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Meth use among HIV-infected MSM poses multiple physical & behavioral problems

Scientists are closer to understanding why

Methamphetamine abuse has been an acknowledged problem among HIV-positive and at-risk men who have sex with men (MSM) since 2000. But there is still much HIV clinicians and researchers do not know about how it interacts with HIV to create greater physical and behavioral problems.

"Methamphetamine is a risk factor for contracting HIV," says **William F. Maragos**, MD, PhD, an associate professor at the University of Kentucky Medical Center in Lexington, KY.

"Meth use does disinhibit people, and it contributes to further promiscuous sexual behaviors," Maragos says.

MSM often use methamphetamines, which are part of the circuit drug or party drug culture. Those who do are considered high risk for HIV transmission because the drug is associated with a number of risk factors.

These risk factors include multiple partners, unprotected insertive and receptive anal sex, casual partners, decreased use of condoms, and prolonged sexual activity, says **Shirley Semple**, PhD, a project scientist with the University of California - San Diego.

"Historically, San Diego County has the highest rates of methamphetamine use in the general population, and meth has been popular in the MSM community in San Diego since the 1990's," Semple says.

In a recent study, Semple and co-investigators examined the relationship between meth use and impulsivity, and they found that MSM who had the highest levels of impulsivity also had the strongest relationship between intensity of meth use and total unprotected sex.[1]

"This whole concept of impulsivity is a promising, but underdeveloped target concept in HIV prevention research," Semple says. "This study suggests it's important and related to sexual risk and also to meth use."

But investigators can't answer questions about causation, and so more research, including studies involving developing and testing clinical intervention strategies, is needed, Semple adds.

What nearly a decade of research into the connection between methamphetamine use and at-risk MSM has demonstrated is that HIV

clinicians need to screen patients for methamphetamine use and suggest treatment when necessary.

"Heavier meth users who are high in impulsivity have higher sexual risk behaviors," Semple says.

It would be helpful to screen patients for both methamphetamine use and impulsivity, which at high levels could indicate the patient has an impulse control disorder diagnosis, she adds.

"It's difficult for clinicians because meth use makes people seem like they're impulsive because they're high on the drug," Semple notes. "So does that mean they have an underlying personality trait? We don't know."

The University of California - San Diego has a sexual risk intervention for meth-using, HIV-infected MSM that was begun in 2000, Semple says.

"The primary goal of the intervention was to reduce sexual risk behaviors in this population of active meth users," she says. "We didn't try to change their drug use behavior."

The program has evolved, and now there's an intervention to teach participants how to manage urges and cravings for methamphetamines using cognitive behavioral therapy and technique, Semple says.

Semple was a co-author of the new EDGE study, which assessed the efficacy of a theory-based behavioral intervention for increasing safer sex behaviors among meth-using MSM who were HIV positive.[1]

The study found that the EDGE intervention, which involved eight sessions designed to reduce high-risk sexual behaviors of meth-using MSM, was superior to the control condition for increasing self-efficacy for condom use.[2]

Another study found that it isn't easy to identify and reach meth-using MSM in some regions of the country because of geographic and cultural obstacles.

Researchers, who looked at the characteristics of meth-using MSM in North Carolina, found that methamphetamine users were not part of demographic groups that Southeastern clinicians typically associate with the drug. For example, MSM who reported using methamphetamine were more likely to report having higher education and health insurance coverage.[3]

"We hear a lot about meth use in urban centers, but we're in a part of North Carolina that isn't quite urban," says **Scott D. Rhodes**, PhD, MPH, an associate professor at Wake Forest University's division of public health sciences/social sciences and health policy in Winston-Salem, NC.

"There are some misconceptions about who is your typical meth user, especially in the South," Rhodes notes.

Due to popular media depictions of meth labs, methamphetamine users typically are associated with abandoned house meth laboratories or housewives in trailer parks, he notes.

"Providers on some levels may not realize what potential users look like in the sense that these people have health insurance, decent incomes, and they're professionals," he adds. "So they think, 'I don't have to screen them.'"

The problem is that broad-scale, social marketing campaigns warning MSM about meth use are

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difficult to employ in the Southeast, Rhodes says.

"We don't have parts of town where gay men and women congregate or hang out," Rhodes says. "There are a few bars around, but there is no gay center."

