AMERICAN HEALTH CONSULTANTS®

AIDS ALERT

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INSIDE

MARCH 1999

VOL. 14, NO. 3 (pages 25-36)

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Research confirms HIV virus still may be transmitted after HAART

Public health efforts must focus on safe-sex practices

While highly active antiretroviral therapy (HAART) has been reducing HIV to undetectable levels in patients for some time now, clinicians have always said the fight to prevent HIV infection must continue unchecked. A study published in the Dec. 17 issue of *The New England Journal of Medicine* has now confirmed that assertion. The study concludes that HIV-infected men on HAART still may harbor the virus in seminal cells, even if they have no detectable levels of viral RNA in plasma.[1]

"If you pass these cells to uninfected men or women, these cells could potentially produce virus and infect those people," says **Roger J. Pomerantz**, MD, professor of medicine, biochemistry, and molecular pharmacology, chief of the division of infectious diseases, and director of the center for human virology at Thomas Jefferson University in Philadelphia. Pomerantz was one of seven co-authors of the study.

"The risk is probably very low, but it's not nonexistent," Pomerantz says. "So the fact that these cells can still be grown in vitro suggests these people should still have safe-sex practices and consider themselves not cured of the disease."

The study suggests that people who adhere to their antiretroviral regimen may have residual virus that can transmit, says **Kenneth Mayer**, MD, chief of the infectious disease division of Memorial Hospital in Pawtucket, RI, and professor of medicine at Brown University in Providence, RI.

While getting people into treatment might help decrease transmission on a population basis, it does not mean individuals should behave as though they are no longer infected, Mayer says.

"For that individual person, just because your sexual partner is taking triple therapy and it's undetectable in the blood, it doesn't mean your partner might not be infectious at any given point in time," he explains.

Earlier research has shown that HIV infectiousness is highly variable between individuals and even within a particular person. A person may have positive viral semen cultures at one point in time and negative cultures a few months later, Mayer notes. Thus, the Thomas Jefferson University study underscores the importance of teaching

HIV-positive people to prevent transmission for the rest of their lives, he says.

"We always stress that patients, regardless of their viral load, should be viewed as infectious," says **Aaron E. Glatt**, MD, chief of the division of infectious diseases at Catholic Medical Centers of Brooklyn and Queens and professor of clinical medicine at Albert Einstein College of Medicine in the Bronx, NY.

"I try not to say you have a negative or zero viral load," Glatt adds. "I stress to patients that we are not able to detect virus because the tests we use are at fault and can't detect low levels."

The research implies important policy messages that should be reinforced continually, especially to young people, says **Cliff Morrison**, ACRN, FAAN, director of staff development for Telecare Corp., a behavioral health company in Oakland, CA. Morrison is the former deputy director of the AIDS Health Service Program in the Institute for Health Policy Studies in San Francisco.

"I think after almost 20 years of looking at prevention policy relating to the epidemic, it's obvious that any time there's new information, we have to get it out there quickly," Morrison says.

Researchers in the Thomas Jefferson University study collected peripheral blood and semen samples from seven men with HIV-1 infection. The men were identified from more than 400 men with HIV-1 infection who were treated in the university's clinics. The seven had received HAART for five to 41 months, and they had no detectable RNA in plasma. They had plasma levels of HIV-1 RNA below 400 copies per milliliter when measured by a reverse transcriptase polymerase chain reaction assay on three occasions at least one month apart. When blood and semen samples were obtained for the study, their plasma HIV-1 RNA levels were below 50 copies per milliliter.

Researchers isolated cells and analyzed the samples using a quantitative polymerase-chain-reaction assay, looking for proviral DNA, Pomerantz says. They then cultured the cells with uninfected blood cells from an uninfected individual and stimulated the cells to see if the virus would replicate, he explains.

The study's findings included the following:

• HAART inhibited viral replication in the bloodstream and in the genital tract, although cell-associated viral DNA was detected in peripheral-blood mononuclear cells from all the men.

• Cell-associated proviral DNA was detected in the seminal cells of four men, with the number of copies of HIV-1 DNA ranging from fewer than five to 90 per million seminal cells.

• Researchers recovered replication-competent HIV-1 from peripheral-blood lymphocytes from three men and from seminal cells from two of the three.

• The virus isolated from seminal cells of two men is potentially capable of initiating a primary infection in a sexual partner even though the men were receiving HAART and had undetectable levels of viral RNA in plasma.

The findings suggest that at least two of the men were still infectious, Pomerantz says.

Researchers also examined whether the men's virus showed any resistance mutations to the protease inhibitors, and they found no real resistance. This means the medication successfully suppressed the virus, although it did not totally eradicate it.

"These viral strains are fossil or archival viruses that were there lying fallow for many years, probably from the time after infection," Pomerantz says.

