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New York City case of multidrug-resistant, rapid AIDS progression baffling

Health officials continue investigation

HIV physicians and public health officials say the recent discovery of a man in his mid-40s with both rapidly progressing AIDS and a highly resistant strain could portend an ominous turn in the epidemic, particularly in light of evidence that the transmission of antiretroviral resistant HIV is increasing in some cities.

"This type of case should serve as a wake-up call that HIV remains a formidable adversary despite the fact that we're living in an era where there are multiple effective antiretroviral drugs," explains **Ron Valdiserri**, MD, MPH, deputy director of the National Center for HIV, STD, and TB Prevention at the CDC.

The New York City Department of Health and Mental Hygiene issued a medical alert Feb. 11, 2005, to notify physicians that a New York City man had been diagnosed in January with primary HIV infection with HIV-1 that was resistant to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). The medical alert also noted the increase in transmission of resistant virus in New York City.[1]

In New York City, the percentage of HIV patients who have resistance to two or more classes of

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antiretroviral drugs increased from 2.6% to 9.8% between 1995-1998 and 2003-2004.[1]

With the possible exception of efavirenz (Sustiva) and the fusion class drug T-20 (Fuzeon), genotypic and phenotypic testing demonstrated complete antiretroviral drug resistance.[1] Less than 1% of people newly diagnosed with HIV are resistant to three or more classes of drugs, Valdiserri says.

The case involved a man who has sex with men (MSM) who tested negative for HIV in May 2003, and then tested positive on Dec. 16, 2004. He reported symptoms of acute retroviral syndrome during early November 2004, and he said he used crystal methamphetamine while engaging in unprotected insertive and receptive anal intercourse with multiple partners, including those met through the Internet, in mid-October 2004.[1]

What made this case extraordinary was that it combined in one man the rare event of newly acquired, highly resistant HIV and rapid progression to AIDS, HIV experts say.

"It could be a perfect storm of two bad things happening at the same time," says **Jay F. Dobkin**, MD, associate professor of clinical medicine at Columbia University Medical Center. The key question is whether there is something about that particular strain that leads to more rapid progression or whether the rate of progression has more to do with that particular HIV patient, he says.

The man's virus appeared to be dual-tropic, meaning his virus was able to use both CCR5 and CXCR4 as coreceptors, which HIV experts say may be a factor in why his disease has progressed so rapidly.[1]

"Most often, we don't see dual-tropism until later stages of disease," says **James Braun**, DO, president of New York City-based Physicians' Research Network Inc.

"This infection is not only rapidly progressive, but also it's potentially untreatable — not a good combination," he says. "From a public health standpoint, it's extremely important to make people aware of this because you don't want to wait and see an enormous number of people who have been infected with it."

New York City officials defined the man's disease as AIDS in January 2005 after a physical exam showed that he had lost weight, continued to have fatigue and malaise, and had a CD4 cell count of fewerVIADO than 100 cells, along with an elevated viral load.[1]

"The most intriguing debate about this case is

DOHMH recommendations for treating at-risk patients

In a medical health alert issued Feb. 11, 2005, the New York City Department of Health and Mental Hygiene (DOHMH) issued these recommendations for providers in New York City, where it's believed a three-drug class resistant HIV (3DHR HIV) strain may become more prevalent:

1. Consider acute retroviral syndrome in patients who may have risk factors for recent HIV infection. Acute retroviral syndrome is a flu-like illness which may include fever, lymphadenopathy, pharyngitis, rash, myalgias, diarrhea, headache, nausea, vomiting, hepatosplenomegaly, weight loss, thrush, and neurologic symptoms lasting 1-2 weeks, generally within 1-2 months of risk behavior. Obtain thorough risk factor history and, for all people who have such a history and symptoms consistent with acute retroviral syndrome, test for HIV infection both by serology and tests for HIV nucleic acid (e.g., HIV-1 RNA PCR or bDNA).
2. Test for drug resistance in all people with newly diagnosed HIV. Genotypic assays detect resistance-conferring mutations. Phenotypic assays directly measure resistance of the patient's HIV strain to specific individual drugs. If you suspect a patient has been infected with 3DCR HIV, report the case immediately to the DOHMH's Bureau of HIV/AIDS Prevention and Control at (212) 442-3388.
3. Drug-resistance testing also should be obtained, along with a careful assessment of patient adherence, in all cases of clinical deterioration, incomplete viral suppression, or virologic failure. Use results of resistance testing to guide treatment.
4. Ensure adherence in patients receiving antiretroviral treatment to prevent further development and spread of drug-resistant HIV. Adherence improves with simpler regimens, housing support, mental health services, and drug and alcohol treatment.
5. Obtain, or refer to the DOHMH to obtain, partner names and contact information from all who test HIV+. Notify partners and recommend or obtain HIV testing; for HIV antibody-negative people with symptoms of acute seroconversion, additional testing for HIV nucleic acid (e.g., HIV-1 RNA PCR or bDNA) is indicated. Those with primary HIV infection have enhanced transmission efficiency due to their high viral loads. Partner notification results in prompt diagnosis of HIV and reduces spread of HIV; HIV+ people who are aware of their status are more likely to reduce risky behavior. Call DOHMH's Contact Notification Assistance Program (212) 693-1419 for help with partner notification. For more information, go to www.nyc.gov/html/doh/pdf/chi/chi23-7.pdf. ■

whether this [strain] really is as aggressive as it seems," Dobkin explains. "The man's T cell count could rebound to a more normal level. We don't know exactly how long it's been going on, so there's a remote possibility that after the dust settles, his disease won't look as bad as it does now.'

There's also a possibility that even if this man has transmitted multidrug resistance to other people, his rapid progression to AIDS is unique to his own situation.

