AMERICAN HEALTH CONSULTANTS

AIDS ALERT

The most comprehensive source of HIV/AIDS information since 1986

January 2003 • Volume 18, Number 1 • Pages 1-12

IN THIS ISSUE

Attention CE/CME participants: To serve you better, *Aids Alert* has changed the procedures for receiving continuing education credit. **See directions' box, p. 11.** Or for more information on the CE/CME program, call customer service at (800) 688-2421.

In This Issue **continued on next page**

New research confirms role of heart disease as a treatment by-product

Studies shed light on this and other med problems

While the exact cause remains to be found, it is no longer a mystery whether certain antiretroviral drugs can lead to metabolic changes associated with heart disease. Recent studies have made it clear that there is a direct connection between some protease inhibitors (PIs) and other anti-HIV medications and health problems that could affect HIV patients over the long term.

"In the past couple of years, there's been increasing concern about atherosclerosis and coronary heart disease in patients with antiretroviral therapy," says **Marshall Glesby**, MD, PhD, assistant professor of medicine at Weill Medical College at Cornell University in New York City.

"The most carefully studied patients have a number of abnormalities associated with heart disease, including abnormal lipids, changes in body shape, diabetes, increased truncal fat, and others." Moreover, there's good evidence of a direct cause and effect with regard to certain PIs, Glesby says. "From data on certain PIs given for short periods of time to people without HIV infection, you can see increased elevation in cholesterol, triglycerides, and insulin resistance," he explains.

For example, one recent study found that PI use is associated with coronary artery calcification, atherogenic lipid changes, and increased erythrocyte volume.[1]

Some additional metabolic complications of antiretroviral therapy include hyperlipidemia,

(Continued on page 4)

In This Issue **continued from cover**

FDA Notifications

COMING IN FUTURE ISSUES

- Southern states are having an especially hard time coping with a largely minority, poor, and rural HIV epidemic
- Depression and denial are major clues to patients who won't take drugs effectively
- How gay men negotiate condom use and deal with taboo subjects may affect their ability to remain HIV-free
- Liposuction is finding a cosmetic role among HIV patients

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

Subscriber Information

Customer Service: (800) 688-2421. Fax: (800) 284-3291. Hours of operation: 8:30 a.m-6:00 p.m. M-Th, 8:30-4:30 F EST. E-mail: customerservice@ahcpub.com. Web site: www.ahcpub.com.

Subscription rates: U.S.A., one year (12 issues), $467. Approximately 18 nursing contact hours or Category 1 CME credits, $467. Outside U.S., add $30 per year, total prepaid in U.S. funds. One to nine additional copies, $374 per year; 10 to 20 additional copies, $280 per year. For more than 20 additional copies, call customer service for special handling. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue date. **Back issues**, when available, are $78 each. (GST registration number R128870672.)

This continuing education offering is sponsored by American Health Consultants ®, 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 Consultants ® designates this continuing medical education activity for up to 18 hours in category 1 credit towards the AMA Physicians' Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

American Health Consultants® (AHC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. This CME activity was planned and produced in accordance with the ACCME Essentials.

Statement of Financial Disclosure: In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Advisory Board Member Dr. Tapper is a consultant for Abbott, GlaxoSmithKlein, Amgen, Boehringer Ingelheim, Serono, Merck, Roche, and Ortho Biotech; is a stockholder in Merck; and is on the speakers bureau at Bristol Myers-Squibb, Ortho Biotech, and Boehringer Ingelheim. Dr. Thompson reports research connections with Abbott, Bristol Myers Squibb, Chiron, DuPont, GlaxoSmithKlein, Roche, Triangle, Boehringer Ingelheim, Amgen, Gilead, Serono, VaxGEN, and Oxo Chemie. Dr. Bartlett works as a consultant for Merck, GlaxoSmithKlein, Abbott, and DuPont. Board member Kalinoski reports nothing to disclose. Responses were not received from Gostin or from Drs. Bihari, Glatt, Mayer, Cottone, or Richman.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

