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AIDS ALERT

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Coverage of the 2001 IDSA Conference

HAART patients can face greater risk of developing heart disease — studies

Study shows connection with myocardial infarction

Some of the strongest evidence to date suggesting that patients on highly active antiretroviral therapy (HAART) are at greater risk for developing cardiovascular disease was presented at the 39th Annual Meeting of the Infectious Diseases Society of America (IDSA), held Oct. 25-28, 2001, in San Francisco.

While a large focus of the IDSA meeting was on anthrax and bioterrorism, which were a national obsession in the fall, the research presented about the connection between HIV and cardiovascular disease is something HIV clinicians will want to keep in mind when starting new patients on HAART or making adjustments to existing HIV treatments.

"HAART therapy is associated with a variety of changes that go under the umbrella of lipodystrophy and hypercholesterolemia," says **John Bartlett**, MD, chief of the Division of Infectious Diseases at Johns Hopkins University School of Medicine in Baltimore. "And increases in cholesterol and triglycerides are like it is for other populations without HIV infection — it confers risk for heart disease."

Investigators from the HIV Outpatient Study (HOPS) group, which is located at 10 sites in the United States, found that after a few years of taking protease inhibitors, HIV patients were beginning to show a significantly increased rate of myocardial

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■ ICAAC special report: Coverage of the latest HIV/AIDS news and research presented at the 2001 Interscience Conference on Antimicrobial Agents & Chemotherapy

■ World HIV/AIDS update: The world may be distracted from concerns about the AIDS pandemic, but the virus marches on, flaring up in various regional hot spots

■ Dual resistance test launched: New combination resistance test provides phenotypic and genotypic information on one report

■ Deaths cut among children: Four-year study shows combining protease inhibitors with standard AIDS drugs cut risk of death by two-thirds

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Editor: **Melinda Young**, (828) 859-2066.
Vice President/Group Publisher: **Donald R. Johnston**, (404) 262-5439, (don.johnston@ahcpub.com).
Editorial Group Head: **Glen Harris**, (404) 262-5461, (glen.harris@ahcpub.com).
Managing Editor: **Robin Mason**, (404) 262-5517, (robin.mason@ahcpub.com).
Production Editor: **Brent Winter**.

Editorial Questions

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

infarctions, says **Scott D. Holmberg**, MD, MPH, senior epidemiologist in the Division of HIV/AIDS Prevention at the Centers for Disease Control and Prevention in Atlanta.

"When we looked at the rate of myocardial infarction in the HOPS cohort overall, the rates start significantly increasing after 1996, the time the protease inhibitor drugs were introduced," Holmberg says.

The main argument of the research, which was presented at the IDSA conference, was that the HIV patients who were on PI-containing regimens were several times more likely to have a myocardial infarction, even after controlling for traditional cardiovascular risk.[1]

This increased risk also appears when HIV patients on PI regimens are compared with HIV patients on non-PI regimens, including those that contain nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors, Holmberg adds.

"Also, it's consistent and biologically plausible that PI drugs increase lipid and glucose levels in the blood and perhaps increase hypertension, as well," Holmberg says.

Diagnoses verified against clinical records

The HOPS data came from two groups of 3,000 HIV patients. One group had taken protease inhibitors, and the other had not. The study's findings are particularly noteworthy because researchers looked specifically at myocardial infarctions and verified hospital discharge diagnoses against clinical records.

"We found a couple of MIs that were actually angina, and some angina that were not angina," Holmberg says. This is what makes the HOPS outcomes unique.

"Some other cohorts have been limited in their ability to look at actual drugs patients have taken and at the patients' cardiovascular risk factors," Holmberg adds. "Some previous studies may not have followed patients long enough."

Still, the HOPS patients will need to be followed even longer to verify what CDC researchers have seen thus far, Holmberg notes.

The HOPS findings confirm what HIV clinicians and researchers have suspected for the past few years, but it's too soon to base clinical decisions solely on the risk of cardiovascular disease, experts say.

"It's way too early to say that PIs by themselves are going to automatically guarantee serious cardiovascular problems," says **Kenneth Mayer**, MD, professor of medicine and community health at Brown University and Miriam Hospital in Providence, RI, and medical research director of Fenway Community Health in Boston.

However, it is time for clinicians to consider assessing HIV patients' risk factors for cardiovascular disease and to make recommendations for prevention programs, such as smoking cessation programs, increased exercise, and weight loss, in the event an HIV patient is taking protease inhibitors and also has other risk factors, Mayer says.

