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Truvada trials hold promise for new HIV prevention strategy

Once-a-day might keep HIV away

Researchers and public health officials say they hope ongoing research will eventually show efficacy with a new prevention strategy that involves giving uninfected people at risk for HIV a simple combination reverse transcriptase inhibitor (RTI) therapy. But it's too early in the research to draw conclusions or for individuals to attempt the strategy, says Lynn Paxton, MD, MPH, team leader for the antiretroviral prophylaxis and microbicides team at the Centers for Disease Control and Prevention (CDC).

The good news is that there are ongoing trials in Botswana to study the use of tenofovir (Viread) and emtricitabine (Emtriva) in a combination drug called Truvada for the prevention of HIV infection among a population of people, ages 18 to 29 years, she adds.

"Animal data suggest tenofovir may be a potentially promising strategy for pre-exposure prophylaxis," says **Albert Liu**, MD, MPH, director of HIV prevention intervention studies at the HIV Research Section of the San Francisco Department of Public Health in San Francisco.

Called pre-exposure prophylaxis (PrEP), the combination of antiretroviral drugs could one day serve as a daily prophylactic for people at high risk for HIV infection. The idea is for people to take antiretroviral medicine before they have a potential exposure.

CDC literature notes that a daily oral preventive of tenofovir or Truvada could help meet the need for a female-controlled prevention method for women worldwide who are unable to negotiate condom use.

This approach also might appeal to at-risk men and women who would like an additional safety net. But the idea is that it would be taken daily by uninfected adults and not in response to any particular HIV exposure.

"So PrEP is not a morning-after pill," says Liu. The CDC already has issued guidelines for post-exposure prophylaxis (PEP), he points out. "After a high risk exposure, under PEP, people take a combination of antiretroviral drugs — two or three drugs — for 28 days," Liu explains.

Any hope for public health success with PrEP shouldn't turn into

action on the part of clinicians or their patients until the data are in, Paxton says.

Widespread national media reports in March 2006 touted the drug combination's potential in combating HIV, but the important research has a long way to go before the strategy can be employed.

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"What we've been worried about is we're afraid the news of this strategy is coming out a little too positive with this bent that it works," Paxton says.

"Obviously, we think there's merit to this or we wouldn't be studying it, and there's a strong background in the literature," Paxton says. "We're just very worried because a lot of people jump on the newspaper article headline and go ahead with using drugs."

CDC officials are worried that people at high risk for HIV infection will self medicate with Truvada and stop using condoms and other proven prevention strategies, Paxton says.

Although animal data showed promise, it was limited in that only six monkeys were given the tenofovir/emtricitabine combination, Liu notes. "And there are significant limitations in extrapolating data from monkeys into what will happen in humans. So while we feel that the data are encouraging for the field, it's still very important that we gather both safety and efficacy data in people."

It's the CDC's role to explore all promising interventions, and the Truvada PrEP is one possibility, but that's all it is at this time, Paxton says. "We find it worrisome that people might be using this drug, so we want to get the word out that people should not be using [ART] under the assumption that it will protect them because we simply do not know that yet," Paxton says.

Anecdotal evidence suggests that some people are using PrEP either through finding antiretroviral drugs on their own or by convincing physicians to prescribe them the medication, Liu says. "We don't know the extent to how this is happening, so we've launched a survey of 400 men who have sex with men in the San Francisco bay area," Liu says. "We're asking whether they've heard about PrEP, whether they've heard of people using it, or whether they've used it themselves in an unmonitored fashion."

Liu is involved in a CDC-sponsored trial involving giving tenofovir to HIV-negative men. It's called Project T, and trial locations are in San Francisco and Atlanta. The study was designed with tenofovir because many animal studies have looked at PrEP, using tenofovir, and because it is a once-a-day pill that has a relatively favorable safety profile and resistance profile, Liu explains.

"I believe that looking at daily tenofovir or other HIV medications is one of several promising new HIV prevention strategies, and it's worth exploring," Liu says.

In San Francisco, there are 15 to 20 new HIV infections per week, and there are 14,000 new infections per day worldwide, Liu notes. "While we know behavior change remains the cornerstone of all prevention, we need a range of prevention strategies to further drive down infections, because no one size fits all," Liu says.

"Our hope is that PrEP when combined with condoms and other proven prevention strategies can further reduce infections around the world, but we need to first look at the safety of this approach," Liu adds.

"We're studying 400 healthy, HIV-negative gay and bisexual men, first looking at the biological safety of tenofovir in this population, including looking at side effects and tolerability of this medication," Liu says. "Secondly, we're looking at the behavioral safety of taking an HIV pill on a daily basis, and specifically, we're looking at whether men, as a result of taking a daily pill, might change or increase or decrease risk behavior."