For example, the man's immune system could be affected by his drug use or other factors, Braun says. But if the man's virus is transmissible and has a similar affect on other people, it could have a devastating impact on communities at risk for HIV, he continues. "Personally, I hope this is an isolated case, but if it's not an isolated case, then greater action needs to be taken toward early diagnosis, and there needs to be a great deal more effort at all levels in diagnosing primary HIV infection," Braun adds.

While it's generally accepted that it takes 10 to 11 years for the typical HIV infection to progress to AIDS, there have been people who progressed much faster, and others who progressed more slowly since the epidemic began, Dobkin says.

"There's always a question about why some people handle the virus so well and others so poorly, and the great bulk of data say it has to be with the host and not the virus. So even if this man transmits it to others, most of them won't have such an aggressive disease."

For this particular man, the news is grim because it's unlikely he'll survive long enough to benefit from treatment with new classes of HIV drugs, he adds.

While he could be treated with the one available fusion inhibitor for a while, the response likely will be transient, eventually putting him back to where he began, Dobkin notes.

The CDC and New York City public health officials say this case is yet another sign that unsafe sex practices, coupled with substance use, are on the rise in the MSM community. Other indications include rising syphilis rates and recent reports of lymphogranuloma venereum (LGV) in HIV-positive MSM.[1]

"It is significant that this individual had problems with crystal methamphetamine use, and much of the unsafe sex took place under the influence of crystal meth use," Valdiserri says.

"Crystal meth use has been associated with higher STDs, and some jurisdictions have observed what they believe to be increases in HIV transmission associated with crystal meth use." The fact that unsafe sex practices may be on the rise and that drug use may be associated with unsafe sex should affect prevention efforts, he says. "An important national message is that HIV prevention efforts have to keep pace with emerging challenges. We really need to be careful not to grow complacent about HIV."

This one case, which has made it to the front pages of newspapers across the country, serves as a reminder to the general public that people engaging in high-risk activities are in real danger, Dobkin notes.

Valdiserri and other health officials also point to the need for a public health investment in better HIV surveillance systems and data about drug resistance. "We're going to have to invest in systems that monitor drug resistance," Valdiserri says.

Clinicians in the New York City area are asked by the city health department to test for drug resistance in all people with newly diagnosed HIV and to report to the city's Bureau of HIV/AIDS Prevention and Control any cases in which a patient is suspected to be resistant to three classes of HIV antiretrovirals.[1] **(See NYC health department recommendations, p. 39.)**

As of mid-February, New York City and CDC health officials were continuing to investigate the case to identify people who might have been exposed to the highly resistant strain and to see if they were in danger of a fast progression to AIDS. A more detailed report is expected later this year.

Reference

1. New York City Department of Health and Mental Hygiene. DOHMH Alert #7: *Primary 3-Drug-Class-Resistant HIV-1 Infection with Rapid CD4+ T Cell Depletion and Progression to AIDS in a New York City Man Who Has Sex with Men.* Feb. 11, 2005. ■

President's budget concerns advocates

Prevention money cuts are dark omen

President George W. Bush expressed support for the reauthorization of the Ryan White Care Act in his State of the Union address, but his budget for the 2006 fiscal year provided mostly flat funding. AIDS advocates say cuts in prevention activities are a sign that trouble is ahead for

state budgets and AIDS service organizations struggling to provide prevention, care, and other services to growing HIV populations.

"The president talked about the Ryan White Care Act and the need to attend to the HIV epidemic among African Americans in the State of the Union address. Less than a week later, he launches a budget with not one dollar more for minority AIDS initiative prevention," says **Paul Feldman**, public affairs director of the National Association of People with AIDS (NAPWA).

"Given his rhetoric around the need to attend to the AIDS epidemic among African Americans, the fact that he didn't fund the instrument designed expressly for that purpose makes the point that talk is cheap," he adds.

It hasn't escaped Feldman's and other AIDS advocates' notice that while the overall HIV spending picture is bleak, the president did find money to increase abstinence-only education, which recently was criticized for inaccurate curriculum **(See *AIDS Alert*, March 2005, p. 30.)**

"It bugs me a lot that we're letting politics a nd ideology get in the way of public health and attending to the most vulnerable among us," Feldman says. "AIDS is a disease of poverty, and most people living with AIDS in this country are poor. They need help to get care and treatment and prevention services."

Flat funding through 2006

HIV/AIDS spending for the fiscal year 2005 was cut across-the-board because of a 0.80% rescission included in the Omnibus Appropriations bill. While the percentage is small, it came on the heels of several years of flat funding, and the president's FY 2006 budget makes it clear that next year's funding will be as bleak, AIDS advocates note.

"The Ryan White Care Act has been flat funded another year, except for a small increase to the AIDS Drug Assistance Program (ADAP)," says **Carl Schmid**, director of federal affairs for The AIDS Institute in Washington, DC.

"So it's disappointing we're not getting higher increases. We're going to have to take our arguments to Congress to get increased numbers, and we haven't been that successful in current years," he adds.

Meantime, HIV caseloads are on the rise because of new infections and people living longer with HIV, Schmid says.

ADAP funding was offered by the president's proposal of a $10 million increase, which is a small fraction of the $250 million increase requested by ADAP advocates and the AIDS Budget and Appropriations Coalition, which would like to bring total ADAP spending for FY 2006 to $1.037 billion to meet the funding challenges of a program now burdened heavily by waiting lists and growing need. **(See AIDS Budget Coalition's chart of HIV funding for FY 2005 and what's needed for FY 2006, inserted in this issue.)**

CDC prevention activities were cut by $4.6 million, 0.05%, and the housing budget for people with AIDS was cut $13.7 million in the president's proposed budget, says **Mark Del Monte**, JD, director of policy and government affairs at the AIDS Alliance for Children, Youth & Families.