"Ten years ago, patients may not have lived long enough to be concerned about heart disease, but now they are," Mayer adds.

A second study that assessed coronary heart disease (CHD) among HIV patients also suggested that young men ages 18-34 with HIV infection were more likely than non-HIV men to have coronary heart disease.[2]

The study, conducted on behalf of Bristol-Myers Squibb of Plainsboro, NJ, looked at claims codes and data from the California Medicaid (MediCal) population, which has a large HIV-infected population, says **Sally Lynn Hodder**, MD, director of clinical analysis for Bristol-Myers Squibb Virology.

HIV patients who were not receiving therapy were excluded from the study, Hodder says.

"It appeared that young men with HIV had an increased incidence of coronary heart disease as opposed to their non-infected counterparts," Hodder says. "Older individuals with HIV had a lower incidence of coronary heart disease."

The study had some limitations, including that the claims databases did not have information on smoking and some other coronary heart disease risk factors, but it at least suggests that there is an acceleration of atherosclerosis in young HIV-infected people receiving HAART, Hodder says.

"In the study design, people had to be continuously medically eligible for three years to be included, and the first year was a wash-out period in which the individual had to be free of any coronary heart disease diagnoses," Hodder explains. "We were looking at incidence, not at prevalence."

The bottom line is that clinicians caring for HIV-infected patients should give important consideration to modifying a patient's risk for coronary heart disease.

"While it's unclear whether HIV infection, antiretroviral agents, or both are affecting the

incidence of coronary heart disease, you clearly want to minimize an individual's risk factors for CHD," Hodder adds.

A third IDSA study looked at the characteristics of HIV-infected patients who had a myocardial infarction. It concluded that these patients were predominately middle-aged African-Americans with relatively preserved immune function, and 80% were on HAART.[3]

Yet, it would be a mistake if clinicians concluded that they should not be giving patients PI drugs because of the increased cardiovascular risk, Bartlett notes.

'Like every drug, it has risks'

"PI therapy has been the miracle of the decade in terms of medical treatment and has had an astonishing record of success in every parameter," Bartlett says. "But like every drug, it has risks."

Still, there are three potential strategies clinicians might consider, Bartlett says:

- They could refrain from making changes because the risk of cardiovascular disease isn't very high.
- They could treat according to current medical guidelines and give HIV patients with increased cholesterol and cardiovascular disease risk factors a statin drug.
- They could try to switch certain patients to HAART regimens.

"I think switching is a reasonable thing to consider, but you wouldn't switch if the person didn't have hyperlipidemia," Mayer says. "Clinical judgment says you don't have a one-size-fits-all strategy."

On the other hand, keeping patients on PI regimens and then adding a statin drug to their daily pill-taking routine means HIV patients will have one more medicine and its side effects to contend with, and that could pose adherence problems, Mayer says.

"Unfortunately, because we don't have a cure, we're still in the realm of learning more about this phase of HIV disease and the interaction of people living long periods of time and being on chronic medications that potentially have significant side effects," Mayer explains. "It's a set of interactions that we can't predict."

The actual risk of cardiovascular disease to any particular HIV patient on PI drugs appears to be very small, Holmberg says.

Still, there's the potential for the complications and risk to increase as HIV patients age, Mayer says.

If a patient and clinician are uncomfortable with the risk, consider these questions:

- What are the patient's modifiable cardiovascular risk factors?
- How long has the patient been on PI drugs?
- How well is the patient doing on PI drugs?

"All of these factors need to be weighed before the physician starts immediately swapping patients out," Holmberg says. "But the patient's wishes are always something to consider."

If a clinician and patient decide that switching off PI therapy would be the most desirable strategy, then there are a few suitable options.

One strategy would be to replace PIs with abacavir, efavirenz, or nevirapine regimens. For instance, the triple-drug pill Trizivir, which contains abacavir, lamivudine (3TC), and ATC, appears to work well, Bartlett says.

In another study presented at the IDSA conference, investigators found that HIV patients randomly assigned to be switched from a PI regimen to an abacavir substitute retained viral load suppression at 24 weeks, says **Joseph J. Pulvirenti**, MD, director of inpatient HIV services for Cook County Hospital in Chicago.

"There was an improvement as far as cholesterol was concerned at 24 weeks, and it was considered to be significantly improved in the abacavir arm," Pulvirenti says. "We also saw a difference in triglycerides, with people who swapped out to abacavir having a significant improvement as far as lipid studies."

