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IN THIS ISSUE

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Male circumcision in some nations may be the best available HIV prevention tool

Evidence growing for safety, efficacy

Randomized clinical trials and other recent studies have confirmed earlier work showing a strong public health benefit for the use of male circumcision to prevent HIV infection in high-prevalence areas of the developing world.

Investigators who once were somewhat isolated in their pursuit of this question, and who have had to deal with nasty emails, phone calls, and even protests by fringe anti-circumcision groups, now can see the benefits of their research.

"We now have three clinical trials that show how male circumcision approximately cuts in half the risk of HIV infection," says **Robert C. Bailey**, PhD, MPH, a professor of epidemiology in the School of Public Health at the University of Illinois at Chicago.

Bailey is principal investigator of a clinical trial of more than 2,700 HIV-negative, uncircumcised men in Kenya, who were randomly assigned to groups that were circumcised or not circumcised. The trial was halted early because results within the first two years showed that the circumcised men had half as many HIV infections as the uncircumcised men.

"If we had a vaccine that was 50 to 60 percent effective, the world would be scrambling to make it available," Bailey notes. "Because circumcision is a surgical procedure, people are less enthusiastic about it."

Nonetheless, Bailey's research and other studies showing similarly positive results are expected to result in some changes in prevention strategies in parts of sub-Saharan Africa.

"I think the international public health community has been waiting for the results of these trials," Bailey says. "And now that they've arrived, the evidence is very compelling that circumcision has a protective quality against HIV infection."

At the same time the clinical trials have shown strong evidence of the protective effect of circumcision against HIV infection, there have been numerous other studies looking at psychosocial issues,

cultural/religious issues, financial impact of circumcision, and whether circumcised men engage in more and riskier sex than uncircumcised men.

Another recent study shows that in sub-Saharan Africa, male circumcision is significantly associated with lower cervical cancer incidence and lower HIV prevalence, independent of whether participants were Christian or Muslim.[1]

"We found that male circumcision is strongly associated with less HIV prevalence in sub-Saharan African countries and in non-sub-Saharan countries that have primarily heterosexual transmission," says **Paul Drain**, MPH, MD-candidate, an investigator at the University of Washington in Seattle, WA.

"And male circumcision is associated with low cervical cancer incidence [among a population], and it's associated with lower herpes virus, type 2," Drain adds. "All three of those are sexually transmitted diseases [STDs]."

When investigators compared circumcision rates with diseases that are not sexually transmitted, such as tuberculosis and malaria, they found no such association, Drain says.

There are various other studies that have had results overwhelmingly positive with regard to employing circumcision as a prevention strategy. (*See article in the "AIDS Alert International" section of the upcoming April 2007 issue of* AIDS Alert, *about the variety of research involving HIV infection and circumcision.*)

For example, a study published in January 2007 in the *Journal of Acquired Immune Deficiency Syndrome* found that in the first year after being circumcised, men did not engage in more risky sexual behaviors than uncircumcised men.[2]

"The circumcised men did not assume they were insulated from HIV," says **Kawango Agot**, PhD, MPH, director of the Impact Research and Development Organization of Kisumu, Kenya.

While the circumcised men studied did not engage in risky sexual behaviors for HIV infection, this was a short study and the situation could be different with a longer follow-up, Agot notes.

Other research found that male circumcision is a cost-effective HIV prevention strategy in sub-Saharan Africa settings that have high or moderate HIV prevalence among the general population.[3]

Investigators studied the question of how many infections likely will be prevented if 1,000 men are circumcised, says **James G. Kahn**, MD, MPH, professor of health policy and epidemiology at the Institute for Health Policy Studies at the University of California, San Francisco.

"We compared what it costs to deliver the intervention to the potential savings when people aren't getting HIV infected and sick," Kahn says. "What we found is that if you circumcise 1,000 men over 20 years, using our epidemic modeling, you would avert an estimated 308 infections over 20 years."

The averted infections would include women

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partners, he notes.

Such a strategy would have a net savings of $2.4 million.[3]

Investigators conducted a sensitivity analysis, changing all of their assumptions, including changing the assumption that circumcision results in 50 to 60 percent fewer HIV infections to an assumption that it prevents only 40 percent, Kahn notes.

"We looked at what if the intervention costs more and if the area's HIV incidence is substantially lower," Kahn says. "But the bottom line is for the range of things we looked at, there never is a net cost — all of scenarios we looked at yielded net savings."

