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## IN THIS ISSUE





# Clinicians, researchers starting to understand impact of depression

*Study shows that depressed HIV patients cost more*

Recent research drives home the point that HIV patients are at risk for becoming depressed, and their progression to AIDS may be affected by their psychological status and the level of stress in their lives. Also, untreated depression in HIV patients results in higher medical care costs, a study has shown.

"HIV intrudes on your life, has financial costs, and affects your sex life," says **Margaret Chesney**, PhD, professor of medicine at the University of California – San Francisco (UCSF).

"So the persons living with HIV and their closest family and friends and providers all tend to become at times overwhelmed by this," Chesney explains. "Sometimes it's depression; sometimes it's just being stressed or having a depressed mood."

### *Data confirm it*

While clinicians may have been alert to this problem through anecdotal evidence and intuition previously, now there's a growing body of research confirming their suspicions that HIV patients fare worse when they are depressed or under excessive stress.

"There's beginning to be an outpouring of data that psychological factors affect disease progression in HIV," says **Jane Leserman**, PhD, research associate professor of psychiatry at the University of North Carolina School of Medicine in Chapel Hill.

Other research shows a high rate of depression among older adults with HIV.

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## COMING IN FUTURE ISSUES

■ **Raising satisfaction among HIV patients:** Researchers look at strategies clinicians can employ with patients

■ **Physicians have changed perceptions of lipodystrophy:** Study explains how the medical view has evolved

■ **Quick response to HIV infection could jump-start immune system:** New study shows how it might be possible to keep virus under control without long-term antiretroviral therapy

■ **Potential causes of muscle-wasting disease uncovered:** Scientists hope research will lead to new treatments

■ **Methadone treatment affects antiretroviral therapy:** Methadone decreases bioavailability of didanosine and stavudine

"About 54% of older adults with HIV infection have some form of depression, whether mild, moderate, or severe," says **Timothy Heckman**, PhD, associate professor of psychology at Ohio University in Athens. "This is higher than in the general population of HIV patients," Heckman adds.

Two trends make this finding more alarming, Heckman notes. First, the success of antiretroviral medications in extending the lives of HIV patients means it is likely many of the people who become infected while in their 20s and 30s will live until their late 50s and 60s. Second, there is an increase in HIV infection among older adults.

Together, those trends indicate that clinicians need to be aware that their older patients are at greater risk for depression and that their younger patients may face an increasing risk as they age.

"I'm very concerned about not just extending the life expectancy of people with HIV, but also improving their quality of life," Heckman says. **(See story on depression among older HIV patients, p. 132.)**

### *Watch for depression at diagnosis*

A University of Florida researcher has found that HIV patients are particularly prone to develop depression at two specific times: right after they receive their HIV diagnosis and when their symptoms first appear, explains **Gail Ironson**, MD, PhD, professor of psychology and psychiatry at the University of Miami in Coral Gables, FL.

"So a physician should be on the lookout for that," Ironson says, "and also ask patients if they have had any particularly difficult stressors in the last six months, any major stressful events in their lives."

Although the prospects of a longer and healthier life now exist for HIV patients, the disease still carries a stigma, and depression is common among those who are infected, says **Jerry Durham**, PhD, RN, FAAN, dean and professor at the Barnes College of Nursing at the University of Missouri in St. Louis.

"HIV is a life-threatening condition, and it carries with it a sense of loss and the potential of not having a very good outcome," Durham says.

Treating depression, whether through a variety of cognitive and behavioral therapy interventions, stress management, support groups, or

## Quick study guide on the cost of depression

Researchers at Rutgers University of New Brunswick, NJ, investigated a population of more than 5,000 New Jersey Medicaid recipients who tested positive for HIV between 1991 and 1996 to assess the prevalence and predictors of diagnosed depression and to compare utilization and costs between those treated with antidepressants and those untreated.[1]

The investigation resulted in the following findings:[1]

- 18.2% were diagnosed with depression.
- 54.2% of the total population were men, but only 15.3% of those diagnosed with depression were male.
- 21.6% of the females in the group were diagnosed with depression.
- 22.5% of the white patients were depressed, and whites consisted of 19.2% of the total group.
- 16.2% of the African-Americans were depressed, and 62.6% of the overall group was African-American.
- 20.3% of the Hispanics were depressed, and 17.6% of the total group was Hispanic.
- Injection drug users, whether or not in a methadone treatment program, were much more likely to be depressed than nonusers, with 30.5% consistently on a methadone maintenance program and 26.2% on no program diagnosed with depression, compared with only 8% of noninjection drug users diagnosed as depressed.
- Those patients diagnosed with depression who were treated with antidepressants had an average monthly inpatient expenditure of $1,531, compared with an average monthly inpatient expenditure of $1,884 for those patients who were depressed and not treated with antidepressants.
- Nearly 40% of patients diagnosed with depression were not prescribed antidepressants.
- Patients receiving antidepressants were more likely to be prescribed antiretroviral drugs.

### *Reference*

1. Sambamoorthi U, Walkup J, Olfson M, Crystal S. Antidepressant treatment and health services utilization among HIV-infected Medicaid patients diagnosed with depression. *J Gen Int Med* 2000; 15:311-320. ■

medications often is necessary. **(See story on interventions for treating depression in people with HIV, p. 134.)**

Untreated depression is associated with higher medical costs for HIV patients than is treatment with antidepressants, according to a study published this year in the *Journal of General Internal Medicine*. **(See box on study's chief findings, above.)**

The study assessed antidepressant treatment and health services utilization among Medicaid patients who had HIV and were diagnosed with depression. The patients who were treated with antidepressants had significantly lower monthly medical care expenses and were more likely to receive appropriate HIV care.[1]

The study concludes that depression is a major health risk for people with HIV and is associated with a variety of other problems, including lowered immune response, disease progression to AIDS, shorter survival, increased disability, and a lower quality of life.[1]

Leserman has been studying how psychological factors impact the immune system and disease process in HIV patients. The preliminary findings indicate that psychosocial status and neuroendocrine functioning might lead to the acceleration of HIV disease.[2]

"Often when we think about HIV, we focus only on the biological aspects of illness, and the psychological aspects are only thought about in terms of whether someone has a major psychiatric disorder," Leserman says. "In our study, we find psychological factors may be important in terms of disease progression."