The double-blinded, placebo-controlled trial has a unique design in that there's an immediate tenofovir group and a delayed tenofovir group, along with two placebo arms. Two arms to the study begin taking a pill at the enrollment visit, and then two arms wait nine months before they start taking the pills, Liu says.

"So they're still in the study and come in for a visit, but they don't take the pill until nine months later," Liu says. "What this design enables us to study is the direct result of taking the pill on risk behavior."

Investigators will see if there are any changes in risk behavior, and they'll look at the issue of antiretroviral adherence among a healthy population, Liu adds. "We'll see whether people experience any types of social harms while being in the clinical trials," Liu says.

The study's extensive informed consent process involves describing the nature of the study and reinforcing the fact that they might receive a placebo and even if they receive the drug, there's no evidence that tenofovir can work to prevent HIV. The participants are given risk reduction counseling, free condoms and lubricants, and they receive a test for HIV at each of the three-month visits, Liu says.

More than 100 volunteers, ages 18 to 60, have been enrolled in the two-year trial in San Francisco, and altruism is listed as their main reason for participating, Liu says.

"They want to contribute to HIV prevention in some way," Liu says. "This is one way they can give back to their community, and that's the most common reason we hear for why they enroll."

The study results will probably be available in late 2008 or 2009, Liu says.

Meantime, the CDC has changed one tenofovir study to include the combination therapy of Truvada. The Botswana study had begun as a tenofovir study, but was retooled as a phase III study to look at Truvada, Paxton says.

"It may be five more months to get all the required protocol approvals from IRBs and to get the drug imported into Botswana," Paxton says.

When that work is complete, the study will begin to enroll 1,200 young adults, who are within the age group of the highest incidence of HIV infection, Paxton says.

It probably will take about 15 months to fully enroll participants, and then all participants will be followed until the last person enrolled has been followed for 12 months, Paxton explains.

Since the phase III study was built upon extensive work involving the study of tenofovir alone, phase II preliminary data are available, and this information contains both safety and efficacy results, Paxton says.

"What we originally planned was a combined phase II/III study, but after the first 200 persons were enrolled, we put the study on hold, looked at safety data to make sure there was nothing untoward going on, and we rolled it over into a phase III trial, Paxton says.

Safety data will continue to be collected, and ongoing data will be reviewed by a data safety monitoring board, Paxton notes.

Some literature reports have discussed possibly lowering the viral set point among people who get early antiretroviral therapy, so it's possible that these people who had ART during the early days of their infection might end up with an attenuated course of infection, Paxton says.

It's a theoretical idea, but investigators will watch for it, she adds. "If a person becomes HIV infected during the trial they will go into the seroconverter protocol where — at specified intervals — they will have intensive follow-up, getting CD4 cell counts checked, viral resistance profile followed," Paxton explains. "And we'll see whether there are any differences in their HIV course that may possibly be due to having been exposed to an antiretroviral early on."

Researchers don't expect very many seroconverters during the trial, and even for those who do seroconvert, they won't be on the drugs very long, Paxton says.

"They're tested for HIV every month, and as soon as they turn positive they are taken off the drugs, so the longest amount of time they would be Truvada would be a month," Paxton says.

The seroconverters will be provided with intensive counseling and follow-up care, but they won't meet the criteria for ART until their CD4 cell count lowers to below the 200 to 250 range, Paxton says.

Trial participants who do not seroconvert will remain on the study drug until the last person enrolled has been on the drug for 12 months, Paxton says.

The costs of Truvada, which was developed by Gilead Sciences, are provided at cost for the trial, Paxton says. "It costs about 57 cents per pill for tenofovir and 87 cents per pill for Truvada," she says.

Even if Truvada as PrEP proves effective in clinical trials, it will always be promoted in conjunction with condoms, abstinence, knowing your partner's status, and all the other things that public health officials know works, Paxton says.

"And studying PrEP doesn't prevent us from exploring microbicides, vaccines, and other things, as well," she adds. "We do think this could show promise, but we won't know if it works until the trials are completed." ■

A completely new target for fighting HIV infection?

Target involves DNA repair genes

Investigators have discovered a natural host defense against HIV thanks to a little help from yeast virus research. Researchers have found that two DNA repair genes can defend cells from HIV infection.[1]

The DNA repair genes are XPB and XPD, which are major pathways for destroying HIV, says **Richard Fishel**, PhD, a professor of molecular virology, immunology, and medical genetics and a professor of human cancer genetics at the Ohio State University Comprehensive Cancer Center in Columbus, OH.