"The housing cuts come on the heels of a cut last year for that program of $13.1 million," he adds.

"I think, generally, the president's commitment to reauthorization of the Ryan White Care Act and increased support for ADAP in this budget environment are positive things," Del Monte says.

"On the other hand, we're faced with a situation of overwhelming need, and we've got to find a way even in tough budget times to meet our basic obligations to people with HIV or who are at risk for HIV infection," he explains.

Cuts to Medicaid?

AIDS advocates say they fear an even bigger problem if the signs coming from the Bush administration about Medicaid changes are followed through.

Mike Leavitt, the new secretary of Health and Human Services (HHS), spoke to the World Health Care Congress Feb. 1, 2005, about Medicaid, in a speech, "Medicaid, A Time to Act."

"The most important signal, the secretary said, was the Bush administration's interest in blowing out guaranteed entitlement to needed medical service," says **Michael Kink**, legislative counsel for Housing Works Inc., based in New York City. Housing Works relies heavily on Medicaid and private donations to provide medical care and other services to HIV patients.

Housing Works, HIV Medicine Association of Alexandria, VA, and NAPWA were among about 300 organizations that sent President Bush a letter, dated Jan. 26, 2005, requesting he not propose cuts in Medicaid funding or make any changes in the program's structure that would alter the open-ended financing for states.

"Medicaid works so well for HIV/AIDS because it covers necessary benefits and services for people who qualify," Kink says. "The Bush administration would like the states and private companies like HMOs to decide how much and what kind of medical treatment folks would get."

This practice would lead to HMOs deciding which antiretroviral drugs and high-cost interventions they would cover or not cover, he notes.

"Right now Medicaid is an entitlement, and in most states if it's needed and you're covered, you can get it. What we're looking at [with the Bush plan] is not just the creation of 50 different Medicaid programs, but probably thousands of different Medicaid benefits, depending on how much a state is willing to give power to private companies and depending on how much private companies are willing to spend on beneficiaries," Kink explains.

Leavitt suggested the change would enable Medicaid to expand to more people who need some help, while reducing costs by eliminating some high-cost care. In his speech, Leavitt said, "Wouldn't it be better to provide health insurance to more people, rather than comprehensive care to a smaller group? Wouldn't it be better to give Chevies to everyone rather than Cadillacs to a few?"

Leavitt's words and other signs coming from the Bush administration have led to a belief among AIDS advocates and others that there soon will be a dramatic Medicaid restructuring proposal with the primary aim of limiting federal Medicaid expenditures, says **Christine Lubinski**, executive director of the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA).

"He forwarded such a program two years ago, and it didn't take off," she points out. "But he has strengthened his support in Congress, and the concern is that with resources needed to continue the war and make tax cuts permanent and revamp Social Security that Medicaid is one of the places where he's looking to get some of those resources."

Medicaid expert **Jeffrey Crowley**, MPH, project director at Georgetown University's Health Policy Institute in Washington, DC, says the gist of Leavitt's speech is that the government needs to protect critical services for children, the elderly, and people with disabilities — the mandatory populations — while not providing comprehensive coverage to optional populations.

The problem with that logic is there is no distinction with regard to disability or medical needs between the mandatory and optional populations, he says.

"The distinction is income," Crowley explains.

People who live on disability income are subsisting on money that still puts them below the federal poverty level, but if their low income is $5 more than the Medicaid cutoff for mandatory populations, then it would mean their benefits are cut off, he notes.

"The vast majority of adults with AIDS qualify because they are disabled, so we're not talking about people who are healthier and need coverage less than others," he adds. "We're talking about people who are severely disabled by AIDS and have $5 more in disability payments than others."

What would happen on the proposal that Leavitt discussed is that the people administering Medicaid funds could make arbitrary decisions about whether to cover new medications for HIV treatment or whether to provide coverage for other medical care to some disabled people, Crowley says.

"The [Bush administration] is saying that states should be able to say to optional coverage people that they'll give them fewer benefits than other people," he notes.

"They start going down this road and pick winners and losers, and it's all based on politics and the budget — a very dangerous road to travel," Crowley adds. ■

CDC releases detailed guidelines for PEP use

Agency focuses on nonoccupational exposure

While post-exposure prophylaxis (PEP) has been available to medical employees and first responders for years, public health officials have routinely dismissed the possibility of extending PEP to the general public, citing the inefficiency of its use even after potential exposure to HIV from rape.

This philosophy has changed with the recent release of guidelines for nonoccupational PEP (nPEP) by the CDC.

For the first time, the CDC has provided a detailed blueprint for how clinicians might recommend nPEP among patients who might have

been exposed to HIV within the previous 72 hours.[1]

"It's recommended only in limited circumstances," says **Lisa A. Grohskopf**, MD, MPH, epidemiologist in the CDC's Division of HIV/AIDS Prevention.

"It can be administered no more than 72 hours after exposure from a person known to be HIV infected, and it's for those who have an occasional lapse, condom breakage or slippage, or who were assaulted," she says. "If the person's HIV status is not known, then it can be used only on a case-by-case basis."

In introducing the guidelines in late January, CDC officials noted that far too many Americans are infected with HIV each year.

"African Americans are hardest hit with the burden of infection at a significantly higher rate than their counterparts in other ethnic and racial groups," says **Ronald O. Valdiserri**, MD, MPH, deputy director of the CDC's National Center for HIV, STD, and TB Prevention.

"The severity of this epidemic dictates we utilize all available tools to reduce new infections," he says. "And if used appropriately with other prevention methods, nPEP may provide a safety net to prevent new infections."

The nPEP guidelines apply to nonoccupational exposures from sexual intercourse, sexual assault, drug use, bite wounds, and needlesticks outside of health care settings, Valdiserri says.