Investigators looked at the issue of swapping HIV therapies because of the problems patients have experienced in recent years with PI therapies, including resistance, adherence, adverse events, and chronic problems, Pulvirenti says. **(See story on abacavir study, p. 5.)**

Also, two studies presented at the 8th European Conference on Clinical Aspects and Treatment of HIV Infection, held in October 2001 in Athens, Greece, showed that HIV patients taking a nevirapine-based therapy had an improved lipoprotein profile. The 96-week data showed that patients treated with nevirapine, ddI, and d4T demonstrated a 40% increase from baseline in HDL cholesterol and a decrease in the total cholesterol / HDL cholesterol ratio. By comparison, patients receiving the protease inhibitor indinavir showed significant increases in total and LDL-cholesterol and an increase in the total / HDL cholesterol ratio. The study has not produced

results evaluating the effectiveness of nevirapine in a combination therapy to treat HIV-1 infection.[4]

"The data are getting stronger and stronger to say [non-PI regimens] will work, but we have to take the individual patient into account," Bartlett adds. "So if this patient has no risk for heart disease, elevated cholesterol for a few years is quite acceptable."

Alternatively, if the patient has previous heart problems or diabetes, hypertension, or a bad family history, a clinician may say that's too great a risk, Bartlett says.

References

1. Holmberg S, Moorman AC, Tong T, et al. Protease inhibitor drug use and myocardial infarction in ambulatory HIV-infected patients. Presented at the 39th Annual Meeting of the Infectious Diseases Society of America. San Francisco: Oct. 25-28, 2001. Abstract 941.

2. Hodder S, Burtcel B, Kawabata H, et al. Coronary heart disease in patients with human immunodeficiency virus infection. Presented at the 39th Annual Meeting of the Infectious Diseases Society of America. San Francisco: Oct. 25-28, 2001. Abstract 18.

3. Castro JG, Fischl M. Characteristics of HIV-infected patients who had a myocardial infarction. Presented at the 39th Annual Meeting of the Infectious Diseases Society of America. San Francisco: Oct. 25-28, 2001. Abstract 730.

4. van der Valk M, Kastelein J, Murphy R, et al. Nevirapine-containing potent antiretroviral therapy results in a sustained anti-atherogenic plasma lipid profile: 96 weeks results from the Atlantic Study. Presented at the 8th European Conference on the Clinical Aspects and Treatment for HIV Infection. Athens: Oct. 29, 2001. Abstract 126. ■

Coverage of the 2001 IDSA Conference

Easier abacavir regimen has promising results

Patients improved adherence on abacavir

HIV patients, understandably, are sometimes unenthusiastic about taking their protease inhibitor (PI) drug therapies because of the numerous pills, the side effects, and chronic problems such as lipodystrophy.

To address these problems, researchers have been studying non-PI drug therapies that are potent against HIV. An abstract presented at the 39th Annual Meeting of the Infectious Diseases Society of America (IDSA), held Oct. 25-28, 2001, in San Francisco, demonstrated successful viral suppression for at least 24 weeks when patients were switched from a PI regimen to an abacavir regimen.

"The reason we did this study was to try to address an issue that a lot of clinicians are running into, and that is the difficulty with chronic management of PI regimens," says **Joseph J. Pulvirenti**, MD, director of inpatient HIV services for Cook County Hospital in Chicago.

"We were trying to achieve a decrease in adverse events and develop regimens that were more patient-friendly," Pulvirenti says.

Investigators selected patients who were on their first antiretroviral regimen and who had a good response to that regimen, remaining undetectable for a period of time, Pulvirenti says.

Patients were placed in random groups with a two-to-one ratio: For every two patients who were discontinued on PI therapy and switched to an abacavir therapy, there was one patient who continued on the PI therapy, he explains.

At 24 weeks, the two groups were compared with regard to viral load, adverse effects, cholesterol levels, triglyceride levels, and adherence.

Abacavir group maintained viral suppression

The study found that patients who had been switched to the abacavir regimen maintained viral suppression and adherence and had an improved lipid profile, Pulvirenti says.

Both groups had improved their adherence during the study, and there was no significant difference in whether patients achieved an undetectable viral load, he says.

However, the patients who had been switched to abacavir had an improvement in triglycerides and cholesterol levels, as well as improvement in adherence, which suggests this was a more tolerable regimen, Pulvirenti says.

"If the study were carried out to 48 weeks or further, the study in adherence may have had more of an effect," he adds.

The abacavir group had to take only four pills a day, as opposed to PI regimens, which can require patients taking more than 10 pills per day, Pulvirenti notes.