Bailey's research has looked into the acceptability of male circumcision as an HIV prevention tool, and the results have been promising.

In one review of acceptability studies, the median proportion of uncircumcised men who were willing to become circumcised was 65 percent, and 69 percent of women favored circumcision for their partners.[4]

"There now are 13 studies of acceptability from nine different countries in sub-Saharan Africa, and the general findings are that the main barriers for men in non-circumcising religions are cost, fear of pain, and fear of infection," Bailey says. "Adverse events, in other words."

This suggests that if the world's public health community was to make circumcision available at minimal or no cost in these non-circumcising areas, then many men who are not circumcised would consider the procedure, Bailey says.

Even before the HIV and circumcision clinical trial results were known, studies of male perceptions of circumcision in these areas showed that men considered circumcision a positive action to take for better hygiene, to prevent STDs, and to protect them from HIV infection, Bailey notes.

"About 50 percent of the men thought circumcision would protect them from HIV," Bailey says. "They could look around at tribal groups and see that the circumcised men were not infected."

Investigators also are studying the perceptions of newly circumcised men about their sexual pleasure and any changes, and so far the men haven't reported any differences in before and after circumcision, Bailey says.

The next step will be for the World Health Organization (WHO) of Geneva, Switzerland, to weigh in on the issue, and for medical experts to come up with a plan for providing male circumcision in a safe, affordable, voluntary setting within research-poor areas where medical training and resources are limited, Bailey adds.

Bailey has studied this issue since 1995 after reading an article about how the areas of Africa where HIV prevalence was the highest were areas where men do not traditionally get circumcised.

"That caught my attention, and I looked further into the literature, and there were quite a few studies where individuals who were not circumcised were at twice to eight times greater risk of HIV infection," Bailey says. "These were observational studies where both uncircumcised and circumcised men were observed."

As a biological anthropologist who also has trained in epidemiology, Bailey thought this would be the ideal topic to marry his experience in epidemiology and anthropology.

"This is a culturally and religiously loaded practice, and we also needed more information about the distribution of circumcision and HIV infection," Bailey says.

Bailey has experienced first-hand the controversy surrounding circumcision and any science that proves it is beneficial medically. People who are against circumcision demonstrated at one his talks, he says.

Kahn has received unpleasant emails from anti-circumcision groups.

"There is a bit of a backlash in this country against circumcision," Bailey says.

"A lot of nurses have been trained to advise against circumcision, and the American Pediatric Association says to do it out of religious or cultural preference, but not on a medical basis," Bailey says.

"I think their position is wrong," he adds. "I think there are a lot of medical and health benefits to circumcision, even beyond preventing HIV infection."

For example, circumcision results in a reduction in urinary tract infections in adults, and it results in lower rates of cervical cancer among sexual partners of circumcised men, Bailey says.

While this doesn't mean that it should be performed routinely on infants, there is evidence supporting voluntary circumcision among adult men, he adds. ■

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Aging and AIDS: Special series on older patients

Experts offer this advice for improving care of older HIV patients

[*Editor's note: This issue of* AIDS Alert *presents the second part of a series about the problem of HIV infection among Americans who are 50 years old and older. This story addresses how clinicians can improve care and treatment of older HIV patients. The February 2007 issue covered the increasing numbers of older people infected with HIV, screening issues, and the psychosocial problems and dual stigma older HIV patients experience.*]

Clinicians caring for older HIV patients increasingly need specific experience and training to deal with the treatment issues that are more commonly seen in this group.

There are additional polypharmacy issues and screening needs, as well as additional comorbidities and opportunistic infections (OIs) that will require attention, experts say.

And there often are psychosocial issues that require some knowledge about the disease's impact on people who are age 50 and older.

Less than a decade ago, HIV clinicians did not need to give much thought to specific problems experienced by older HIV patients, because the population of such patients was so small. That has changed as people diagnosed with HIV in their 30s and 40s now are living into their 50s and 60s, and as increasing numbers of older people are being diagnosed with HIV.

"Now we have to manage an overlapping effect of the aging process itself and age-related comorbid conditions, says **Kris Ann Oursler**, MD, ScM, deputy director of the Infectious Disease Clinic at the VA Maryland Health Care System in Baltimore, MD. Oursler also is an assistant professor of medicine at the University of Maryland School of Medicine in Baltimore.