Clinicians should use studies like this to emphasize to HIV patients that safe sex still should be the norm, Mayer says. "Having a partner treated for HIV is not a chemical condom," he says.

Reference

1. Zhang H, Dornadula G, Beumont M, et al. Human immunodeficiency virus type 1 in the semen of men receiving highly active antiretroviral therapy. *N Engl J Med* 1998; 339:1,803-1,848. ■

Urine test could become early detection device

But first, researchers must confirm HIV infection

Researchers have detected HIV antibodies in the urine of 24 low-risk people who tested negative for HIV in blood tests.

While these people appear to have been exposed to HIV, they may not have become infected with the virus. But the study's findings also suggest that it is possible that one person in 1,000 who has tested negative for HIV in blood tests actually has been exposed to the virus and could become infected.

"At the very least, they've been exposed to HIV, and at the worst, they are infected with HIV," says **Robert Stout**, PhD, a biological

chemist and president of Lenexa, KS-based Clinical Reference Laboratory, which conducted the study.

"Of great scientific interest is, if they are infected, how have they confined the infection to the urogenital tract?" Stout asks.

The study examined urine samples of 25,118 low-risk people who had given informed consent. They found that 24 samples had antibodies reactive to HIV, with companion blood samples that were HIV non-reactive. Research testing shows that IgA antibodies reactive to HIV were present in most of these urine samples. IgA is an antibody secreted by immune cells that provides protection for the mucosal surfaces of the body. The urine test was developed and is marketed by Calypte Biomedical Corp. in Berkeley, CA. The commercially available urine test has approval from the Rockville, MD-based Food and Drug Administration and currently is used on a limited basis.

The study will be presented at the annual American Association of Clinical Chemists meeting in New Orleans on July 25-29.

Explaining the findings

Here are three possible scenarios for what the findings mean:

- These individuals were exposed to the virus but may be immune to the virus and avoid any infection.
- They were exposed to the virus and are infected at a level that cannot be detected through current blood tests.
- They were exposed to the virus, harbor the virus in their urogenital tract, and may one day become systemically infected.

HIV blood tests screen for the IgG antibody, which is present in concentrations 10-20 times that of IgA. The IgA HIV test is currently used for research purposes only. The medical community has overlooked the urine test despite its potential research and clinical benefits, Stout says.

"We've always predicated our detection of HIV infections on IgG antibodies," Stout says. "I think we've overlooked one additional class of antibody that might be present, and it's coming around full circle now for researchers to look for the presence of antibodies in non-serum fluids, such as urine."

Stout's laboratory will conduct molecular tests on 10 of the urine samples over the next six months to see if the subjects' urine samples contain HIV genetic material. If genetic material is found, these individuals are probably infected with HIV in their urogenital tract. Researchers can only speculate whether the virus could later spread to their blood and other parts of their bodies.

"What we have discovered is that some serum HIV-negative individuals have antibodies to HIV in the urogenital tract that typically are produced after an infection," Stout says.

When a person is exposed to HIV through sexual activity, it's possible the virus and antibodies to it would appear in the urogenital tract before spreading to the bloodstream, Stout explains. This is one possible explanation for how someone could be infected with the virus and have no signs of it when given a blood test.

If the urine findings are correct, it could have a significant impact on health care clinics that offer screening for HIV because they then could have a tool that would detect HIV infection at a much earlier stage than what the blood test permits.

Screen for high-risk individuals

The urine test could be a way to screen high-risk individuals. If they are found to have HIV antibodies and infection, they could be given highly active antiretroviral therapy (HAART) before the infection becomes systemic, possibly even clearing their bodies of HIV, Stout says.

The study also examined urine samples of 128 high-risk individuals who had tested negative for the virus in the blood test. It found 10 incidences of HIV exposure in that group.

However, Stout says the urine test so far only establishes exposure to the virus. "We have to answer the question: Are these people carrying the infection?" he says.

Some long-term carriers of HIV have had the infection for 15 years or more and still have not progressed to AIDS. Stout says the study and use of the urine test could begin to explain why some people seem to be immune to the disease.

"But it's premature to go down that line until we've established whether or not these people are infected," he adds.

The urine test is a relatively inexpensive way to detect HIV exposure, costing about $10,000 per 1,000 samples, Stout says.

Calypte officials say they sell the urine test to laboratories for $3 per sample.

By contrast, to screen 1,000 people for HIV using the molecular test would cost $100,000, Stout says. ■

Gene mutation speeds up progression to AIDS

Up to 13% of population has susceptible genotype

Researchers at the National Cancer Institute (NCI) in Frederick, MD, have concluded that some people progress to AIDS more rapidly if they possess a recessive genetic variation that makes their cells more receptive to HIV infection.[1]

The researchers studied the CCR5 gene. This gene's promoter region determines how often and when the gene manufactures cell surface receptors, which are the points at which a new virus enters a cell to make copies of itself.