While some researchers propose using the Internet to reach this at-risk group, it's less than ideal of a strategy, he says.

"I think not having a visible gay community is challenging, and requires us to think creatively about how to reach these men," Rhodes says.

"Create an environment conducive to disclosure," Rhodes suggests. "Don't make assumptions about sexual behavior or drug use behavior."

One potential strategy is to have HIV clinicians screen patients for meth use by asking both direct and indirect questions. For example, one indirect question could be to ask whether the man has mail-ordered Viagra, or another such drug.

Many MSM who use methamphetamines, which can enhance sexual desire, but makes it more difficult to achieve sexual satisfaction, also use an erectile dysfunction drug that they've been prescribed from a doctor or from an Internet source, Rhodes says.

"If you have a 25-year-old patient who you realize is buying drugs for treating erectile dysfunction, or if the patient is trying to get a prescription to one of those drugs from you, then there probably is something going on other than the patient's need for that drug," Rhodes explains.

While more behavioral studies are needed to fully understand the impact of methamphetamine use among MSM who are HIV infected, there also is a need for additional basic research about what methamphetamines do to the bodies of infected patients.

For instance, what investigators have not yet demonstrated is whether, and how, methamphetamine use results in increased infectivity in the brains of HIV patients, Maragos says.

"We don't know how that is, but there seems to be a somewhat larger [viral] burden in the brains of people who use methamphetamines," Maragos says.

Maragos' research involves looking at toxic HIV proteins, including the tat protein, which enhances the replication of the virus.

"The tat protein has a number of other interactions, and one of them is toxic to cell neurons," Maragos says.

"So there are several things that are very interesting about HIV and methamphetamine and/or tat, and that is they both affect the same area of the brain called the basal ganglia, which is the part of the brain that impacts Parkinson's disease," Maragos explains. "Also, they both involve free radical formation."

Investigators directly injected the tat protein into the basal ganglia of a rat, and after 24 hours, they exposed the rat to methamphetamine, Maragos says.

"We chose concentrations that alone were not toxic and did not cause any damage to this area of the brain," Maragos says. "But when given 24 hours apart, they cause 65 percent loss in the transmitter dopamine, which is an important transmitter in the basal ganglia."

This basic research may eventually answer why clinical studies have found that HIV-positive patients who abuse methamphetamines have increased deficits in their brain's metabolic processes, he adds.

"A lot of people who have HIV develop an HIV-associated dementia," Maragos says. "And people who are methamphetamine abusers tend to have more severe cognitive deficits, as well as an increased risk of these defects."

The goal is to clarify the mechanism of what's happening with tat and methamphetamine exposure, he notes.

"People have established the mechanism of meth toxicity, but we really don't know in detail what the tat is doing to make meth so much more toxic," Maragos says. "So we're looking at pathways that might prime the brain in such a way that nontoxic doses of methamphetamine become highly toxic."

For instance, investigators are looking closely at the effect tat has on dopamine compartmentalization of basal ganglia and transporter function, he adds.

"We've only demonstrated that there are some motor deficits due to this interaction of HIV and methamphetamine," Maragos explains. "That's not published and that's just motor deficits."

What has been published is evidence of an impact on cognitive behavior and higher cortical functions, and this could be what leads to increased risky behavior, Maragos says. ■

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Circumcision does not affect women's STD risk

By Rebecca Bowers

With findings suggesting that male circumcision reduces risk of HIV acquisition for men, researchers now are turning attention on circumcision's impact on acquisition of sexually transmitted diseases (STDs) for women. Findings presented at the recent International Society for Sexually Transmitted Diseases Research in Seattle indicate that the protective effect of male circumcision may not transfer to STD risk reduction in female sexual partners.[1]

An international expert consultation was convened in March 2007 by the World Health Organization (WHO) and the UNAIDS Secretariat, with a recommendation issued that male circumcision be recognized as an additional important intervention to reduce the risk of heterosexually-acquired HIV infection in men. The consultation was held following publication of evidence from three randomized, controlled trials undertaken in Kisumu, Kenya; Rakai District, Uganda; and Orange Farm, South Africa, that showed male circumcision reduces the risk of heterosexually-acquired HIV infection in men by about 60%.[2-4]

In contrast to HIV, the effects of circumcision on other sexually transmitted infections have been studied much less, states **William Miller**, MD, PhD, MPH, associate professor of medicine and epidemiology at the University of North Carolina at Chapel Hill. Miller and fellow researchers analyzed data from a prospective cohort study on hormonal contraception and incident HIV and STDs conducted among women from Uganda, Zimbabwe, and Thailand, for the report presented at the Seattle conference.

