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IN THIS ISSUE

■ Special Report: Bridging the gap for inmates.....cover

■ NY state program helps ex-offenders prevent HIV.....87

■ Changing attitude is part of re-entry for ex-offenders.....89

■ Ongoing study looks at an adaptation of Safety Counts..90

■ Lumbar Puncture in HIV-infected Patients91

■ Young and untested...HIV spread continues92

■ FDA Notifications.....93

— *Raltegravir indication extended*

— *Tentative approval for lamivudine*

— *New labeling for Videx*

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Special Report: Bridging the gap for inmates

CDC researchers find that too many people are diagnosed late

Other studies confirm problem

Too many Americans with HIV infection continue to be tested late in their disease, despite decades of HIV awareness, prevention, and testing campaigns and efforts.

Although data from the last few years are not yet available, information from the 1990s through 2005 suggest the problem continues nationwide.¹⁻⁴ Without effective antiretroviral therapy, most people with HIV will progress to full-blown AIDS in approximately 10 years. Testing, diagnosis, and medical care soon after HIV infection and before developing AIDS can prevent unnecessary morbidity and mortality and reduce further HIV transmission, the Centers for Disease Control and Prevention reports. People who receive an AIDS diagnosis concurrently or soon after receiving their initial HIV diagnosis (less than three years) represent missed opportunities for prevention and treatment.

African Americans and other minorities are diagnosed with HIV even later in their disease than most white people in the United States.

The CDC studied late HIV testing from 1996 to 2005 by examining data from 34 states. Although 2005 was the cutoff year for follow-up purposes, CDC investigators used data collected through June, 2008, says **Luke Shouse**, MD, MPH, a medical officer in the CDC's division of HIV/AIDS prevention. "We looked at the initial diagnosis date and then when they were diagnosed with AIDS," he says.

They found that 38.3% of patients had received an AIDS diagnosis within one year of their HIV diagnosis, and another 6.7% — for a total of 45% had received an AIDS diagnosis within three years of their HIV diagnosis.¹

The data collection period preceded the CDC's revised recommendations for HIV testing, which were released in 2006, Shouse notes.

The CDC now recommends routine testing for ages 16 to 64 years.

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"We're examining a period prior to the testing guidelines," Shouse says. "This might be a baseline, and we could repeat this in a couple of years and see if people appear to be getting tested earlier."

Another researcher who has examined late diagnosis of HIV infection at two urban hospitals

compared data between timelines and found no progress in early HIV diagnoses through 2004.²

"It was surprising," says **Muriel Jean-Jacques**, MD, MA, an assistant professor in the department of medicine at Northwestern University in Chicago, IL.

"We expected that with increased awareness of HIV and AIDS and increased attention paid to early diagnosis that even in the absence of a formal early diagnosis program that early diagnoses would increase," Jean-Jacques says. "We were surprised to find the median CD4 cell count was so low and the viral load so high, and there was no change or improvement in that."

One reason for this finding could be that hospital culture continues to focus on acute HIV/AIDS problems, overlooking opportunities to test patients in either inpatient or outpatient settings, Jean-Jacques suggests.

"Providers have been taught that you think about HIV and AIDS and whether people have symptoms," she explains. "There's not a lot of emphasis on using the inpatient setting as an opportunity for preventive care because that's not generally what it's for."

CDC recommended strategies

Still, the CDC's 2006 recommendations are for routine HIV testing in all health care settings. The Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Healthcare Settings suggests these strategies:

- All health care patients, ages 13 to 64, should be notified that HIV testing will be performed unless they opt-out of the screening;
- People who are at high risk for HIV infections should be tested annually;
- Health care professionals should incorporate screening into their general medical care consent form and not require a written consent.

Jean-Jacques' research has shown that 12% of patients diagnosed late with HIV had been hospitalized at some point within the five years prior to their diagnosis. Since many of these patients had CD4 cell counts of less than 50 when they were diagnosed, it suggests they were HIV positive earlier, but had not been screened for HIV.

Also, 48% of the people with a late diagnosis had a prior outpatient visit within five years of their HIV diagnosis, Jean-Jacques says.

"This shows there are potential other encounters with the health care system where they could have been diagnosed," she adds.

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Editorial Questions?

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There have been some efforts by health care organizations to incorporate the 2006 recommendations into practice, but it's difficult to say how widespread the practice has become, Jean-Jacques says.

If insurance companies would require it or if HIV screening became a quality indicator for hospitals and health care providers, then it would become more routine, she notes.