Researchers discovered that HIV-infected people whose CCR5 gene contains the promoter allele CCR5P1 progress to AIDS two years faster than those who don't. This variation is not in the coding region of the gene, but in the regulatory region, which determines how much of the receptor protein is produced on the cell's surface. The gene is recessive, meaning it works only when both of a person's parents carried it.

"This is not the first gene that was discovered to have genetic sensitivity to HIV; it's the fourth," says **Stephen O'Brien**, PhD, a geneticist and head of the Laboratory of Genomic Diversity at NCI. O'Brien led the team of NCI researchers.

"The first discovery was a mutation in the center of CCR5 that caused it to be completely resistant to HIV infection," O'Brien says, adding that these types of mutation discoveries have provocative implications for HIV therapy.

Tracking a moving target

AIDS progression is a competition between a rapidly replicating virus and the body's T-cells that are fighting the infection, O'Brien explains. So far, the war on AIDS has focused on arming the body's immune system with powerful chemical weapons that help it fight the virus. But that strategy has not worked well because the virus is a moving target that mutates at a rate of once per replication, with one billion replication mutations each day, O'Brien says.

Researchers also are studying defense strategies that would prevent the virus from beginning its replication process.

"If we can interfere with the cellular protein made by the host that's required for infection and replication, then you don't have a moving target, you have a fixed target," O'Brien suggests.

"If you knock out CCR5, you shut out HIV from replicating because CCR5 is the doorway by which HIV enters a new cell," he adds.

The NCI study and other receptor research may have important implications for vaccine research, says **Kenneth Mayer**, MD, chief of the infectious disease division of Memorial Hospital in Pawtucket, RI, and professor of medicine at Brown University in Providence, RI.

"The research lets us assess what's needed for HIV entry," Mayer says. "The better we understand what causes resistance to HIV, the better we can try to replicate the ways in which the cells in the body are either more resistant or susceptible to HIV."

Drugs could block viral entry

This knowledge could result in a vaccine that gives protective immunity to HIV, or it could lead to the development of drugs that would block HIV access to certain receptors, Mayer adds.

Scientists have tried for more than a decade to develop drugs that block HIV access to certain receptors, Mayer says. "Part of the reason they haven't succeeded is because they haven't understood the mechanisms of viral entry that these genetic studies are helping us to understand."

The NCI study's researchers compared the genes of more than 2,600 people infected with HIV with the genes of 474 healthy people. The study includes a genetic association analysis of five cohorts of people with AIDS. It showed that infected individuals whose CCR5 regulatory region contained the promoter allele CCR5P1 progressed to AIDS more rapidly than those with other CCR5 promoter genotypes, particularly in the early years after infection.

The researchers estimate that 10% to 17% of patients who develop AIDS within three and a half years of HIV-1 infection also have the CCR5P1 genotype. The study shows that 12.7% of Caucasians and 6.7% of African-Americans carry a CCR5P1 genotype. This genotype's influence on accelerating AIDS is strongest in the initial four to six years after infection. This is because CCR5 is the primary manufacturer of HIV-1 receptors in the early years of infection.

The study authors described an individual's acceleration to AIDS by using AIDS endpoints that reflect advancing morbidity. These were

defined by the Atlanta-based Centers for Disease Control and Prevention as individuals with CD4 counts of fewer than 200 cells / milliliter or individuals that died from the disease.

Reference

1. Martin M, Dean M, Smith M, et al. Genetic acceleration of AIDS progression by a promoter variant of CCR5. *Science* 1998; 282:1,907-1,911. ■

Herpes drug suppresses HSV in people with HIV

Famvir is only drug approved for HIV patients

Clinicians now have a potent treatment for herpes simplex virus (HSV) infections in HIV patients. A recent study shows that Famvir (famciclovir), manufactured by SmithKline Beecham Pharmaceuticals in Collegeville, PA, suppresses recurrent HSV infections in people with HIV.

During a four-month period, 97% of patients treated with Famvir did not experienced any culture-confirmed HSV recurrences, according to **Clarence Young**, MD, director of antivirals, clinical research and development, and medical affairs at SmithKline Beecham.

In an open-label clinical trial, the researchers gave 500 mg of Famvir twice daily for four months to 65 patients (49 men and 16 women) co-infected with HSV and HIV. Each month, clinicians evaluated patients with a clinical exam. If lesions were present, they took a viral culture. Thirty-eight of the patients (58%) had AIDS or AIDS-defining illnesses. The median CD4 cell count at study entry was 168 cells / milliliter, with a range of two to 969. Thirty-three of the patients (51%) had CD4 counts of less than 200.

