccine due to their low levels of pre-existing immunity to the adenovirus.

The interim analysis concluded that the vaccine did not prevent infection. In volunteers who received at least one dose of the three-dose vaccine series, 24 cases of HIV infection were observed in the 741 volunteers who received vaccine and 21 cases of HIV infection were observed in the 762 participants in the placebo group. In the subgroup that had received at least two vaccinations and who were HIV negative for at least the first 12 weeks of the trial, 19 cases of HIV infection were observed in the 672 volunteers in the vaccine arm, and 11 cases were observed in the 691 volunteers in the placebo arm. Data also indicated the vaccine did not reduce the amount of virus in the bloodstream of those who became infected. HIV RNA levels were similar in the vaccine and the placebo arms about eight to 12 weeks after diagnosis of infection.[2]

Study volunteers were followed for about 13 months. Overall adverse event rates generally were similar among the two groups, except for a higher rate of local injection site-related reactions in the vaccine group.

Researchers also have halted a second Phase II trial of the Merck vaccine candidate, known as the Phambili trial, as well as two additional Phase I trials. The Phambili trial was begun earlier in 2007 in South Africa by the HVTN to see whether the Merck vaccine would be effective at preventing infection, reducing viral levels, or both from HIV subtype C, which is more common in southern Africa.

"The next step is really to learn as much as we can about why this vaccine didn't work and then continue to work with the vaccines in the pipeline to keep testing until we find one that will," says **Sarah Alexander**, HVTN spokeswoman.

More vaccines on way

In a conventional vaccine, the immune system is triggered into manufacturing antibodies against an infectious organism. Scientists have been stymied in developing an effective vaccine against the rapidly mutating HIV.

Over the past decade, science has focused on the T cell approach, stimulating T lymphocytes that can identify and kill HIV-infected cells in an effort to prevent/limit viral replication and delay disease progression.[3] Researchers have zeroed in on this approach after results of early studies showed that monkeys receiving such vaccines against simian immunodeficiency virus (similar to HIV) lived longer or had lower than usual viral levels.[3]

One vaccine using this premise is nearing an efficacy trial, says Alexander. Developed by the Dale and Betty Bumpers Vaccine Research Center (VRC), part of the National Institutes of Health (NIH), the vaccine uses a recombinant DNA as a prime and then an adenoviral vector vaccine as a boost. The vaccine contains synthetic versions of four HIV genes: gag, pol, nef, and env. The gag, pol, and nef genes come from HIV subtype B, the primary virus found in Europe and North America. Env, the fourth gene, codes for an HIV coat protein that allows the virus to recognize and attach to human cells.[4] The first portion of the vaccine strategy uses DNA to prime an immune response to internal HIV proteins and external HIV proteins, with the booster portion designed to stimulate specific antibody responses to HIV envelope proteins and internal proteins.[3]

The DNA components of the vaccine were

manufactured by Vical in San Diego; the adenovirus vector was developed by the VRC in collaboration with GenVec of Gaithersburg, MD, which also manufactured the adenovirus vector vaccine.[4]

Funding pushes search

An Atlanta-based biotechnology company, GeoVax Labs, has just been awarded an estimated $15 million grant from the NIH's National Institute of Allergy & Infectious Disease to support its HIV/AIDS vaccine program. How does GeoVax's vaccine differ from the Merck candidate? There are multiple differences, says **Harriet Robinson**, PhD, chief scientific advisor for the company and chief of microbiology and immunology at the Yerkes National Primate Research Center based at Emory University in Atlanta.

"The Merck vaccine used a recombinant adenovirus to introduce HIV proteins into cells," she explains. "We use recombinant DNA, followed by a recombinant poxvirus, so the platforms are different."

GeoVax scientists believe that the company's vaccine raises a form of protection not seen in the Merck candidate, says Robinson. Also, while both candidates raise a T cell response, the GeoVax vaccine includes high frequencies of T cells associated with good long-term control of HIV, she says. "We feel that we have raised a type of T cell that has greater potential for protective responses for battle," Robinson says. Consider the analogy of soldiers, she says. "You want your soldiers to demobilize and rest, and you can't keep them continually in the field," Robinson says.