For example, providing pneumococcal vaccines to people over age 65 has been a publicly-reported goal and benchmark, and that's led to a greater rate of vaccination, Jean-Jacques says.

If someone reported a measure of the proportion of a health care organization's patients who had been screened or offered testing for HIV, then this practice would improve, she adds.

The CDC study found that older people, heterosexual men, injection drug users, and minorities tended to have higher rates of late HIV diagnosis.¹

"Whites were the least likely group to have an AIDS diagnosis at three years," Shouse says.

The CDC data and analysis didn't address why people were being diagnosed late, although stigma likely plays a role, Shouse says.

"I do think the 2006 recommendations for all adults to be tested routinely as part of their health care is an important recommendation, and I think it might have an impact on stigma," he adds. "It might reduce the stigma and make testing more accessible to more people."

Heterosexual men might have been diagnosed later because they don't feel like they're at risk for HIV, Shouse says.

"Some of the reasons people get tested or not tested depend on their perception of risk," he adds.

Jean-Jacques has found in her medical practice that people will often turn down the offer of an HIV test, saying they aren't sure whether they could deal with it or handle a positive finding.

"Or people will say, 'I don't think I'm at risk for that,'" she adds. "Then when you do a sexual history, you find out they're having unprotected intercourse, but they don't see themselves as at risk."

Once health care organizations adopt the opt-out HIV screening approach, it likely will help to reduce HIV stigma, Jean-Jacques notes.

"Personally, I like to ask people if they'd like an HIV test at a separate time from when I ask about their sexual history because I don't want them to think I'm judging them," she adds. "I try to ask about the HIV test when I ask about their having a mammogram or having their chole-

sterol checked or having a flu vaccine."

When clinicians ask patients about the HIV test in the context of obtaining their sexual history, it might make patients defensive.

Another strategy to increase HIV testing acceptance would be to provide more oral testing so people don't have to have their blood drawn for an HIV test if they are not already having their blood drawn for something else, Jean-Jacques suggests.

Some people will need more frequent HIV tests because of their risk factors, but if the nation's health care policy becomes to routinely test everyone from 16 to 64, then the test needs to be taken out of the context of risk assessment, Jean-Jacques adds.

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NY program provides HIV interventions for inmates

Both condoms and jobs are focus

[Editor's note: This is the second part of a special report on how prisoners returning to the community often need specific HIV prevention interventions. In this issue of *AIDS Alert* we highlight the efforts of a New York prison re-entry program that serves as a vehicle for HIV prevention, as well as a way to reduce prison recidivism. In the July, 2009 issue of *AIDS Alert*, we featured a study that found a large portion of HIV-positive prisoners released into the community do not immediately access care or treatment.]

A New York AIDS service organization (ASO) has found that a good HIV prevention program for people who were incarcerated in state

prisons involves a multi-step program that includes health/HIV education, finding them a place to live, finding them a job, and following up with community support.

In the nearly three decades the world has been dealing with HIV/AIDS, it's become clear to public health officials, ASOs, and clinicians that effective HIV prevention, particularly for some of the most vulnerable and highest-risk populations, requires a holistic approach.

"When guys are first getting out of prison they have much more immediate needs than HIV prevention," says **Nancy Fisher**, director of prevention services for AIDS Council of Northeastern New York in Albany, NY. The AIDS Council has five offices that work with 15 counties in Northeastern New York, and it's located 160 miles from New York City.

The organization also works with HIV positive inmates, providing them with services in their home communities through a case management model.

"They have issues with housing and employment, so we stabilize them in most things and make referrals, and then we deal with teaching them safer behaviors," Fisher explains.

Here's how the organization handles HIV prevention for newly-discharged prisoners:

- **A community re-entry specialist works with men and women upon prison discharge.**

"I work with people who are at risk for HIV simply because of their lifestyles before they went into prison," says **David Howard**, community re-entry specialist with AIDS Council of Northeastern New York.

The re-entry prevention program's goal is to slow down the prisoner recidivism rate by helping prisoners returning to the community receive positive support and reinforcement. **(See story about how program helps with attitude change, p. 89.)**

"I see men in the department of parole who I develop a positive relationship with," Howard says. "Parole officers refer them to me."

The newly-released men and women have to contact Howard, but once they do he is flexible about when and where they'll first meet.

The stigma of HIV/AIDS leads to many ex-offenders choosing to meet outside of AIDS Council's offices, he notes.