Of the 65 patients, 48 (74%) had baseline HSV lesions. After treatment with Famvir, which cleared the initial lesions, 59 of the patients (91%) remained free from clinically diagnosed recurrences during the four-month observation period, and 63 (97%) remained free from culture-proven viral recurrences.

• Patients tolerated the drug well. The most commonly reported side effect was diarrhea, followed by headaches and nausea. However, Young notes that people who took placebos in other studies reported the same symptoms at similar incidence rates. "It's fair to say that the adverse events we saw were comparable to what we saw in other controlled studies where the incidence was comparable to a placebo," he says.

Herpes/HIV co-infection high

Young says the findings could have a big impact on the quality of life experienced by HIV patients.

"Studies show that as many as 90% of HIV-infected people have concurrent infection with herpes simplex virus," Young says. "It's possible people could have been exposed to herpes I as a child and then herpes II later in life before they acquired HIV."

Also, people who have herpes lesions are more susceptible to HIV infection, and they may be more likely to spread HIV, he adds. "Researchers have shown that you can culture HIV in these lesions."

While herpes outbreaks can be painful and uncomfortable for anyone, they can especially be a problem for HIV patients.

"Genital herpes impacts their sense of well-being," Young says. "Most studies that look at this have found that HIV-infected patients who have prior evidence of herpes have more outbreaks, and these last longer [than in non-HIV infected people]." Also, herpes outbreaks are more severe in HIV-infected people, sometimes spreading to their liver or lungs and causing potentially life-threatening complications.

An earlier Famvir study showed that treating HIV patients with the drug over an extended period of time reduced the amount of time the patients had any evidence of HSV shedding, Young notes.

"They were looking for herpes even on normal skin daily for the whole 16-week study," he explains. "Famvir was pretty effective at significantly reducing the finding of herpes virus in the genital region."

The Rockville, MD-based U.S. Food and Drug Administration (FDA) has approved Famvir for treatment of recurrent herpes simplex virus infections, including genital herpes and cold sores, in HIV-infected people.

SmithKline Beecham pursued the famciclovir study at physicians' requests for information on the drug's use in HIV-infected patients.

Famvir's protocol calls for a dosage of 500 mg twice a day for seven days. The study followed patients who were taking the drug over a four-month period to observe the medication's impact on preventing outbreaks of genital herpes. However, the FDA has given approval only for treatment of acute recurrences, Young says.

"It has not been approved in HIV-infected patients for prevention of outbreaks, and it's likely that studies involving large numbers of patients would be required in order to obtain that approval," Young says.

Unlike other herpes medications, Famciclovir has excellent viability. The amount of the active drug that gets into a person's bloodstream is very high, somewhere in the 70% to 80% range, Young says.

"What happens is, once you take the Famvir pill orally, the drug gets metabolized in the bloodstream to form penciclovir, and that's the active form of the drug," he explains. "These drugs are called pro-drugs because you give a form of the drug that enhances the ability to absorb it, and then it's quickly metabolized and releases an active form of the drug."

SmithKline Beecham also sells a herpes penciclovir cream that is used to treat herpes simplex cold sores. The company is studying an intravenous form of penciclovir for treatment of herpes simplex infections in immunocompromised patients, including patients who have been receiving chemotherapy for cancer. ■

HAART reduces virus in women's genital tracts

Researchers followed 176 women over four years

Researchers at a Rhode Island hospital have found that women on highly active antiretroviral therapy (HAART) have lower levels of HIV in their genital tracts than women who have not received HAART. Study results indicate a close correlation between the level of HIV in the blood plasma and the level of HIV in the genital tract.

The study may be the largest ever undertaken in the United States to measure the effects of HIV treatment on the genital secretions of women. Several previous studies have measured the effects of HIV treatment on men's semen.

"I think the basic message here is, if you are on good therapy, which we equate with HAART therapy in this day and age, then you have a better chance of having a smaller amount of HIV in your blood and genital tract," says **Susan Cu-Uvin**, MD, assistant professor of obstetrics and gynecology at Miriam Hospital at Brown University in Providence, RI. **(See related story, p. 31.)**

The researchers presented the study in November at the 36th Annual Meeting of the Alexandria, VA-based Infectious Diseases Society of America, held in Denver.

Cu-Uvin says HAART also may have an impact on perinatal transmission of HIV, although more research is needed.

Looking beyond the bloodstream

The researchers decided to study HIV levels in women's vaginal secretions to answer several major questions.

"We are giving the medications, and we know they are affecting the blood, but are they affecting the other areas of the body where the virus might be hiding?" Cu-Uvin says.

"The next question is how much medication reaches the vaginal tract, and that's a big question," she adds. "We're encouraging drug companies to take a look at this."

Collecting samples from women presents problems that researchers have not had with men. "The problem with vaginal secretions is there are many diverse ways to get it," she explains. "This is unlike men, where there's only one way to collect it, by having them masturbate and collecting semen."