"There is more than enough data out there to suggest that swapping out is a perfectly viable way to go," Pulvirenti says. "When it comes to my patient population and people who are well-controlled but who remain on protease inhibitors, I discuss the options with them."

Some patients have refused to swap therapies, but Pulvirenti says he will discuss changing therapies for patients who have evidence of lipodystrophy or other problems that suggest greater risk for heart disease.

"In order for a patient to get to the position where he can swap out, he has to be compliant with medication for a good long period of time," Pulvirenti notes. "So these people who are candidates for swapping regimens are generally very compliant and more highly educated than other patients."

That's why it's essential to always obtain the patient's opinion and discuss the plan for swapping medications, working toward obtaining patient buy-in for the strategy, Pulvirenti says. ■

Coverage of the 2001 IDSA Conference

Opportunistic infection improvements level off

Six diseases have shown no decrease at all

One of the greatest achievements of protease inhibitor (PI) therapy and highly active antiretroviral therapy (HAART) has been the dramatic decrease in the incidence of opportunistic infections (OIs) related to AIDS.

In the first couple of years after the advent of PI therapy, clinicians found that fewer HIV / AIDS patients developed some of the more common OIs, such as Kaposi's sarcoma and pneumocystosis.

However, new research shows the decline in OI rates has ended. The declines experienced between 1995 and 1998 did not continue through 1999 for all except for two OIs, according to a study by researchers with the Centers for Disease Control and Prevention

The exceptions to the new trend are the OIs cerebral toxoplasmosis and CMV retinitis, both of which showed lower rates among men in 1999 than in 1998.

"Possible reasons for the leveling incidence include the achievement of the maximum benefits of HAART among this cohort," says **A.D. McNaghten**, PhD, MHSA, an epidemiologist with the CDC.

"Medication side effects, poor patient compliance, the development of resistant strains of HIV, and late presentation and diagnosis may diminish the effects of HAART," McNaghten says. "These possibilities need to be investigated further."

The CDC study, which was presented at the 39th Annual Meeting of the Infectious Diseases Society of America (IDSA), held Oct. 25-28, 2001, in San Francisco, also found that six OIs did not decrease at all between 1995 and 1999. These included disseminated histoplasmosis, pulmonary candidiasis, Burkitts lymphoma, disseminated coccidioidomycosis, and recurrent salmonella septicemia. The sixth, cervical cancer, actual had an increasing trend during this time period, McNaghten says.

OIs decreased less for women

When the incidence trends were analyzed by gender, it was found that men had significant decreases for 19 of 25 OIs, while women had decreasing trends for only 11 of 26 OIs.[1]

"These women may be diagnosed with HIV later and enter care later than men," McNaghten says. "There may also be differences in treatment."

For example, a recent ASD analysis showed that among patients eligible for antiretroviral therapy according to treatment guidelines in 1999, female gender was associated with a decreased likelihood of HAART prescription, McNaghten says.

CDC investigators will continue to study the incidence of OIs, including conducting an analysis of OI incidence in 2000 and 2001 to determine if specific OIs are increasing, decreasing, or remaining level, McNaghten says.

Meanwhile, clinicians should keep these findings in mind as they initiate and adjust antiretroviral treatment for HIV patients.

"These findings reinforce the importance of antiretroviral therapy and OI prophylaxis, which are vital to preventing OIs," McNaghten says. "It is important for clinicians to be aware of the recommendations in the *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents and the USPHS/IDSA Guidelines for the Prevention of OIs in Persons Infected with HIV*."

Reference

1. McNaghten AD, Hanson DL, Nakashima AK, Swerdlow DL. Incidence of AIDS-defining opportunistic infections in the US may be leveling from 1998-1999. Presented at the 39th Annual Meeting of the Infectious Diseases Society of America. San Francisco: Oct. 25-28, 2001. Abstract 751. ■

Coverage of the 2001 IDSA Conference

New research adds support for ED at-risk testing

Strategy reaches high-risk heterosexuals

A study conducted at the University Hospitals of Cleveland in Ohio adds to the growing body of research that suggests it's a good strategy to offer HIV testing to patients admitted to hospital emergency departments.

"People that are in HIV high-risk groups . . . use traditional HIV testing sites, but offering testing to emergency room patients reaches a different group that's at risk, such as African-American women," says **Michelle Kucia**, Ryan White grants administrator for the University Hospitals of Cleveland.

During a five-month period, investigators compared 123 people tested for HIV at a local clinic with 105 people who were tested in the emergency department after being admitted for common illnesses, such as sexually transmitted diseases (STDs), minor trauma, upper respiratory infection, or pelvic inflammatory disease, according to a study that was presented at the 39th Annual Meeting of the Infectious Diseases Society of America (IDSA), held Oct. 25-28, 2001, in San Francisco.