"We have a one-on-one consultation and evaluation," Howard says. "I ask at every intake: 'Have you been tested for HIV?'"

Nearly all of the people say they were tested

while in prison, so Howard offers to have them retested if they wish. He also hands out condoms and information, along with making them referrals for housing and employment services.

- **Provide support services to released prisoners.**

"The thing is that when a guy comes home from prison he paints a picture that everything is all right, but the reality is that he doesn't have a place to live, he doesn't have Medicaid, and he doesn't have too much to look forward to," Howard says. "So they come in and meet with me, and they can be honest with me because I'm an ex-offender, and I identify with not having anyone out there that I can talk with."

Howard helps them both find and prepare for job interviews, and he cultivates contacts throughout the region with the goal of finding people who will hire ex-offenders.

"David has many connections with employers who will hire ex-offenders, so he knows where to send them so they'll have a better chance of success," Fisher says. "He tells them how to dress and how to carry themselves, and they can hear it from him because they see him as a mentor."

Howard also helps ex-offenders address substance abuse problems by helping them attend group support meetings.

"Ninety% of the people who return from prison have substance abuse issues," he says. "I'm also in recovery, and I serve as a model for them."

- **Work with other organizations that target same population.**

AIDS Council also works with other organizations that help ex-offenders, including ROOTS — Re-entry Orientation and Opportunity Toward Success, which is a group for ex-offenders, Fisher says.

"They've developed a curriculum that points ex-offenders toward success," she explains. "And we have a subcontract with them where we provide twice monthly meetings."

The meetings are small group interventions that discuss HIV prevention, along with behavior change strategies, including changing one's attitude toward life and work.

"I have a lot of young men who show up and who are serious about changing their criminal thinking and who don't want to go back to the corner to sell drugs," Howard says. "They want to make a contribution to their community."

The problem is their low frustration tolerance and proclivity toward easy boredom.

“We have some young men on a waiting list to enroll in a community college,” Howard says. “We have to create things to keep people occupied and busy so they won’t fall back into recidivism.”

Within this context, teaching ex-offenders about HIV prevention is one part of the package, while teaching them how to be happy and productive members of society is another part, he explains.

- **Provide HIV prevention classes within prison walls.**

Howard has taught basic HIV information in correctional facilities in 16-session classes of 1.5 to 2 hours duration per session.

“I taught basic HIV information and about how if you are getting high with someone, here’s how to sterilize the utensils you’re using,” Howard says. “If you don’t have a constant partner, here’s how to properly use condoms, and I teach communication skills and how to adjust and deal with HIV.”

- **Provide peer associate program.**

For ex-offenders who are staying in AIDS Council’s region, there are opportunities for them to become peer associates, Fisher says.

“For folks who are ready, we provide training and individual interventions,” Fisher says. “They’re dealing with their own risk reduction behavior, and we provide opportunities and outreach for them to share the HIV information they’ve learned with others in their community.”

This reinforces HIV education among a high-risk population, and it helps peer associates build their own HIV risk reduction behavioral skills, Fisher adds.

“This is a positive thing for them to do and to spend their time,” she says.

The peer associates program helps teach ex-offenders responsibility, and it gives them something positive to do rather than to just hang out on their block, Howard says.

Howard also hoped that informal peer educator relationships would be built during the prison HIV prevention sessions.

“So maybe the guys with younger siblings could take it back and share it with their families,” Howard says.

“I have some inmates who returned to the community who had peer education training for HIV,” Howard adds. “These men received education about HIV and a certificate, and then they shared HIV prevention information with their family and close friends.”

For the men who received the certificate upon completing all of the HIV sessions, this was a proud moment, Fisher says.

“For some, it’s the first time they’ve stuck with something all the way through, and they’re very proud,” she adds. ■

HIV prevention program for ex-offenders succeeds

Teaching listening, patience

Before HIV educators can hope to change HIV risk behavior among high-risk ex-offenders, they need to help these men and women change their attitudes about their lives in general, an expert says.

“They’re so used to getting new pairs of sneakers by going to the street corner and selling drugs,” says **David Howard**, community re-entry specialist with AIDS Council of Northeastern New York.

Howard tries to teach them how they’ll appreciate what they have more if they work, wait, and save for them.

“Life’s a slow walk,” Howard says.

Ex-offenders often listen to what Howard says because he is an ex-offender too: “They know the passion in me to help people,” he says.