While it's unethical to perform a randomized, placebo-controlled clinical trial of nPEP, data from animal transmission models suggest that it can be effective.[1]

Also, the short antiretroviral regimens used to reduce mother-to-child HIV transmission have been very successful and also suggest that a properly administered nPEP could prevent infection.[1]

Further, PEP studies involving needlestick injuries to health care workers found that prompt initiation of zidovudine was associated with an 81% decrease in risk of acquiring HIV.[1]

Feasibility studies of nPEP also have pointed to its potential success.[1]

"It's important to note that nPEP is not for everyone," Grohskopf says. "It's not recommended for individuals whose HIV exposure risk is negligible or for people who seek care after 72 hours after exposure."

It's also not recommended for people whose behaviors put them at frequent risk for HIV exposure, she explains.

"People who are repeatedly exposed to HIV would need continuous courses of nPEP, which is not recommended," Grohskopf adds. "They need other interventions that are more likely to reduce their risk to HIV infection."

The guidelines recommend that baseline HIV testing with a rapid HIV test should be performed on all people seeking evaluation for nPEP and that nPEP initiation should not be delayed beyond 72 hours.[1]

Clinicians should evaluate patients who have had a potential nonoccupational exposure, assessing these factors, the guidelines say:

- **HIV status:** The person seeking nPEP already could be infected with HIV.
- **Timing and frequency of exposure:** If a patient requests nPEP more than 72 hours after exposure, the potential benefit may not outweigh the risks.
- **HIV status of source:** When the source's HIV status is unknown, the risk varies according to whether the source is part of a high-risk group.
- **Transmission risk from the exposure:** Some types of transmission pose higher risk of infection, including blood transfusion, needle sharing by injection drug users, receptive anal intercourse, and percutaneous needlestick injuries.[1]

The CDC guidelines outline a 28-day course of antiretroviral therapy involving two or three drugs that are selected based on potential adherence, side effects, and cost.

"At this time, no evidence suggests any specific medications are optimal," Grohskopf says. "Regimens containing nevirapine should be avoided because the long-term use is associated with liver damage, and efavirenz may increase risk of birth defects."

Evidence from the nPEP feasibility study in San Francisco suggests the availability of nPEP may not lead to increases in risk behaviors, the guidelines note.

According to that study, 62% of participants reported a decrease in risk behavior over the next 12 months, 14% reported no change, and 14% reported an increase. Seventeen percent of participants requested a second course of nPEP during the year after the first course, which shows that some participants did not eliminate risk behaviors entirely.[1]

"Anyone who works in this field wants to make sure this intervention is understood and that people don't see this as a morning-after pill," Valdiserri notes.

The use of nPEP is considered a safety net and

not a substitute for other interventions that might reduce risk behaviors, Grohskopf says.

Each clinician should assess a risk-benefit ratio before using nPEP with a particular patient, adds Valdiserri.

"The clinician should know enough about the patient to understand if this incident truly is an episode, such as a gay man who very consistently practices safer sex and has a relapse of unsafe sex, and it's an unusual event," he says. "The benefit of nPEP should outweigh the risks involved, and it's a decision reached jointly between the health care provider and the client seeking nPEP."

Among the risks are side effects from the drugs and a cost of $600 to $1000 for the 28-day supply of antiretrovirals, Grohskopf notes.

"It's unclear at this point to what degree nPEP would be covered by insurers," she says. "We hope that because there are federal guidelines, it will initiate a dialogue for what kind of coverage there might be."

Reference

1. Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States. *MMWR* 2005; 54(RR-2):1-20. ■

Adherence tips included in IDSA care blueprint

Guidelines for primary care of HIV patients

The first guidelines written explicitly for the primary care of HIV patients include two pages about antiretroviral adherence, demonstrating how management of HIV disease increasingly is incorporating behavioral factors with medical practice.

According to the guidelines — *Primary Care Guidelines for the Management of Persons Infected with Human Immunodeficiency Virus: Recommendations of the HIV Medicine Association [HIVMA] of the Infectious Diseases Society of America [IDSA]* — research has shown that a greater than 95% adherence is necessary to achieve nondetectable virus load in most HIV patients taking antiretroviral medications.

However, only about half of HIV patients in some clinical practices are able to achieve a maximum suppression of HIV, indicating that most HIV patients are not achieving the optimal adherence, the guidelines state.[1]

"The guidelines' section on adherence is the section that maybe gets taken for granted," says **Joel Gallant**, MD, MPH, associate professor of medicine and epidemiology at Johns Hopkins School of Medicine in Baltimore. Gallant is one of the authors of the HIVMA/IDSA guidelines.

"People forget they have to keep discussing adherence on an ongoing basis," he says. "This section on adherence is very helpful and reminds physicians how important it is to keep emphasizing it."

The guidelines advise clinicians to avoid making assumptions about patients' adherence because they're usually incorrect. Instead, clinicians should find a specific method for measuring antiretroviral adherence.[1] Examples of methods for measuring adherence include patient self-report, electronic medication monitoring devices, pill counts, and checking pharmacy refill records.[1]

The guidelines discuss factors that negatively impact adherence, including depression, alcohol and drug use, lack of education about HIV, frequency of dosing, etc.[1]

Adherence strategies are divided into patient-focused, regimen-focused, and provider-focused strategies. The advice varies depending on the strategy. For example, with patient-focused strategies, the first advice is to screen all patients for depression before initiating antiretroviral drug therapy. For regimen-focused strategies, clinicians are advised to prescribe simpler antiretroviral regimens; and for provider-focused strategies, the guidance says they should develop a set of adherence-focused activities that are provided for each patient, including an assessment of readiness for antiretroviral therapy.[1]

The HIVMA/IDSA guidelines also pull together information about the metabolic complications of highly active antiretroviral therapy (HAART), including serum lipid abnormalities, morphological changes, dysregulation of glucose metabolism, lactic acidemia, and reduced bone mineral density.[1]

"We have guidelines on metabolics because we felt it was important to focus on this area," says **Judith Aberg**, MD, an associate professor of medicine at New York University and director of HIV at Bellevue Hospital Center, New York University AIDS Clinical Trials Unit, both in New York City. Aberg is the first author of the new HIVMA/IDSA guidelines on HIV primary care.