Older HIV patients tend to be treated with more medications for other conditions than younger HIV patients, and so the polypharmacy issues are challenging, says **Kathleen Casey**, MD, chief of infectious disease at Jersey Shore University Medical Center in Neptune, NJ.

HIV doctors treating older patients need to be on the same page as the other specialists who see the patient for comorbid conditions so there won't be dangerous drug interactions, Casey says.

"You can't say, 'I'll take care of the HIV, and you take care of the diabetes and blood pressure,'" Casey adds.

"A lot of these health conditions overlap, and that's why it will be difficult to tease out the pathogenesis and develop treatment guidelines for those who are HIV infected," Oursler says. "There are not a lot of older, HIV-infected individuals in clinical trials, and there just now are some longitudinal studies starting, such as the Veterans Aging Cohort Study."

Oursler collaborates with gerontologists on clinical research focused on older HIV patients.

"I found that as an infectious disease-trained specialist, working with gerontologists has allowed me to appreciate the complexity of caring for older individuals," Oursler says.

It's important for clinicians to screen older HIV patients for hypertension, diabetes, and high cholesterol, says **Kelly A. Gebo**, MD, MPH, an assistant professor of medicine, epidemiology, and director of the Public Health Studies Program and director of the infectious diseases, post-doctoral fellowship program at Johns Hopkins University in Baltimore, MD.

"They often have more cancers and other kinds of comorbid conditions that occur with age," Gebo says. "We suspect that those comorbidities are going to be part of the reason these older HIV patients are going to have long-term reduced longevity."

This is why HIV clinicians should not forget to screen for these common age-related conditions, as well as schedule older HIV patients for mammograms, PSAs, colonoscopy exams, and other procedures, Gebo adds.

Older HIV patients are at increased risk for osteoporosis, cardiovascular disease, and cancer, but the biggest challenge is managing the metabolic toxicity of antiretroviral (ARV) therapy, Oursler notes.

One study on HIV in the elderly found that 40 percent had hypertension, 15 percent had dia-

betes, 12 percent had cancer, and 9 percent had coronary artery disease.[1]

"We looked at comorbidities specific to HIV and found that 40 percent were co-infected with hepatitis C," says **Daniel Hart**, MD, an assistant professor of medicine at the Robert Wood Johnson Medical School in New Brunswick, NJ. Hart was a co-author of the study on HIV in the elderly.

Of 163 patients age 55 and older included in the study, nearly 50 percent had been diagnosed after age 50, Hart says.

One of the confounding factors is that older individuals still are diagnosed concurrently with an opportunistic infection, meaning they were found later in the disease progression.

"Clinicians are still not thinking of HIV when a 50-year-old person comes in with weight loss," Oursler says.

"An HIV diagnosis often isn't considered in the older population," Hart notes. "There's a tendency for physicians to attribute symptoms to other things."

Then when older patients are diagnosed, it's difficult for clinicians to determine whether some comorbid conditions are made worse by the disease or antiretroviral treatment.

"We need to conduct longitudinal research to determine if older individuals on antiretrovirals in the long term are at increased risk for age-related diseases or more severe forms of age-related diseases," Oursler says. "Teasing out the pathogenesis of these overlapping problems will be a challenge, but will be necessary to create age-specific HIV care guidelines, which we are going to need."

Oursler, Casey, Gebo, and Hart offer these suggestions for caring for older HIV patients:

1. Metabolic problems are a chief concern.

"What is most studied so far is metabolic toxicity associated with lipodystrophy syndrome, specifically, glucose intolerance and diabetes, dyslipidemia, and fat redistribution," Oursler says.

Older age is one of the independent risk factors associated with lipoatrophy.[2,3]

"It's fair to assume that older individuals are at increased risk for lipodystrophy syndrome," Oursler says. "The problem you have in studying this question is there's so much overlap between ARV metabolic toxicity, comorbidity, and older age."

For instance, suppose an HIV clinician is presented with a 60-year-old patient who has no obvious health problems other than the HIV infection and being a little overweight, Oursler says.

"Then you give him antiretrovirals and get his HIV under control, and he gains 20 pounds — all in his midsection," Oursler says. "His fasting glucose is 200 and total cholesterol is 250, and so the question is how that individual got to this point in two years' time."