Researchers collected vaginal secretions through a cervical vaginal lavage method, which involves putting 10 cc of normal saline in the vaginal area and then collecting the secretions. HIV was detected via cervical vaginal lavage in 40 of the 176 women (23%). This compares to virus being found in plasma in 122 (69%) of the women, with a median of 22,500 copies per milliliter and a range of 420 to 3 million copies. Researchers used an assay that can detect only 400 copies or greater. From 2% to 3% of women who had no detectable HIV in the bloodstream were found to have HIV in the genital fluids.

Sixty-three women (36%) were on HAART; 61 (35%) were on non-HAART treatment; 52 (29%) had no therapy at all at the time researchers collected samples. When the study first began in 1995, protease inhibitors were not available, so early samples included women who had used mono or dual drug therapies. Then, as protease inhibitors became the normal treatment a couple of years into the study, researchers began collecting samples from women who had received HAART, Cu-Uvin says.

The women involved in the study had a median age of 37. They were 52% white, 23% African-American, 23% Latino, and 1% other races, including Native Americans. Forty-six percent of them were injection drug users and probably contracted HIV through dirty needles, and 54% likely contracted HIV through sexual intercourse.

Forty-two (24%) of the women had CD4 counts of less than 200, 88 (51%) had CD4 counts between 200 and 500, and 43 (25%) had CD4 counts greater than 500. The median CD4 count was 343, and the CD4 count range was from four to 1,862. "So it's a wide range of patients," Cu-Uvin says. "Some were very sick, and some were very healthy."

Duration of medication use remains unknown

Researchers assessed the women's medication use through a retrospective review of their charts and having them answer a questionnaire. They were asked: Are you currently on therapy? If yes, what medications are you taking? "That's our gauge of their medication history," Cu-Uvin says. "But we don't know whether they have been taking this for two months, three months, or one week."

Researchers now are going back to the women's medical charts to try to determine how long they have been on therapy and when it was prescribed to them, and to compare this information to the time when researchers took samples to determine in more detail how medication use affected the study results.

Among women with a viral load of greater than 10,000 copies of HIV RNA per milliliter of plasma, 47% had detectable HIV in the genital tract. When the plasma viral load was between 400 and 9,999 copies, 8% had HIV in the genital tract. When the women's plasma viral load was below 400 copies, or undetectable, only 2% had detectable virus in their genital secretions.

About 42% of the women with CD4 cell counts below 200 had detectable virus in their genital tracts, compared with 14% of patients with CD4 counts above 200.

About 15% of the women who reported receiving no therapy had a plasma viral load of less than 400; 21% of those on non-HAART treatment had a plasma viral load of less than 400; and 52% of the women on HAART had a plasma viral load of less than 400. "So it made sense," Cu-Uvin comments. "If you don't go on therapy, the likelihood of your clearing the virus from your blood is very low."

Cu-Uvin says the research raises more questions that should be studied. For example, if HIV is reduced in women's genital tracts, will that reduce the likelihood of an HIV-infected mother transmitting the virus to her baby? "We don't know the answer to that, but in theory we're hoping that would be the case," she says.

Another big question, Cu-Uvin points out, is whether or not HAART significantly decreases heterosexual transmission of HIV.

The researchers have begun a longitudinal study to determine if HAART benefits hold up over time. ■

Program increases HAART adherence in HIV patients

Nonadherence rates drop drastically

Clinicians at Miriam Hospital in Providence, RI, have drastically increased HIV patients' adherence to highly active antiretroviral therapy (HAART) during a six-month pilot program.

About 75% of the patients reported prior to the program's intervention that they had missed a dose of AIDS drugs within the previous four days. After one month of the program, only 22% said they had missed a dose. So far, only one month's worth of data has been analyzed, but the outcomes look promising, says **Jennifer A. Mitty**, MD, MPH, assistant professor of medicine at Brown University in Providence and an attending physician at Miriam Hospital.

"Adherence is so important because poor adherence results in drug-resistant virus," Mitty says.

The program, which has grown to 23 HIV patients, began in June 1998. The patients were referred by physicians after they had reported nonadherence to their medications. The group's demographics are:

- a mean age of 39;
- 76% female;
- 29% white;
- 33% black;
- 29% Hispanic;
- 65% have been in jail or prison;
- 26% are active substance abusers;
- 85% are not working.

At baseline, 48% accurately reported their medication, and 14% correctly reported their dosage; at one month, 60% accurately listed their medications and dosage.

Drugs delivered by community members

The program works this way: Two peer outreach workers who are not health care professionals deliver medications to the patients each day, Monday through Friday. They meet patients at their homes or at some other place that the patients choose. On Friday, they leave medication for the weekend. A nurse packages the medication in daily doses.