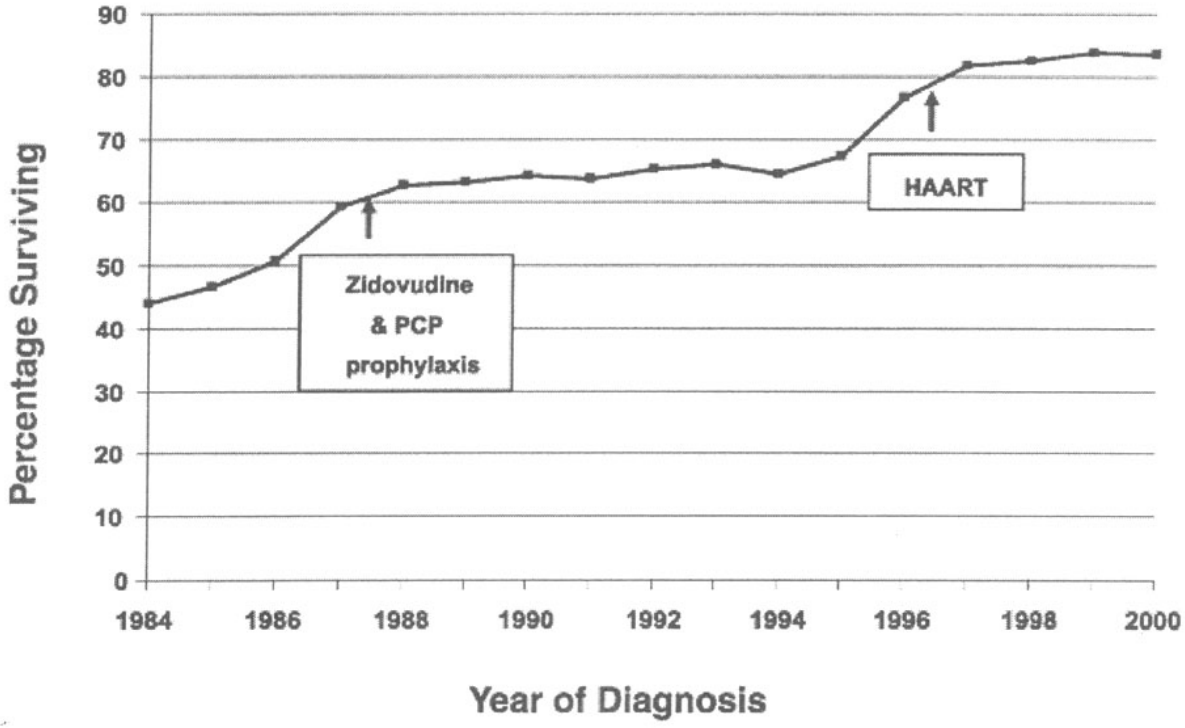
Editor: **Melinda Young**, (828) 859-2066.
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@ahcpub.com).
Editorial Group Head: **Glen Harris**, (404) 262-5461, (glen.harris@ahcpub.com).
Managing Editor: **Robin Mason**, (404) 262-5517, (robin.mason@ahcpub.com).
Senior Production Editor: **Ann Duncan**

AMERICAN HEALTH CONSULTANTS
THOMSON HEALTHCARE

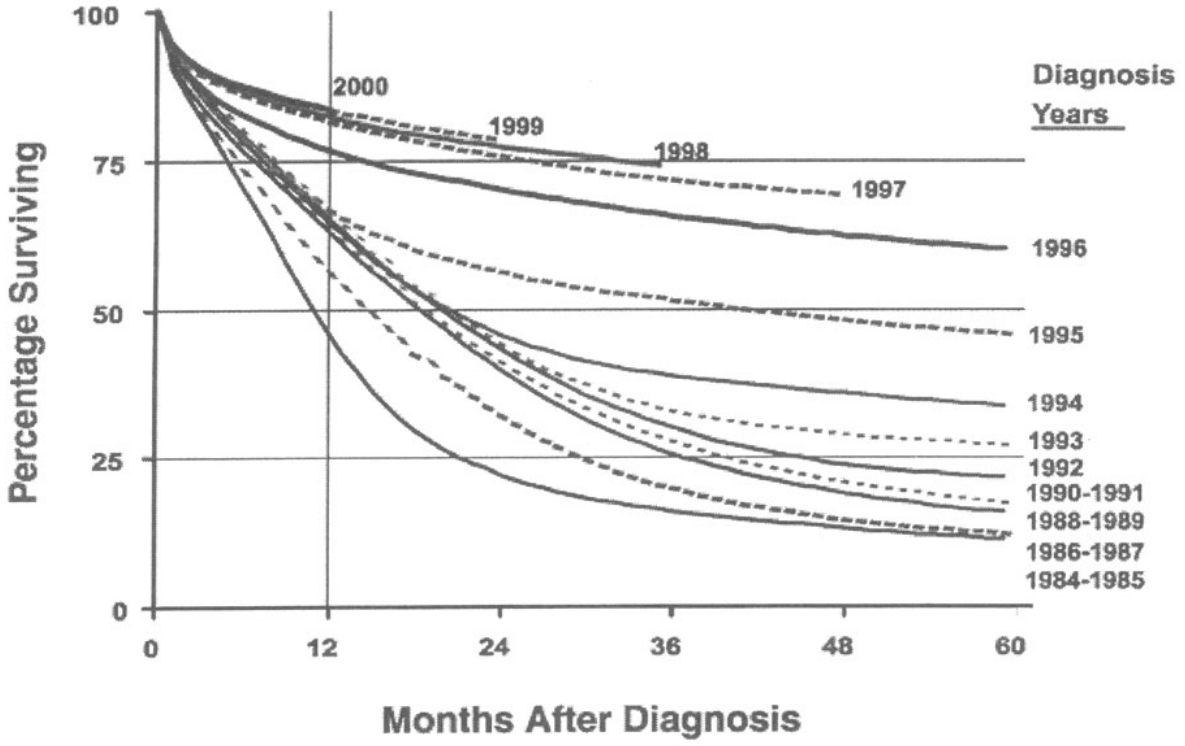
Editorial Questions

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

Proportion of AIDS patients surviving at least 1 year after diagnosis of their first AIDS-defining opportunistic illness, by year of diagnosis of opportunistic illness, 1984-2000, United States



Cumulative proportion of AIDS patients surviving by number of months after diagnosis of first AIDS-defining opportunistic illness, for different years of diagnosis, 1984-2000, United States



Source for both charts: Centers for Disease Control and Prevention, Atlanta.