Was the individual's metabolic decline due to the antiretroviral therapy, or was it because of his advancing age combined with being at higher risk for obesity, diabetes, and high cholesterol?

"There's no way to tease out cause and effect," Oursler says.

2. Older HIV patients may have some unique psychosocial problems.

"Having HIV is not something you talk about at the family dinner table when you're an older person," Casey says. "You can talk about your blood pressure and heart attack, but not about HIV."

As a result, older HIV patients are much more private about their HIV status, and they often do not share this information with their adult children, Casey says.

"This makes it more difficult for them to find support," Casey adds. "And they can't just assume their children know what's wrong with them when they're hospitalized."

For instance, Casey says she doesn't even acknowledge her patients when she's in the grocery store or elsewhere in public because unless they approach her first, she assumes they want to keep the fact that they know an HIV doctor private.

"HIV is a different animal altogether," Casey says. "It's more difficult to cope with when the elderly person is surrounded by caring children who want to know what's wrong with mom or dad, and the parent cannot tell them."

Older HIV patients often deal with feeling isolated from their peers, friends, and families, Gebo says.

"They feel like they're the only ones who have the disease, and they worry that if they tell their children they might not be allowed to see their grandchildren," Gebo adds.

"We have a support group for older HIV patients, and we've found it to be very helpful because then patients feel that they're not the only ones at their age with the disease," Gebo explains. "There also is a National Association of HIV over 50 that has many resources and will

speak at meetings, providing help to older patients."

Another issue that has arisen lately has to do with the way HIV medication is funded under the new Medicare prescription formulary, Casey notes.

"All of the HIV patients who have had their prescriptions rolled over to Medicare Part B have had their medication interrupted," Casey says. "No one has been denied their petition, but they aren't allowed to have their drugs until the petition is heard."

This type of treatment interruption is not safe for any disease, but it's especially dangerous with HIV when increasing evidence shows treatment interruption can result in a resurging viral load and other problems, she adds.

3. There's greater potential for adverse drug interactions and side effects.

In the recent study of HIV and the elderly, investigators found that older HIV patients use multiple drugs to treat a variety of conditions, including many associated with aging, Hart says.

"We found this cohort of patients were on an average of nine daily prescription drugs," Hart says. "So it's reflective of not only their comorbidities, but also the potential for drug interactions and issues along those lines."

Interestingly, the study found that one of the most common side effects among the older HIV patients was neuropathy, which impacted 31 percent of the group, Hart says.

"That's reflective of having older people who started on nucleosides in the early to mid-1990s," Hart says. "This finding was more of a result of the type of nucleoside reverse transcriptase inhibitors [NRTIs] they were started on, and these [initial ones] carried a risk of neuropathy."

4. There is an increase in age-related disorders.

Recent research has shown that older HIV-infected patients are more likely to have neurocognitive problems, including dementia and depression, and Parkinson's disease may be more common among the older HIV cohort.[4-7]

"The cause of death in HIV-infected individuals has changed, and we're seeing deaths now due to non-AIDS-related illnesses," Oursler says.

"The older HIV-infected individuals may be at increased risk for non-HIV conditions compared to younger patients, partly because they've been infected for a longer time," Oursler says. "That's why I believe that a key management strategy will involve prevention and treatment of comorbid conditions in the older HIV-infected individual."

Findings from the Veterans Aging Cohort Study (VACS-5) show that HIV-infected veterans with common comorbid conditions, such as hypertension and lung disease, have limited physical functioning that is similar to age-matched HIV-negative veterans.[8]

Clinicians also should screen older HIV patients for osteoarthritis and avascular necrosis when patients present with hip pain, and they should check for pneumonia when these patients have shortness of breath, Gebo suggests.

Oursler led a study that looked at physical functioning among older HIV-infected patients.[9]

The research team, including gerontologists and exercise physiologists, took patients into an exercise lab at the Baltimore VA Geriatric Research, Education and Clinical Center, and tested functional performance, Oursler says.

They found that patients had a 41 percent reduced aerobic capacity when compared with the expected values of healthy age- and gender-matched individuals. However, ambulatory function and strength were relatively intact, reduced only eight to 10 percent when compared to healthy individuals of that age.

"The reason this is important is because we need to figure out what's causing their severe impairment in aerobic capacity," she adds.

We hypothesize that older patients have a combination of effects from aging, ARV toxicity, and comorbidities that combine to hinder their bodies' ability to use oxygen, Oursler says.