Howard’s approach combines the practical with the emotional. He’ll hand out a dozen condoms, along with job leads, to men who have just re-entered the community. And he’ll behave as a good friend or counselor who will listen to their concerns and patiently show them the way to make themselves marketable in what is always a difficult job environment.

When he finds a job for an ex-offender the reaction is often that it pays too little and requires too much.

Howard helps them put this in perspective.

“I tell a lot of gentlemen and women when I work with them that ‘I can’t do your job, but here’s what will help you keep your job and move onto a better job,’” he says.

For example, Howard teaches them how to listen and follow what their employers or teachers are telling them.

“Listening means following directions and taking suggestions,” Howard says. “A lot of people miss that point.”

Occasionally there are success stories that show that ex-offenders can make lifetime changes, given the right kind of support and education.

"We had one guy who was in prison for 15 years for murder," Howard recalls. "I met him at a re-entry support group."

The man was big and intimidating, but Howard saw that he wanted to change.

"He liked what I said, and he latched on to some of the things I said at a re-entry program," Howard says. "He got a job eight days later as a part-time worker at a deli."

Within two weeks, the man had become a full-time employee, and a month later he received a raise and was considered to be one of the owner's best hires.

With help from the re-entry support group, the man then met the owners of a weatherization business. He went to work for them and was eventually promoted to being a supervisor with a decent income, Howard says.

When the weatherization company hired another ex-offender, the older man served as a mentor, helping out his younger assistant, earning high praise from the business owner, Howard adds.

"I work with people who will listen to what I say and who are willing to have an opportunity to prove themselves," Howard says. ■

The 'Safety Counts' HIV prevention model

Early snapshot holds promise

Investigators are using an adaptation of the Safety Counts model for HIV prevention to evaluate the impact of HIV education, hepatitis education, and a substance abuse intervention on people who are at high-risk for HIV infection in New York.

"We are looking to see if people change," says **Kristin Stainbrook**, PhD, an assistant director of research at Advocates for Human Potential in Albany, NY. The advocacy program is studying the intervention, which is being administered by the AIDS Council of Northeastern New York.

"We want to know if their understanding of HIV increases, whether they change risky behav-

iors, whether they decrease substance use and decrease their risk factors," Stainbrook says.

Safety Counts, which is one of the approved HIV interventions listed by the Centers for Disease Control and Prevention (CDC) in Atlanta, GA, was designed for a substance abuse population.

The prevention intervention includes face-to-face group and individual sessions, educational activities, creative strategies for reducing risk behaviors, and a graduation session.

"I think we've had some good results," Stainbrook says of the ongoing study. "We're in the middle stages of the study and have been collecting data for about 1.5 years, following up with people who've completed the program."

About 60 people have received the intervention so far, and the early findings suggest the intervention has helped to reduce drug use and binge drinking, as well as to reduce participation in unsafe sexual practices, Stainbrook says.

"There has been some slight increase in people feeling comfortable talking with their partner about using protection or saying, 'No,' to risky behaviors," she adds. "Also their knowledge of HIV has increased, which has been one of the best findings."

While people participating in the intervention are not necessarily remaining abstinent and are still using drugs and drinking, they say they are less likely to practice unsafe sex and are more likely to use clean needles, Stainbrook says.

The study will continue and the sample so far is small, she notes.

The clients like the group session environment and say they learn a lot from each other, Stainbrook notes.

"The sessions are fun and include food, games, and prizes," Stainbrook says. "We also have some very engaging staff."

The intervention includes having people get together to discuss their personal issues regarding HIV prevention. They also participate in games intended to increase their awareness and improve their behavioral change skills.

For example, one game is based on Jeopardy and includes questions about HIV.

"One thing the program has tried to do, and we don't know if it's been successful, is to develop peer associate groups," Stainbrook says. "The incentive is the possibility of clients becoming a peer and participating in some of the outreach activities." ■

Lumbar puncture in HIV patients with syphilis

By **Dean L. Winslow, MD, FACP, FIDSA**, Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor, Stanford University, School of Medicine.

Synopsis: In this study, 202 patients with HIV infection and syphilis and no neurologic symptoms were studied, and 61 underwent either immediate or delayed lumbar puncture (LP). Using a combination of rapid plasma reagin (RPR) titer \geq 32 and CD4+ lymphocyte count \geq 350 cells/uL or serologic response to treatment improved the ability to identify asymptomatic neurosyphilis (ANS).

Source: Ghanem KG, et al. Lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms. *Clin Infect Dis.* 2009; 48:816-821.