"We felt that there was the potential that circumcision could also reduce a woman's risk for acquiring these other STDs," says Miller of the report's genesis. "The mechanism could either be through reducing men's risk, which would secondarily reduce women's risk, or alternatively, there could be reduced transmission associated with circumcision, perhaps through effects on organism burden."

The report's findings indicate that male circumcision was not associated with women's risk of acquisition of gonococcal or trichomonal infections. Circumcision had no effect on chlamydia when all participants were considered together; however, when analysis was restricted to monogamous women, those with circumcised partners appeared to have increased risk for chlamydial infection.[1]

Miller's study was done as a secondary data analysis, he says. "I would think that a study specifically designed to assess this relationship would have a better chance of identifying any protective — or even increased risk — relationship," Miller says. "Furthermore, I think that as programs are developed for circumcision to prevent HIV infection, the potential consequences and/or benefits for women should be carefully monitored."

Review the results

To perform the study on women's risk of chlamydial, gonococcal, and trichomonal infections, scientists looked at 5,925 women from Uganda, Zimbabwe, and Thailand, who were seen quarterly for up to two years. The women underwent physical exams with specimen collection and were given face-to-face questionnaires to gather sexual and behavioral data.

Women were asked about the circumcision status of their partners: 18.6% reported a circumcised primary partner at baseline, 70.8% reported an uncircumcised partner, and 9.7% did not know their partner's circumcision status. During follow-up, 411, 307, and 373 participants had a first incident chlamydial, gonococcal, or trichomonal infection, respectively.

In multivariate analysis, after controlling for contraceptive method, age, age at coital debut, and country, the adjusted hazard ratio (HR) comparing women with circumcised partners to those with uncircumcised partners for chlamydia was 1.22 [95% confidence interval (CI): 0.94 to 1.59]; for gonorrhea, adjusted HR: 0.93 (95% CI: 0.70 to 1.24); for trichomoniasis, adjusted HR: 1.05 (95% CI: 0.81 to 1.37), and for all three infections combined, adjusted HR: 1.02 (95% CI: 0.86 to 1.22). Sensitivity analysis excluding women reporting multiple sexual partners had little influence on the estimates for gonorrhea and trichomoniasis; however, for chlamydia, analyses restricted to women with only one sexual partner revealed those with circumcised partners had increased risk of acquisition compared to participants with uncircumcised partners (restricted HR: 1.33, 95% CI: 1.01 to 1.75).[1]

Further research should be aimed at determining male circumcision's potential effects of genital ulcer diseases, such as chancroid, herpes, syphilis, and human papillomavirus (HPV), says **King Holmes**, MD, PhD, director of the Center for AIDS and Sexually Transmitted Diseases at the University of Washington in Seattle. Skin-to-skin transmission routes may be the link to any protective effect, he observes.

For example, earlier research has indicated that women whose male partners were uncircumcised were more likely to acquire/develop cervical cancer,[5] says Holmes. Does this mean that men who don't have a foreskin are more likely to acquire or transmit HPV? Such a hypothesis remains to be fully tested in future studies, he notes.

Hypothesis on circumcision

Results of a meta-analysis presented at the Seattle conference indicate that male circumcision is associated with a reduced risk of symptomatic genital ulcer disease.[6] The report, based on a meta-analysis of observational studies and one randomized trial, hypothesizes that while the protective effect may be due to a reduction in infection with ulcerative STDs, it also is possible that circumcision reduces the frequency and duration of symptoms. This reduction in infection may contribute to reduced acquisition of HIV infection found in circumcised men, the report concludes.[6]

Another area of potential research lies in determining male circumcision's impact on bacterial vaginosis (BV), says Holmes. Scientists have speculated that the bacteria that cause BV can survive under the foreskin of an uncircumcised man, observes Holmes. A man with multiple partners may be more likely to transmit infection to an uninfected partner by just transporting the bacteria he has acquired from the woman who has the infection, he notes. Findings indicate circumcision may have a protective effect. A statistical review of the past medical files of more than 300 couples in Uganda, where the female partner was HIV-negative and the male was HIV-positive, indicates that male circumcision reduced rates of trichomonas and bacterial vaginosis in female partners.[7]

Does male circumcision extend its protective effect to women when it comes to HIV? Researchers at Johns Hopkins University in Baltimore currently have an ongoing trial to answer that question. The study will not be completed until 2008. ■

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ADHERENCE STRATEGIES

New model of adherence teaches IMB skills

Motivation often is the biggest barrier

HIV patients who are better informed, have some social support, and who are not concerned about medication side effects have a higher self-reported adherence, a new study shows.