Researchers asked adult homosexual men with HIV to fill out questionnaires about the stresses that had occurred in their lives within the past six months. "We took their blood at a certain time in the morning and did neuropsychological and psychiatric evaluations," she says. Investigators measured the men's social support and coping mechanisms based on their answers to the questionnaire, and they measured stress levels based on an objective scale that rated various life stressors.

"So if their dearest friend had died, it received a higher rating than if an acquaintance had died," she explains. "Our rating was based on the idea of how would the typical person, given these circumstances, assess this, rather than using the men's own rating, which was biased."

Researchers viewed stress as something that could affect the men's health even when the men downplayed its importance. "A lot of people are just stoic, and if you ask them how stressful an event was, they say it wasn't so bad, and yet they're suffering," Leserman says. "And other people say they're stressed no matter what's happening to them — they might just get a traffic ticket and that's the biggest stress."

The men answered questions about how satisfied they were with their social support and how they coped with the prospect of developing AIDS and watching their disease grow worse. They were given choices among their answers, such as "I pretend it's not real" or "I pretend it's not happening." Those types of responses indicated their level of denial about the disease.

> "There are not too many good studies on cortisol . . . . Our own findings showed that cortisol was not a very beneficial hormone for these men."

Blood tests revealed their cortisol measures, which tended to predict which men would have a faster progression to AIDS, Leserman says.

"Cortisol is associated with lowering the immune system, and it might have had a direct effect on immune response," she says. "There are not too many good studies on cortisol, and the research is controversial."

Some findings show that high cortisol levels are harmful, while others have not reached that conclusion. "Our own findings showed that cortisol was not a very beneficial hormone for these men," Leserman says.

### References


1. Sambamoorthi U, Walkup J, Olfson M, Crystal S. Antidepressant treatment and health services utilization among HIV-infected Medicaid patients diagnosed with depression. *J Gen Int Med* 2000; 15:311-320.

2. Leserman J, Petitto JM, Golden RN, et al. Impact of stressful life events, depression, social support, coping, and cortisol on progression to AIDS. *Am J Psychiatry* 2000; 1,578:1,221-1,228. ■


# Older patients especially prone to depression, stress

*Elderly often need targeted interventions*

An estimated one in five people with AIDS are men age 45 or older, a rate that has doubled since 1995.[1] Also, an estimated one in four women newly infected with HIV are between 35 and 44.[1] This suggests the HIV population will shift more to the middle years, particularly with the long-term success of antiretroviral drugs. This population requires special attention because people with HIV who are middle-age or elderly have a variety of other health, social, and emotional concerns.

"Depressive symptoms are not uncommon among older adults, and this is particularly true of older adults with cognitive impairments," says **Timothy Heckman**, PhD, associate professor of psychology at Ohio University in Athens. He has been involved with two recent studies of depression among older persons living with HIV disease.

Older people commonly live alone and experience anxiety and social isolation in addition to feelings of depression. In addition, HIV-infected persons often suffer from multiple bereavements, loss of physical and financial independence, discrimination, and other HIV-related difficulties.[2] That combination can lead to life distress and a greater risk for suicide, Heckman says.

People between 45 and 65 years of age have higher suicide rates than do other adults, and suicide is one of the 10 leading causes of death for this age group.[1] Add HIV infection to the group's other life stressors, and the danger is even higher. Investigators have found that one in four middle-age and older persons with HIV infection involved in a recent study reported having had thoughts about suicide within the past week.[1]

The study also found that men had higher rates of suicidal ideation, which were associated with physical symptoms related to HIV disease.[1]

Heckman and other investigators have studied how health care professionals can help this at-risk population, both preventing suicide and improving older HIV patients' general quality of life. Here are some strategies the research suggests:

- **Help improve social support.** In a pilot intervention Heckman and other investigators tested, they found that older adults with HIV were very happy to get together in a group setting with other people like themselves.

Those who had attended support groups consisting of younger HIV-infected people said they couldn't identify with the younger group members. On the other hand, the older adults often said they would love to participate in groups involving other older HIV-infected people. "They need a place where they can talk openly about difficulties they've had in the past and difficulties they're having now," he says. "A support group is a good environment to share personal stories and access support they might not get other places."

• **Teach coping effectiveness training.** Such training can be done in a group setting. "We have them identify stressors in their lives, and then they talk with other group members about the ways they might more effectively deal with these stressors," he says. "They talk about maladaptive coping, such as high alcohol use."

Then the group creates goals for implementing adaptive coping strategies. For example, one event that can lead to stress is the loss of a friend or loved one, which is common among many older HIV-infected people; they were adults when the AIDS epidemic was new 20 years ago and often have lost friends and partners to the disease. Also, older people with HIV may have lost family members to other diseases, and they often have lost jobs and financial independence. Loss is a big issue and an easy stress trigger. "So we spend a lot of time talking about loss," Heckman says. "If people experience bereavements and don't deal with them effectively, that can lead to greater stress."

## HIV disclosure also is a major stressor

Another major stressor has to do with when to disclose one's HIV status. "Older adults have to tell children and grandchildren and friends, who might never have known they were gay or bisexual," he explains. "We discuss who to tell, how to tell, and whether it is safe to tell this individual or this group." The support group creates a safe environment for practicing HIV disclosure. Members might talk about how a particular person will react to the news and whether this could be used against them in a job or housing situation.

"The nice thing about the group environment is that people who've been in similar situations can share with their peers how they handled it and what the response was," he adds.