"HIV specialists watch HIV treatment and follow T cells and viral loads, but they are not

comfortable with complications like lipodystrophy, bone disease, etc.," she says. "And primary care providers have to be aware of this — they're looking at the routine management of health issues."

While primary care physicians might be comfortable managing a general population's metabolic disorders, they may be less experienced in dealing with metabolic problems related to complications from HIV antiretroviral medications, Aberg notes.

"Whether it's from HIV itself or the drug therapies or a host of risk factors, we're not still sure, but there is an increase in lipid abnormalities and bone disorders among HIV patients, and we want to alert physicians to incorporate screening for these into the patient's primary care," she says.

For example, the IDSA guidelines discuss premature osteopenia, osteoporosis, and osteonecrosis with avascular necrosis of the hips, which all have been found in HIV-infected patients. The guidelines advise clinicians to consider having patients who take antiretroviral drugs and who have other risk factors for premature bone loss to undergo bone densitometry at baseline and to prescribe to these patients calcium and vitamin D supplements, as well as prescribing exercise and the cessation of cigarette smoking.[1]

The guidelines also provide HIV experts strategies for better managing their patients' primary care issues, Gallant says. "People are getting older and living longer with HIV, so issues like blood pressure and blood sugar need to be managed. Pre-HAART physicians forgot about those issues because they were so trivial, and now we need to refresh their memories."

The HIV Medicine Association of IDSA created the guidelines as an acknowledgement of how HIV medicine is evolving into treatment of a chronic disease, requiring more attention to primary care of patients, Aberg notes.

"Since the guidelines have come out, I've gotten interesting e-mails from HIV specialists and primary care physicians, saying, 'Thanks for putting those out because I realize there were things I was missing,'" she says. "We've had a very good response."

Reference

1. Aberg JA, Gallant JE, Anderson J, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2004; 39:609-629. ■

FDA Notifications

BMS issues letter about omeprazole

Bristol-Meyers Squibb has issued a "Dear Healthcare Provider" letter regarding important new pharmacokinetic data concerning the coadministration of atazanavir (Reyataz) and ritonavir (Norvir) with omeprazole (Prilosec).

Omeprazole is a proton-pump inhibitor (PPI) for the treatment of acid-related diseases that works by suppressing gastric acid secretion.

The following observations were made from a randomized, open-label, multiple-dose drug interaction study:

- A 76% reduction in atazanavir area under the concentration-time curve (AUC) and a 78% reduction in atazanavir trough plasma concentration (Cmin) were observed when atazanavir/ritonavir 300/100 mg was coadministered with omeprazole 40 mg.

Based on the study results, the recommendations are:

- Do not coadminister atazanavir or atazanavir/ritonavir with omeprazole due to the reduction in atazanavir exposure levels. This recommendation is consistent with the current atazanavir U.S. package insert.
- It is not known whether the over-the-counter dose of omeprazole (20 mg once daily) would produce similar results; therefore, coadministration is not recommended.
- Increasing the atazanavir/ritonavir dose to 400/100 mg in combination with omeprazole did not result in atazanavir exposures comparable to those observed with a regimen of atazanavir/ritonavir 300/100 mg without omeprazole.
- Simultaneous administration of 8 ounces of cola given in an effort to decrease (acidify) gastric pH did not appear to affect this reduction.

Investigations regarding the potential drug interaction between atazanavir sulfate and H2 Receptor antagonists (another type of gastric medication) when coadministered are ongoing. Until data are available, clinicians should note the following statements from the atazanavir

(Reyataz) package insert: "Reduced plasma concentrations of atazanavir are expected if H2 Receptor antagonists are administered with Reyataz (atazanavir sulfate). This may result in loss of therapeutic effect and development of resistance. To lessen the effect of H2 Receptor antagonists on atazanavir exposure, it is recommended that an H2 Receptor antagonist and Reyataz be administered as far apart as possible, preferably 12 hours apart."

To view the complete letter, go to www.adobe.com/products/acrobat/readstep2.html. ▼

Copackaged drug regimen approved for PEPFAR

The FDA announced the tentative approval of a copackaged antiretroviral drug regimen, consisting of lamivudine/zidovudine fixed dose combination tablets and nevirapine tablets for the treatment of HIV-1 infection in adults. It is manufactured by Aspen Pharmacare of South Africa.

A tentative approval means the FDA has concluded a drug product has met all of the required quality, safety, and efficacy standards, even though it may not yet be marketed in the United States due to existing patents and/or exclusivity. It does, however, make the product eligible for use under the President's Emergency Plan for AIDS Relief (PEPFAR) program.

The copackaged drug products are a complete antiretroviral drug regimen that have met the FDA's quality, safety, and efficacy standards and will be available for potential procurement by PEPFAR for use in South Africa and developing nations. It is the first tentative approval of a product to treat HIV/AIDS under the new expedited FDA review process for PEPFAR, and the first tentative approval of an HIV drug regimen manufactured by a non-U.S.-based generic pharmaceutical company.

Aspen's lamivudine/zidovudine fixed-dose combination tablets are a version of the FDA-approved Combivir tablets manufactured by GlaxoSmithKline, and the nevirapine tablets are a version of Viramune tablets manufactured by Boehringer-Ingelheim.