(Continued from cover)

elevated lactate and lactic acidosis, and osteopenia / osteoporosis.

Research presented at the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, held in September in San Diego add to the body of evidence that antiretroviral therapy can lead to hypertriglyceridemia. Research also has found that patients receiving antiretroviral regimens containing the nucleoside reverse transcriptase inhibitors (NRTIs) stavudine were at an increased risk of hypertriglyceridemia.[2,3]

Other long-term problems associated with HIV and antiretrovirals are morphologic changes, including the loss of subcutaneous fat and fat accumulation, such as gynecomastia and a dorsocervical fat pad, says **Paul Sax**, MD, clinical director of the HIV Program at Brigham & Women's Hospital and a medical professor at Harvard Medical School, both in Boston.

NRTIs are associated with fat wasting or fat atrophy, and some of the NRTIs are associated with peripheral neuropathy, while PIs are closely associated with increased insulin resistance, he says.

Recent research has concluded that both stavudine- and zidovudine-based antiretroviral therapy are associated with significant gluteal subcutaneous adipocyte depletion, and that lamivudine is associated with more adipocyte depletion than the drugs didanosine or zalcitabine.[4]

In analyzing data from fat redistribution and metabolic changes (FRAM) research, Sax says, investigators have drawn these conclusions about antiretroviral treatment and metabolic changes:

- Some protease inhibitors cause fat accumulation and insulin resistance.
- Mitochondrial toxicity associated with NRTIs leads to fat wasting.
- When PIs and NRTIs are combined in therapy, there is an acceleration of fat wasting due to fat cell apoptosis.

Patients who experience acidosis as a result of NRTI therapy are not always easy to identify because the symptoms typically are nonspecific, Sax says. "Symptoms include nausea, anorexia, fatigue, breathlessness," he explains. "Sometimes, it's only very late that physicians realize it's lactic acidosis."

Other antiretroviral complications resulting in long-term side effects include the association between some NRTIs, including DDI and D4T, and peripheral neuropathy, Sax says.

"Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have a different side-effects profile that doesn't appear relevant to morphologic changes," Sax notes. "Although they do sometimes cause alterations in lipids, it's been observed that these alterations are favorable."

Current research has examined the incidence of accelerated atherosclerosis and PI medications, and there seems to be solid evidence that PIs contribute to symptoms associated with heart disease. However, the jury still is out on whether this means there is an increased risk of death from heart disease among HIV patients treated with PI therapy.

"The bigger issue and question is to determine whether people with HIV have an increased risk of cardiovascular disease and to what extent that is due to metabolic and lipid changes with therapy," says **Judith Currier**, MD, an associate professor of medicine at the David Geffen School of Medicine at the University of California, Los Angeles. Currier also is director of clinical trials unit of the UCLA Care Center.

She spoke about coronary heart disease and PIs at the 40th Annual Meeting of the Infectious Diseases Society of America (IDSA), held in October in Chicago.

"Several studies say there's an increased risk with PI use, and others don't," Currier says. "What we need to focus on now is trying to determine to which extent it's due to HIV in itself, the metabolic changes associated with treatment or the prevalence of other risk factors for cardiovascular disease that exist in this population."

There is no question that some HIV drugs cause patients to experience lipid and metabolic changes, but the contribution of these changes to heart disease risk in this population is not known, she adds. "We're still a ways off deciphering these factors."

A study presented at the IDSA conference concluded that the highest mortality rate when HIV-infected and noninfected individuals with and without coronary heart disease (CHD) were compared was among the HIV-infected people with CHD.[5]

Investigators found a significant increase in the risk of CHD among HIV patients in the 18 to 34 age group, but not among older HIV patients, says Currier, who was a co-author of the IDSA study about CHD and HIV.

The study found that the youngest group (ages 18-24) of HIV patients who also had CHD diagnoses were at an 8.67 times greater risk of death

from all causes than HIV-infected individuals of that age range who did not have a CHD diagnosis, says **Beth Burtcel**, PharmD, manager of Virology and Scientific Operations for Bristol-Myers Squibb Co. in Plainsboro, NJ. Burtcel also co-authored the IDSA study on CHD and HIV.

"These patients could have died of something besides a CHD event," Burtcel notes. "But the take-home message is that for younger individuals with CHD and HIV, the risk of death is significantly higher."

There was not such a large difference in the rate of death among the 18-24 age group of people who had CHD but did not have HIV infection, Burtcel adds.

The study used California's MediCal data in the retrospective study, examining claims from more than 28,000 HIV-infected men and women and more than three million non-HIV infected people.

Both the HIV-positive and negative cohorts had to be free of all CHD diagnoses and claims for at least one year to be included in the study, Burtcel says.

Antiretroviral medication and its possible role in CHD were not investigated as part of the IDSA study, Burtcel adds.

"This study just gives us a general idea of what role coronary heart disease is playing in HIV-infected people," Burtcel says. "These data suggest there is an association between CHD and all-cause mortality rates in HIV-infected individuals."

Clinicians should put these findings in perspective and not rush to switch antiretroviral therapy that otherwise is saving a patient's life, Sax advises.