The study found that HIV cDNA had greater stability in mutant XPB and XPD cells, which suggests that XPB and XPD could play an important role in defending against HIV infection.[1]

The key to this discovery was having the flexibility to look at yeast research, Fishel says. Yeast can be infected with a TY1 virus that has some similarities to HIV, he explains. With yeast, investigators earlier had set up a genetic selection to determine which host genes will impact the selection of TY1, Fishel says.

"The problem with TY and yeast is it's really hard to figure out the mechanism for how this works," Fishel says. "But the research conclusion was that when you knock out these DNA repair genes, you get elevated integration of TY, so they must defend against TY integration."

Fishel recalled the TY1 findings later when he heard of another researcher's work in studying HIV integration into DNA. By taking the yeast research ground work and seeing if the cell lines discovered in the earlier investigations would have an effect on HIV, HIV investigators were able to find out how the integration process works with HIV, Fishel says.

The reverse transcribed RNA is called cDNA, and for the integration of HIV, cDNA is an obligatory step in the life cycle, because if the virus does not integrate, nothing happens, Fishel says.

"HIV injects RNA into the cell and as it gets into the cytoplasm inside the cell, it takes RNA and copies it into DNA by reverse transcription," Fishel explains. The result is cDNA. "So the cDNA gets into the nucleus and pathway that involves the genes and degrades DNA before it gets into the genome," Fishel explains.

"The majority of cDNA is degraded or lost, and [little] more than 10% of cDNA can ever integrate into the virus, so the majority is lost by some mechanism, and we think 80% of that is degradation."

If researchers could discover a way to degrade the extra 10% then the virus would enter oblivion, Fishel notes. "We're pretty sure that access to cDNA is through the ends, which are protected by integrase. If you mutate DNA repair genes so they're nonfunctional, integration goes up pretty dramatically. In yeast it's 10 to 1,000 fold; in humans it's two to five fold."

When these genes are functional they are suppressing integration, and that's the defense against viruses, Fishel says. These findings suggest possible targets for future HIV drugs, including a host-targeted drug, Fishel notes.

"We want to know all the components of this pathway," Fishel says. "We would like to screen for small molecules which might alter this."

Also, investigators would like to identify other defense pathways and mechanisms, which might be DNA pathways too and which could have

been predicted by the yeast research results, Fishel says.

Funding and time are the major obstacles to building on this research and creating a new antiretroviral drug, Fishel says. For example, the development of an integrase inhibitor has taken a considerable amount of time and money, he says.

"Pharmaceutical companies are a little gun-shy about going after something else that's new," Fishel says. "Instead, they'll take one mechanism and then vary the drug, as they did with reverse transcriptase inhibitors, as the virus mutates to become resistant."

Nonetheless, the potential of a drug that would use the natural defenses of the DNA repair genes is appealing because this type of drug probably would last far longer, Fishel says.

Essentially, the drug would strengthen HIV's degradation process by assisting the two DNA repair genes in the destruction of HIV cDNA in cells. This way, there is a reduced pool of HIV cDNA that can integrate into host chromosomes, and this protects cells from infection, Fishel says.

It's far less likely HIV would be able to develop resistance to this type of host-targeted drug than it does to drugs that target viral proteins, he adds.

"For DNA repair genes, there is no way around degradation," Fishel says. "I think HIV would have to change its whole life cycle in some sense, change the whole picture so it wouldn't allow access to degradation machinery, and it would be very difficult." ■

Reference:

1. Yoder K, et al. The DNA repair genes XPB and XPD defend cells from retroviral infection. *Proc Natl Acad Sci USA*. 2006;103(12):4622-4627.

Metabolic problems in children on ARTs found

Solution is finding balance in treatment

Conducting clinical trials involving HIV-infected children is very challenging, so the evidence has slowly trickled in, but researchers now believe HIV infection among children can lead to similar metabolic and other problems long noted in adults with the disease.

Many of the complications recognized as a result of HIV disease and/or treatment, including insulin resistance, lipodystrophy, mitochondrial toxicity, and others, may also appear in HIV-infected children, says **Grace McComsey**, MD, division chief of the pediatric infectious diseases and rheumatology, and an associate professor of pediatrics and medicine at the Case Western Reserve University in Cleveland, OH.

"Another complication is bone abnormalities, which is especially important in children," McComsey says.

"Adults with HIV seem to be prone to have a loss of bone density or bone mass, and we have done studies in children with HIV where they have had a very high rate of osteopenia and osteoporosis."

The children's bones were very thin for what is expected at their age, and the investigations could not answer definitively the question of whether the problem was the HIV disease, medication, or both, McComsey says.

"It's very much a concern, because if you have a teenager with low bone mass, then they won't reach peak bone mass which is reached at age 30," McComsey says.

"I deal with that problem in the clinic every day; if children have very thin bones they'll be at risk for fracture, and you can't restrict their activities very much."