"Adherence is an extremely complex phenomenon, and it needs to be tailored to each individual person and to where they are in the process of thinking about medications," says **Deborah Konkle-Parker**, PhD, FNP, of the University of Mississippi Medical Center, division of infectious diseases in Jackson, MS.

Adherence requires a multi-factorial approach because of the complex reasons why people will choose not to take a medication that is saving their lives, experts say.

This is why investigators have been exploring the use of a long-standing model of health behavior in psychological literature, called the information-motivation-behavioral (IMB) skills model, in an intervention to improve antiretroviral medication adherence.

"The better informed and motivated a person is, the more likely it is that he/she will seek information through other functions to help develop the necessary behavioral skills," says **K. Rivet Amico**, PhD, an assistant research professor at the Center for Health, Intervention & Prevention, University of Connecticut in Storrs, CT.

Amico and Konkle-Parker are among the researchers who are studying using the IMB skills model among a population of HIV-infected people in the Deep South, which they define as including the Carolinas, Georgia, Mississippi, Alabama, and Louisiana.

These southern states were singled out because they carry a disproportionate share of the AIDS epidemic, Amico notes.

"One-third of the U.S. population resides in the south, but 44 percent of AIDS cases are there," she says. "When you look further into it, you see that there was a 38 percent increase in new AIDS cases in the Deep South, compared with a 13 percent increase in all other southern states and 17 percent in the rest of the United States."

So, the AIDS epidemic is a crisis in the Deep South, which makes treatment adherence of critical importance, Amico says.

The study had a convenience sample of 150 participants at a large infectious disease clinic in Jackson, MS. Konkle-Parker approached patients as they waited for an HIV care appointment in the clinic, asking them if they were prescribed antiretrovirals and if they would be willing to complete a computer-delivered survey of medication adherence.[1]

The IMB approach looks at the HIV patients' personal motivation, which addresses their beliefs. These beliefs include their thoughts about their medication and the side effects, Amico explains.

"It also looks at barriers that come from the difficulty of having to adhere at a time when there is no end point," Amico says.

The behavioral skills addressed include patients' actual set of skills for adhering and their confidence in doing so, she adds.

"How hard is it for you to take your meds at work? Do you have the skills for taking medication in these different contexts?" Amico says.

It's not enough to inform patients about their disease and treatment and then to obtain their buy-in to adhering to their drug regimen, Amico notes.

"If patients don't have the skills they need to be confident in the action of taking medications in different situations, then they won't be able to sustain adherence over time," she explains. "Motivation and information are important, but these have to be combined with behavioral skills."

In the IMB model, it is motivation that might present HIV patients with the biggest difficulty, Konkle-Parker says.

"This has a lot to do with the cultural context," she says. "Stigma is very huge against HIV and against homosexuality in the South."

In Konkle-Parker's Mississippi clinic, the HIV population mainly involves African Americans who have a low income and typically a high school education.

"Stigma is very big in that community," she says.

One key to combating stigma is to show patients that their medications and clinic visits are things that will help them improve their health, even if the antiretrovirals might make them feel worse initially, Konkle-Parker says.

"A lot of times if patients have antiretroviral drug side effects, they'll stop coming back to get medical care," she adds. "They think, 'Oh, I feel fine, so I didn't need to come in anymore.'"

Through an IMB intervention, they learn how to manage their symptoms on a daily basis, as well as look at the bigger picture involving the physical costs of taking the drugs versus the physical benefits.

The IMB research so far suggests that helping HIV patients become better informed and helping them foster social support are important steps to assisting patients in implementing better health behaviors on a daily basis, Amico says.