Knowing that exercise and physical activity improve many comorbid conditions in older non-HIV patients, Oursler's team at the Baltimore VA is focusing on developing exercise interventions for older HIV patients. ■

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FDA Notifications

FDA approves lipidatrophy drug

On Dec. 22, 2006, the Food and Drug Administration (FDA) approved Radiesse, an injectable (under the skin) implant to restore or correct signs of facial lipidatrophy, or fat loss, in people with human immunodeficiency virus (HIV). Radiesse, a sterile, semi-solid cohesive implant consisting of synthetic calcium hydroxylapatite suspended in a gel carrier, is a medical device. It is already approved for use as a tissue marker, for treatment of vocal fold insufficiency, and to correct certain dental defects.

The safety and effectiveness of Radiesse for the treatment of facial lipoatrophy was evaluated in a prospective, open-label, multi-center study of 100 patients with HIV and facial lipoatrophy. Study subjects were at least 18 years of age, HIV positive, with a CD4 count $\geq$ 250 /mm^3 and viral load $\leq$ 5000 copies/mL, had been receiving HAART therapy for a minimum of 3 years, and had HIV-associated facial lipoatrophy that was a grade 2, 3, or 4 on the Facial Lipoatrophy Severity Scale. The study population consisted predominantly of multi-ethnic, non-smoking males (94% male) with a mean age of 48 years. Forty-four (44) percent of patients were Black, Hispanic or Asian. Fifty-six (56) percent were Caucasian.

Patients received an initial treatment (initial injection and an additional injection at 1 month as needed). Six months later, all patients were assessed for the need for a touch up injection. Effectiveness was assessed at 3, 6 and 12 months from initial treatment by means of a Global Aesthetic Improvement Scale (GAIS) rating, cheek skin thickness measurements, and patient satisfaction assessment. Safety was assessed by the recording of adverse events through 12 months.

All treatments were performed with a 25-gauge, 1½-inch needle. Mean initial treatment volumes were 4.8 mL for the initial treatment and 1.8 mL at 1 month if necessary (85% of patients were treated at 1 month). At 6 months, the mean touch up volume was 2.4 mL (89% of patients). Four (4) percent of patients received only one treatment, 18% of patients received a total of two treatments, and 78% of patients received a total of three treatments. No patient received more than three treatments.

Mean left cheek thickness measurements at baseline was 4.7 mm (N=100). At 3 months, the mean thickness was 7.3 mm (N=100), representing an increase of 2.6 mm from baseline, with p-Value = 0.0001. At 6 months the mean thickness was 7.1 mm (N=97), representing an increase of 2.4 mm from baseline, with a p-Value = 0.0001.

Mean cheek thickness at baseline for the right cheek was 4.9 mm (N=100). At 3 months, the mean thickness was 8.0 mm (N=100), representing an increase of 2.1 mm from baseline, with a p-Value of 0.0001. At 6 months the mean thickness was 7.5 mm (N=97), representing an increase of 2.7 mm from baseline, with a p-Value of 0.0001.

The most common adverse events reported were temporary edema (swelling), ecchymosis (bruising), erythema (reddening), and/or pain at the injection site.

The calcium hydroxylapatite (CaHA) particles in Radiesse can be seen in X-rays and CT scans. It is important that patients inform their doctor and other health care professionals that they have had Radiesse injected in the face. In a radiographic study of 58 patients, there was no indication that Radiesse potentially masked abnormal tissues or was interpreted as tumors in CT scans.

Radiesse is a product of BioForm Medical Inc., of Franksville, WI.

FDA grants tentative approval of generic efavirenz

The Food and Drug Administration (FDA) has granted tentative approval for efavirenz capsules, 50 mg, 100 mg, and 200 mg, manufactured by Aurobindo Pharma Limited Inc., of Hyderabad, India.

This is a generic version of the already-approved Sustiva capsules, 50 mg, 100 mg, and 200 mg, manufactured by Bristol Myers Squibb Co.

Efavirenz is a member of the class of drugs known as non-nucleoside reverse transcriptase inhibitors, which help keep the AIDS virus from reproducing. This antiretroviral drug is intended to be used in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The application was reviewed under expedited review provisions for the President's Emergency Plan for AIDS Relief (PEPFAR).