Recent data on AIDS deaths from the Centers for Disease Control and Prevention (CDC) in Atlanta may offer some broader perspective on the issue about antiretroviral medications and increased risk of coronary heart disease. CDC data offer continued testimony to the increased longevity of HIV patients since the advent of PIs and other potent antiretroviral drugs. **(See charts on proportion of AIDS patients surviving by months after diagnosis, and proportion of AIDS patients surviving at least one year after diagnosis, p. 3.)**

"We HIV specialists are unanimous in agreeing that people with AIDS need therapy," Sax says. "But the important thing is to be aware of the side effects so that you can treat them and manage them if necessary."

Also, clinicians should factor these long-term side effects into their decisions about when to start a healthy, HIV-positive patient on antiretroviral treatment, Sax adds. "We may be delaying treatment a little bit longer than before for patients who are asymptomatic."

Some guidelines have been introduced in the past year to assist HIV clinicians in making decisions about managing lipid disorders and metabolic complications. For instance, the International AIDS Society USA recently published its guidelines on managing metabolic complications, and in August, the Adult AIDS Clinical Trials Group (AACTG) issued its metabolic complications guide. **(See story about AACTG recommendations, p. 6.)**

Meantime, HIV clinical practice already has changed because of the metabolic complications, says **David Haas**, MD, director of Vanderbilt AIDS Clinical Trials Center and associate professor of medicine at the Vanderbilt Medical School in Nashville, TN.

"Right now, management of HIV has become as much about management of medication side effects such as lipid abnormalities as it is about management of the virus itself," Haas says.

"I think treating HIV infection has been like being on a roller coaster where enthusiasm for treating sometimes has been offset by concerns of drug toxicity," he adds. "For some patients, their cardiovascular disease poses greater risk in the immediate future than their HIV disease."

One new PI, called atazanavir, that has been available in expanded access programs but still awaits approval by the Food and Drug Administration, is a possible alternative to antiretrovirals that cause metabolic problems, Haas says.

The once-a-day drug has been shown to have favorable lipid profiles in HIV patients, according to new research. **(See story about atazanavir study, p. 7.)**

References

1. Meng Q, Lima JAC, Lai H, et al. Coronary artery calcification, atherogenic lipid changes, and increased erythrocyte volume in black injection drug users infected with human immunodeficiency virus-1 treated with protease inhibitors. *Am Heart J* 2002; 144:642-648.

2. Galli M, Gervasoni C, Adorni F, et al. Factors associated with the development of high serum triglyceride levels in patients receiving two NRTI combinations. Presented at the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. San Diego; September 2002. Abstract 40.

3. Morlese J, Qazi N, Orkin C, et al. Both stavudine and zidovudine-based therapy is associated with gluteal

subcutaneous adipocyte depletion. Presented at the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. San Diego; September 2002. Abstract 30.

4. Walmsley S, Montaner J, Saag M, et al. Nucleoside reverse transcriptase inhibitor treatment as a risk factor for hyperlipidemia: Results from the FOCUS trial. Presented at the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. San Diego; September 2002. Abstract 52.

5. Burtcel B, Kawabata H, Dezil C, et al. Increased mortality in HIV infected Individuals with Coronary Heart Disease. Presented at the 40th Annual Meeting of the Infectious Diseases Society of America. Chicago; October 2002. Poster 466. ■

AACTG recommendations for metabolic problems

Guide covers insulin resistance and diabetes

The Adult AIDS Clinical Trials Group (AACTG) has responded to research showing a link between HIV antiretroviral treatment and metabolic disorders with guidelines that offer recommendations for assessing, monitoring, and treating the problem.

According to the AACTG guides, up to 40% of HIV patients on a protease inhibitor (PI)-containing regimen will have impaired glucose tolerance caused by significant insulin resistance, which can lead to increased risk of cardiovascular complications. Here's a brief look at the guidelines, which were published Aug. 13, 2002:

- Clinicians should assess HIV patients' fasting glucose before and during PI treatment, at intervals of three to six weeks after initiating therapy, and annually after that.
- All HIV patients should be educated about following a healthy, balanced diet with regular exercise as a way to prevent diabetes mellitus, and clinicians should recommend weight loss to patients who are obese and at a higher risk of developing diabetes.
- HIV patients who need diabetes drug therapy might first be prescribed metformin or thiazolidinedione, while oral sulfonylureas, meglitinides, and insulin may be appropriate for patients who have severe fasting hyperglycemia.
- Clinicians also might consider not starting HIV patients on a PI therapy in cases where patients have pre-existing abnormalities of glucose metabolism or diabetes risk factors.
- Patients should be carefully monitored for potential adverse effects, including hepatic dysfunction and lactic acidemia, both of which may be caused by the diabetes drugs. Likewise, liver enzymes need to be monitored every two months for the first year of thiazolidinedione treatment.
- HIV clinicians should perform a fasting lipid profile prior to starting antiretroviral therapy, including an assessment of total cholesterol, HDL cholesterol, triglycerides, and a calculated LDL cholesterol. Every three months after starting a new antiretroviral regimen, clinicians should repeat this fasting lipid profile, and if the results are normal, then the profile should be assessed annually.
- When considering interventions for dyslipidemia, clinicians should evaluate and intervene for hypogonadism, hypothyroidism, liver disease, and alcohol abuse.
- It's also advisable to perform a complete cardiovascular risk assessment and to encourage patients to make lifestyle changes, including stopping smoking, adhering to a lipid-lowering diet, and engaging in regular aerobic exercise.
- When an HIV patient is at significant risk for cardiovascular disease, a clinician might consider substituting a non-PI-containing regimen and/or using a lipid-lowering drug. ■

FDA approves new rapid HIV test

The U.S. Department of Health and Human Services has announced that the U.S. Food and Drug Administration (FDA) has approved a new rapid HIV diagnostic test kit that provides results with 99.6% accuracy in as little as 20 minutes.