Researchers found that 97 (92%) of those tested in the emergency department were African-American and eight were Caucasian. Also, 63 (60%) were female. By comparison, of the population tested at the local HIV clinic, 79 (64%) were Caucasian, 25 (21%) were African-American, and the rest were mixed-race, Asian-American, and Hispanic. Of those tested at the clinic, 45 (36%) were female.

Also, the people tested in the emergency department were more likely to be heterosexual, have a history of STDs, and have prior intravenous drug use compared with those tested at the clinic. Men who have sex with men (MSM) were more likely to be tested at the HIV clinic, as were those who had sex with a known HIV-infected partner.

The study found no significant difference in the number of positives found in the emergency room vs. the HIV clinic, Kucia says.

"By offering testing in the ER, we got people to think about HIV infection," Kucia says. "Especially at a time when women are coming to the rapid care center for something STD-related or prenatal, this gets them to think about risk and transmission."

Grants covered the cost of emergency department HIV testing, and the project included two medical students who would go to the rapid care center, make contact with patients, give them background information about HIV, and then offer testing. Medical students would obtain the patients' consent, and nurses would draw their blood. Patients were instructed to return within a week to the outpatient HIV clinic for their results, Kucia says.

"HIV tests are run for free through the Ohio Department of Health, but it was something our ER was very hesitant to do," Kucia says. "They didn't want to deal with all of the counseling and giving patients results, and that's why we had patients come to the HIV clinic for their results." ■

Infection with GBV-C linked to longer life

Odd benign virus is related to hepatitis C

New research has established a link between HIV patients being infected with a virus that is similar to hepatitis C and having a slower HIV disease progression.

Investigators first began to look at GBV-C in the mid-1990s as a possible cause of chronic hepatitis, but they quickly lost interest when the virus was shown to have no direct link to the disease, says **Jack Stapleton**, MD, a researcher and physician at the Veterans Affairs Medical Center in Iowa City, IA, and a professor of internal medicine at the University of Iowa in Iowa City.

"The virus was discovered in late 1995, and by 1998 it was determined it didn't cause hepatitis, so most people quit studying it," Stapleton says. "But we're slow, and we had some interesting questions about the virus, and so we continued to work on it."

Stapleton and fellow investigators searched for differences between GBV-C and hepatitis C in an effort to understand how hepatitis C causes hepatitis. Their other goal was to examine GBV-C for use in gene therapy.

"The virus is a persistent and common human infection that doesn't cause disease," Stapleton

explains. "So we reasoned that it might be useful as a gene therapy factor as a way to express foreign genes."

GBV-C is a bloodborne virus that is more efficiently transmitted sexually than hepatitis C, Stapleton says. "People who have sexually transmitted diseases have a higher rate of infection of GBV-C than the general population, and the virus is easy to transmit from mother to child."

Then in 1999, the investigators came across reports by German and Japanese researchers. They found that people who are infected with HIV and co-infected with GBV-C had better clinical outcomes than HIV patients without GBV-C infection.

"One of my projects was to look at hepatitis C and GBV-C in HIV-positive people to look at different issues related to viruses and responses," Stapleton says. "Somewhat to our surprise, when I looked at patients who were in the clinic for more than 10 years — the first 14 patients — 13 of them had GBV-C infection."

The investigation changed focus and began to involve a look at samples from HIV patients that dated back to 1988. Researchers studied blood samples and mortality data from 362 HIV patients, including 144 who had a GBV-C co-infection.

Of the 144 people co-infected with HIV and GBV-C, 28% had died, compared to deaths among 56% of those with HIV and no GBV-C infection. The study also found that nearly 40% of the HIV patients studied had GBV-C co-infection, while in the United States, among healthy blood donors, only 1.8% of people are infected with GBV-C.[1]

"When we looked at their CD4 cell counts, treatment, prophylaxis, parameters, and survival, we found that the group with the GBV-C co-infection had a much lower death rate," Stapleton says. "It really was quite striking."

Armed with more information, researchers returned to the lab and examined the cells infected with GBV-C to see if they could measure any differences between cells lacking the co-infection. It was possible that GBV-C co-infection had nothing to do with prolonged survival with HIV disease and that the coincidence had some other explanation, Stapleton notes.

However, lab tests showed that cultured human T-cells co-infected with GBV-C had less HIV cell growth than those that didn't, Stapleton says.