When they deliver the medication, they watch the patient take the morning dose, and they check to see if the previous day's evening dose has been taken. One of the workers speaks Spanish, and both are members of the community in which the patients reside.

The program, which cost less than $40,000 for the first six months, was funded by a Lifespan/Tufts Center for AIDS Research grant in Boston and Providence. The program received money from three pharmaceutical companies: Glaxo Wellcome, Bristol-Myers Squibb, and Merck. The patients' AIDS drugs are covered through Medicaid or the Rhode Island Drug Assistance Program.

Mitty says the program began with the daily visits and eventually weaned the patients down to visits three times a week, then two times a week, and finally once a week.

HIV patients who have trouble adhering to their drug regimens probably should be followed indefinitely, Mitty says.

"We'd like to observe people by giving them a weekly pill pack, and if we see someone going through a major life stress, then we could increase the visits," she explains. "For example, if someone has picked up a substance abuse problem or has become homeless, then we could say that once a week is no longer good enough."

Although the pilot program was developed for six months, Mitty says it will be continued as a weekly outreach project.

The nine patients who first began on the program had an average viral load decrease of 1.2 log after one full month. Also, their average CD4 cell count increased from 215 to 283, Mitty says.

"The program's effectiveness still needs to be determined, but it is feasible for others to implement a program such as this, and it's been very well accepted by patients," Mitty says.

She suggests other communities and medical centers could start such a program fairly inexpensively, perhaps even using volunteers as outreach workers.

The program's future may include incorporating patient education in the outreach work, Mitty adds. The outreach workers already serve as links to the medical clinic because if they see a patient has a medical problem, they'll contact Mitty or another professional.

"I don't know if this program is for everyone, but it definitely serves the needs of certain populations," Mitty says. "The whole point is to design interventions appropriate to the population being served." ■

AIDS patients with ARF treated for wrong infection

Cryptococcus seen in immunodeficient patients

Houston researchers have shown through a retrospective study that clinicians sometimes attribute acute respiratory failure (ARF) in AIDS patients to *Pneumocystis carinii* pneumonia, when the true culprit is *Cryptococcus neoformans* meningoencephalitis.[1]

Pneumocystis is so common among people who come into hospitals to be treated for ARF that clinicians often assume AIDS patients with ARF symptoms have this disease, says **Richard J. Hamill**, MD, associate professor of medicine, microbiology and immunology at Baylor College of Medicine in Houston, and staff physician of the Section of Infectious Diseases of the VA Medical Center in Houston. Hamill co-wrote

an article on the study, published in *Clinical Infectious Diseases.*[1]

The study showed that the incidence of ARF in AIDS patients who have cryptococcosis is underestimated in the literature and sometimes overlooked by clinicians. Hamill's research confirms anecdotal evidence that cryptococcal disease is often seen in people with compromised immune systems.

John Perfect, MD, professor of medicine at Duke University Medical Center in Durham, NC, says he's seen cryptococcal infection relatively commonly in HIV patients and others with compromised immune systems.

"In our situation and in our location, cryptococcus is still a major opportunistic fungal pathogen in patients with HIV and organ transplants, and occasionally in normal individuals," says Perfect, who is co-author of a book called *Cryptococcus Neoformans* (Washington, DC: ASM Press; 1998).

Raising cryptococcosis awareness

Perfect says he has spoken and written about cryptococcal disease to raise clinicians' awareness of it. If physicians thought about cryptococcal disease when they are presented with ARF symptoms, pulmonary lesions, and chronic meningitis, they could easily test patients for it and make a correct diagnosis.

The problem is that when physicians assume ARF patients have pneumocystis, they treat them with a sulfa antibiotic called trimethoprim/sulfamethoxazole, which works for pneumocystis but has no effect on cryptococcal disease, Hamill says.

"For cryptococcus, we usually give patients amphotericin B, which is an antifungal drug," he adds.

Only 11 of 19 case patients in the study had been given the antifungal drug. All of these patients had died, and most within four weeks of diagnosis with cryptococcal disease.

The cryptococcosis study also showed there is a significantly higher incidence of cryptococcal disease in black AIDS patients than in other races. Hamill speculates one reason for this higher incidence may be that black AIDS patients fail to access the health care system as early in their disease as do white AIDS patients.

"We didn't look at socioeconomic levels or anything like that," Hamill says. "They may have had the same level of CD4 as someone else, but they waited until their cryptococcal became worse before coming in for treatment."

There also is the possibility that cryptococcal disease is worse in blacks for genetic reasons, although this theory has not been studied.

Consider other etiologies

Hamill says it would be easy for physicians and clinics to find cryptococcal disease in AIDS patients if they would simply think of etiologies other than pneumocystis when they're presented with a case of ARF.