Using less than a drop of blood collected, this new test can quickly and reliably detect antibodies to HIV-1, the HIV virus that causes infection in most cases in the United States. Unlike other antibody tests for HIV, the test can be stored at room temperature, requires no specialized equipment, and may be considered for use outside of traditional laboratory or clinical settings.

The newly approved HIV test is The OraQuick Rapid HIV-1 Antibody Test, manufactured by OraSure Technologies Inc. in Bethlehem, PA.

Federal officials note that each year, 8,000 HIV-infected people who come to public clinics for

HIV tests do not return to receive their test results. The new test will allow the results while the patient is present, enabling practitioners to start treatment immediately.

To perform the test, a fingerstick sample of blood is collected from an individual and transferred to a vial where it is mixed with a developing solution.

The test device, which resembles a dipstick, is then inserted into the vial. In as little as 20 minutes, the test device will indicate if HIV-1 antibodies are present in the solution by displaying two reddish-purple lines in a small window on the device.

Although the results of rapid screenings will be reported in point-of-care settings, as with all screening tests for HIV, if the OraQuick test gives a reactive test result, that result must be confirmed with an additional specific test. The OraQuick test has not been approved to screen blood donors.

FDA waiver available

The FDA currently categorizes the OraQuick test as "moderate complexity" under the Clinical Laboratory Improvements Amendments of 1988 (CLIA).

Under CLIA, new tests are categorized as either moderate or high complexity. This designation means that the OraQuick test only can be given in CLIA-approved labs by CLIA-certified laboratory technicians or medical staff.

If the test manufacturer applies for a CLIA waiver, the FDA can evaluate it for use under less stringent conditions.

Federal officials are urging the OraSure company to apply for a CLIA waiver. If the FDA finds that the company's data proves that the OraQuick test is both easy and safe to use, it can get a CLIA waiver.

Then the test could be given in many more health care settings, perhaps even administered by social workers in HIV counseling centers.

The Centers for Disease Control and Prevention (CDC) has estimated that one-fourth of the approximately 900,000 HIV-infected people in the United States are not aware that they are infected.

Because of the potential public health benefits of rapid HIV testing, the CDC and the Centers for Medicare & Medicaid Services (CMS) are working with state and other health officials to make the test widely available and to offer technical assistance and counseling training for its use.

"This test will be a great help in identifying pregnant HIV-infected women going into labor who were not tested during pregnancy so that precautionary steps can be take to block their newborns from being infected with HIV," says FDA Deputy Commissioner **Lester M. Crawford**, MD.

"It will also be a critical resource in helping identify HIV infection in health care and emergency workers who are accidentally exposed to HIV-infected blood while doing their job," he says. ■

Atazanavir found to help improve lipid profile

IDSA study offers good news for HIV care

A new protease inhibitor (PI) called atazanavir was found to actually improve the lipid profile of HIV patients in a 48-week study presented at the 40th Annual Meeting of the Infectious Diseases Society of America (IDSA), held in Chicago.

"Our most important conclusion is that therapy with a regimen that includes atazanavir is likely to have beneficial effects on lipid profiles as compared to other comparable PIs," says **David Haas**, MD, director of the Vanderbilt AIDS Clinical Trials Center and an associate professor of medicine at the Vanderbilt Medical School in Nashville, TN.

Haas was the lead author on a study that compared the total cholesterol from baseline and at 48 weeks following treatment with atazanavir.

Atazanavir has been submitted for approval by the Food and Drug Administration (FDA).

"This study was a head-to-head comparison of salvage therapy in patients with fairly early virologic failure," he says. "These were patients who had a good virologic response to previous potent regimens for at least 24 weeks, but were now failing therapy based on virologic criteria."

After treatment with atazanavir, HIV patients had a lipid profile that either did not change or actually improved, compared with an increase in abnormal lipids among the PI control group.[1]

While investigators wouldn't want the study to be seen as evidence that atazanavir lowers pre-HIV treatment lipids, it is possible that since many of the patients already had experienced elevated lipids from previous antiretroviral therapies that the atazanavir treatment helped to improve these abnormal lipid profiles, Haas says.

"What makes this very important is that presently in clinical practice, treatment decisions in many situations are being driven at least as much, if not more, by toxicity considerations than by virologic and immunologic considerations," he adds. "For many patients in our clinic when we're trying to choose a treatment regimen, the criteria for that regimen is [that it be] a potent regimen that does not affect lipids."

Investigators also found that patients receiving atazanavir, administered in once-daily doses along with saquinavir had comparable virologic responses as the control group of patients who received traditional PI and nucleoside reverse transcriptase inhibitor (NRTI) therapy, Haas explains.

Atazanavir is the only once-a-day PI administered without the boost of ritonavir, which has been associated with lipid abnormalities, he adds.

"Atazanavir dramatically boosts saquinavir levels and acts as an enhancer for saquinavir without boosting side effects," he says.