• **Reach rural HIV patients through phone groups.** Older HIV patients, especially those in rural or small-town areas, often lack support groups of people in their own age bracket. "In rural areas, it's complicated because you have HIV-infected people who live long distances from traditional sources of support, and they can't make it to support groups because of geographical distances or physical limitations," he says. "Often these people will not have cars or driver's licenses. Or they'll have issues of confidentiality and may be concerned about meeting with other HIV-infected people in a small community because word spreads about what's going on and who attends these groups."

A possible solution is a telephone support group in which several HIV-infected rural people are linked across the country, all on the same telephone line at the same time. "They can talk about life histories, perceptions of loneliness, discrimination, perceptions of isolation, and all the things that everybody talks about such as finances, relationship difficulties," Heckman says.

Telephone support groups can be similar to everyday conversations, only with strangers who share similar life circumstances.

Although it is not the same social dynamic as a face-to-face group encounter, the telephone support groups provide participants with the knowledge that other people are experiencing the same sort of difficulties they face. And they can discuss and identify strategies that will help them cope with their daily stressors.

This type of support also can be provided through the Internet in chat rooms and on message boards. But because computer technology is cost-prohibitive for low-income people, the telephone conference, supported by a grant or HIV clinic, may be a more realistic option.

Investigators are studying the outcomes of telephone support services when used to assist HIV-infected people in rural areas. This could be a relatively inexpensive way to provide services to a hard-to-reach population.

"If we find you can effectively disseminate services through the telephone, then others can make a stronger argument to do this and request money to support this type of program," says Heckman.

## References

1. Kalichman SC, Heckman TG, Kochman A, et al. Depression and thoughts of suicide among middle-aged and older persons living with HIV-AIDS. *Psychiatr Serv* 2000; 51:903-907.

2. Heckman TG, Kochman A, Sikkema KJ, Kalichman SC. Depressive symptomatology, daily stressors, and ways of coping among middle-age and older adults living with HIV disease. *J Ment Health Aging* 1999; 5:311-322. ■

# Research offers clues on treating depression, stress

*Many interventions show success*

Ongoing research suggests there are many successful strategies to help people with HIV cope with depression and stress.

Clinicians and psychologists who have worked with HIV-positive patients emphasize how important it is for clinicians to screen all such patients for depression. HIV treatment should include questions about whether patients are having difficulty sleeping, a change in appetite, feelings of sadness, a loss of interest in daily activities, a depletion of normal energy level, trouble concentrating, and any thoughts of harming themselves.

Patients who appear to have mild depression could be referred to an HIV support group or a mental health professional. Those who have more severe signs of depression may be candidates for antidepressant medications.

## Strategies now being used

Here is a look at some of the strategies featured in ongoing and recent research to prevent and alleviate depression and stress:

**1. Accentuate the psychological factors that contribute to long-term survival with HIV.** A Florida researcher has been involved in studies that offer clues to why some HIV patients remain healthier and live longer than others and how to help patients manage stress.

"We have another year to go on the study, but our preliminary results show some psychological factors related to staying healthy with HIV," says **Gail Ironson**, PhD, MD, professor of psychology and psychiatry at the University of Miami in Coral Gables, FL.

The psychological factors that appear to be important are these:

• The patient has a good, collaborative relationship with his or her doctor. "Often we find that the people who are doing well had changed doctors if they had a doctor they didn't like," Ironson says. "They needed a doctor they could talk to and maybe ask, 'I'm using this alternative treatment. What do you think about this?' or say, 'I don't like the side effects of this medication. Can we work to find some other combination?'"

• The patient uses psychological protectors, such as optimism and staying involved. "A lot of long-term survivors have gotten involved in helping other people with HIV," Ironson says.

• The patient has good social support. "Some people will be wonderful, and others will reject you, so you have to move on to creating a support system for yourself and realize that not everyone is going to be supportive," Ironson says.

• The patient has a clear, comfortable idea of his or her spirituality. "Often patients wouldn't find the support they needed in traditional religion," Ironson explains. "So long-term survivors, instead of rejecting religion altogether, would redefine their spirituality so they could still have comfort from some of the beliefs without feeling they were rejected by their religion."

• The patient can express emotions. This may involve a gay HIV-infected man finding another gay man to confide in and discuss what he's going through. This also is a way for the HIV-infected person to come to terms with the illness and find some meaning in it.

Alternatively, Ironson says, the two variables that predicted faster disease progression were stressful life events and having an angry personality. People with an angry personality fared all right until they were confronted with a major stressful event, such as the death of a loved one, job loss, or loss of a relationship.

**2. Focus on improving coping skills and effectiveness training.** "Living with HIV disease, like living with other chronic conditions, can be really psychologically draining," says **Margaret Chesney**, PhD, professor of medicine at the University of California – San Francisco (UCSF). "In addition to the day-to-day effort that's required to maintain and take medications and to try to maintain optimal health, you have a very stigmatized disease."

Chesney is the co-director of the Center for AIDS Prevention Studies at UCSF, and she has received federal grants to study how clinicians can help people living with HIV cope with their infection. The studies have assessed a model for coping-effectiveness training for HIV-infected people.

The program trains people, either in groups or individually, to identify what is causing them stress, whether it's the disease itself, job troubles, family troubles, or other problems. Then they identify what can be changed to reduce the stress.

The intervention is based on a model that compares maladaptive coping strategies with adaptive ones. Maladaptive strategies include using

emotion-focused coping in situations that can be changed and problem-solving solutions in situations that cannot.[1]

"There are a lot of things about life we can't change right now," Chesney says. "But what we can do is teach people how to manage their moods when they're confronted with something they can't do anything about."

Adaptive strategies include using emotion-focused coping — such as cognitive restructuring, relaxation, and humor — when confronted with a stressful situation that cannot be changed and using problem-focused coping — such as problem-solving, social/communication skills, and negotiation — when confronted with a situation that can be changed.[1]

"We tell people, 'Take a break from having HIV. This weekend, go have fun. Remember your medicines, but let's not think about or talk about HIV until Monday,'" Chesney offers as one adaptive coping strategy.