The most rapid bone growth occurs between ages eight and 15, but in HIV-positive children, a recent study showed that 43% to 74% had osteopenia and 23% to 48% had osteoporosis, he says.

Another recent study has shown that tenofovir disoproxil fumarate (TDF) is associated with decreases in bone mineral density among children infected with HIV and on TDF treatment.[1]

McComsey also has seen evidence of lipodystrophy and lipatrophy among children in her clinic, and these metabolic problems are particularly difficult for teenagers, she says.

"I know by experience that several of my teenagers, as soon as they start to notice body fat changes and they know it has something to do with HIV drugs, we have a significant difficulty keeping them on the drugs," McComsey says. "Two teenage girls stopped taking the drugs without telling us, and they admitted they were throwing out the pills and telling their parents they were taking them."

On a positive note, the newer antiretrovirals appear to result in less lipodystrophy, McComsey says. "So we're hoping we won't see a lot of new cases as we see newer and newer drugs."

HIV-infected children on antiretroviral drugs

also appear to be at a higher risk for increased lipid levels and atherosclerosis, McComsey says.

Hyperlipidemia is a problem even in children under age 10, and this is a difficult group to treat because statin drugs have not been approved by the Food and Drug Administration (FDA) for prescriptions to young children, McComsey says.

So pediatricians with HIV patients are put in the dilemma of deciding whether it's more harmful to give statin drugs to young children with HIV infection or whether it's more dangerous to leave their lipid levels high, McComsey says.

One study found that there were higher cardiovascular markers in ART-treated HIV-positive children when compared with healthy children.[2]

The study suggests that children with HIV disease may be at significant risk for atherosclerosis while they are young.[2]

"We found that HIV-infected children without any other risk factor other than being HIV positive and being on antiretrovirals, had arteries with underlying atherosclerosis," McComsey says. "That's why my study and other such studies in kids are so important," she adds. "This tells us we shouldn't stay comfortable with saying the children have high lipids, but don't worry about them."

McComsey's study, which measured carotid intima-media thickness, produced evidence that the high lipid levels have a significant effect on the children's hearts.

In treating HIV infected children, a physician's challenge is to balance the pros and cons of every treatment, including ARTs, McComsey says.

"If someone has very high lipid levels that I can't control with diet, then first I try to switch their HIV medications to those less likely to cause this lipemia," McComsey says.

"I've been successful in this approach except in one child who I had to start on statins at age nine," McComsey says. "I tried to do strict diet control, which you can imagine in children is a nightmare." ■

References:

1. Gafni R, et al. Effect of tenofovir disoproxil fumarate-containing HAART on bone mineral density in HIV-infected children. Presented at the 13th Conference on Retroviruses and Opportunistic Infections, held Feb. 5-8, 2006, in Denver, CO. Abstract: 694.

2. McComsey G, O'Riordan M, Hazen S, et al. Carotid intima media thickness and cardiovascular markers in HIV-infected children. Presented at the 13th Conference on Retroviruses and Opportunistic Infections, held Feb. 5-8, 2006, in Denver, CO. Abstract: 691.

Research findings suggest new course against HIV

Nef protein plays major role

New research provides some answers to long-standing questions about how HIV proliferates despite the initial strong immune response. Investigators have discovered evidence that HIV-1 evades some immune cell responses by hijacking physiological feedback inhibitors in B cells via the negative factor (Nef) protein, an HIV-1 protein that is expressed by infected cells.[1]

"Nef is a viral protein known to be involved in the development of AIDS, and it has a profound effect in viral replication," says **Andrea Cerutti**, MD, an assistant professor of pathology and laboratory medicine at Weill Medical College of Cornell University in New York, NY.

"Previous studies have shown that this viral protein is important in the development of immune deficiency in primates," Cerutti says. Among humans, there are long-term HIV survivors who lack the Nef protein and never progress with their disease, Cerutti notes.

"We know there are people who are exposed to HIV and yet do not develop the disease, and this can happen for several reasons: First, they lack CCR5, the receptor for HIV," Cerutti says. "Another reason is that they lack the viral protein Nef and were infected by viruses that for some reason lack function of the Nef protein."

The latter cases involve people who have developed an attenuated form of the disease or who have not developed the disease at all. "The role of Nef in antibody production was not known, and that's why we wanted to do this study," Cerutti says. "Antibodies play an important role in HIV infection."

The immune system's two arms include T cells that recognize infected cells and destroy them and the B cells which make antibodies, which work like molecular bullets, neutralizing targets, Cerutti explains. "So Nef is known to play an important role in the T cell response, but nothing was known about the response of the B cells, which make antibodies," Cerutti says.

Also, immunologists have been puzzled for years by the way HIV-infected people are unable to make effective antibody responses against the virus and opportunistic agents despite having high blood levels of immune T cells, he adds.