The new copackaged product consists of both lamivudine/zidovudine fixed-dose tablets and nevirapine tablets, one of each tablet to be taken twice daily, after the initial two-week initiation phase of this nevirapine regimen. ▼

FDA issues final guidance on nucleic acid tests

The FDA has issued final guidance on the *Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components (including Source Plasma and Source Leukocytes) to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV.*

FDA's blood-testing rules require establishments that collect blood and blood components (e.g., whole blood and blood components, including source plasma and source leukocytes) to test each donation of human blood or blood component intended for use in preparing a blood product for evidence of infection due to specific communicable disease agents. The purpose is to reduce the risk of transfusion-transmitted transmission of communicable disease.

The purpose of the guidance is to inform blood collecting and processing establishments that:

1. The FDA has licensed nucleic acid tests (NAT) as tests to screen blood donors for HIV-1 ribonucleic acid (RNA), and HCV RNA.
2. These licensed tests can detect evidence of infection at a significantly earlier stage than is possible under previously approved tests using antibody or antigen detection technology; including the HIV-1 p24 antigen test.

NAT is a nucleic acid amplification technology that includes polymer chain reaction, or PCR, to detect certain viral components. NAT enables the earliest and most sensitive detection of disease-causing human viruses in blood and plasma donations. A recently infected person would have virus particles in the bloodstream.

Although the blood or plasma could be infectious, the infection may not be detected using current antibody tests because the person may not yet have developed antibodies. This time frame before measurable antibody production is called the "window period." Over time, the person would make enough antibodies for the antibody test to be effective. However, because NAT can detect RNA or DNA from a very small number of virus particles, it can reduce the window period by detecting the infection earlier.

This guidance combines and finalizes the NAT draft guidance [www.fda.gov/ohrms/dockets/98fr/01d-0584_gdl0001.pdf dated December 2001, 67 FR 4719 (Jan. 31, 2002)] and the draft guidance *Use of Nucleic Acid Tests on Pooled and*

Individual Samples from Donors of Whole Blood and Blood Components for Transfusion to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV [www.fda.gov/ohrms/dockets/98fr/040902c.pdf dated March 2002, 67 FR 17077 (April 9, 2002)].

The complete final guidance document can be found at www.fda.gov/cber/gdlns/hivhcvnatbld.htm. ▼

Consumers warned about unapproved test kits

The FDA is warning consumers not to use unapproved home-use diagnostic test kits that have been marketed nationwide via the Internet by Globus Media of Montreal, Canada. In fact, no home-use test kits intended for diagnosing HIV, syphilis, and dengue fever are approved for sale in the United States.

The use of these products could result in false results (though there is no confirmed evidence of false positives) that could lead to significant adverse health consequences.

The illegal kits are labeled as:

- Rapid HIV Test Kit
- Rapid Syphilis Test Kit
- One Step Cassette Style Cocaine Test
- One Step Cassette Style Marijuana (THC) Test
- One Step Cassette Style Amphetamine Test
- Rapid Dengue Fever Test
- One Step Midstream Style HCG Urine (Home) Pregnancy Test

The FDA has not approved or evaluated the performance of any of Globus Media's products. As a result, consumers cannot know with any degree of certainty that test results are correct. For example, a person testing positive for HIV or the AIDS virus using one of these tests may not be infected with HIV, or worse, someone infected with HIV may test negative and not seek medical treatment, or spread the virus to others.

The tests were sold through web sites and distributed throughout the United States, usually by overnight delivery services.

They have been made available for sale on several web sites, including www.htkit.com and www.hstkits.com.

The kits usually are contained in a paper envelope with instructions inside the packaging. The envelope, instructions, and packaging may not accurately identify the manufacturer, packer, or

CE/CME *questions*

13. New York City health officials alerted the public in February that they had discovered a case of a man infected with an HIV-1 strain that was resistant to three classes of antiretroviral drugs, although he head never been on antiretroviral drug therapy. What was the other unusual problem that made this man's case so alarming?
    A. He was an injection drug user.
    B. The man's virus appeared to have a rapid progression to AIDS, which, in part, may be because his virus was dual-tropic, meaning his virus was able to use both CCR5 and CXCR4 as coreceptors.
    C. The virus also appeared to be resistant to the new fusion class inhibitor.
    D. all of the above
14. After the discovery of the highly resistant HIV strain, New York City health officials made clinical practice recommendations in a medical alert issued in the New York City area. Which of the following is not one of the recommendations?
    A. Consider acute retroviral syndrome among patients who may have risk factors for recent HIV infection and flu-like symptoms.
    B. Test for drug resistance in all people with newly diagnosed HIV.
    C. Treat anyone found with multidrug resistant virus with the new fusion inhibitor.
    D. Ensure adherence among patients receiving antiretroviral treatment to prevent further development and spread of drug-resistant HIV.
15. The CDC has issued its first guidelines for the use of nonoccupational post-exposure prophylaxis (nPEP). CDC officials say nPEP must be started within how many hours of the potential exposure to HIV to be effective?
    A. 24 hours
    B. 36 hours
    C. 48 hours
    D. 72 hours
16. The HIV Medicine Association of the Infectious Diseases Society of America has issued the first guidelines for HIV primary care. These new guidelines include a section on adherence. Which are the three adherence strategies outlined in the guidelines?
    A. pill reminder tools, patient counseling and support, directly-observed therapy
    B. patient-focused, regimen-focused, and provider-focused strategies
    C. social-behavioral, clinical, and pharmaceutical strategies
    D. none of the above

distributor. The name of the kit appears on the instructions.

Consumers who have these products should not use them. Anyone who has used one of these test kits should be retested using valid test methods.