"We're helping people develop strategies for getting to clinics and how to take their medications despite issues of nondisclosure," Amico says. "To the extent you can do those things in an intervention, you will have effective responses in increasing and sustaining adherence over time."

The main point is to tailor the intervention to the individual, Konkle-Parker says.

"Any particular person may have barriers that are completely different from someone else," she says. "Giving one person pill boxes may not help, but for another person it may be the exact thing they need."

Konkle-Parker uses the IMB skills assessment to guide her to patients' particular deficits, and in any intervention, she addresses those specific barriers.

Assessing patients' obstacles or deficits is not time consuming, Amico says.

Clinicians could use a checklist or options protocol, asking questions that will lead them to what is most problematic for a particular patient, Amico says.

"The more you help patients get some ideas of what's getting in their way, the better you are able to offer suggestions on what to do about that," Amico says.

"In my intervention study, I specifically did a very low labor intensive, low tech intervention," Konkle-Parker says. "I tested an intervention

that involved two face-to-face sessions with myself as the interventionist and not a clinical care provider."

This would be similar to if an adherence counselor conducted the intervention, she notes.

The intervention included telephone check-ins after the two meetings, so it was not time consuming, Konkle-Parker says.

Another strategy could be using computer software to provide an assessment that patients complete while waiting in a clinic for their appointment, Amico says.

"There is active research into how we can best utilize that clinic situation," she adds. "Many clinics have long waits."

An IMB assessment tool would not measure specific barriers, such as transportation and housing, but it addresses behavioral skills that influence adherence, Konkle-Parker says.

"The assessment tool would ask how easy it is for the patient to pick up his or her HIV medications," she explains. "When the clinician sees from the assessment that one thing is hard for the patient to deal with, then the clinician can say to the patient, 'Tell me about it.'"

This approach starts a dialogue between clinicians and patients, and from that dialogue, solutions will follow.

All of these approaches are patient-centered, meaning they address what the needs are of a particular patient, and follow-up from there.

"You find out what the patients' needs and situations are and you think about how to deal with these situations," Konkle-Parker says.

Motivational interviewing is one strategy to doing this, she says.

"If it's clear from the assessment that a patient is not highly motivated to taking medications in a public setting, for instance, then you ask the patient how he feels about that," Konkle-Parker says. "You may need to provide the patient with information, and through motivational interviewing, you could create a sense in the patient that this is a problem that he has to deal with."

Many clinics are moving toward a more patient-centered approach, Amico notes.

"When the diagnosis is A, the problem is B, and the solution is C is a more prescriptive approach," Amico says. "Seeing the patient as a valuable player in his or her own solution is a strategy that supports people in doing their own assessments of what gets in the way of their adherence."

Sometimes, just asking the right questions, such as through an assessment tool, can be an intervention.

"One of the findings in my intervention pilot study was that every person, whether in the intervention group or not, improved in all of the outcomes of self-reported adherence from the beginning to the end of the study," Konkle-Parker says. "The only thing they had in common was they all did the assessment tool throughout the study, so it does bring up the question of whether the assessment itself is bringing issues to mind." ■

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Veterans have higher rate of non-AIDS-related cancers

Clinicians should screen for certain cancers

New research finds that HIV-infected veterans are significantly more likely to have a non-AIDS-defining malignancy (non-ADM) than are HIV-negative veterans.[1]

The study found that incidence rates were highest for anal cancer, Hodgkin's, liver, and lung cancer. The research was presented at the American Society for Microbiology's 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held Sept. 17-20, 2007, in Chicago, IL.[1]

About five years ago, some researchers began to note that HIV providers were diagnosing a number of cancers unrelated to AIDS in their patients, says **Roger Bedimo**, MD, MS, FACP, an assistant professor of medicine and chief of the infectious disease section of the VA North Texas Health Care System in Dallas, TX. Bedimo also is the director of the infectious diseases fellowship training program at the University of Texas Southwestern Medical Center in Dallas.

"We did one study on this in 2004, and then we went back to our database and looked at all the cancer diagnoses we had in patients," Bedimo says. "We divided them into AIDS-defining cancers, and the rest were called non-AIDS-defining cancers."

Investigators examined the incidence rates in two eras, including 1997 to the present and 1996 and earlier, he says.