While HIV enhances nonspecific IgG and IgA

production on one hand (this phenomenon is known as hypergammaglobulinemia), it decreases protective IgG and IgA responses against invading microorganisms and prevents patients from responding to vaccines on the other, Cerutti says.

"They cannot make effective antibodies of IgA and IgG types, particularly IgA against HIV itself," Cerutti says. "There is a lack of HIV-1-specific IgA at the level of intestinal and urogenital mucosa surfaces, which are an important site of entry for HIV in general," Cerutti explains.

"IgA plays an important role in blocking infections at those mucosal sites because the IgA can be secreted at those sites," Cerutti adds. "The reason why there is a lack of virus-specific IgA at mucosal sites during HIV-1 infection has long puzzled immunologists.?

Also, it's unclear why HIV-1 prevents infected patients from mounting effective IgG and IgA responses to vaccines, even at the early stage of the disease, when T cells are relatively normal, Cerutti says.

This conundrum prompted scientists to hypothesize that the process involved in generating IgA and IgG antibodies somehow was defective or impaired in HIV patients, Cerutti says.

"So we started looking at the presence of Nef in the areas of lymph nodes where IgG and IgA antibodies are made and found an increased concentration of Nef," he says. "We hypothesized that since Nef was present there it has a role in inactivation of the process, and we found that Nef is able to penetrate B cells even though B cells are not infected."

By studying the lymph nodes where the B cells make antibodies, investigators found that in HIV patients Nef is present in the B cells, Cerutti says.

"We don't know the mechanism by which Nef goes from infected cells to B cells," Cerutti notes. "It's present in the B cells, although B cells are not infected by HIV, so future research will focus on the mechanisms by which Nef penetrates B cells."

The implications of the findings involving Nef's important role in HIV infection could lead to new antiretroviral agents. "If Nef is so important in general for the impairment of the immune system, then one possibility is to utilize synthetic inhibitors of Nef to attenuate the immune deficiency of people already infected," Cerutti says. "This could be used, also, to prevent infection in subjects at risk for infection."

For example, there could be a vaccine that attenuates Nef, Cerutti suggests.

"Some investigators are testing the ability of an attenuated HIV virus that lacks Nef to stimulate the immune system of non-infected primates," Cerutti says. "An attenuated virus would be able to stimulate a robust immune response, generate memory, and create a potential for protection against subsequent infection."

Because of the lack of Nef, the attenuated virus would not generate any disease, Cerutti adds.

Another possibility is the development of a chemical agent, a small compound, that would neutralize the activity of Nef, and that could be used to improve the immune response and decrease the spread of HIV throughout the body, Cerutti says.

Scientists have been aware of how crucial Nef is because Nef has very profound effects on T cells and macrophages, two cell types central for the initiation of protective immune responses, Cerutti says.

"Nef seems to disrupt the immune response in several ways, and one of the ways is to impair the ability of T cells to orchestrate the immune response and kill cells infected by HIV-1," he says.

"Our study suggests Nef is also important in the impairment of the B cell response, which is essential because it leads to production of IgG and IgA antibodies against HIV and opportunistic agents."

The role of Nef in HIV infection is very interesting and should be further studied, Cerutti suggests. ■

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1. Qiao X, et al. Human immunodeficiency virus 1 Nef suppresses CD40-dependent immunoglobulin class switching in bystander B cells. *Nat Immunol* 2006;7:302-310.

Adherence Strategies

Therapy for family, patient improves adherence

Intervention designed to reduce drug abuse relapse

Investigators have found that an intensive one-on-one therapy that involves HIV patients and their families holds promise as an effective adherence intervention.

"Structural ecosystems therapy is a systemic family therapy that targets the way families are grouped and interact," says **Daniel J. Feaster**, PhD, an associate professor of biostatistics at the

Stempel School of Public Health, Florida International University in Miami.

Families are defined broadly, and the goal is for the therapist, typically a master's level social worker, to gain the family's trust and observe how the members relate to one another, Feaster explains.

Initially, a study using this technique was aimed at improving patients' adjustment to HIV infection, but it was modified to measure HIV adherence, as well, he notes.

Therapists receive extensive training of up to five months, depending on their level of experience in systemic work, Feaster says.

The therapists' meetings with patients and their families primarily take place in person, although some crisis intervention could be conducted by telephone, Feaster says.

"The overriding theme is building support," Feaster says. "As much as possible we try to get the family in at the first session with the therapist," Feaster says. "It really is a matter of dropping in and getting to know the family, feeling out what they think of the therapist."

A key component is to create an atmosphere of trust in which the patient does not feel as though she is being judged or given orders.

Therapists might let the patient and family tell their stories in the beginning, Feaster explains.