"Tentative approval" means that the FDA has concluded that a drug product has met all required quality, safety, and efficacy standards, although it may not yet be marketed in the U.S. because of existing patents and/or exclusivity rights. This tentative approval, however, does make the product eligible for consideration for purchase under the PEPFAR program.

Update on the CNS Adverse Effects of Sustiva® (Efavirenz)

By Kiron Punwani, Shannon Suedkamp, Diem Nguyen, and Jessica C. Song.

Kiron Punwani, Shannon Suedkamp, and Diem Nguyen are PharmD Candidates at the University of the Pacific School of Pharmacy. Jessica C. Song, MA, PharmD, is Pharmacy Residency Coordinator, Santa Clara Valley Medical Center. Kiron Punwani, Shannon Suedkamp, Diem Nguyen, and Jessica C. Song report no financial relationships relevant to this field of study. This article originally appeared in the October 2006 issue of Infectious Disease Alert.

The US Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents recommends efavirenz (EFV) as part of the preferred non-nucleoside reverse transcriptase inhibitor-based regimen for HIV patients.[1] EFV represents a frequently used component of several antiretroviral combination regimens, even though many patients report CNS (central nervous system) side effects.

Studies, to date, have limited data on non-Caucasian patients, despite the fact that according to the DHHS, the AIDS rate for Hispanic adults and adolescents was 25 per 100,000, compared to 7.1 for Whites and 72.1 for Blacks.[2] Hence, there is a compelling need to study this population segment. Of note, post-marketing surveillance of EFV revealed numerous cases of CNS adverse effects associated with elevated plasma concentrations of this drug, especially in the non-Caucasian patient population.[3-6]

This article will present a review of: 1) case reports of EFV-associated CNS effects observed in patients with elevated concentrations of this drug; 2) differences in pharmacokinetic profiles between Caucasian and non-Caucasian populations; and 3) monitoring recommendations for patients receiving this drug.

Previous studies have evaluated CNS side effects associated with EFV plasma levels.[3-6] A study conducted by Marzolini and colleagues showed that EFV plasma concentration levels help predict treatment failure and CNS side effects. Virologic failure occurred in 22% of patients with EFV levels of 1000-4000 ug/L, and CNS toxicity was 3 times more frequent in patients with EFV levels greater than 4000 ug/L compared with patients whose levels ranged from 1000 to 4000 ug/L. This study also confirmed the presence of marked inter-patient and low intra-patient variability, suggesting that therapeutic drug monitoring may be useful for individualizing treatment.[3]

Various patient populations have been studied, but Hispanic patients were often under-represented. For example, Gutierrez and colleagues demonstrated that a predominantly Caucasian patient population (94.1%) with EFV plasma concentrations greater than 2.74 ug/mL were 5.68 times more likely to experience CNS toxicity.[4] Findings from a study performed by Ribaudo and colleagues supported the strong association of race with the clearance of EFV. The clearance increased by 32% in White non-Hispanic subjects, compared with Black and Hispanic subjects; possibly due to differences in metabolism. Of note, patients in this study consisted of 53% Caucasian, 32% Black, and only 15% Hispanic.[5]

A report published by Hasse and colleagues described the case of a 33-year-old, HIV-infected Taiwanese woman who exhibited symptoms of acute psychosis, resulting from her EFV- based antiretroviral

(ARV) regimen. About a week after treatment cessation, all psychiatric symptoms disappeared. Since the patient's symptoms were attributed to an interaction between EFV and fluconazole, interventions included a lowering of her fluconazole dose from 400 mg to 200 mg once daily and re-initiation of her EFV-based ARV regimen. Her psychiatric symptoms reappeared, and her EFV level was discovered to be 30-fold higher than the upper normal limit. EFV is metabolized by cytochrome (CYP) 2B6, and the inter-individual differences in CYP2B6 activity may be responsible for the differences in susceptibility to EFV associated CNS side effects.[6]

EFV undergoes metabolism by cytochrome p450 (CYP) 2B6 to form inactive hydroxylated metabolites that include 8- and 7-hydroxy efavirenz.[7] Genetic polymorphisms of the CYP2B6 isoenzyme have been shown to increase plasma concentrations of EFV in susceptible individuals exposed to this drug.