Eligible subjects in this study included all patients with concurrent HIV infection and syphilis in a prospective cohort who had no neurologic symptoms at time of lumbar puncture. Retrospective stratification was applied as follows: 1) LP in patients with late latent syphilis or syphilis of unknown duration regardless of CD4 count or RPR titer, 2) LP if CD4 \geq 350 cells/uL and/or RPR titer \geq 1:32 regardless of syphilis stage, and 3) LP in the context of serologic nonresponse to syphilis therapy (lack of \geq 4-fold decrease in RPR titer \geq 12 months after receipt of appropriate treatment or \geq 4-fold increase in RPR titer \geq 30 days after receipt of therapy).

The results showed that 202 patients with syphilis and HIV did not have neurologic symptoms. Immediate LP was performed in 48 patients, and 10 cases (22%) were found to have ANS using standard CSF analysis criteria (any of: WBC $>$ 10/uL, protein $>$ 50 mg/dL, CSF VDRL reactive). With use of criterion 1, two (14%) of 10 cases of ANS would have been missed. With use of criterion 2, no cases of ANS would have been missed but would have

required an LP be performed in 88% of all patients. Performance of LP in 13 patients meeting criterion 3 (serologic nonresponse to treatment) yielded four cases (31%) of ANS.

Commentary

From an historical perspective, following the advent of the use of penicillin for treatment of syphilis following World War II, the rates of neurologic complications of syphilis declined dramatically and resulted in the abandonment of routine LP for staging of patients with syphilis in the absence of neurologic symptoms. By the 1980s, a number of case reports of neurosyphilis developing in HIV-infected patients, often following treatment with approved antibiotic regimens, including standard doses and schedules of penicillin, prompted the need to revisit the issue of LP for these co-infected patients. Obviously, patients with neurologic symptoms and syphilis need to undergo LP, but controversy exists regarding the need for LP in patients without neurologic symptoms.

While this study has many limitations, including small sample size of patients actually undergoing LP and the retrospective application of stratification criteria, the data are useful. Using the criteria of CD4 \geq 350/uL, RPR titer \geq 1:32, or serologic nonresponse to treatment results in the need to perform LP in 70%-90% of HIV/syphilis co-infected patients but avoids missing significant numbers of patients with ANS. Unfortunately, no "gold standard" exists for the diagnosis of asymptomatic neurosyphilis. It should be kept in mind that while reactive CSF VDRL is specific for the diagnosis of neurosyphilis, this test lacks sensitivity and has been suggested to be negative in 50% of patients with neurosyphilis. While CSF pleocytosis is sensitive for the diagnosis of neurosyphilis, this lymphocytic pleocytosis lacks specificity since this finding is commonly present in HIV-infected patients without syphilis, particularly in patients not receiving antiretroviral therapy.

We have been following these guidelines in our HIV clinic for several years and perform LPs in our clinic routinely. In individuals found to have evidence of ANS, we generally admit these patients to our hospital and administer 10-14 days of intravenous penicillin G. ■

Young and untested, HIV spread continues

In 2007 only 12.9% of high school students overall and 22.3% of students who ever had sexual intercourse had been tested for HIV, the Centers for Disease Control and Prevention reports.¹

“Although the results of this report show that the prevalence of HIV testing was higher among female than male students and increased with increasing grade, 73% of female students who had sexual intercourse had never been tested for HIV,” the CDC found.

In the United States, an estimated 1.1 million persons were living with human immunodeficiency virus (HIV) infection in 2006, of whom an estimated 232,700 were undiagnosed and unaware they were HIV infected. Adolescents and young adults aged 13–24 years represented 4.4% of the total but disproportionately comprised an estimated 9.9% of the undiagnosed cases.

These results are similar to those of the 2000 National Survey of Teens on HIV/AIDS that determined that 10% of adolescents overall and 27% of sexually active adolescents aged 15–17 years reported ever being tested for HIV. The results for non-Hispanic black students are especially relevant, because, as of 2007, non-Hispanic blacks accounted for 72% of HIV diagnoses among adolescents aged 13–19 years. This analysis indicated that non-Hispanic black students had the highest overall race/ethnicity-specific percentage of students tested (22%), and among all students who had sexual intercourse, non-Hispanic black students in 12th grade had the highest testing prevalence. These findings suggest that, with respect to race/ethnicity, students with the highest group risk are getting tested at higher rates.