The government grant will propel GeoVax's research, says Robinson. At this point in time, the company's research team is moving along through its clinical trials to build up its safety and immune response data, she reports. "The next most important result we will have from our vaccine is when we get to the point that Merck is, and at that point, we'll know whether or not we protected humans or not," states Robinson.

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FDA Notifications

FDA approves half-strength Kaletra

On Nov. 9, 2007, the FDA approved a new half-strength Kaletra tablet formulation. Each film-coated tablet contains 100 mg lopinavir and 25 mg ritonavir. The major changes to the label include clear instructions regarding the importance of accurate calculation of the dose of Kaletra to minimize the risk for medication errors and overdose or under dose, and the addition of tablet dosing to section 2.2 Pediatric Patients, as described in the pdf attachment.

Kaletra is a combination protease inhibitor product containing lopinavir and ritonavir, manufactured by Abbott Laboratories. The original formulation was approved on September 15, 2000.

FDA's final guidance on HIV resistance testing

The FDA is publishing its final "Guidance for Industry on the Role of HIV Resistance Testing in Antiretroviral Drug Development."

This final guidance discusses the nonclinical studies (mechanism of action; antiviral activity in vitro; cytotoxicity/therapeutic index; and the effects of serum protein binding on antiviral activity) the agency recommends be completed prior to the initiation of phase I clinical studies in HIV-infected patients. In addition, the guidance addresses the use of resistance testing in the clinical phases of drug development, and recommends the type of information that should be collected and the types of analyses that should be conducted to characterize an antiretroviral's resistance profile.

The guidance also discusses the role of resistance testing in initial activity and dose-finding, for study enrollment criteria, for background regimen selection, and to establish an indication.

The guidance represents the agency's current thinking on the role of HIV resistance testing in antiretroviral drug development. As with all FDA guidance for industry, it does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

A copy of the final guidance document is attached. You may find this and other Guidance for Industry on the FDA web site at http://www.fda.gov/cder/guidance/index.htm

FDA's tentative approval for generic Tenofovir

On Nov. 30, 2007, FDA granted tentative approval for a generic version of Tenofovir Disoproxil Fumarate Tablets, 300 mg, manufactured by Matrix Laboratories Limited, of Hyderabad, India. The application was reviewed under the expedited review provisions of the President's Emergency Plan for AIDS Relief (PEPFAR).

"Tentative Approval" means that FDA has concluded that a drug product has met all required quality, safety, and efficacy standards, even though it is not yet eligible to be marketed in the United States because of existing patents and/or exclusivity rights. However, this tentative approval does make the product eligible for consideration for purchase under the PEPFAR program.

This is a generic version of Viread Tablets, 300 mg, manufactured by Gilead Sciences, Inc,, which is subject to existing patent protection.

Effective patent dates can be found in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the "Orange Book."

As with all generic applications, FDA conducts an on-site inspection of each manufacturing facility and of the facilities performing the bioequivalence studies prior to granting approval or tentative approval to these applications to evaluate the ability of the manufacturer to produce a quality product and to assess the quality of the bioequivalence data supporting the application.

CE/CME*questions*

1. Researchers are studying new ways and technologies for delivering HIV prevention messages. Which of the following is one of the most novel methods being explored?

A. Steering at-risk persons to a prevention message Web site
B. Sending high-risk individuals prevention messages by email
C. Sending prevention messages to high risk individuals via cell phone text messaging on weekend nights or other times when the message most is needed
D. None of the above

2. North Carolina researchers have discovered a way to spread HIV prevention messages through social networks of Latinos in the Southeast. Which social network has been used successfully?

A. Churches
B. Civic centers
C. Soccer leagues
D. Latino grocers

3. The latest HIV/AIDS epidemic data from the World Health Organization (WHO) and UNAIDS show that HIV prevalence has leveled off. This finding occurs after the numbers were revised due to better surveillance and methodology. The 2006 numbers were changed from an estimated 39.5 million to what new number for 2006?