The coping effectiveness training study found that this type of program results in less psychological distress, improved coping, and better mood among HIV-infected men.[1] "Our intervention did reduce depression, and it reduced burnout, which is a combination of anger and exhaustion," Chesney says.

Ongoing research is evaluating how to help HIV patients maintain positive coping strategies over time. Investigators also are adding focus-on-the-positive enhancements to the training, Chesney says. "Our patients said, 'You never talk about any of the positive things in our lives,'" she explains. "'HIV has taught me to live life to the fullest, and you don't ask anything about that.'"

That led researchers to the conclusion that people can experience stress and stressful events while finding something positive to focus on. For instance, contracting HIV is a stressful negative event, but if a person can find meaning in his or her life because of the illness, then it becomes something positive, as well.

**3. Include a psychosocial component in HIV medical treatment.** "Clinicians have to be very astute and mindful of the high likelihood of depression and anxiety disorders," says **Jerry Durham**, PhD, RN, FAAN, dean and professor in the Barns College of Nursing at the University of Missouri in St. Louis. "If it comes to the point of becoming clinical depression, then the clinician needs to evaluate the individual for medical interventions, talk therapy, or some kind of therapy that the individual can participate in."

A variety of therapies will work, including group therapy, couples therapy, relaxation therapies, and self-managed therapies in which people are trained to handle their own psychological needs.

The chief difference between people who experience depression and have HIV and people who experience depression and have some other chronic illness is the availability of a support network.

Most people who suffer from a chronic condition are able to find community, religious, or family support fairly routinely. Even if the person suffers from a rare chronic condition and there are no support groups in the person's immediate area, it's possible that person could talk to a stranger on an airplane about the disease without fear of social repercussions.

### Still fighting prejudice

This is less likely to be true of HIV. While HIV-infected patients often can find support groups consisting of other people with the disease, they often are stigmatized by their church, community, and even family. Although more people have become compassionate about HIV in the past decade, it's still common for HIV-infected individuals to be rejected when their HIV status is made public. Discrimination and religious condemnation also continue across the United States.

"One has to be very careful with whom one shares information," Durham says. "There's a higher burden among people with HIV, and, in some cases, they blame themselves for their condition, which is part of their guilt and depression, as well."

That's why it's important for clinicians to encourage HIV patients to share their troubles with an intimate friend or group of people who will not judge and can understand what they are going through, he adds.

"For many people, it's important to find support from family, friends, or support groups," Chesney says. "People with HIV need to look at themselves and say, 'I'm carrying a heavy load, and I need someone to help me carry this."

### Reference

1. Chesney M, Folkman S, Chambers D. Coping effectiveness training for men living with HIV: Preliminary findings. *Int J STD & AIDS* 1996; 7(Suppl 2):75-82. ■

# Resistance testing grows in treatment importance

*HIV pioneer researcher shares some insights*

*(Editor's note:* ***David D. Ho****, MD, is the scientific director and chief executive officer of the Aaron Diamond AIDS Research Center and a professor at The Rockefeller University, both in New York City. Ho received his medical doctorate from Harvard Medical School and is renowned internationally for his pioneering studies on the dynamics of HIV infection and its effects upon the human immune system. Ho also is an expert on antiretroviral drug therapy and resistance testing for HIV and is a member of the ViroLogic Scientific Advisory Board.* AIDS Alert *asked Ho to explain how HIV resistance testing has evolved and how important a role it will play in future treatment planning.)*

***AIDS Alert:*** When the first research was published about HIV resistance testing, and even up until a year ago, there was some doubt that such a tool could ever become practical for regular use in HIV treatment planning. Now the International AIDS Society – USA Panel has published recommendations for using antiretroviral drug resistance testing, and the panel says such testing should be incorporated into some patients' HIV management.

What has changed with regard to resistance testing technology and availability within the past year, and will resistance testing ever become a routine part of HIV treatment?

**David Ho:** The shift toward resistance testing is due to three reasons. First, the tests have become easier and better, and several are now readily available commercially. Second, as AIDS physicians confront cases with complicated treatment histories, there is a growing sense of realization that having knowledge about the resistance profile of the viral population would be helpful. Third, there are preliminary studies suggesting that the use of resistance testing could improve patient outcome.

***AIDS Alert:*** At the 4th International Workshop on HIV Drug Resistance and Treatment Strategies held in Sitges, Spain, in June, ViroLogic Inc. of San Francisco presented research showing that its phenotypic resistance testing assay, called PhenoSense HIV, could determine resistance profiles of AIDS drugs that are still in development, including drugs in the new class of integrase inhibitors.

How difficult do you believe it will be in coming years for resistance tests to keep up with all of the new antiretroviral medications? And do you predict there will be a time when drug manufacturers will no longer have any new drugs to add to the AIDS arsenal and so resistance testing and juggling the available antiretroviral treatments will be the only means for clinicians to keep patients a step ahead of disease progression?

**David Ho:** It will take some work to develop commercial assays to test for resistance to new classes of antiretroviral agents. However, it is certainly within our capabilities. For example, we already have HIV entry inhibitors that are in clinical development. Assays to measure for resistance against such entry inhibitors will be needed in the near future. As for the second part of this question, I truly believe that drug development effort will continue. However, it is difficult to predict the pace of their development. There will always be a need to optimally use the drugs in our current arsenal, and resistance testing will add to that.

***AIDS Alert:*** When should physicians consider using a phenotypic resistance test instead of a genotypic resistance test, and vice versa?

**David Ho:** Our knowledge level is insufficient to be able to translate every genotype into a phenotype. Phenotyping is much more direct. It is also consistent with many years of clinical practice in managing bacterial infections, where resistance to antibiotics had traditionally been determined using simple phenotyping techniques.