"That's an important period because the therapist is joining with the family and is supportive and understands their issues," he says.

Therapists encourage family members to assist patients in creating a plan for what will happen if the woman relapses into drug abuse, Feaster says.

"We break the barriers to talk about the issue and to try to make the woman understand that if she slips up, it's not forever and she need not be afraid to draw on her family support," Feaster says.

"In some families there are huge issues, but in others there are other issues that may prevent the family from adequately supporting the woman," Feaster says. "The whole basis of this theory is that as groups we get into repetitive interactions, and everyone has a way of pushing buttons, and so sometimes you have to change the way you interact to keep those buttons from being pushed and from triggering a relapse."

Each session may last up to an hour, and it's typically conducted inside the patient's home. For purposes of the research study, the sessions were videotaped, but they were reviewed only for providing feedback to the therapists, Feaster says.

The therapist supervisor might provide feedback to the therapist about how she over-supported a particular person in the family group and did not make all of the family members feel as though their issues were as well acknowledged, he says.

Each weekly sessions builds on the establishment of rapport, and they may last for up to four months, Feaster says.

"It is fairly intensive, and for some families there may not be a need for it to continue that long," he says.

The initial study found that women in the intervention arm had significantly better adherence than did the control arms, Feaster says.

"So we're testing a modification of that original therapy, involving mostly African American women who have just received drug abuse treatment," Feaster says. "We're focusing on drug abuse relapse, HIV medication adherence, and sexual risk behaviors."

Investigators felt the intervention should focus on sexual risk behaviors so that women could prevent themselves from being exposed to sexually transmitted infections, which are difficult to treat in the HIV population, Feaster says.

The second study will eventually enroll about 150 women, including both English and Spanish-speaking women, he says.

The first study, which enrolled 209 African American women of whom about 60% had a history of drug abuse, found that the women who were in the therapy intervention had significant declines in distress relative to the community control group and to a group of women who had a person-centered therapy, Feaster notes.

"We saw a significant decline in family hassles," Feaster says. "Since we did look at medication adherence outcomes, we saw improved medication adherence relative to the person-centered group."

Also, the intervention group receiving structural ecosystems therapy had a lower rate of drug abuse relapse than those in the person-centered therapy, Feaster says.

"We feel this program is a good relapse prevention type of therapy and after care," Feaster notes. "So if people have drug problems, we feel they could go through an extensive drug therapy and then we'd help to reintegrate them with their families."

This integration is time-consuming because their family-oriented relationships may have been strained in the past, he says.

The reason this type of intervention is ideal also for the medication adherence among an HIV population with a drug abuse history is because this group often are not prescribed HIV antiretroviral medications if physicians fear they are active drug users, Feaster says.

Through the intervention, involving the patients' families, investigators have shown that antiretroviral drug adherence can be improved, and so there is no reason to be afraid of prescribing to this population, Feaster says.

If the second study's results are similarly positive, investigators are hopeful the model will be used by others. It could be adapted for different populations, as well, Feaster notes.

"We're also testing an adaptation of this model among HIV-infected prisoners in California," Feaster says. "In that model the sexual risk behaviors has more prominence because they're just getting out of prison."

Once the model has been proven in studies, it is possible it could be extended to work with other ecosystems and family sessions, Feaster says. ■

DM program keeps AIDS patients out of hospital

One-on-one education is the key to success

An intensive one-on-one case management program helps people with AIDS stay adherent to their medication regime, avoid hospitalizations and emergency department visits, and learn to self-manage their disease. The disease management program of the AIDS Healthcare Foundation, received a score of 98.4% out of a possible 100% during the survey.

RN care managers with extensive HIV-AIDS expertise oversee the care of 10,000 Medicaid patients with AIDS across the state of Florida.

"We've been successful because of the intense one-on-one and face-to-face work with the patients. The core of our program is education and one-on-one coaching to improve the patients' quality of life and to keep them out of the emergency department and out of the hospital," says **Gene Bundrock**, MS, RN, CCM, statewide director for AIDS Healthcare Foundation's Positive Healthcare Florida.

The field-based care managers work out of their homes and manage the care of patients in the counties in which they live. They work closely with the patients' physicians, often accompanying patients for their office visits and working with them to coordinate care.

"Positive Healthcare takes a different approach to disease management. We do a lot of face-to-face assessments. The care managers get to know the provider and work closely with them. They meet with social service agencies in the community and incorporate them in the plan of care," says **Donna Stidham**, chief of managed care for the AIDS Healthcare Foundation.

Publicly supported patients with AIDS present a challenge to providers. They are poor. Many don't have telephones. They often live with relatives and move around a lot, Bundrock says. The program uses representatives from the community who help find patients and call the care manager. The representative makes an appointment for the patient with the care manager, who sees him or her within three days.