A. 43.5 million
B. 32.7 million
C. 30.2 million
D. 26.4 million

Answers: 1. (c); 2. (c); 3. (b)

COMING IN FUTURE MONTHS

- CDC responds to report of HIV infection upswing among MSM
- Here's the latest on HIV/AIDS funding
- New ART resistance guidelines outlined
- Try this medication adherence program

Tenofovir is a nucleoside reverse transcriptase inhibitor (NRTI) indicated for treatment of HIV infection in adults and adolescents in combination with other antiretroviral agents.

FDA approval for generic lamivudine/zidovudine

On Nov. 29, 2007, FDA granted tentative approval for a generic formulation of combination lamivudine/zidovudine tablets, 150 mg/300 mg, manufactured by Matrix Laboratories, Inc. of Hyderabad, India, under expedited review provisions developed for the President's Emergency Plan for AIDS Relief (PEPFAR).

As with all generic applications, the FDA conducts on-site inspections of each manufacturing facility and of the facilities performing the bioequivalence studies prior to granting approval or tentative approval to evaluate the ability of the manufacturer to produce a quality product, and to assess the quality of the bioequivalence data supporting the application.

This is a generic formulation of Combivir Tablets, 150 mg/300 mg, marketed by GlaxoSmithKline, which is subject to existing patent and pediatric exclusivity protections.

Effective patent dates and additional marketing exclusivities can be found in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the "Orange Book."

Lamivudine and zidovudine are both Nucleoside Reverse Transcriptase Inhibitors (NRTI) indicated for used in combination with other antiretroviral agents in the treatment of HIV infection. ■

CE/CME objectives

The CE/CME objectives for *AIDS Alert*, are to help physicians and nurses be able to:
• Identify the particular clinical, legal, or scientific issues related to AIDS patient care;
• Describe how those issues affect nurses, physicians, hospitals, and clinics;
• Cite practical solutions to the problems associated with those issues.

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any question answered incorrectly, please consult the source material.

After competing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a letter of credit. When your evaluation is received, a letter of credit will be mailed to you.

AIDS ALERT®
INTERNATIONAL

Epidemic leveling off globally, with fewer people living with HIV/AIDS

The latest data by UNAIDS of Geneva, Switzerland, show that the global HIV pandemic has leveled off, with an estimated 33.2 million people infected, 2.5 million new infections last year, and 2.1 million AIDS deaths in 2007.[1]

International media focused on the revisions UNAIDS has made to its annual estimates, a downward projection that eliminates about six million infections. It decreased from the estimate in 2006 of 39.5 million infected worldwide to the new 2006 estimate of 32.7 million infected.

The revised numbers mainly are due to better estimates of infections in six countries, with India topping the list, UNAIDS officials say.

Along with India, 70 percent of the changes were due to surveillance changes in Angola, Kenya, Mozambique, Nigeria, and Zimbabwe.

But the real news, UNAIDS officials say, is that AIDS deaths have declined worldwide, and the number of people living with the disease has leveled off.

"In sub-Saharan Africa, prevalence has declined in recent years in the continent as a whole," says **Kevin De Cock**, MD, director of the HIV/AIDS department at the World Health Organization (WHO) in Geneva. De Cock and other UNAIDS representatives spoke about UNAIDS' annual report at a media teleconference late last year.

Even with the decline, sub-Saharan Africa is disproportionately impacted by the epidemic, De Cock says.

"Sixty-eight percent of people estimated to be living with HIV are in sub-Saharan Africa, and 76 percent of the estimated deaths occurred there," says De Cock. "Just eight countries of Southern Africa account for almost one-third of all new HIV infections and deaths."

Therefore, the international health community's focus on reducing new infections in sub-Saharan Africa, and the increase in access to antiretroviral therapy among those infected can have reverberations felt across oceans.

"It's not possible from these sorts of global estimates and examination of trends to be absolutely certain about the reasons for some of the trends and the impact of prevention or treatment programs, but I think one can draw some conclusions from specific situations," De Cock says. "There are some countries where we really do believe that the reductions in HIV prevalence are the result of behavioral change and of prevention programs, and such countries would include Kenya, Zimbabwe, Cote d'Ivoire, and some countries of Southeast Asia, such as Cambodia."