***AIDS Alert:*** The International AIDS Society's recommendations state that HIV drug resistance testing should not be used as the principal criterion for decisions on changing antiretroviral therapy, that such decisions still should be based on plasma viral load. So how should a clinician handle a patient's treatment when a resistance report predicts the failure of certain antiretrovirals, even though the patient's viral load remains low?

**David Ho:** If the viral load remains low in the presence of some drug-resistant viruses, there is no rush to change the regimen. However, given HIV's propensity to change, it is likely that increasing drug resistance, followed by increasing viral load, would be an expected outcome in the future. Thus, more careful monitoring of the patient would be warranted. On the other hand, some physicians/patients may use the phenotyping data to modify

the regimen in order to achieve better viral suppression. These choices are generally made on a case-by-case basis.

***AIDS Alert:*** The resistance testing recommendations also speak of unresolved technical issues, including a need for adequate standardization and clinical validation. Can those issues be resolved and, if it's likely, how long do you predict it will take to do so?

**David Ho:** As for any commercial test, there are many quality assurance and quality control issues to address. I have no doubt that such technical matters will be resolved within the coming year. However, more definitive clinical studies are required to prove that the use of resistance testing can indeed improve prognosis of a patient. Several such studies are already under way, but they may need a year or two to complete. ■

# Studies link bone disease, antiretroviral meds

*NIH, California surgeon have similar findings*

Recent findings by medical experts from coast to coast suggest clinicians need to be aware that HIV patients on antiretroviral medications may be at greater risk for developing osteonecrosis, also called avascular necrosis (AVN) of the hip joint area.

"In late 1996, I started noticing that I was seeing more cases of avascular necrosis of the femoral head among HIV patients," says **Guy Paiement**, MD, associate professor of orthopedic surgery at the University of California – San Francisco and San Francisco General Hospital Medical Center. Paiement presented some of his research results at the annual meeting of the American Orthopedic Association on June 16 in Hot Springs, VA.

An increase in AVN cases among HIV patients has been confirmed by the National Institutes of Health (NIH) in Bethesda, MD.

"We had heard some anecdotal reports of cases of AVN from community physicians, and over a four-day period a couple of years ago, we had two patients in whom we diagnosed symptomatic AVN of the hip," says **Joseph Kovacs**, MD, senior investigator of the NIH's critical care medicine department. The NIH study results were presented at the Infectious Diseases Society of America's annual meeting on Sept. 8 in New Orleans. "This raised concern that this would be a potentially new problem in HIV patients," Kovacs says.

NIH investigators tested the hypothesis that HIV patients were at greater risk for AVN by using magnetic resonance imaging to evaluate 339 HIV patients. Another 118 people who were HIV negative also were scanned as a control group. Investigators found that 15, or 4.4%, of the 339 HIV patients had the disorder, although it had not yet become symptomatic. None of the 118 people in the control group had osteonecrosis.

The 15 HIV patients had lesions in one or both hips, and some of the lesions were large enough to raise concerns that they would lead to clinical symptoms.

"In our study, we tried to look at potential factors, and certainly one hypothesis is that this is related to protease inhibitors," Kovacs says. "About 90% of our HIV patients are on protease inhibitors and highly active antiretroviral therapy regimens, so that makes it difficult to identify specific drugs."

The NIH study did find that patients with osteonecrosis were more likely to have taken corticosteroids, testosterone, and lipid-lowering drugs. They also were more likely to have engaged in weight-training and body-building activities.

While it is logical to assume that the recent rise in AVN cases among HIV-infected patients is due to antiretroviral drugs, this also could be a result of the fact that HIV-infected people are living longer than they did before the drug therapies, so HIV now has time to make them susceptible to AVN, Kovacs says. However, it would take a large population of HIV patients who are not on antiretroviral therapies and who are living for a long period of time to test that possibility, he adds.

"My gut feeling is that maybe some other factor and not just HIV itself [that] is related to this disease," Kovacs says.

The NIH will continue to study AVN among HIV patients and follow the patients who showed signs of it on the MRI scans to see how many of them need hip replacement surgery.

AVN is not common in the general population. Most of the people who have it had some other risk factors, such as chronic alcoholism or a disease such as lupus that requires them to take prednisone, Paiement says. "Chronic use of prednisone has a lot of musculoskeletal complications, and the most common is osteoporosis," he adds. "But a small number develop AVN."

When Paiement first mentioned his observations of increasing numbers of AVN cases among HIV patients to other orthopedic physicians and HIV doctors, he was met with skepticism, he recalls. "So I decided to pull out these charts, and I realized that all the cases of HIV patients with AVN were people on protease inhibitors. Before 1996, I had seen one or two cases a year among HIV patients, but starting in late 1996, it was like an epidemic."

Paiement reviewed 30 cases of AVN among HIV patients. The hospital's number of HIV cases had remained fairly steady at about 3,500 active HIV patients. The only difference in recent years has been that the demographics of the HIV patients have shifted more toward women, injection drug users, and minorities, he says.

When this sudden increase in AVN cases occurred, it seemed that something else was contributing to it. "For 18 of the patients, the only risk factor was chronic use of protease inhibitors," he says.

He since has reviewed a post-exposure prophylaxis study in which 600 people were given short-term doses of protease inhibitors, and none of those people developed AVN, he notes. "I strongly believe protease inhibitors will cause AVN only if used chronically, and just a short course of four to six weeks isn't long enough."

While screening all HIV patients for AVN through use of an MRI scan is not cost-effective, both Kovacs and Paiement recommend clinicians watch for signs that a patient has developed osteonecrosis of the hip. "If someone is complaining of a pulled groin muscle that's not getting better, think of AVN as a possible explanation for that," Kovacs says.

Paiement recommends clinicians order an X-ray for patients who complain of groin or hip pain or refer them to an orthopedic surgeon. "If you strongly suspect AVN, then get an MRI," he adds. "Let's say the patient presents with groin pain that hasn't improved over six to eight weeks, then refer the patient to an orthopedic surgeon."