Single nucleotide polymorphisms of CYP2B6 arise from the 2B6*6 allele (15631G > T (Q172H); 18053A > G (K262R)), with the highest frequencies seen in African-Americans.[8-9] Less is known about the incidence of CYP2B6 polymorphisms in the Hispanic population. One study conducted by Ribaudo et al demonstrated that Caucasians exhibited a 32% higher clearance of EFV compared with the clearances observed in African-Americans and Hispanics.[5]

Several studies have documented the effects of various drugs on CYP2B6 activity.[7,10-17]

In order to anticipate EFV-associated CNS effects, physicians should monitor for drug interactions of this drug with CYP2B6 inhibitors. Furthermore, plasma concentration level monitoring may be warranted in patients with intolerable CNS adverse effects, with levels being drawn 12 hours post-dose.[3-4]

To date, numerous studies have demonstrated that high plasma levels of EFV are associated with CNS side effects, and some have shown inter-patient variability that may be due to race and/or genetic polymorphisms involved in the metabolism of EFV. Although the populations studied have included Hispanic patients, they have represented only a small percentage, and the focus has been primarily on Caucasian populations. In light of the fact that Hispanics account for an estimated 19% of total AIDS diagnoses in the United States,[2] physicians should be particularly alert for signs of EFV-induced toxicity in this under-studied population. ■

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Mentally ill patients with HIV suffer worse outcomes

This article originally appeared in the November 2006 issue of Case Management Advisor.

Research shows that people with severe mental illness are at greater risk of becoming infected with HIV, their care is more costly when they are infected, and their health outcomes are worse than populations without mental illness.[1-4]

While health care providers need to pay closer attention to people with severe mental illness in order to provide specialized HIV prevention interventions, HIV screening among this population could be improved.[5]

Also, Medicaid recipients with mental illness often die younger and have a higher rate of HIV infection than Medicaid recipients who are not mentally ill, says Michael B. Blank, PhD, assistant professor of psychiatry, assistant professor in the School of Nursing, and senior fellow at the Leonard Davis Institute for Health Economics all at the University of Pennsylvania in Philadelphia. Blank also is assistant professor of nursing at the University of Virginia in Charlottesville, and he's on the executive committee of the national Social and Behavioral Sciences Research Network.

"Severely mentally ill people are more likely to be HIV-positive and less likely to adhere to their pharmacologic regimen," Blank says.

"We have data showing that people with severe mental illnesses are at much higher risk — over five times the risk — of becoming HIV-infected as the general population," Blank says. "Other data show that people who are HIV-positive and have a comorbid mental illness have much higher rates of opportunistic infections than the general HIV-positive population."

Recent national reports highlight the health care issues affecting Americans with mental illness and outline the fragmentation of the health care system, which serves an estimated 33 million Americans who use health care services for mental health problems. These reports note the problems with having a health care system that provides piecemeal services to the mentally ill, rather than closing gaps, improving access, and making screening, assessment, and referrals the best practice model.[6]

Mentally ill people are stigmatized and marginalized in society, says Nancy P. Hanrahan, PhD, RN, assistant professor for the Center for Health Out-comes and Policy Research at the University of Pennsylvania School of Nursing in Philadelphia.

"They have a lot of difficulty accessing very well-documented, evidence-based treatment that helps people get better," Hanrahan says.

For example, people with mental illness are less likely to receive primary care, which leads to more serious health conditions later, she says.

"The people we care for are very sad stories," Hanrahan says. "The people are generally very poor and they've been in the [Medicaid] system a long time."

Often, the patients have a cognitive or mood disturbance that negatively affects their quality of life, she adds.

With appropriate care and treatment, mentally ill people can live a fairly normal life, Hanrahan notes.

"One study showed that 65% of people with schizophrenia could live a normal life with minimal symptoms," she says.

While evidence-based treatment is available, too few are receiving it, Hanrahan says.

"One reason we're looking at this vulnerable HIV population is because if people don't take their HIV medications at least 80% of the time, they can develop mutant strains of the virus," Hanrahan says. "This is a very serious public health problem because mutant strains of the virus result in greater research costs to develop new antiretroviral medications."

Blank began to look into the HIV epidemic among mentally ill populations after a colleague's investigation found elevated AIDS deaths among a Medicaid population in Massachusetts.

"Bruce Dembling [University of Virginia senior research scientist] used Massachusetts Medicaid claims data," Blank says. "He found 14 years of lost life associated with a mental health diagnosis in the Medicaid system."