Visits to health-care providers are opportunities for HIV testing. Data collected during 1994–1996 for the National Longitudinal Study of Adolescent Health reveal that two thirds of adolescents aged 15–17 years had a physical examination in the preceding 12 months. In the 2000 National Survey of Teens, two thirds of the adolescents who reported being tested for HIV had asked to be tested, and most had been tested in health-care settings, including general health clinics (50%), private physician offices (31%), and HIV clinics (9%).

In 2006, CDC recommended routine HIV screening for all patients aged 13–64 years. Certain persons at high risk for HIV should be tested at least annually: 1) injection-drug users and their sex

partners, 2) persons who exchange sex for money or drugs, 3) sex partners of HIV-infected persons, and 4) men who have sex with men or heterosexual persons who have had more than one sex partner since their most recent HIV test or whose sex partners have had more than one sex partner since their most recent HIV test. In addition, all patients seeking treatment for STDs and those attending STD clinics should be screened routinely for HIV during each visit for a new health concern, regardless of known or suspected risk behaviors for HIV infection.

The Society for Adolescent Medicine recommends offering testing and effective risk-reduction counseling and assistance as part of routine care of sexually active adolescents, especially those who live in high HIV prevalence areas. The American College of Obstetricians and Gynecologists also recommends HIV screening for sexually active women under age 19.

Routine HIV screening in health-care settings, as recommended, could increase the proportion of adolescents who are tested for HIV among those who receive medical care, the CDC emphasizes. Adolescents who have had sexual intercourse or are considering having sexual intercourse should know their HIV status and the HIV status of their sex partners. Previously published data for 2007 showed that 15% of high school students had had sexual intercourse with four or more persons during their lifetime. Such students and adolescents at high risk for HIV infection should be tested at least annually.

“HIV testing among sexually active adolescents is an important strategy to reduce the incidence of HIV infection,” the CDC concluded. “The results of this analysis showed that students who had been taught about AIDS or HIV in school were more likely to have had an HIV test than were those who had not been taught about AIDS or HIV. Although approximately 90% of high school students have been taught about AIDS or HIV, only 12.9% have had an HIV test.”

High schools can enhance their HIV prevention curricula by including information on locations and procedures for obtaining free, confidential HIV testing. In accordance with state and local policies, school health professionals could refer at-risk students for HIV prevention, counseling, and testing services. Many schools collaborate with local health centers and community-based organizations to help students receive screenings and some school-based health clinics offer HIV testing on-site. Health-care providers, educators, and

parents or guardians play critical roles in providing support and guidance to adolescents in making decisions about the timing and frequency of HIV testing. Because adolescents might be sexually active but unwilling to discuss this information, health-care providers should provide HIV testing routinely to all patients age 13 and older, the CDC recommends.

Reference

1. Centers for Disease Control and Prevention. HIV Testing Among High School Students --- United States, 2007. *MMWR* 2009; 2009 / 58;(24):665-668. ■

FDA Notifications

Raltegravir indication extended for treatment-naïve patients

On July 8, 2009, FDA granted approval to raltegravir (ISENTRISS) for the treatment of HIV-1 infection in treatment-naïve patients. An integrase inhibitor made by Merck & Co, the recommended dose for treatment-naïve adult patients is raltegravir 400 mg twice daily, with or without food.

The use of raltegravir in treatment-naïve patients is based on a 48-week randomized, double-blind, active control trial to evaluate the safety and efficacy of raltegravir 400 mg twice daily + emtricitabine + tenofovir versus efavirenz 600 mg + emtricitabine + tenofovir. The proportion of patients with HIV RNA < 50 copies/mL was 87% for the raltegravir group compared to 82% for the efavirenz group. The difference between raltegravir and efavirenz with respect to HIV RNA < 50 copies/mL and the 95% confidence intervals is 4.7% (-1.3%, 10.6%).

Several other changes were made to the package insert and include the following major revisions:

A drug interactions heading was included along with a warning about use with UGT (UDP-glucuronosyltransferases) inducers other than

rifampin, specifically, "Coadministration of raltegravir with drugs that are strong inducers of UGT1A1 may result in reduced plasma concentrations of raltegravir"

Indications and usage was changed to incorporate use in treatment-naïve patients: "Raltegravir is indicated in combination with other anti-retroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients. This indication is based on analyses of plasma HIV-1 RNA levels up through 48 weeks in three double-blind controlled studies of raltegravir. Two of these studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults and one was conducted in treatment-naïve adults. The use of other active agents with raltegravir is associated with a greater likelihood of treatment response."