It's important to find AVN early in the disease process because if it's identified after the femoral head collapses, it will result in arthritis and require a more costly procedure, such as hip replacement surgery, to correct it.

"If you pick up AVN before the femoral head collapses, you can do a small procedure to relive the pressure, and it could be self-limited, with the bone repairing itself," Paiement explains. ■

# Research sheds light on heterosexual transmission

*Test for potential blocking agents may be possible*

HIV investigators have long found it difficult to study the way the virus is transmitted in cervical tissue. Replicating the factors important to heterosexual transmission is not easy, particularly when conducting animal studies.

"People have done work with felines, but felines don't have the typical cell structure that presents in women's vagina or cervix," says **Phalguni Gupta**, PhD, professor in the department of infectious diseases and microbiology at the University of Pittsburgh's graduate school of public health.

Gupta and co-investigators have found at least one solution to this problem. "What we did was develop an organ culture using squamous cervical tissue from premenopausal women, and we have shown in the culture that it maintains a lot of different properties of cellular structure," he says. "In using these organ cultures, we have shown that you can show transmission across the mucosal layer, and you can even show which of the cells get infected."

Investigators place a dime-size piece of squamous cervical tissue in a top chamber of a transwell device. HIV is added on top of the epithelium layer, and HIV transmission is measured in the bottom chamber. Their technique provides a natural in vivo tissue architecture that includes stratified squamous epithelium, submucosa, and immune cells.[1]

## A model to test agents

The research paves the way for a system that will test the efficacy of antimicrobials and compounds typically applied in the vagina to see if they can block transmission, Gupta adds. "This is a model to test and screen potential agents that block transmission. This will be available for use before a clinical trial."

That possibility could be a significant improvement in the methods currently available for testing antimicrobials designed to prevent HIV transmission during sexual intercourse.

Women's health activists and international health organizations have promoted microbicide research as a possible solution for women in

developing nations who need an agent to block transmission of HIV that is cheap, easy-to-use, and entirely within their own control.

In addition to financing problems, that research has had a number of setbacks, including the recent study that showed the once-believed promising spermicide nonoxynol-9 does not reduce the rate of HIV, gonorrhea, or chlamydia infection in a group of sex workers who used the treatment. The African women involved in the research also were given condoms and had a 90% use rate.

A new model for studying such spermicides within the laboratory could prevent unfortunate results as produced by the nonoxynol-9 clinical trials, Gupta says. "If this organ culture model was available, we could have said, 'Don't do these clinical trials, because we have seen these results.'"

The University of Pittsburgh researchers have received a grant from the National Institutes of Health in Bethesda, MD, to test a number of different creams, suppositories, and other products that might be able to block transmission of HIV, Gupta says.

Here are some more details about the research:

- The organ culture system method proved durable. Stratified squamous epithelial layers remained unchanged after one day in culture, although the thickness of the epithelial layer started to decrease after three days. The basal layer of the epithelium remained intact for five to six days in culture, and there was no evidence of necrosis or autolysis in the tissues.[1]
- The model demonstrated transmission of infectious HIV-1 across the mucosal barrier. When HIV-1 was inactivated by ultraviolet irradiation, it was not transmitted.[1]
- Between 20% and 30% of tissues did not support HIV-1 transmission in this organ culture system, supporting the theory that not all exposures result in infection.[1]
- An estimated risk of HIV infection for every vaginal exposure to infected semen is only about 0.01%, according to Rhesus macaque studies.[1]
- The model's results in a localization of cells expressing HIV-1 immediately below the epithelial layer were similar to those of the Rhesus macaque studies.[1]
- The model may be very useful in determining the types of cells that become infected initially during heterosexual transmission of HIV-1.[1]
- The model can help determine whether transmission efficacy is higher with cell-free virus or cell-associated virus, and it can be used to determine whether viral transmission is dependent on the phenotypic and genotypic properties of HIV-1.[1]

Gupta says additional research using this model might be able to determine at which stages of a woman's menstrual cycle she is more susceptible to HIV transmission.

## Reference

1. Collins KB, Patterson BK, Naus GJ, et al. Development of an in vitro organ culture model to study transmission of HIV-1 in the female genital tract. *Nat Med* 2000; 6:475-479. ■

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

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

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# Dual infections with HIV and *M. tuberculosis* complicate prevention and treatment initiatives in Africa

*Problem is growing in other parts of world*

More than 34 million people worldwide are infected with HIV, and about one-third of them are co-infected with *Mycobacterium tuberculosis*. The dual infection has created a deadly and expensive dual epidemic, particularly in sub-Saharan Africa, where more than 24 million HIV-infected people reside.

International health organizations estimate that only 20% to 25% of all TB patients worldwide have access to effective diagnosis and treatment provided under the directly observed therapy, short-course strategy (DOTS), which is acknowledged to be the best TB control method.

In many countries in sub-Saharan Africa, up to 70% of patients with sputum smear-positive pulmonary TB are HIV-positive, and half of people with HIV develop TB. While precise statistics are not available, most international health officials would agree that TB is the single leading cause of death among HIV-infected Africans.

HIV infection has made TB infection even more deadly by promoting rapid development of TB disease in people who are newly infected with TB or whose TB infection has been dormant, says **Dermot Maher**, BM, BCh, a medical officer with the Communicable Diseases Control, Prevention, and Eradication of the World Health Organization (WHO) in Geneva.

Likewise, studies show that a person's immune response to *M. tuberculosis* infection enhances HIV replication and may accelerate the progression of HIV disease. Together, the two epidemics have wreaked misery and death throughout sub-Saharan Africa.

While WHO and other international organizations have been focusing on Africa — the region of the world in which the problem is the most critical — they've kept an eye on other potential hot spots. Cambodia and northern Thailand both have high HIV infection rates coupled with high TB infection rates, Maher says. "In those parts of India where HIV is more common, [there's a] risk of fueling the TB epidemic," he adds. "But in India, overall HIV infection rates still are relatively low."