"Our care managers will meet with them anywhere — the home, the doctor's office, in a restaurant, or even under a bridge. We'll go anywhere the patient feels comfortable and where their confidentiality won't be breached," Stidham says.

When new patients are identified for the program, the nurse contacts them and makes an appointment to see them, preferably at their home."It helps the nurses manage the care if they can see their patients in the home environment and become aware of their living conditions. Some don't have electricity. Others may not have a refrigerator or cooking facilities. It helps us tailor a care plan when we can see firsthand what the patient is facing," Bundrock says.

The care managers conduct an extensive assessment that categorizes patients by severity level and acts as a guideline for the number of interventions the patient received. They determine the patients' needs and barriers to care, such as transportation, and get a consent form allowing them to go into the physician's office and examine the patient's medical record.

"These patients are not good historians on previous hospitalizations. They may know they had a cough but not whether it was pneumonia. Our nurses examine the medical record to find out what we need to know to manage the disease," Bundrock says.

The care managers zero in on patients with a high acuity level who are frequently hospitalized, not adherent to their medication regime, and are substance abusers.

"Once the nurse has seen the patient in

person, some of the work can be done [by telephone]. She might not need to see patients every month if they are doing OK, the lab work looks good, and she knows they are being adherent with their medications," Bundrock reports.

The disease management nurses remind patients if they have physician appointments, check to see that the appointment has taken place, and visit the physician office to review the chart. They give the patient a pillbox to help them organize their medications and stress the importance of taking the medication until the physician discontinues it.

Because confidentiality is an issue with AIDS patients, Positive Healthcare mails AIDS-related educational materials only to patients who have given their permission. Otherwise, introductory and follow-up letters are very generic.

The care managers know their community well, often serving on local health planning councils. They know the practitioners in the community and know how to guide their patients through the complex medical system to get help.

The care manager can mine the database for claims data and talk to the physician if a patient is making frequent trips to the emergency department.

"These patients have a lot of mental health issues as well. Depression is a huge problem, and many are on psychiatric medication. Physicians can't get the patients interested in caring for themselves until their mental status is stable," Bundrock says.

Dental care is another problem for AIDS patients on Medicaid. "The state doesn't pay for dental work of any kind, but Medicaid patients still get toothaches. We try to get them access to dental care so they won't go to the emergency department or hospital with an infection that's the result of a dental problem," he says.

A team of nurses and an LPN care partner manage the care of the population in each area. The LPN takes care of telephone calls and other reminders for patients who are on severity level 1, allowing the care manager to concentrate on the more complex patients who are in and out of the emergency department, helping them avoid admissions.

For instance, AIDS medications often cause adverse reactions until the patient gets used to them, causing trips to the emergency department for pain and nausea. The care managers encourage them to try alternatives.

"Now instead of going to the emergency department when they start a new medication and have cramps, they call the care manager who helps them understand that it might be a side effect of the medication. They suggest that they use an over-the-counter medication rather than going to the emergency department," Bundrock explains.

The care managers work closely with the physicians and nurses in physician offices to make sure that the patients are getting the recommended care. They refer any problems they spot to Bundrock or the medical director, who contacts the physician and educates him or her about evidence-based guidelines for the treatment of HIV-AIDS.

Positive Healthcare holds six educational programs a year in each region, informing physicians about the latest information from the scientific community.

"We stay up on new treatment regimes and make sure the physicians know about them. A bad regime can have a bad outcome, which in turn can cost hundreds of thousands of dollars," Bundrock says.

Physicians in the AIDS Healthcare Foundation's disease management programs work with the physicians who care for the patient. "They don't want to interrupt the physician-patient relationship but they do want to enhance the physician's access to knowledge about the condition," Stidham says.

In California, the AIDS Healthcare Foundation began operating one of the first Medicaid managed care programs specially designed for people with AIDS in California in 1995. The foundation has recently received approval to operate a Medicare Advantage plan, allowing the patients to get their drugs through Medicare Part D.

The Medicaid program covers the sickest of the sick, only people with AIDS. HIV-positive patients are not eligible. The state of California compares the foundation's costs to the fee-for-service Medicaid program and splits the savings with the foundation on a 50-50 basis.

"Our patients have always had better outcomes, shorter lengths of stay, and less cost that the fee-for-service patients," Stidham says.

Patients in both the Medicare and Medicaid programs are assigned an RN case manager who has HIV expertise. All of the primary care physicians and specialists in the network have experience working with people with AIDS, and the formulary is designed with people with AIDS in mind. ■

HIV subtype efficient mortality predictor

Subtype D and AD lead to rapid deaths

A surprising finding from the research-rich Rakai (Uganda) cohort shows that a person's HIV subtype is a significant predictor of whether a person might die quickly from AIDS than viral load, CD4 cell count, and other common predictors of disease progression.