Likewise, the decline in AIDS deaths in the past two years can be attributed to the scale-up of antiretroviral therapy, De Cock says.

"There are well over two million, between two and three million people, on antiretroviral therapy in low and middle income countries," De Cock says. "So I think there are some positive elements in this report, some positive elements that are encouraging."

For instance, there are true HIV prevalence declines in Kenya and Zimbabwe, says **Karen Stanecki**, MD, senior advisor on demographics and related data at UNAIDS' department of social mobilization and information.

"In those two countries, we have done extensive research of the data that's available," Stanecki says. "The work that has been done indicates that this decline in prevalence cannot be attributed solely to deaths, but also it is attributable to behavior changes and the reduction in new infections in those two countries."

The revised estimate numbers represent an improvement in country data collection, including the types of surveys undertaken, says **Paul Delay,** MD, director of evidence monitoring and policy at UNAIDS.

"One of the big assumptions that has been put into this latest round is increasing survival, which

HIV/AIDS Epidemic Key Points

UNAIDS recently released its 2007 estimates of the HIV epidemic worldwide, and included these essential findings in its 2007 AIDS Epidemic Update, which is available on the UNAIDS Web site at www.unaids.org:

- Each day, more than 6,800 people become infected with HIV and more than 5,700 people die from AIDS.
- The global prevalence of HIV infection is at the same level, although the global number of persons living with HIV is increasing because of ongoing accumulation of new infections with longer survival times.
- Sub-Saharan Africa accounts for 35 percent of all people living with HIV/AIDS and 32 percent of all new HIV infections and AIDS deaths worldwide in 2007.
- South Africa has the largest number of HIV infections in the world, but recent data suggesting HIV prevalence is leveling off.
- Eight countries have an adult HIV prevalence of greater than 15 percent. These countries are Botswana, Lesotho, Mozambique, Namibia, South Africa, Swaziland, Zambia, and Zimbabwe.
- In Swaziland, 26 percent of adults are HIV positive.
- In Namibia, 20 percent of women attending antenatal clinics tested positive for HIV in 2006.
- In Lesotho, 38 percent of women attending antenatal clinics in the 25 to 39-year age group tested positive for HIV in 2005.
- Some countries have had reductions in prevalence.
- The recent scaling up of access to antiretroviral treatment has helped to reduce HIV-associated deaths.
- New HIV infections have declined globally, and in some countries declines can be attributed to behavior changes.
- HIV prevalence among pregnant women in Kenya dropped by more than 25 percent.
- HIV prevalence among pregnant women in Zimbabwe has dropped from 26 percent in 2002 to 18 percent in 2006.
- Data show reductions in some risk behaviors among young people in Kenya and Haiti.
- Reported condom use among young people in Cameroon, Kenya, Haiti, Malawi, and Zimbabwe has increased.
- In Vietnam, the number of people infected with HIV has increased from 120,000 in 2000 to 260,000 in 2005.
- In Pakistan, the epidemic is exploding among injection drug users (IDUs): HIV prevalence among IDUs was less than 1 percent in 2004; it was 26 percent in March 2005.
- In Indonesia, the epidemic is Asia's fastest growing one, and most of the infections involve contaminated injecting equipment, unprotected paid sex, and unprotected sex between men who have sex with men (MSM).
- In 2005, more than 40 percent of IDUs in Jakarta, Indonesia, were HIV positive.
- In Cambodia, HIV prevalence among adults has fallen from 2 percent in 1998 to 0.9 percent in 2006.
- The epidemic in the Russian Federation is increasing, but its rate of increase has slowed. The annual number of new HIV cases had dropped from a peak in 2001 of 87,000 to 34,000 in 2003. In 2006, there were 39,000 new HIV diagnoses.
- HIV diagnoses each year have doubled in the Ukraine since 2001, where there were 8,700 new diagnoses in the first six months of 2007.
- In Tajikistan, HIV prevalence among IDUs has risen from 16 percent in 2005 to 24 percent in 2006 in the cities of Dushanbe and Khujand. ■

is the amount of time from being infected to living without treatment," Delay says. "This has gone from nine to 11 years, and this changes overall [AIDS death] numbers, based on measured prevalence."