"We have noticed a decline in AIDS-defining malignancies, but we saw an increase in non-AIDS-defining malignancies, and it was a clear increase,"

Bedimo says. "But our dataset was so small that we couldn't make a lot of inferences from it."

The problem was that investigators didn't have a population with which to compare their findings.

"It's one thing to say you have an increasing rate of cancers, but if you do not know what the denominator is, then the next step is to try to find a comparative group and see if the rates of cancer are different," Bedimo explains.

Bedimo and co-authors discovered that Veterans Administration's electronic medical records could identify HIV positive and HIV negative veterans who had malignancies.[1]

"Having an HIV population and a non-HIV population is what makes these findings so valuable," Bedimo says. "We can assert that the risk of many cancers, including lung cancer, liver cancer, skin cancer, and others were significantly higher in the HIV group."

The 2004 study was criticized for its findings, since it contradicted other observational research, Bedimo notes.

But it was the study's timeframe that likely made the difference, he says.

"Our rationale of why other people have not seen those increases before was because if you follow patients long enough, you'll find an increased rate of cancer," Bedimo says.

"One year is not enough time to develop cancers," Bedimo says. "We followed HIV positive patients for five years and 6.4 years for non-HIV patients."

It's taken a long time for the issue to be accepted, but it's important for research to continue and move on, he notes.

"I do have some hypotheses about why the cancer rates are higher among HIV patients," he says. "Some studies are underway to analyze and explore those hypotheses."

The first hypothesis is that many of the cancers are caused by viral infections, Bedimo says.

For example, anal cancer can be caused by HPV infection, and hepatitis C infection can lead to liver cancer.

"Even for those cancers that are not known to have a virus behind them, that's still a possibility," Bedimo says.

A second hypothesis is that HIV patients receiving antiretroviral therapy are living a lot longer than they used to, but there still are questions about whether their immune systems function completely normally under the chronic condition, he says.

"So we might be improving their immune systems, but they're still sort of vulnerable and more predisposed to illness," Bedimo says.

"It is hypothesized, and some studies have shown, that the immune system helps us deal with cells that have become abnormal, either through DNA damage or those that progress to cause cancer," he explains. "So they're either repaired or killed, and if an HIV patient has a subnormal immune system, then the immune system is not adequate enough to reign in or kill that cell that's been tossed out by the virus or an ionizing agent."

This means the HIV patients' bodies are not able to suppress or control cancer as it develops.

An example of this phenomenon can be found in transplant patients who are kept on immunosuppressant medication. Within five years, most will develop cancer — mostly skin cancers, Bedimo says.

"So it's clear that by suppressing the immune system, you can promote cancer, and HIV is suppressing the immune system," he says.

The key factor is time.

"It may take years for an HIV patient who survived to develop cancer," Bedimo adds. "The only reason we're seeing this now is because we're starting to see a large number of patients who've had HIV and are on antiretroviral drugs."

The third hypothesis is that HIV treatment is causing cancer, he notes.

"That is unlikely, but possible," Bedimo says. "If drugs are present in the body for 10-plus years and the cells have been damaged, then you might have a possibility, but we don't have evidence of this."

Bedimo and colleagues will continue to explore this connection, next looking at the cancers involved to see if they carry evidence of another type of infection, or have damage that can be attributed to something else.

"We think it's important to raise questions and look for answers," Bedimo says.

Also, clinicians need to be more suspicious of potential cancer in their HIV patients and maybe screen for certain common cancers, he suggests.

"People should be aware of the fact that these cancers are significantly higher in HIV-positive patients," Bedimo says. ■

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FDA Notifications

FDA provides more info in response to Viracept recall

Nelfinavir mesylate (Viracept) is a protease inhibitor antiretroviral medicine used in combination with other anti-HIV medications to treat infection with HIV. It is approved for use in adults and in children older than 2 years of age who are infected with human immunodeficiency virus (HIV-1), the virus that causes AIDS.

Earlier this summer, Viracept was recalled from the European market due to high levels of a harmful substance known as ethyl methane mesylate (EMS), a byproduct of the Viracept manufacturing process. EMS is known to be an animal carcinogen (can cause cancer) mutagen (can be harmful to DNA, the genetic material in cells) and a teratogen (can be harmful to the development of an unborn child). The level at which EMS may become carcinogenic in humans is not known.