The FDA has issued an import alert which alerts FDA field personnel to the possible importation of these devices, provides guidance as to their detention and refusal of admission into the United States and also advises U.S. Customs officials about these products.

Other unapproved tests also may be available through the Internet. You can find a list of FDA approved/licensed tests for HIV and hepatitis at www.fda.gov/cber/products.testkits.htm. ▼

Roche issues drug interaction warning

Roche Laboratories Inc. has issued a "Dear Health Care Provider" letter to communicate an important drug interaction warning for saquinavir/ritonavir, used as part of combination therapy for treatment of HIV infection. It reads:

"Drug-induced hepatitis with marked transaminase elevations has been observed in healthy volunteers receiving rifampin — 600 mg once daily in combination with ritonavir 100 mg/saquinavir 1000 mg twice daily (ritonavir boosted saquinavir)."

As a result of high incidence of hepatotoxicity in a Phase I, randomized, open-label, multiple-dose clinical pharmacology study in healthy volunteers, Roche now advises prescribers that: "Rifampin SHOULD NOT be administered to patients also receiving saquinavir/ritonavir (ritonavir boosted saquinavir) as part of combination antiretroviral therapy (ART) for HIV infection." Rifampin is known as Rifampicin outside of the United States.

Roche is collaborating closely with the FDA on this issue, and appropriate changes to the package insert will be made as soon as possible.

Health care professionals are encouraged to report any unexpected events associated with the use of saquinavir/ritonavir directly to Roche Laboratories at (800) 526-6367 or to the FDA MedWatch program by phone at (800) FDA-1088, by fax at (800) FDA-0178, or by mail to MED WATCH, 5600 Fishers Lane, Rockville, MD 20852-9787. ■

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. ■

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 **below**. 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 *answers*

13. B **14. C** **15. D** **16. B**

AIDS Budget and Appropriations Coalition

FY 2005 Appropriations for Federal HIV/AIDS Programs and Preliminary FY 2006 Requests[1]

(January 2005; Increases or decreases from previous fiscal year are shown in parentheses)

PROGRAM	FY 2004 Final	FY 2005 President's Budget Request	FY2005 Coalition Request	FY 2005 Final[2]	FY 2006 Coalition Request
Labor/HHS Portfolio					
Total - HIV, STD, TB line[3]	$963.9 m	$963.9 m (+ $0 m)	$1,536.2 m (+ $572.3 m)	$961.2 m (- $2.7 m)	$1,545.3 m (+ $584.1 m)
CDC: HIV Prevention and Surveillance	$667.9 m	$667.9 m (+ $0)	$1,035.6 m (+ $367.7 m)	$662.6 m (- $5.3 m)	$1,049.2 m (+ $386.6 m)
CDC: STD Prevention	$158.6 m	$158.6 m (+ $0)	$274.2 m (+ $115.6 m)	$159.7 m (+ 1.1 m)	$269.7 m (+ $110 m)
CDC: TB Prevention	$137.4 m	$137.4 m (+ $0)	$226.4 m (+ $89 m)	$138.9 m (+ $1.5 m)	$226.4 m (+ $87.5 m)
CDC: Viral Hepatitis (Infectious Disease line)	$17.5 m	$17.5 m (+ $0)	$100.0 m (+ $81.3 m)	$17.36 m (- $.14 m)	$40 m (+ $22.64 m)
CDC: DASH - HIV Prevention Education	$47.02 m	$47.02 m (+ $0)	$67.02 m (+ $20 m)	$46.64 m (- $.376 m)	$66.64 m (+ $20 m)
HRSA: Ryan White CARE Act Total	$2,019.86 m	$2054.86 m (+ $35.0 m)	$2,445.4 m (+$425.5 m)	$2,048.1 m (+ $28.24 m)	
Title I	$615.02 m	$615.02 m (+ $0)	$702.0 m (+ $86.98 m)	$610.1 m (- $4.92 m)	$725.02 m (+ $114.92 m)
Title II: Care	$337.03 m	$337.03 m (+ $0)	$387.03 m (+ $50.0 m)	$334.3 m (- $2.73 m)	$384.3 m (+ $50 m)
Title II: ADAP	$748.87 m[4]	$783.87 m (+ $35.0 m)	$965.87 m (+ $217.0 m)	$787.28 m (+ $38.7 m)	$1,037.28 m (+ $250 m)
Title III	$197.2 m	$197.2 m (+ $0)	$224.5 m (+ $27.3 m)	$195.6 m (- $1.6 m)	$236.6 m (+ $41 m)
Title IV	$73.11 m	$73.11 m (+ $0)	$101.0 m (+ $27.89 m)	$72.53 m (- $0.58 m)	$113.25 m (+ $40.72 m)
Part F: AETCs	$35.34 m	$35.34 m (+ $0)	$46.0 m (+ $10.66 m)	$35.06 m (- $0.28 m)	
Part F: Dental Reimbursement	$13.33 m	$13.33 m (+ $0)	$19.0 m (+ $5.67 m)	$13.22 m (- $0.11 m)	$19.0 m (+ $5.78 m)
(SPNS[5])	($25.0 m)	($25.0 m)	($25.0 m)	($25.0 m)	($25.0 m)
HRSA: Community Health Centers	$1,617.4 m	$1,835.9 m (+ $218.5 m)	$1,867.6 m (+ $250.2 m)	$1,733.8 m (+ $116.4 m)	$2.0 b (+ $266.2 m)
HRSA: Title X	$278.3 m	$278.3 m (+ $0)	$350.0 m (+ $71.7 m)	$285.9 m (+ $7.6 m)	$350 m (+ $64.1 m)
Minority HIV/AIDS Initiative (across multiple programs)	$401.8 m	$407.6 m[6] (+ $5.8 m)	$610.0 m (+ $208.2 m)	$398.4 m (- $3.4 m)	
ACF: Abandoned Infants Assistance	$12.052 m	$12.086 m (+ $0.034 m)	$18.0 m (+ $5.95 m)	$12.052 m (+ $0)	$20.052 m (+ $8 m)
NIH	$27.66 b	$28.8 b (+ $980 m)	$30.6 b (+ $2.78 b)	$28.28 b (+ $620 m)	$30 b (+ $1.72 b)
AIDS Research thru OAR	$2.825 b	$2.9 b (+ $50 m)	$3.135 b (+ $285 m)	$2.9 b (+ $75 m)	$3.1 b (+ $200 m)