## Community TB Care in Africa Project

| Project site | Intervention cohort (community DOT option) | Control cohort (no community DOT option) | Type of control |
|---|---|---|---|
| Machakos, Kenya | 90% (537) | 85% (600) | Historical 1996 |
| Lilongwe, Malawi | 68% (1,455) | 61% (914) | Historical 1997 |
| Kiboga, Uganda | 78% (135) | 61% (148) | Historical 1997 |
| Kawempe, Uganda | 52% (298) | 33% (unknown) | Historical 1997 |
| Hlabisa, S. Africa | 86% (37) | 68% (638) | Concurrent |
| Guguletu, S. Africa | 69% (548) | 66% (82) | Concurrent |
| Ndola, Zambia | 77% (40) | 49% (59) | Concurrent |

*Source:* Dermot Maher, World Health Organization, Communicable Disease Control, Prevention, and Eradication, TB-LIFE Meeting, Atlanta, Aug. 28-29, 2000. Percentages (and numbers) represent treatment completion of project participants.

## Five keys to reducing TB/HIV co-infection

The World Health Organization in Geneva says any program geared to eradicating a tuberculosis epidemic must include these five features:

1. Political commitment.
2. Diagnosis by sputum smear microscopy of people presenting with coughs of more than three weeks duration when they go to general health services because of their coughs.
3. Standardized short-course chemotherapy.
4. Regular uninterrupted supply of anti-TB drugs.
5. Standardized recording and reporting of all TB cases, allowing assessment of treatment results. ■

But the dual TB/HIV epidemics in those Asian nations are dwarfed in comparison to sub-Saharan Africa's troubles.

"We've had the chance to observe over the past decade — and very many sub-Saharan African countries have seen — terrific escalations of TB due to HIV and poverty," Maher says. "A number of countries have seen their TB case rates go up threefold or fourfold."

### *Double whammy*

The symbiotic way in which the two infections promote progression to disease and death also fuels the transmission rates. Tuberculosis is not contagious when it's in a latent form. Because HIV infection causes people also infected with TB to progress rapidly from latent TB infection to full-blown TB disease, it also increases the pool of people who are contagious with TB and therefore spreading it to many others, says **Kenneth Castro**, MD, director of the Division of TB Elimination at the Centers for Disease Control and Prevention (CDC) in Atlanta.

CDC researchers have found increased viral replication in lymphocytes and macrophages of HIV patients who have active tuberculosis. Co-infection with *M. tuberculosis* and HIV-1 resulted in a 1,000-fold higher level of viral replication in cells than that seen in a person infected with HIV alone, according to posters presented in June at the Tuberculosis 2000 conference in New York City.

All of the recent research and surveillance data point to a problem that will only escalate unless comprehensive measures are taken to stop the co-infection rate.

"Our responsibility is to declare this situation as intolerable, that the status quo is intolerable, and it calls for action," Castro says. "If nothing is done, it's only going to get worse."

### *Coming together*

Until recently, health ministries and support organizations tackled each disease separately, rarely working together. WHO and others now recognize that this approach will not succeed. TB organizations need to collaborate with HIV organizations, combating the epidemics with a united front.

"To address the problem, you have to do two things to turn off the TB epidemic," Maher says. "You need to stop TB transmission by identifying and curing the infectious cases using the DOTS strategy, and you need to stop HIV transmission since HIV is fueling TB."

Good collaboration between HIV and TB programs, therefore, is key. In trying to make the solutions to stopping both epidemics widely available, the world's health community has some new initiatives that should help. WHO, the CDC, UNAIDS, USAID, and other organizations are promoting community-based initiatives aimed at providing testing, treatment, and counseling for people who may have HIV and TB.

While HIV antiretroviral treatment continues to be cost-prohibitive for most people and nations in sub-Saharan Africa, TB treatment is much more affordable, costing as little as $10 to $20. However, the same lack of health care infrastructure that makes HIV testing, counseling, and treatment so elusive in those nations also makes it difficult to treat tuberculosis patients successfully.

Patients need to adhere strictly to the TB medication, sometimes for as long as eight months, for treatment to succeed. Low adherence rates have been associated with a rise in drug-resistant TB strains in many countries. In the United States, this type of strict adherence has been possible among homeless and marginal populations when the drugs are administered in a direct observation therapy program, meaning someone watches the TB patient take the medication each day.

International organizations are working with health ministries in many countries in sub-Saharan

Africa to ensure all TB patients have access to the type of support necessary to enable them to adhere to and complete therapy.

One such project, called "Community TB Care in Africa," is investigating how to engage community participation in tackling tuberculosis. Another initiative, called "ProTEST," is investigating how health officials and others may provide interventions designed to prevent HIV infection from fueling the tuberculosis epidemic through voluntary counseling and testing for HIV and other measures.

The Community TB Care in Africa project, begun in 1996, is evaluating the community contribution to effective tuberculosis control in countries with high HIV prevalence. Projects based in districts of Botswana, Kenya, Malawi, South Africa, Uganda, and Zambia began implementing community TB care interventions in early 1998. Their chief intervention is DOTS for people with TB. WHO also provided technical support for community TB projects in Tanzania and Ethiopia. Most pilot sites have demonstrated high rates of treatment success. **(See chart, p. 1.)**

Also, the program resulted in lower health care costs for the communities involved. The health systems saw cost savings of between 16% and 72%. The average length of stay for these TB patients dropped by 73% to 98%, and the average family costs also dropped substantially. In Kiboga, the district hospital has closed its TB ward because all of the TB patients were successfully treated in the community, resulting in a considerable cost-savings to the hospital, Maher says.

"Community-member volunteers identified through the parish development committee were doing direct observation therapy," he adds.