While Roche manufactures and distributes Viracept in Europe, Pfizer manufactures and markets Viracept in the United States. The levels of EMS detected in Viracept manufactured by Pfizer are lower than the levels of EMS detected in Viracept manufactured by Roche.

The FDA and Pfizer have agreed to specific limits of exposure of EMS to allow for continued use in populations where the benefit of using Viracept outweighs the potential risk.

At this time, the FDA and Pfizer consider the risks of unintended interruption of HIV treatment that may result from a recall to be greater than the risks associated with taking Pfizer-manufactured Viracept.

Pfizer is issuing the following Dear Healthcare Professional letter to describe the current situation:

VIRACEPT® (nelfinavir mesylate) 250 mg, 625 mg tablets, and Powder for Oral Suspension:

IMPORTANT INFORMATION FOR PRESCRIBERS

Dear Healthcare Professional:

The purpose of this letter is to inform you of the presence of ethyl methanesulfonate (EMS), a process-related impurity in Viracept (nelfinavir mesylate) and to provide guidance on the use of Viracept in pregnant women and pediatric patients.

In June 2007, excess levels of EMS were detected in Roche Ltd-manufactured active pharmaceutical ingredient of Viracept; subsequently Roche recalled Viracept from all their European Union (EU) markets. EMS is a process-related impurity formed during manufacture of Viracept. EMS is a potential human carcinogen (Class 2B). Data from animal studies indicate EMS is teratogenic, mutagenic and carcinogenic; however, no data from humans exists.

In response to the Roche EU recall, the Food and Drug Administration (FDA) asked Pfizer to implement a new specification to limit the presence of EMS in Pfizer- manufactured Viracept products marketed in the United States. Pfizer commenced testing all active ingredients and found levels of EMS substantially lower than those associated with the Roche EU recall. Testing continues. Pfizer and FDA have agreed on interim and long term specifications of EMS in Viracept at levels substantially lower than those that prompted the Roche EU recall. Only product meeting the interim specifications will be released for patient use in the US. Pfizer is taking this step to balance the need to maintain the availability of Viracept as a therapeutic alternative for patients and prevent unexpected interruption of HIV-1 antiretroviral treatment with the need to minimize patient exposure to a potential carcinogen.

The agreed interim specification limits the theoretical lifetime increased cancer risk in adults to less than 17 cases per 100,000 exposed. The long term specification for levels of EMS limits the theoretical lifetime increased cancer risk in adults to less than 1 case per 100,000 exposed. Current estimates of the background incidence of cancer in the HIV population are about 20-30 cases per 1000 patient-years.

MANAGEMENT OF PEDIATRIC PATIENTS:

While no data on the impact of high EMS levels in humans exist, toxicology experts generally agree that the lifetime risk associated with exposure to a carcinogen is about 3-fold greater among pediatric patients between 2 and 16 years of age and even higher among pediatric patients younger than 2 years of age; this potentially greater risk was used to determine acceptable levels of EMS in formulations used in the pediatric population. For pediatric patients who are stable on Viracept-containing regimens, the FDA and Pfizer agree that the benefit-risk ratio remains favorable and those patients may con-

tinue to receive Viracept. Pediatric patients who need to begin HIV treatment should not start regimens containing Viracept until further notice.

We encourage you to refer to specific recommendations for the use of antiretroviral agents in pediatric HIV-1 infected patients from the United States Department of Health and Human Services (DHHS) guidelines.[1]

MANAGEMENT OF PREGNANT WOMEN

We currently do not have information on the ability of EMS to cross the placenta nor enter breast milk. In the Antiretroviral Pregnancy Registry involving over 6000 HIV infected pregnant women, no significant difference in the prevalence of birth defects between women who used Viracept and those who used other antiretroviral therapy was observed. Nonetheless, FDA is recommending that pregnant women limit their exposure to EMS during pregnancy. Pregnant women who need to begin antiretroviral therapy should not be offered regimens containing Viracept until further notice. As a precautionary measure, pregnant women currently receiving Viracept should be switched to an alternative antiretroviral therapy while Pfizer and FDA work to implement the long term EMS specification for Viracept. We encourage you to refer to specific recommendations for the use of antiretroviral agents in pregnant HIV-1 infected patients from the United States Department of Health and Human Services (DHHS) guidelines,[2] *in determining an alternative treatment option.*

Maintaining the health of the mother and preventing transmission of HIV to the fetus are of paramount importance. For pregnant women with no alternative treatment options, FDA and Pfizer agree that the risk-benefit ratio remains favorable for the continued use of Viracept.