- Section 6.1: Clinical trials experience, treatment-naïve studies: This section now includes 48-week safety and laboratory data from Protocol 021.

- Section 6.2: Postmarketing experience: addition of paranoia and anxiety.

- Section 7.1 Effect of raltegravir on the pharmacokinetics of other agents adds information for CYP1A2, CYP2B6 and methadone.

- Section 12.4 Microbiology was updated to include the following headings and information: Antiviral Activity in Cell Culture

In addition, 5 clinical isolates of HIV-1 subtype B had EC₉₅ values ranging from 9 to 19 nM in cultures of mitogen-activated human peripheral blood mononuclear cells.

Resistance: Treatment-naïve subjects: By Week 48 in the STARTMRK trial, the primary raltegravir resistance-associated substitutions were observed in 3 (1 with Y143R and 2 with Q148H/R) of the 6 virologic failure subjects with evaluable paired genotypic data. ■

Tentative approval for lamivudine

On June 22, 2009, FDA granted tentative approval for lamivudine tablets, 150 mg and 300 mg, manufactured by Matrix Laboratories Ltd of Hyderabad, India, for use in combination with other antiretrovirals in the treatment of HIV-1 infection in adults. The application was reviewed under expedited review provisions for

the President's Emergency Plan for AIDS Relief (PEPFAR).

The FDA originally granted tentative approval for the Matrix Laboratories formulation of lamivudine 150 mg on March 19, 2007. The current tentative approval adds lamivudine tablets 300 mg, and also addresses scoring issues associated with the 150 mg tablet.

"Tentative approval" means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, but is not eligible for marketing in the U.S. because of existing patent protections applied to Epivir Tablets, 150 mg and 300 mg, made by GlaxoSmithKline. Tentative approval does, however, make the product eligible for consideration for purchase outside the United States under the PEPFAR program.

Effective patent dates for all approved drugs can be found in the agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the "Orange Book."

As with all generic applications, FDA conducts an on-site inspection of each manufacturing facility, and of the facilities performing the bioequivalence studies, to evaluate the ability of the manufacturer to produce a quality product and to assess the quality of the bioequivalence data supporting the application prior to granting approval or tentative approval to these applications.

A list of all Approved and Tentatively Approved Antiretrovirals in Association with the President's Emergency Plan is available on the FDA website. ■

New labeling for Videx pediatric powder

The FDA recently approved new labeling for didanosine (Videx pediatric powder and Videx EC capsules). The revisions to the Dosage and Administration, Contraindications, Warnings and Precautions, and Drug Interactions sections in both package inserts are outlined below. Other minor changes to the package inserts were made for consistency. In addition the Videx pediatric powder package insert was converted to Physician Labeling Rule (PLR) format.

Summary of Revisions:

I. Section 2.3 Dosage Adjustment was modified to remove statements for dose reductions for

adverse events such as pancreatitis or peripheral neuropathy. Dose reductions for didanosine other than for weight have not been established.

In the Videx pediatric powder package insert, Section 2.3 Dosage Adjustment was revised to state that no didanosine dosage adjustment is required with hepatic impairment. This information has already been incorporated into the package insert for Videx EC capsules.

II. Two contraindications were added to both package inserts as shown below. The changes reflect re-interpretation of previously known drug information in the current setting of HIV infection and available antiretroviral therapy. The rationale for the change are summarized below.

These recommendations are based on either drug interaction studies or observed clinical toxicities.

Coadministration of didanosine and allopurinol is contraindicated because systemic exposures of didanosine are increased, which may increase didanosine-associated toxicity [see Clinical Pharmacology (12.3)].

Coadministration of didanosine and ribavirin is contraindicated because exposures of the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) are increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving both didanosine and ribavirin.

Rationale: Contraindicating Use of Didanosine with Allopurinol:

Previously the coadministration of didanosine and allopurinol was 'not recommended', however, the potential for didanosine toxicity was re-evaluated in the current context of other available NRTIs and other available drugs for gout therapy. Coadministration of allopurinol with didanosine increases didanosine AUC by 113% and C_{max} by 69% in healthy subjects. Contraindicating administration of didanosine with allopurinol is recommended based on the increase potential for didanosine-associated toxicity due to increase in didanosine levels.

Contraindicating Use of Didanosine with Ribavirin:

Previously the combination of didanosine and ribavirin was 'not recommended' due to serious adverse events including fatal hepatic failure. Given availability of other NRTIs and the concern for potential didanosine-induced hepatotoxicity in patients with underlying liver disease (those receiving ribavirin as part of Hepatitis C

treatment), the coadministration of ribavirin and didanosine is now contraindicated.