The serum antigen test to identify cryptococcal disease is simple and inexpensive and can be done in a few minutes, Hamill says. "It's a little slide test where you look for a clumping of latex beads."

ARF patients often have been on prophylaxis for pneumocystis, and this prophylaxis is very effective.

"So if a patient who is taking prophylaxis comes in for treatment, physicians should consider the possibility of other etiologies," Hamill says. "They should do other tests to make a diagnosis, and one of those tests is serum cryptococcal antigen."

Patients with cryptococcal disease sometimes experience cranial pressure that can cause brain damage. If a clinician suspects the patient is experiencing this symptom, the clinician could do a spinal tap that would immediately show whether the patient has meningitis due to cryptococcal infection, Hamill suggests.

"If I have an AIDS patient with a low CD4 count and a fever and no obvious source of infection, I do the serum cryptococcal antigen test," he adds.

Hamill has suspected for years that cryptococcal disease has a higher incidence rate than most clinicians think. Since 1992, he has been involved with a project sponsored by the Centers for Disease Control and Prevention that involves collecting cryptococcus fungal isolates mostly from AIDS patients in Houston. So far, his research group has collected 500 to 600 isolates of cryptococcal pathogens from different patients, 95% of whom have AIDS.

The ARF and cryptococcosis study offers some proof that this incidence rate is underestimated. Here are some of the study's findings and methodology:

Researchers conducted a case-control, referent study, selecting 210 HIV-positive patients from

existing databases from January 1993 to May 1996 at four major teaching hospitals in Houston. Researchers identified cases by active surveillance of positive cryptococcal antigen tests and / or recovery of *C. neoformans* from any body site in 14 microbiology laboratories.

Twenty-nine of the 210 patients (13.8%) had acute respiratory failure. Ten patients were excluded from analysis, leaving 19 cases that met the case definition of acute respiratory failure due to cryptococcal disease. Among the 19 cases, 100% died, with a median survival time of only two days. More than 50% of referents had been alive for more than a year, and 25% of referents had died.

When patients had neurological manifestations, they were more likely to have their disease diagnosed and treated. This finding emphasized how clinicians often failed to recognize the respiratory syndrome associated with cryptococcal disease.

Researchers postulate that cases had a fulminant course due to acute dissemination shortly after acquisition of a primary pulmonary infection. They base this belief on the lack of cryptococcal disease in all except for one case; respiratory symptoms that often preceded neurological manifestations; common systemic symptoms that suggest dissemination; and the detection of fungemia in at least two patients more than a week before onset of neurological signs and symptoms.

Variables independently predictive of ARF in patients with cryptococcal disease were black race, a lactate dehydrogenase level of greater than or equal to 500 IU / L, the presence of interstitial infiltrates, and the presence of cutaneous lesions.

Reference

1. Visnegarwala F, Graviss E, et al. Acute respiratory failure associated with cryptococcosis in patients with AIDS: Analysis of predictive factors. *Clin Infect Dis* 1998; 27:1,231-1,237. ■

AIDS • NEWS • ALERTS

Study shows high efficacy of female condom

A recent Japanese study showed that the female condom, if used correctly with every sex act, had a six-month failure rate of 0.8%.

The condom's efficacy rate refers to the rate of pregnancy. However, the female condom also is used by women to prevent the spread of HIV and other sexually transmitted diseases.

Previously, a U.S. study showed a six-month failure rate of 2.6%. Also, in the Japanese study, the failure rate when the condom was not used correctly with every sex act was 3.2% for six months, as compared with 12.4% in the U.S. study.

"The mostly likely reason for the difference was that coital frequency was much lower in the Japanese study," says **James Trussell**, PhD, professor of economics and public affairs at Princeton (NJ) University. Trussell, who analyzed the two studies for an article in the journal *Contraception*, also is a faculty associate at the Office of Population Research at Princeton.

"The protocols were the same; participants were supposed to have coital frequency of a certain amount," Trussell explains. "But the mean coital frequency in the U.S. study was 12 acts per month, and in the Japanese trial it was 4.9 acts per month, 60% lower."

The Japanese study is good news for clinicians and public health officials who promote AIDS prevention. "If it works against pregnancy, that means it's not breaking or slipping," Trussell says. "And because of its physical design, it clearly will protect women against sexually transmitted diseases."

The female condom is manufactured and distributed by The Female Health Co. in Chicago.

COMING IN FUTURE MONTHS

- New model could help clinicians increase HAART adherence
- Race to HIV vaccine is updated
- Clinicians working with HIV patients are safe from TB
- After HAART treatment, immune systems might be reconstituted
- Causes of wasting syndrome explained

The company holds patents on the condom in the United States, the United Kingdom, Japan, France, Italy, Germany, Spain, China, Canada, New Zealand, South Korea, and Australia. **(See story on the female condom in *Common Sense about AIDS,* inserted in this issue.)** ▼

African-American women are hard hit by AIDS

African-American women represent 56% of all AIDS cases reported among women, and they have three times the number of new cases that are reported for white women, according to the Henry J. Kaiser Family Foundation in Menlo Park, CA.