"We found that 10% of the people with subtype D and recombinant virus incorporating D were dead within three years of being infected," says **Oliver Laeyendecker**, MS, MBA, senior research associate at The Johns Hopkins University School of Medicine in Baltimore, MD, and a senior research assistant at the National Institute of Allergy and Infectious Disease in Bethesda, MD.

The data tells investigators when people were infected, within a six-month window, so the timeline from HIV infection to death was well documented, Laeyendecker notes. "The shocking thing is those individuals did not have a significantly higher viral load than the general population of HIV patients."

Investigators also found that individuals with HIV subtype A had an average survival rate of nine years, whereas those with subtype D had an average survival rate of seven years, and those with a recombinant AD had an average survival rate of six years, Laeyendecker says.

All of the people who died within three years did not have a significantly higher viral load than those who took longer to die, Laeyendecker says.

"They all had mid-to-high range of viral load," he explains. "The people with really high viral loads were much more likely to die quicker than those who had very low viral loads, but when you stratified those individuals who died within three years and those who didn't, there was no significant difference in viral load."

In the Rakai District of Uganda, where the study drew on a population-based cohort of 12,000 individuals, who have been interviewed and provided blood samples since 1994, 60% of the HIV infected population has subtype D. Another 20% have the recombinant AD, and 16% have subtype A, Laeyendecker notes.

Most studies about disease progression have been done in the United States and Europe where subtype B is prevalent, he says. "In Kenya, Uganda, and Tanzania, subtype D is endemic to these countries. In South Africa and India, the common subtype is C, and Thailand, the common subtype is recombinant AE and subtype B."

The Rakai cohort was part of a sexually transmitted disease (STD) intervention trial from 1994 to 1998. It studied the hypothesis that if people were tested for STDs then health officials could lower the incidence of HIV, Laeyendecker explains.

Since the study was longitudinal, investigators also could study the incidence of HIV infection and the probabilities of HIV transmission. Some of the many studies that have been published as a result of this cohort have found that pregnancy increases the risk of HIV acquisition, for example, Laeyendecker says.

The cohort maintains about 12,000 people in the study, and as some die or withdraw, they are replaced with others. "All of the people in the cohort with HIV infection were provided access to antiretroviral therapy in 2004," he says.

For the subtype study, researchers identified HIV subtypes and screened for recombinant virus, and then analyzed the data to see whether the people who had provided the original blood sample had died, Laeyendecker says.

Why researchers found this difference in subtype remains an unanswered question, he says.

Investigators have looked at co-receptor tropism in the Ugandan individuals and have found that 25% of the people with subtype D have dual tropic virus in which the virus infects both X4 and R5 receptors, Laeyendecker says.

"For subtype A, it's a purely R5 virus, and for the recombinant strains it was about 16% dual tropic," he adds. Dual tropism played a role in rapid deaths, the data suggest. "About two-thirds of the people who had dual tropic virus from the time point that we did the assay were

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- HIV spread among indigenous people threatens culture

dead within three years," Laeyendecker says. "Tropism is determining which co-receptor the virus is using."

Investigators believe the reason why subtype D virus is more pathogenic is because a greater percentage of its virus uses co-receptor CCRX4, Laeyendecker says. "So subtype D is bad and D with X4 tropic virus is really bad," he says.

For researchers and clinicians working in Uganda and other places where subtype D is common, this knowledge suggests they monitor their patients with subtypes D or AD more closely than they do those with subtype A, but this may be difficult to achieve in the resource poor regions, Laeyendecker notes. ■

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, 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.

CE/CME *questions*

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 certificate of completion. When your evaluation is received, a certificate will be mailed to you.

17. The Centers for Disease Control and Prevention (CDC) of Atlanta, GA, is studying the use of a pre-exposure prophylaxis. Which two drugs are being studied for this use?
A. Abacavir and lamivudine
B. Zidovudine and nevirapine
C. Tenofovir and emtricitabine
D. Indinavir and efavirenz

18. Which of the following HIV-related complications are seen in HIV-infected children, as well as adults?
A. Lipodystrophy and atherosclerosis
B. Osteopenia and osteoporosis
C. Lipodystrophy and lipoatrophy
D. All of the above

19. Which viral protein is now known to have a profound effect in viral replication for HIV?
A. Tat
B. Nef
C. Rev
D. Vif

20. Which of the following are DNA repair genes recently were found by investigators to defend cells from HIV infection?
A. XPB and XPD
B. TDG and MPG
C. PNKP and LIG3
D. APEX1 and APEX2

Answers: 17. C; 18. D; 19. B; 20. A