III. Hyperuricemia was removed from Warnings and Precautions section of the package inserts.

A review of postmarketing cases indicated hyperuricemia was listed along with multiple medical issues reported, usually in the context of serious conditions like lactic acidosis, hypersensitivity, general advancement of AIDS. A few cases of only gout were identified; none of the cases were compelling.

IV. Section 7 Drug Interactions was updated to provide information regarding drug-drug interactions with ganciclovir and methadone, as presented below.

A dosing recommendation for administration of nelfinavir with didanosine was added to the enteric coated capsule package insert. This information is already included in the pediatric powder package insert.

The clinical comment for ganciclovir was revised to state: If there is no suitable alternative to ganciclovir, then use in combination with didanosine with caution. Monitor for didanosine-associated toxicity.

The rationale for this change includes the following: Coadministration of didanosine with ganciclovir increases didanosine AUC by 111% (data for didanosine C_{max} is not available). A similar magnitude of increase in didanosine levels is noted with both allopurinol (increase in AUC of 113% and C_{max} of 69%) and ganciclovir, and consideration was given to contraindicating concomitant use of didanosine and ganciclovir. Use of didanosine with ganciclovir is not contraindicated for the following reason: ganciclovir is used for treatment of serious and life-threatening CMV infection and in certain clinical scenarios ganciclovir may be the only agent available for treatment of CMV infection. Therefore, in contrast to allopurinol, concurrent administration of didanosine with ganciclovir is allowed when no suitable alternative to ganciclovir is available and with monitoring for didanosine toxicity.

Information regarding methadone was also included as follows: Do not co-administer

CNE/CME questions

5. The Centers for Disease Control and Prevention (CDC) recently found that which percentage of patients had received an AIDS diagnosis within one year of their HIV diagnosis across 34 states from 1996 to 2005?
A. 13.9%
B. 28.2%
C. 38.3%
D. 45.1%
6. The CDC's 2006 recommendations for routine HIV testing in all health care settings includes which of the following:
A. All health care patients, ages 13 to 64, should be notified that HIV testing will be performed unless they opt-out of the screening
B. People who are at high risk for HIV infections should be tested annually
C. Health care professionals should incorporate screening into their general medical care consent form and not require a written consent
D. All of the above
7. Which of the following is not a common barrier to HIV risk reduction activities among recently-released ex-offenders, according to experts?
A. HIV stigma
B. Substance use
C. Lack of access to condoms
D. Attitude about life and returning to criminal activities

Answers: 5. C; 6. D; 7. C.

methadone with Videx pediatric powder due to significant decreases in didanosine concentrations. If coadministration of methadone and didanosine is necessary, the recommended formulation of didanosine is Videx EC. Patients

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■ Denver clinic has way of normalizing HIV testing

■ Study examines racial differences in ART use and mortality

■ New medication adherence strategy shows promise

should be closely monitored for adequate clinical response when Videx EC is coadministered with methadone, including monitoring for changes in HIV RNA viral load.

The rationale for this recommendation is as follows: An analysis evaluated methadone's effect on didanosine exposure which was separately evaluated for the enteric coated capsules and buffered tablets compared to combined or pooled historical pharmacokinetic data from healthy subjects. The results indicated that while the average didanosine exposure was decreased less than 20% for both Cmax and AUC(0-inf) with the enteric coated capsules, greater decreases in didanosine exposure were observed with the buffered tablets. The buffered tablet average Cmax and AUC(0-inf) decreased by approximately 40% and 30%, respectively.

The clinical relevance of the observed decrease in didanosine AUC and Cmax for both formulations are unknown. In the absence of exposure-response data, it can not be determined whether the decreases in didanosine exposure require a dosage adjustment for didanosine with concurrent administration of methadone.

Videx is a Nucleoside Reverse Transcriptase Inhibitor (NRTI) manufactured by Bristol Myers-Squibb. ■

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CNE/CME objectives

The CE/CME objectives for *AIDS Alert*, are to help physicians and nurses be able to:

- Identify the particular clinical, legal, or scientific issues related to AIDS patient care;
- Describe how those issues affect nurses, physicians, hospitals, and clinics;
- Cite practical solutions to the problems associated with those issues.

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any question answered incorrectly, please consult the source material. After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a letter of credit. When your evaluation is received, a letter of credit will be mailed to you.