The fact that patients could take the atazanavir/saquinavir combination as several pills once a day is another advantage to this option, he notes.

"I think it gives us one more option, which is very important given that therapy must be individualized for each patient," Haas says. "This drug will find use in patients who are treatment naïve where the use of a PI that may be given once a day and that's well-tolerated would be attractive, and we'll also find use in patients who have previously had other agents."

Reference

1. Sension M, Squires K, Cahn P, et al. Change in total cholesterol (as per NCEP ATP III) from baseline at 48 weeks following treatment with atazanavir or comparator protease inhibitors. Presented at the 40th Annual Meeting of the Infectious Diseases Society of America. Chicago; October 2002. Poster 468. ■

DAAT may work where DOT model fell short

Good results for drugs issued by methadone clinics

While there are some similarities between HIV and tuberculosis (TB) treatments, it's the differences in treatment regimens, duration, and end results that have made HIV clinicians and others somewhat hesitant to use the directly observed treatment (DOT) strategy, which has been so successful in treating TB, with HIV patients.

"For a number of years, people have been wondering whether DOT could help at least a subset of people treated for HIV," says **Gregory M. Lucas**, MD, assistant professor at the Johns Hopkins University School of Medicine in Baltimore.

However, the drawbacks to modeling HIV treatment after DOT have been that unlike TB medication, HIV medication always is prescribed daily and that HIV is incurable so medications must continue for the patient's lifetime, rather than for the six months that a typical TB patient might receive treatment, he says.

Johns Hopkins researchers have found a possible solution to these barriers in a treatment modeled after DOT, which they have named directly administered antiretroviral therapy (DAAT), which has demonstrated good outcomes when used with an injection drug using population on maintenance methadone treatment.

"Obviously, in a methadone-maintenance clinic, you have 100% of people who have heroin addiction and a very high HIV prevalence in that population," Lucas says. "Also, a lot of studies have shown that drug users aren't as successful with HIV treatment."

So this is a population that clearly could benefit from a program that works at improving HIV medication adherence, and the population can be served in a setting where patients arrive each day to receive their methadone.

"You could do DAAT indefinitely, and it doesn't require nurses or other community workers to go out into the community and find people to give the medications to," he explains.

"About two years ago, we started a pilot study and, to date, we have enrolled about 35 people who are receiving methadone and who have HIV and are eligible for antiretroviral therapy," Lucas says.

"Somewhere between 70% and 80% of the people enrolled in the program have achieved an undetectable viral load of less than 400 copies," he explains. The pilot study is not randomized, but investigators also are following a large cohort study of 2,500 active HIV patients and so there is a matched control group, he adds.

"Our DAAT group really is doing a lot better than what is occurring with the standard care," Lucas says.

The DAAT project works this way:

- HIV clinicians prescribe antiretroviral regimens to patients who are receiving methadone therapy.
- Trained staff give patients their antiretroviral medications at the methadone clinic and watch as the patients take the pills.
- Staff also give patients a packet with the pills they'll need to take later that day.

"It's a modified DOT protocol, which really is done for feasibility purposes," he points out. "It's hard to track down people and observe them taking medications twice a day, and it's not realistically done in any outpatient setting."

Soon there may be more once-per-day antiretroviral treatment options available, which will make DAAT even easier to monitor, Lucas notes.

"The staff we have who are involved with this are enthusiastic and bond with the patients," he says. "They are involved with their lives and help them get whatever help they need, and there is more to it then just seeing some medications going into someone's mouth."

One of the advantages to this approach is that there are federal funds available for HIV programs that target disadvantaged patients and if studies continue to show that DAAT at methadone treatment clinics work then more of these programs would become eligible for federal grants, Lucas says.

Many of the people who use methadone treatment clinics are racial minorities, women, and have low incomes, all of which contribute to their having a difficult time accessing HIV care through the usual routes, Lucas adds. "It's a hard-to-reach population."

Plus, Ryan White programs already have funded a number of slots for methadone treatment to be provided for uninsured HIV-infected women, Lucas says.

The next step is to study DAAT in a randomized, controlled trial where people either receive DAAT or just take the medications on their own, Lucas says, adding that investigators also are exploring the options of working with larger methadone treatment clinics in the area.

Reference

1. Lucas GM, Weidle PJ, Hader S, et al. Directly administered antiretroviral therapy improves rates of viral suppression compared to standard care or an intensive adherence intervention. Presented at the 40th Annual Meeting of the Infectious Diseases Society of America. Chicago; October 2002. Poster 489. ■

Efavirenz effects worse than reported, study says

Study reaches troubling conclusion

A study conducted at San Francisco General Hospital suggests a greater incidence rate of severe psychiatric illness resulting from HIV treatment with efavirenz than what has previously been reported.

"The serious psychiatric side effects are suicidal depression, including agitation, aggression, and hallucinations," says **Talia Puzantian**, PharmD, an assistant clinical professor at the University of California, San Francisco, and a clinical pharmacist in psychiatry at San Francisco General Hospital.

Puzantian was among the authors of a study about efavirenz that was presented at the 40th annual meeting of the Infectious Diseases Society of America (IDSA), held in Chicago in October.

These serious side effects have less than a 2% incidence rate according to previously published reports, but Puzantian and colleagues questioned this rate after seeing a number of cases of HIV patients on the drug who were admitted to the psychiatry unit, she says.