UNAIDS increased the survival time with untreated HIV because of new information, says **Peter Gece** with UNAIDS.

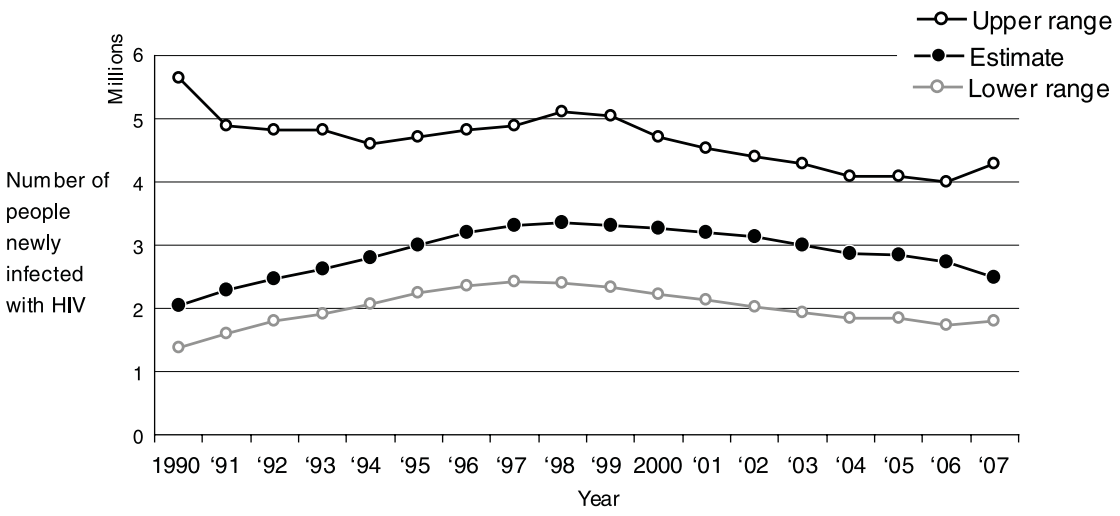
"There is new information on the survival time of people infected with HIV," Gece says. "This has come from a cohort study in different regions of the world, including from Africa, from the Caribbean, and from Asia."

A recent analysis of that new data indicates that average survival is around 11 years, Gece adds.

"So, the 9-year assumption was based on much less information than this new survival of 11 years, which was formed by a larger group of studies and, within those studies, a larger number of people than we had before," Gece explains.

Delay says it would be absurd to suggest that

Estimated number of people newly infected with HIV globally, 1990–2007



Source: 2007 AIDS Epidemic Update. Produced by UNAIDS/WHO. Available at www.unaids.org.

UNAIDS had previously inflated HIV/AIDS estimates out of a political agenda.

"UNAIDS is not an implementing agency," Delay says. "Our budgets are not really affected by these massive changes in resources that are being devoted to the programmatic response. So the idea that this is somehow self-serving is absurd."

Also, there are too many people working with the data, including ministries of health, statistics bureaus, district-level epidemiologists, and others for the data to be skewed fraudulently without someone blowing a whistle, he adds.

The take-home point is that there is positive news in the revised data, Delay says.

"Though it hasn't really been clearly stated here, these are very encouraging trends — stabilization of prevalence, declines of prevalence in sub-Saharan Africa, and the beginnings of declines in mortality," Delay says. "So it's data that we clearly need to continue to be collecting and making the investments so that the quality continues to improve." ■

Reference:
1. 2007 AIDS Epidemic Update. Produced by UNAIDS/WHO. Available at www.unaids.org.

Taking prevention from research to reality is tricky

Investigator offers fresh ideas to make it work

One of the major problems the HIV prevention field has had is translating successful research into success in the real world. This challenge is even more of a hurdle when it comes to sending successful programs designed in the United States to sub-Saharan African and other developing world settings.