"An explanation is that GBV-C is damaging cells somehow, or maybe it's preventing cells from metabolizing protein as fast," Stapleton explains. "We think GBV-C is somehow acting to inhibit HIV from growing."

When researchers infected cells with HIV for 24 hours before inserting GBV-C, they saw that GBV-C inhibited HIV as much as if the cells were infected with both viruses simultaneously, Stapleton says.

"This argues to us that GBV-C is altering cells in some way to make them less hospitable for HIV," he says. "What we don't have evidence for is whether the cells infected with GBV-C are the same as those infected with HIV, and that would be a prerequisite for this to be a direct interference."

There are indirect ways a virus can induce protection, Stapleton adds. "For example, some studies show influenza virus infections and vaccination can make T-cells secrete interferon and be less susceptible and hospitable for HIV."

An alternative theory is that GBV-C is altering cytokine expression within cells, making them less hospitable for HIV, Stapleton says.

"These are substances that can be released by cells and affect surrounding cells and still have an inhibitory effect, — even if the same cells are not infected," Stapleton explains. "We're actively studying this to find out which substances those are, and we're leaning toward that explanation."

Reference

1. Xiang J, Wunschmann S, Diekema DJ, et al. Effect of coinfection with GB virus C on survival among patients with HIV infection. *N Engl J Med* 2001; 345(10):707-714. ■

CDC posts new HIV testing, referral guidelines

One set addresses pregnant women

New HIV testing guidelines released by the Centers for Disease Control and Prevention in Atlanta include strategies for increasing early testing of at-risk people and universal HIV testing of pregnant women.

"Over the course of time, we've ended up with a document that describes state-of-the-art HIV testing, counseling, and referral services," says **Ken Hunt**, senior public health advisor in the Division of HIV / AIDS Prevention.

The guidelines have been in development for nearly three years. CDC officials have taken pains to include various expert opinions and incorporate public comments into the guidelines. They also use information provided at conferences and state meetings, as well as other feedback, Hunt says.

This way, both the public and providers have been actively involved in helping to frame the recommendations, he adds.

"What's important now in the state of the epidemic is that we have better treatment, so we're encouraging people to ensure that early testing is made available and the highest-risk people have the opportunity to be tested," Hunt says.

The updated guidelines, called the *Revised Guidelines for HIV Counseling, Testing and Referral and Revised Public Health Service Recommendations for HIV Screening of Pregnant Women*, are available on-line at www.cdc.gov/hib/ctr or by calling (800) 458-5231.

Here's what's new in each of the guidelines:

1. Pregnant women.

"The revisions really emphasize that every woman who is pregnant should be offered HIV testing," says **Mary Glenn Fowler**, MD, MPH, chief of the Maternal Child Transmission Section of the Epidemiology Branch of HIV/AIDS.

Since the last guidelines were released, research has strongly suggested public health benefits in having every pregnant woman tested because it enables physicians to identify and treat HIV-infected women and provide prevention interventions for their infants.

Make pre-test counseling simpler

In recent years, there have been concerns among private practice physicians that pre-test counseling is onerous and burdensome, Fowler says.

So the guidelines suggest strategies for making pre-test counseling simpler and more flexible by providing women with the basic information they need to make an informed decision, Fowler explains.

"If a woman refuses testing, we need to understand the reasons behind it," Fowler says.

For example, some women were bothered by long waits for the test, and if the test had been offered at a later time they might have agreed to be tested, she says.

Another issue is that some women do not receive prenatal care, so when they are finally seen by a physician, it is when they already are in labor. For these women, the guidelines recommend that rapid testing be offered so that treatment can be offered at the time of delivery in order to prevent mother-to-child transmission.

"That's a group we're trying to target and make testing available to them," Fowler says. "Women are approached around the time of labor and delivery, and they can be offered a rapid HIV test, which is followed up by a standard test."

The CDC now is conducting tests to see how best to offer these tests to women in labor.

HIV educational material, including videos, general information, and user-friendly brochures, may be offered to women while they wait in their doctor's office, Fowler says.

"It's different from the general guidelines where people go to counseling and testing settings and where they have much more need to know certain risk behaviors and need more advice," Fowler explains.

Pregnant women simply need to know that HIV testing is important for their own treatment and to substantially reduce the risk of their babies becoming infected.

2. Adult HIV testing guidelines:

The new guidelines focus on having clinicians encourage the highest-risk people to be tested for HIV.