The AIDS case rate for African-American women is 61.9 cases per 100,000, about 16 times higher than white women's AIDS case rate of 3.8 cases per 100,000.

These alarming statistics have created a sense of urgency about AIDS among African-American women, and this is expressed in a recent survey the foundation conducted. The Kaiser Family Foundation survey showed that many African-American women believe AIDS is the most urgent health problem facing the nation today, with 88% saying AIDS is a major threat to public health in the United States.

The African-American women surveyed also revealed these beliefs:

- About 46% of African-American women surveyed say AIDS is a more urgent problem today for their community than it was a few years ago.
- Fifty percent of the women know someone personally who has AIDS, or has died of AIDS, or has tested positive for HIV.
- Nearly 70% are very concerned about their children becoming infected with HIV, and this concern has increased more among women than men in recent years.
- Sixty percent of the women say they need information about discussing AIDS prevention with children.
- About 58% report they have been tested for HIV, including 36% within the last year. However, only 47% of the women surveyed say they are very concerned about becoming infected with HIV.
- One-third of African-American women have talked with a health care provider about HIV testing, and 53% of these women say they brought up the topic. Only 35% of African-American women have ever talked with a health care provider about the risks of being infected with HIV.
- One in five African-American women incorrectly state that today's HIV tests can determine infection within one month of exposure, and 21% state that they do not know when the tests can determine, with confidence, whether or not someone has been infected with HIV.

Of the African-American women surveyed who have not been tested for HIV, 35% say it is because they are married or in a monogamous relationship; 32% say it is because they are not sexually active; and 14% say it is because they see no need or reason to suspect a problem. ▼

AIDS Alertfi (ISSN 0887-0292), including **AIDS Guide for Health Care Workers**fi and **Common Sense About AIDS**fi, is published monthly by American Health Consultantsfi, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodical postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **AIDS Alert**fi, P.O. Box 740059, Atlanta, GA 30374.

This continuing education offering is sponsored by American Health Consultantsfi, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center s Commission on Accreditation. Provider approved by the California Board of Registered Nursing, provider number CEP 10864. This continuing education program does not fulfill State of Florida requirements for AIDS education. American Health Consultantsfi is accredited by the Accreditation Council for Continuing Medical Education to sponsor CME for physicians. American Health Consultantsfi designates this continuing medical education activity for 18 credit hours in Category 1 of the Physicians Recognition Award of the American Medical Association.

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Editor: **Melinda Young**, (828) 859-2066.
Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@medec.com).
Executive Editor: **Susan Hasty**, (404) 262-5456, (susan.hasty@medec.com).
Managing Editor: **Coles McKagen**, (404) 262-5420, (coles.mckagen@medec.com).
Senior Production Editor: **Brent Winter**, (404) 262-5401.

Editorial Questions

For questions or comments, call **Melinda Young** at (828) 859-2066.

Do-it-yourself kits could lead to unsafe sex

Internet shopping has made it easy for anyone with a credit card to order an HIV test kit for as little as $25, and this prospect has public health officials worried about health hazards, according to a report in the *San Francisco Chronicle*.

The Rockville, MD-based U.S. Food and Drug Administration has approved one test, called Home Access, for home use. However, a *Chronicle* reporter received an unapproved kit by mail after placing an on-line credit card order for $24.95 plus $3.95 for shipping and handling. The test was shipped from Malta by a European company, Health Diagnostics Ltd., and it had a label printed in Russian beneath another label in English.

Bernard Branson, an HIV-testing specialist at the Centers for Disease Control and Prevention, told the *Chronicle* that public health officials do not know enough about these tests to determine if they are accurate.

The danger is if someone who has been infected with HIV uses an unapproved test kit and receives a negative result, then the person may falsely believe he or she is free of HIV and could then spread the disease to others through unsafe sex or other risky practices.

FDA officials say HIV test kits are considered medical devices and therefore are subject to the FDA's jurisdiction. ▼

Study shows PI treatment safe for pregnant women

A study of 37 HIV-infected pregnant women appears to show that protease inhibitor treatment is safe for use during pregnancy.

The study, conducted by scientists at the University of Southern California School of Medicine, found that all 32 babies born thus far have been HIV-negative. In addition, there was a relatively low rate of prematurity and no birth defects among the infants.

Alice Stek, MD, who presented the findings at a meeting of the Society for Maternal and Fetal Medicine in San Francisco, asserted that HIV-positive women should not be denied optimal treatment because of pregnancy. ■

CE objectives

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, 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. ■