"The problem in the AIDS area is the major journals are read primarily by other scientists, but the real users of our work are AIDS service organizations," says **Jeffrey A. Kelly**, PhD, a professor of psychiatry and behavioral medicine and director of the Center for AIDS Intervention Research at the Medical College of Wisconsin in Milwaukee, WI.

"Those organizations generally don't have access to our journals, or they're written in the wrong language," Kelly says. "Or even if they could access the articles, the description of the program is usually a couple of paragraphs long, and no one could possibly replicate an intervention from that description."

So there's a disconnect between good HIV prevention research and the implementation of that research in the field.

"No matter how good our research is, if it isn't transferred to HIV providers, then the research on its own isn't contributing to public health and preventing the disease," Kelly says.

"I think all of us in the HIV prevention area want to see our intervention used, so we think if it works we want to create a manual so other people will use it," Kelly says. "What the field has not done much of is scientifically study how to transfer what we've learned to providers, and that's the area that interests me."

For the 95 percent of HIV infections occurring outside of the United States, most of the prevention work is carried out by non-governmental organizations (NGOs), Kelly notes.

"Researchers know quite a bit about the principles of behavior change, but good NGOs know much more about their community, their community's needs, their community's culture," Kelly explains. "So we're trying to bring together here two bases of knowledge: one in the scientific arena, and the other is what providers know from their experience."

Investigators approached this transfer of prevention program information with the philosophy that there are core elements common across all effective interventions.

"We wanted to get people to carry out adult community programs with these characteristics," Kelly says. "How they did this and what they wanted to emphasize was up to them."

So researchers tried to train NGOs about these core elements rather than focus solely on the intervention, he says.

"A lot of people say, 'We provide manuals for interventions,'" Kelly says. "But we're among the few groups studying the science of dissemination and faster uptake of interventions, and that's a niche that I think is very important."

Since thousands of the NGOs have little access to evidence-based prevention interventions, Kelly has researched how to bring this information to them in a way they can adopt and adapt for their own purposes.

"We developed a curriculum in the popular opinion leader intervention and community level intervention," Kelly says. "This is the kind of model the NGOs said they'd find useful."

Investigators created an interactive curriculum that can use audio and video streaming to model intervention techniques. It has self-pace segments to guide an organization through planning, carrying out, and then sustaining a program based on the model, Kelly says.

It's relatively simple to create a Web-based program for NGOs, but the challenge is in using advanced communication technology as a training tool, Kelly says.

"One immediate issue was that most of the NGOs don't speak English, so we developed everything for the project in four different languages: English, French, Spanish, and Russian," Kelly says. "It was quite a technical undertaking, developing all of these materials in all of these languages."

Researchers contacted leading NGOs in the capitol or large cities of 78 countries, and these NGOs became the study's participants, he says.

Studying how the NGOs adapted and implemented the prevention programs was very difficult logistically, Kelly notes.

Investigators had to assess how interventions worked in these very different environments: "How did the popular opinion leader intervention work when carried out with drug users in a post-Soviet country?" Kelly says. "How did it work with high school kids in Latin America?"

Designing a trial in this way is the first hurdle. Then there is the issue of control over the intervention. For instance, the NGOs likely will want to make changes, but how many changes are too many for it to be meaningfully studied? And is there anyway of proving that the NGOs implemented the intervention in the way they say they did, he asks

"These trials are logistically very difficult to do," Kelly says. "You have to have lots of providers carrying this out, and you have to have ethics research approvals when there are a lot of messy questions."

One of the bigger issues in technology and information transfer across oceans is that interventions often are developed around what is most important to the researcher, Kelly notes.

"I believe that a part of the technology transfer process is not moving interventions from the research arena to providers, but listening to providers and creating an intervention that is needed in the world," Kelly says. "It's bi-directional."

If investigators are studying interventions that cannot be used practically in the real world, then they're developing the wrong interventions, he says.

"We need better, mutual, reciprocal interventions in which providers inform the research," Kelly says. "We have to remember that if what we're researching is not useful in the field, then we're not really helping and being effective." ■