"If you're serving folks concerned about sexually transmitted diseases [STDs], then those same people could be at risk for HIV," Hunt says. "Some folks are more at risk than others, and the recommendations talk a lot about how a facility might provide a screening for folks so that offering testing for HIV, STDs, and hepatitis might be made available."

The guidelines emphasize that once people know their serostatus, they are likely to reduce their risk behaviors.

The guidelines offer detailed and technical information that is fully referenced for managers, administrators, directors, and people involved with public policy at a local level.

"We intend to make good use of the web and expand on the web presence so that we also have a one-stop shopping resource on that page," Hunt says. "As we develop links in the document, it will make it easier for providers to understand the details and the whys and wherefores."

Flexibility has been added to the revised guidelines, giving clinicians several options in counseling.

The guidelines offer a best-of-all-worlds prevention intervention strategy, as well as strategies that take into account policy, resource, and financial constraints, Hunt says.

"For example, some providers will say they don't have the resources to do counseling," Hunt says. "So the recommendations acknowledge that testing is important and missed opportunities to do counseling are important, but perhaps they could refer a patient to someone who could do counseling."

Therefore, even when a provider can't do it all, the provider could at least provide testing and refer patients to networks or clinics where they could receive prevention support or psychosocial support. ■

FDA notifications

Nucleic acid test system approval

On Sept. 21, 2001, the Food and Drug Administration (FDA) licensed the first nucleic acid test (NAT) systems intended for screening of plasma donors. These test systems are expected to further ensure the safety of plasma-derived products by permitting earlier detection of HIV and HCV infections in donors.

Although effective procedures for virus inactivation are required in the manufacturing of all U.S.-licensed plasma derivatives, removal of potentially infectious donations through donor screening adds a safeguard by limiting the amount of virus contamination that the manufacturing process must clear.

The newly approved test systems were developed by National Genetics Institute of Los Angeles for screening plasma used in manufacturing of products such as clotting factors and immune globulins. Alpha Therapeutic Corp. of Los Angeles was also approved to use new testing systems at its plasma collection facilities.

NAT is a recently developed technology that allows detection of very small amounts of genetic material (DNA or RNA) by a process of massive copying (amplification) of a gene fragment. The approved test systems permit highly sensitive detection of RNA from HIV, type 1 (the HIV variant that is responsible for the vast majority of AIDS cases in the United States) and HCV in test pools of 512 plasma samples obtained from multiple donors.

The use of pooled plasma samples for testing makes use of the NAT system cost-effective. However, if a test pool is positive for either virus, the individual donation that is suspected of containing a virus can be identified and not used for further manufacturing, and the donor can be deferred and notified.

Currently, donors of blood and plasma are tested for antibodies to HCV, antibodies to HIV, and HIV-1 antigens, which are the virus' own proteins. However, there is still a "window period" during which a donor can be infected but have negative screening tests. With the use of NAT for HCV, the "window period" for detection of HCV is reduced by 57 days (from an average of 82 days to 25 days). For HIV-1, the average window period with antibody tests is 22 days. Antigen testing cuts the window period to approximately 16 days, and NAT further reduces this period to 12 days.

In the clinical trials that supported these approvals, a total of 342,729 donations from approximately 48,000 donors collected at 33 plasmapheresis centers were tested for HIV-1 and HCV. The NAT systems detected a number of HIV and HCV infections that would have been missed by previously licensed test methods, confirming the effectiveness of these systems. Additionally, use of the NAT system for HIV will allow Alpha Therapeutic Corp. to discontinue antigen testing, although antibody testing will still be done on all plasma donations.

Since 1997, the FDA has encouraged the investigation of NAT technology through the use of experimental protocols, in the hope of improving the safety of plasma derivatives and further reducing the risk of an infectious unit of blood being transfused. ▼

Tenofovir (Viread) receives FDA approval

On Friday, Oct. 26, 2001, the FDA approved tenofovir for treatment of HIV-1 infection in combination with other antiretroviral agents.

Viread (tenofovir disoproxil fumarate) is a new antiviral drug indicated for treatment of HIV-1 infection in combination with other antiretroviral medicines. Tenofovir disoproxil fumarate is the

first nucleotide analog approved for HIV-1 treatment. Nucleotide analogs are similar to nucleoside analogs, and block HIV replication in the same manner.

The FDA based its approval of tenofovir disoproxil fumarate on two clinical studies involving more than 700 patients who had previously been treated with antiretroviral agents but showed signs of continued HIV replication despite drug therapy. The two clinical studies were a placebo-controlled 24-week study and a controlled dose-ranging 48-week clinical trial. Patients who received tenofovir disoproxil fumarate showed significant decreases in the quantities of HIV RNA in their blood compared to patients who received a placebo with the standard antiretroviral regimen.