This question prompted a retrospective study severe psychiatric side effects and central nervous system (CNS) side effects that compared a database of HIV patients from March 2000 to February 2002 who had discontinued use of efavirenz with a group of patients who had discontinued nelfinavir, another antiretroviral medication.[1]

"We wanted to see the numbers in a real-world setting," Puzantian says. "We looked at substance use and psychiatric illness, and the efavirenz and nelfinavir groups were similar, so we controlled for that." Investigators found that of the 25.5% of patients who had discontinued use of efavirenz, 36% had discontinued because of side effects. By comparison, of the 23.6% of patients who had discontinued nelfinavir, 14.4% had discontinued because of side effects.[1] For the HIV patients who had discontinued use of efavirenz because of side effects the main problems noted were psychiatric and CNS side effects, she says.

The study found that 18.3% of subjects on efavirenz reported vivid dreams; 14.7% reported insomnia; 10% were lethargic or fatigued; 8.3% had headaches, and 7.3% had dizziness. Of these symptoms, the only one that was greater than 1.1% among the nelfinavir cohort was fatigue,

which was reported by 7.8%.[1]

Other CNS side effects included subjects having nightmares, feeling like they were stoned or had a hangover, as well as having feelings of euphoria, dysphoria, confusion, and trouble concentrating, Puzantian says.

The most common neuropsychiatric effect reported was depression by 12% of efavirenz subjects and 1.1% of the nelfinavir subjects. No other neuropsychiatric effects were reported by the nelfinavir subjects, while the other more common neuropsychiatric effects reported by the efavirenz group included: anxiety (9.2%); suicidal depression (2.8%); hallucinations (1.8%); agitation (1.8%).[1]

The other, less common neuropsychiatric effects reported by the subjects on efavirenz were paranoia, psychosis, emotional lability, aggressive behavior, and rage attacks.[1]

"We also saw a significantly greater number of the efavirenz patients being referred to psychiatry for new onset psychiatric symptoms, compared with the other group," she adds. "That also indicated to us that the ability to refer patients to psychiatry services would be an important resource to have available for patients using efavirenz."

The study also found that the incidence of CNS side effects among patients who discontinued use of efavirenz was 57%, while the incidence of severe psychiatric side effects was 22%.[1]

"But this was a biased group because they are people who discontinued using the drug and not a whole sample," Puzantian notes. "Now we're doing a second part of the study and are looking at people who stayed on efavirenz."

While the study only suggests that the incidence of severe psychiatric effects may be greater than believed, it does not offer definitive proof. Nonetheless, clinicians should keep the possibility of these effects in mind when educating, and monitoring HIV patients using efavirenz, she says.

"Be aware that these psychiatric side effects can occur and probably occur more than we think," Puzantian says. "We can't really guess who it's going to happen to, so we shouldn't assume that if someone doesn't have a substance use or psychiatric illness that it won't occur."

Other studies have shown that the psychiatric side effects can persist even after the first few weeks of efavirenz drug therapy, so it's important to continue to monitor patients who have been on the drug for longer periods of time, she adds. "In one patient [at San Francisco General Hospital] the side effects persisted for a couple of weeks after the patient stopped taking efavirenz."

Puzantian detailed one case study in the *Pharmacotherapy* journal about a 47-year-old man with AIDS who was admitted to a psychiatry ward with symptoms of depressed mood, suicidal thoughts, insomnia, confusion, feelings of hopelessness, agitation, anxiety, and anhedonia.[2]

The man denied substance abuse and had a negative toxicology screen, but he had been hospitalized for psychosis at age 17 after taking hallucinogenic drugs. He had been on an antiretroviral regimen of stavudine, didanosine, and indinavir until he became unresponsive and was prescribed 600 mg / day of efavirenz. His symptoms appeared shortly after starting the efavirenz regimen, and after a few days the efavirenz was discontinued.[2]

However, the patient's symptoms persisted and he was prescribed mirtazapine for depression and subsequently admitted to the psychiatric ward for evaluation and treatment. He was successfully treated at the hospital, but upon discharge nine days later, the patient refused further antiretroviral treatment, despite being told that a different regimen would not produce the adverse psychiatric and CNS effects.[2]

References

1. Puzantian T, Lee J, Lee RJ, et al. Psychiatric effects associated with efavirenz: A retrospective study. Presented at the 40th Annual Meeting of the Infectious Diseases Society of America. Chicago; October 2002. Poster 481.

2. Puzantian T. Central Nervous System Adverse Effects with Efavirenz: Case Report and Review. *Pharmacotherapy* 2002; 22(7):930-933. ■

FDA Notifications

New guidance assists HIV drug development

Changes affect approvals for antiretroviral drugs

The Food and Drug Administration (FDA) has issued new guidance intended to assist sponsors in the clinical development of drugs for the treatment of HIV infection. Specifically, it addresses the FDA's current thinking regarding designs of clinical trials that use HIV ribonucleic acid (RNA)

measurements to support accelerated and traditional approvals of antiretroviral drug products. It also is intended to serve as a focus for continued discussions among the Division of Antiviral Drug Products (DAVDP), pharmaceutical sponsors, the academic community, and the public. The draft version of this document, first posted in August 1999, was based on a 1997 DAVDP advisory committee meeting to discuss the use of HIV RNA endpoints for traditional approval of antiretroviral drugs. This document has been updated to address public comments to the draft version and to include pertinent information from a 2001 DAVDP advisory committee meeting to address issues relating to trial design in heavily treatment experienced HIV-infected patients. This guidance does not address specific phase-1 and phase-2 development issues, development of alternate dosing regimens, or the use of HIV-1 resistance testing. These issues will be addressed separately in future guidance documents. Sponsors should contact the division to discuss specific issues that arise during the development of an antiretroviral drug product.