PROGRAM	FY 2004 Final	FY 2005 President's Budget Request	FY2005 Coalition Request	FY 2005 Final[2]	FY 2006 Coalition Request
Labor/HHS Portfolio (cont'd)					
SAMHSA: Center for Substance Abuse Treatment	$419.2 m	$517.0 m (+ $97.8 m)	$544.5 m (+ $125.3 m)	$422.5 m (+ $3.3 m)	$456.3 m (+ $33.8 m)
Substance Abuse Block Grant	$1,699.9 m	$1,753.0 m (+ $83.0 m)	$1,904.1 m (+ $204.2 m)	$1,695.8 m (- $4.1 m)	$1,837.8 m (+ $142 m)
SAMHSA: Center for Substance Abuse Prevention	$198.5 m	$196.0 m (- $2.5 m)	$248.6 m (+ $50.1 m)	$198.7 m (+ $0.2 m)	$214.7 m (+ $16 m)
SAMHSA: Center for Mental Health Services (CMHS)	$840.4 m	$890.7 m (+ $50.3 m)	$970.2 m (+ $129.8 m)	$879.4 m (+ $39.0 m)	$982.4 m (+ 103 m)
Subset of CMHS: Mental Health Block Grant	[$412.8 m]	[$414.3 m] [(+ $1.5 m)]	[$489.0 m] [(+ $76.2 m)]	[$410.86 m] [(- $1.94 m)]	[$471.5 m] [(+ $60.64 m])
CDC: Global HIV/AIDS[3]	$118.8 m	$118.8 m (+ $0)	$118.8 m (+ $0)	$123.88 m (+ $5.08 m)	$147.0 m (+ $23.12 m)
CDC: Research	$11.0 m	$11.0 m (+ $0)	$11.0 m (+ $0)	$11.0 m (+ $0)	$13.0 m (+ $2 m)
CDC: TB and Malaria	$17.9 m	$15.9 m (- $2 m)	$10.0 m (- $7.9 m)	$15.9 m (- $2 m)	$16.0 m (+ $.1 m)
NIH: Research	$323.5 m	$355.0 m (+ $31.5 m)	$355.0 m (+ $31.5 m)	$355.0 m (+ $31.5 m)	$382.0 m (+ 27 m)
VA/HUD Portfolio					
HUD: HOPWA	$294.8 m	$294.8 m (+ $0)	$350.0 m (+ $55.2 m)	$281.7 m (- $13.1 m)	$385 m (+ $103.3 m)
Foreign Operations Portfolio					
USAID: HIV/AIDS	$566.9 m	$540.5 m (- $26.9 m)	$540.5 m (- $26.4 m)	$400.7 m (- $166.2 m)	$417.0 m (+ 16.3 m)
USAID: TB and Malaria	$155.0 m	$105.0 m (- $78.9 m)	$105.0 m (- $78.9 m)	$168.6 m (+ $13.6 m)	$195.0 m (+ $26.4 m)
State Department Coordinator	$488.1 m	$1,450 m (+ $961.9 m)	$1,250 m[7] (+ $762.0 m)	$1373.9 m (+ $885.8 m)	$1.9 b (+ $526.1 m)
Other Appropriations Portfolios/Mixed Funding Streams					
Global Fund - Total	$458.9 m	$200.0 m (- $346.7 m)	$1,200.0 m (+ $653.3 m)	$435.0 m (- $23.9 m)	$1.5 b (+$1.065 b)
Global Fund - HHS	[$149.1 m]	[$100.0 m]	—	[$99.2 m]	—
Global Fund - USAID	[$397.6 m]	[$100.0 m]	—	[$335.8 m][8]	—
Other (DOL, DOD, DOA, FMF)	$40.9 m	$2.0 m (- $38.4 m)	—	$36.3 m (- $4.6 m)	$42.2 m (+ $5.9 m)
Total - President's Global AIDS Initiative	$2,268.3 m	$2,798.2 m[9] (+ $529.9 m)	$3,614.3 m (+ $1,346.0 m)	$2,920.3 m (+ $652 m)	$4.7 b (+ $1.78 b)

[1] With gratitude to NASTAD for generating this chart
[2] The Omnibus Appropriations bill calls for an across-the-board 0.80% rescission and is reflected in these figures
[3] Accounting of CDC funding has changed whereby all management and administrative costs have been reallocated to two new accounts: Public Health Improvement and Leadership and Business Services Support and is reflected in the FY04 and FY05 numbers
[4] This figure does not include the $20 million of reprogrammed HRSA money for the bulk purchase of drugs for 10 states with waiting lists as of June 21, 2004
[5] Special Projects of National Significance (SPNS) is funded through an evaluation tap across all PHS programs, the tap in FY2004 is 2.2% and 2.4% in FY2005, and is not included in the RWCA total
[6] The President's budget provides a $3.3 million increase for the Public Health and Social Services Fund at HHS
[7] Request includes bilateral efforts at the State Department, USAID, and CDC
[8] This figure includes $87.8 million appropriated in FY04 that was not provided to the Global Fund due to legislative provisions
[9] Includes $8.8 million for administrative expenses for the Office of the Coordinator