While an exam of the causes of death revealed that suicides were the leading cause, Dembling found that deaths from HIV/AIDS were elevated, Blank says.

Blank, who is a co-director of the Behavioral and Social Sciences Core of the Penn Center for AIDS Research (CFAR) in Philadelphia, was funded by the Penn CFAR to conduct a pilot study of

Medicaid claims. He looked for both HIV and severe mental illness, and found that about 7% of mentally ill people also were HIV-positive.

"We looked at the Medicaid claims and found a much higher seroprevalence among people with mental illnesses than we would have expected," Blank says.

Further research included a prevention study, funded by the National Institute on Drug Abuse in Bethesda, MD, for severely mentally ill people who used substances and who were HIV-negative.

"The idea was to use a case manager to deliver individually oriented HIV prevention messages," Blank explains. "They have knowledge about their clients' cognitive and emotional deficits and were particularly well suited to deliver these programs.

While the social network model for HIV prevention works well for many populations, it is not suited for serving mentally ill people, Blank notes.

"These are people who have difficulty in social situations and who need the messages reinforced over time," he says. "The message needs to be titrated to their constellation of risk factors."

This population's excess risk for infection is due to both their mental illness, substance use, and their risky sexual behavior, Blank notes.

"Because these folks are community-dwelling and vulnerable, they're easily exploited, and they tend to trade sex for food, money, drugs, and a place to stay," Blank explains.

For the approximate 7% of mentally ill patients who already are HIV-positive, investigators developed a program, funded by the National Institute of Nursing Research of Bethesda, called Preventing AIDS Through Health (PATH) Plus.

The PATH intervention includes the use of advanced practice nurses who serve as liaisons between physical health and mental health providers, Blank says.

The intervention is intensive, resulting in an average of 22.9 contacts per participant, including face-to-face interventions with the nurse nearly half of the time.[1]

Despite its cost, it will save money by prevent-

CE/CME*questions*

7. Recent randomized clinical trials of men in sub-Saharan Africa who are circumcised versus those who are not had findings that resulted in the trials being halted early. What were those findings?
A. The uncircumcised men had 20 percent fewer HIV infections within 24 months than the circumcised men.
B. Both groups had equal rates of HIV infection, but the circumcised group had a significant number of side effects related to infections at the surgical site.
C. The circumcised men had 50 to 60 percent fewer HIV infections than the uncircumcised men.
D. None of the above.

8. Research shows that older patients with HIV infection are at increased risk for which of the following?
A. Lipoatrophy/lipodystrophy syndrome
B. Dementia and Parkinson's Disease
C. Depression, social isolation
D. All of the above

9. Which of the following is correct with regard to efavirenz?
A. Plasma levels are not predictive of therapeutic success or failure.
B. Plasma levels are not predictive of central nervous system side effects.
C. It is metabolized by the 2B6 isoform of CYP450.
D. The coadministration of rifampin does not efavirenz exposure.

10. Which of the following is true about people who are mentally ill?
A. They are at greater risk of becoming infected with HIV.
B. If they are HIV-positive and on Medicaid, they are at risk of dying younger than the general Medicaid population.
C. If they are HIV-positive, their health outcomes are worse than for HIV populations without a comorbid mental illness.
D. All of the above

Answers: 7.(c); 8.(d); 9.(c); 10.(d)

COMING IN FUTURE MONTHS

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ing AIDS cases and new HIV infections, Blank says.

Since this population's risk behaviors result in further HIV exposures, the intervention can prevent new infections through keeping clients on highly active antiretroviral therapy, which lowers their viral loads and their risk of transmitting the virus to other people, he says.

"We think preventing even a single case of HIV will save a huge amount of costs," Blank says.

The PATH research, which received National Institutes of Health (NIH) funding, shows that the public health community has grown more aware of the problems facing mentally ill people with HIV infection, Hanrahan says.

"I think the HIV community has begun to open their eyes about this," Hanrahan says. "The funding of our study was very significant — a five-year, funded study at a time when NIH funding is dropping."

NIH's National Institute of Nursing Research, which provided the funding, had the foresight to see this as a multidimensional problem, Hanrahan says.

"Also, it's a significant niche for nurses because of the mental health and physical health needs of this population," Hanrahan says. "They're generally people who are hard to keep track of, and so we go out to their homes or meet them wherever we can find them." ■

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CE/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 competing 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.