Accelerated approvals of antiretroviral drugs have been based for years on changes in surrogate endpoints, such as CD4 cell counts and plasma HIV RNA levels. Traditional approvals were based on clinical endpoint trials assessing the effects of a drug on mortality and/or HIV disease progression. With the availability of potent antiretroviral drug regimens and sensitive assays for assessing plasma HIV RNA, the standards of clinical practice evolved to a paradigm emphasizing maximal and durable HIV RNA suppression. With the successes of combination therapy and the subsequent decline of HIV-related illnesses (Palella et al., 1998; Hogg et al., 1999), it became clear that a requirement for clinical endpoint studies for every traditional approval was neither necessary or feasible.

In July 1997, the agency convened an advisory committee meeting to consider the use of changes in HIV RNA levels as endpoints in clinical trials

CE/CME *directions*

To complete the post-test for *AIDS Alert*, study the questions and determine the appropriate answers. After you have completed the exam, check the answers **on p. 12**. If any of your answers are incorrect re-read the article to verify the correct answer. At the end of each six-month semester, you will receive an evaluation form to complete and return to receive your credits.

CE/CME *questions*

1. Which of the following are adverse effects associated with antiretroviral medication use?
   A. abnormal lipids, changes in body shape, increased truncal fat
   B. increased cholesterol, increased triglycerides, insulin resistance, and diabetes
   C. coronary artery calcification, atherogenic lipid changes, increased erythrocyte volume.
   D. all of the above
2. The August 2002 metabolic disorders recommendations by the Adult AIDS Clinical Trials Group suggest which initial strategy for dealing with metabolic changes caused by antiretroviral regimens?
   A. When side effects first appear, clinicians should change patients' therapy and discontinue use of the specific drugs associated with these side effects.
   B. All HIV patients should be educated about following a healthy, balanced diet with regular exercise as a way to prevent diabetes mellitus, and clinicians should recommend weight loss to patients who are obese and at a higher risk of developing diabetes.
   C. Patients should be educated about side effects but cautioned that current antiretroviral treatment will have greater long-term benefits than risks, so they shouldn't fail to follow the recommended medication regimen.
   D. none of the above
3. Recent studies show that atazanavir, a new PI, is likely to have what impact on lipid profiles?
   A. It appears to increase triglycerides, but lower overall cholesterol.
   B. It appears to increase insulin resistance and increase triglycerides and cholesterol.
   C. It appears to have a beneficial effect on lipid profiles when compared with other PIs.
   D. It appears to significantly improve overall cholesterol and triglycerides in HIV treatment-naïve patients.
4. Johns Hopkins researchers have found a way to model directly observed therapy used for TB patients in a program targeting HIV patients who are at risk of not being adherent to their antiretroviral treatment. A key strategy has been the location at which the directly administered antiretroviral therapy is administered. Which location did they use?
   A. HIV/AIDS treatment clinic
   B. homeless shelter
   C. methadone maintenance clinic
   D. outreach center for injection drug users

supporting traditional approval of antiretrovirals.

To evaluate the feasibility of using HIV RNA levels as a study endpoint, a collaborative group of pharmaceutical, academic, and government scientists investigated relationships between treatment-induced changes in HIV RNA and clinical endpoints from ongoing and completed antiretroviral trials (Murray et al, 1999; Hill et al, 1998).

In several analyses of more than 5,000 patients in multiple trials, a clear association was identified between initial decreases in plasma HIV RNA levels and reduction in the risk of clinical progression and death. This relationship was observed across a range of patient characteristics including pretreatment CD4 counts and HIV RNA levels, prior drug experience, and treatment regimen. Based on these data, the Division of Antiviral Drug Products advisory committee concurred that treatment-induced decreases in HIV RNA levels were highly predictive of meaningful clinical benefit and that HIV RNA measurements could serve as endpoints in trials designed to support both accelerated and traditional approvals.

The division proposed basing accelerated approvals on studies that show a drug's contribution toward shorter-term reductions in HIV RNA (e.g., 24 weeks) while traditional approvals could be based on trials that show a drug's contribution toward durability of HIV RNA suppression (e.g., for at least 48 weeks). The committee agreed and recommended that changes in CD4 cell counts be consistent with observed HIV RNA changes when considering approval of an antiretroviral drug.

To access the guidance document, go to the FDA web site at: www.fda.gov/cder/guidance/3647fnl.pdf. ■

CE/CME *answers*

Here are the correct answers to this month's CE/CME questions.

1. **D — all of the above**
2. **B — All HIV patients should be educated about following a healthy, balanced diet with regular exercise as a way to prevent diabetes mellitus, and clinicians should recommend weight loss to patients who are obese and at a higher risk of developing diabetes.**
3. **C — It appears to have a beneficial effect on lipid profiles when compared with other PIs.**
4. **C — methadone maintenance clinic**

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. ■