Because the approval of tenofovir disoproxil fumarate was based on clinical trials involving patients who were previously treated with antiretrovirals, the risk-benefit ratio for untreated patients has yet to be determined. Furthermore, there are no study results to show long-term inhibition of the clinical progression of HIV by tenofovir.

Tenofovir disoproxil fumarate is available as a 300 mg tablet to be taken orally with a meal. The use of tenofovir disoproxil fumarate should be considered for treating adult patients with HIV strains that are expected to respond to tenofovir as assessed by laboratory testing or treatment history. The most frequently reported adverse events among patients in the clinical trials were mild to moderate gastrointestinal problems including diarrhea, nausea, vomiting, and flatulence. Lactic acidosis and hepatomegaly with steatosis (severe liver enlargement and excess fat in the liver) have also occurred among patients treated with nucleoside analogues alone or in combination with antiretrovirals. These are severe and possibly fatal conditions.

Viread is the brand name for tenofovir disoproxil fumarate and is marketed by Gilead Sciences, Inc. of Foster City, CA.

The complete indication is as follows:

Viread is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in a controlled study of Viread of 24 weeks duration and in a controlled, dose-ranging study of Viread of 48 weeks duration. Both studies were conducted in treatment-experienced adults with evidence of HIV-1 viral replication despite ongoing antiretroviral therapy. Studies in antiretroviral-naive patients are ongoing; consequently, the risk-benefit ratio for this population has yet to be determined.

Additional important information regarding the use of Viread for the treatment of HIV infection:

There are no study results demonstrating the effect of tenofovir on clinical progression of HIV.

The use of Viread should be considered for treating adult patients with HIV strains that are expected to be susceptible to tenofovir as assessed by laboratory testing or treatment history. The Package Insert is located on the FDA/CDER web site in PDF format: www.fda.gov/cder/foi/label/2001/21356lbl.pdf. The FDA Talk Paper is located at: www.fda.gov/bbs/topics/ANSWERS/2001/ANS01111.html. ▼

TrueGene HIV-1 genotyping kit approval

The FDA approved on Sept. 28, 2001, the Visible Genetics, Inc., PMA for its TrueGene HIV-1 Genotyping Kit and Open Gene DNA Sequencing System to be used to identify drug resistance in HIV patients. The approval information is available on the FDA web site at: www.fda.gov/cber/products.htm. ■

CE/CME questions will appear each month

As a service to participants in the *AIDS Alert* Continuing Medical Education program for physicians and Continuing Education program for nurses, the test questions will now be published with each issue of the newsletter. Twice a year, in the June and December issues, participants will be mailed an answer sheet on which they can mark their answers. Participants can then return the answer sheet for grading.

The change will allow continuing education participants to mark their answers each month while the articles are still fresh in their minds and the material is close at hand. The answers can then easily be transferred to the answer sheets when they arrive. ■

CE/CME

1. A recent HIV Outpatient Study conducted by Centers for Disease Control and Prevention researchers made what discovery about the effect of taking protease inhibitors?
   A. Protease inhibitor therapy increases the incidence of hypercholesterolemia, lipodystrophy, and diabetes.
   B. Protease inhibitor therapy is associated with a significantly increased rate of myocardial infarctions.
   C. Protease inhibitor therapy improves mortality and morbidity among HIV-infected people.
   D. None of the above

2. Centers for Disease Control and Prevention research presented at the 2001 Infectious Diseases Society of America conference shows that the trend of declining rates of opportunistic infections (OIs), experienced from 1995 to 1998, has ended for the period of 1998-1999 for all but two OIs. Which OIs continued to show lower rates among HIV-infected men in 1999 compared with 1998?
   A. Kaposi's sarcoma and pneumocystosis
   B. Pneumocystosis and cerebral toxoplasmosis
   C. Cerebral toxoplasmosis and CMV retinitis
   D. Cryptococcal meningitis and human monocytic ehrlichiosis

3. New research suggests that GBV-C infection among HIV-positive people can lead to slower HIV disease progression and better outcomes. What type of disease is caused by GBV-C?
   A. Hepatitis G
   B. Hepatitis C
   C. Non-hepatitis liver disease
   D. No disease is caused by GBV-C.

4. New HIV testing guidelines released by the Centers for Disease Control and Prevention include strategies for increasing early testing of at-risk people and universal HIV testing of pregnant women.
   A. True
   B. False

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, 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. ■