The ProTEST initiative is designed to develop a district-based model for the integrated delivery of health care services to reduce the burden of tuberculosis and HIV. ProTEST programs will attempt to reach some of the 90% of people with HIV who do not know they are HIV-positive.

"The program is promoting testing for HIV to make sure those identified with HIV have access to preventive TB treatment if they don't have TB yet," Maher says.

ProTEST projects are under way in South Africa, Malawi, and Zambia. Uganda is expected to start a project later this year, and Zambia will combine this project with a project that looks at prevention of the transmission of HIV from mother to child. ■

# Mother-to-child advances are closer to reality

*(*AIDS Alert *asked nevirapine researcher John L. Sullivan, MD, to discuss the drug and its potential use in preventing mother-to-child transmission of HIV in developing nations. Sullivan was involved in the discovery of nevirapine in 1990 and first proposed a mother-to-child transmission trial in 1992.*

*He has been involved in much of the nevirapine research since then and most recently was a chief researcher in the SAINT Study, which compares nevirapine favorably with a combination of lamivudine and zidovudine in prevention of mother-to-child transmission. The study was presented at the XIII International AIDS Conference in Durban, South Africa, in July 2000.*

*Sullivan is a professor of pediatrics in the Program in Molecular Medicine at the University of Massachusetts Medical School in Worcester.)*

***AIDS Alert:*** When news first came out last year that one dose of nevirapine was very effective in preventing mother-to-child HIV transmission, many people saw this drug as a possible solution to the infant HIV problem in Africa. What does the new SAINT Study add to the earlier findings?

**Sullivan:** I think the same trial obviously has expanded those findings in demonstrating that this result can be duplicated. In the HIVNET 012 study, the nevirapine was compared with AZT alone. In the SAINT study, nevirapine was compared with AZT and 3TC in combination, a much more potent regimen, and even with that more potent regimen, nevirapine was equivalent in potency in terms of prevention.

I think the other important aspect of SAINT is that it included women who formula-fed their babies as well as women who breast-fed their babies. And we could really look at the efficacy of nevirapine in terms of preventing maternal-to-child transmission in the intrapartum period. When we did that, the efficacy was 80%, so that a single 200 mg dose of nevirapine to the mother and a 6 mg dose to the baby was 80% effective in preventing intrapartum transmission.

***AIDS Alert:*** To put this into perspective, how serious is the mother-to-child HIV transmission problem in Southern Africa?

**Sullivan:** One of the sites for SAINT was in Durban, South Africa, and at the prenatal clinics currently in Durban, approximately 35% of pregnant women are HIV-infected. So we have hospitals in South Africa where there are 12,000 to 14,000 deliveries a year, and if you think about one-third of those women are HIV-infected, and the ultimate transmission rate includes the transmission that occurs in utero, which is 7%, as well as the transmission that occurs in intrapartum period, which is 15% to 16%, and the transmission that occurs by breast-feeding, which is another 10% to 5%, we're looking at overall transmission rates in the 25% to 40% range. So again, a third of the women who are pregnant are at risk for transmission, and a third of their babies are infected.

There are approximately 1,600 babies born a day in the world with HIV infection. So if you think about intrapartum infection accounting for 50% of those when you include in utero transmission and breast milk transmission, you could reduce the number of infected infants by half.

***AIDS Alert:*** How should nevirapine be administered to obtain the best results in preventing HIV transmission through breast-feeding?

**Sullivan:** That's the next research question that needs to be answered. We can prevent the transmission that occurs in the intrapartum period. But some of those babies who escape infection at that point in time will then become infected through breast milk. So we now have to figure out a regimen that's going to protect breast-feeding babies.

There are studies going on now with dosing infants with nevirapine through the breast-feeding period. And I think our hope would be that we could use nevirapine to prevent transmission through the breast-feeding period, along with shortening the breast-feeding period — it looks like one can terminate breast-feeding in the range of three to six months and not lose the effect of breast milk on the prevention of enteric diseases, which obviously are a very serious problem in the developing world.

***AIDS Alert:*** Ingelheim, Germany-based Boehringer Ingelheim GmbH announced right before the XIII International AIDS Conference in Durban, South Africa, that the company would be offering nevirapine at no charge for the use of preventing mother-to-child transmission in developing countries for a period of five years. Do you believe African nations will take advantage of this offer, and how might this impact the HIV pandemic in the developing world?

**Sullivan:** Absolutely. This removes cost of drug as a barrier, and I think the next barrier to implementation of this regimen is an infrastructure to ensure that the drug is going to be given to those women and babies who need it. I think that's where additional funds are needed — to create that infrastructure — and there are a number of organizations providing money to do that, including the Pediatric AIDS Foundation, the USAID, and there was a bill introduced in Congress to make $1 billion available over the next two years to the developing world for HIV prevention.

So I think the monies necessary to create the infrastructure to assure that this free drug will get to the people who need [are going to be provided]. So my guess is that we're going to see over the next two years the implementation of this regimen throughout the developing world.

***AIDS Alert:*** What is your greatest expectation for the next 10 years in the area of mother-to-child transmission of HIV? How might it change from what we are experiencing today?

**Sullivan:** I think this is really a stopgap measure, if you will. Obviously, women who are HIV-infected in the developing world are not receiving antiretroviral therapy for their own disease and eventually are going to die from their HIV infection. So even though their babies are not infected, their babies are going to end up being orphans.

What this does offer is the first hope of having treatments available in the developing world, and I think what we're going to see and what already has happened on a really small scale is the introduction of certain very inexpensive antiretroviral therapies into the developing world for treatment of adults and children with HIV infection.

I think we're going to see that happen increasingly over the next several years, where we're going to be able to prevent maternal-to-child transmission, and we're also going to be able to attenuate the serious HIV infections to the point of people being able to live longer. But this is really a stopgap in itself, as well, because the only hope for the developing world really is a vaccine, and I think we're probably 10 years away from having a vaccine that's efficacious. ■