ALL OTHER PATIENTS

There is no change in the recommended use of Viracept for all other patients. Please see enclosed full prescribing information. In considering the best treatment for patients, please be aware that many HIV antiretroviral medications are carcinogenic in animal studies. In addition, some HIV antiretroviral medications are mutagenic or are teratogenic. Despite these findings, available information shows the benefits of HIV-1 antiretroviral treatment outweigh the risks of using these products or completely stopping HIV treatment. Please see individual product labeling for additional information.

Pfizer and FDA continue to work together to define a long-term, globally harmonized, plan which appropriately limits EMS levels within Viracept while still ensuring an uninterrupted supply of the medication to patients.

Sincerely,
Michael Berelowitz MB ChB, FACP, FCP(SA)

Safety Information

VIRACEPT in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

Nelfinavir is principally metabolized by the liver; it can be used in patients with mild hepatic impairment without any dose adjustment. VIRACEPT should not be use in patients with either moderate or severe hepatic impairment.

Exercise caution when administering VIRACEPT with drugs that induce CYP3A, and with potentially toxic drugs that are metabolized by CYP3A, including those that prolong the QT interval.

In clinical studies (n > 5000), the most common adverse event, diarrhea, was moderate to severe in 14% to 20% of patients.

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including VIRACEPT.

Redistribution/accumulation of body fat has been reported in patients receiving antiretroviral therapy. A causal relationship has not been established, and long-term consequences are not known at this time.

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported with protease inhibitors.

There are no adequate and well-controlled studies in pregnant women taking VIRACEPT. VIRACEPT should be used in pregnancy only if clearly needed.

VIRACEPT use is contraindicated with amiodarone, quinidine, triazolam, midazolam, ergot derivatives, and pimozide. VIRACEPT should not be coadministered with St. John's wort, simvastatin, lovastatin, rifampin, and omeprazole. Rifabutin dose should be reduced by 50%. PDE5 inhibitors should be prescribed with caution.

Increased bleeding in patients with hemophilia type A or B has been reported with protease inhibitors.

For additional information, see FDA's MedWatch page, titled, "Questions and Answers Regarding Health Concerns and Potential Shortage of Nelfinavir" (marketed as Viracept) at http://www.fda.gov/cder/drug/infopage/nelfinavir/qa.htm ■

References

1. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. October 26, 2006; 1-126. Available at http://www.aidsinfo.nih.gov.

2. Public Health Service Taskforce: Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States. October 12, 2006; 1-65. Available at http://www.aidsinfo.nih.gov.

CE/CME *questions*

32. Which of the following describe methamphetamine use among men who have sex with men (MSM) who are HIV-positive?
A. Meth use disinhibits people and can contribute to further promiscuous sexual behaviors.
B. Methamphetamines are part of the MSM circuit drug or party drug culture.
C. Meth use places MSM at high risk for HIV transmission because its use is associated with unprotected, receptive anal sex, casual sex partners, decreased use of condoms, and prolonged sexual activity.
D. All of the above

33. New research shows that self-reported adherence is higher among which of the following?
A. HIV patients who are motivated to take their medications on time, even if the patients have not been taught the best skills for maintaining adherences.
B. HIV patients who are better informed, have some social support, and who are not concerned about medication side effects.
C. HIV patients who believe in their health care providers.
D. All of the above

34. Which of the following statements is *True*?
A. New research finds that HIV-infected veterans are significantly more likely to have a non-AIDS-defining malignancy (non-ADM) than HIV-negative veterans.
B. Incidence rates were highest for anal, Hodgkin's, liver, and lung cancer for HIV-infected veterans.
C. Both A and B
D. None of the above

Answers: 32. (d); 33. (b); 34. (c)

COMING IN FUTURE MONTHS

- More news from ICAAC
- Here are clinical predictors of disseminated histoplasmosis
- Look at the latest research on immune reconstitution inflammatory syndrome
- Research sheds light on hypersensitivity to abacavir

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.

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f. Total Free Distribution *(Sum of 15d and 15e)*			35	35
g. Total Distribution *(Sum of 15c and 15f)*			156	152
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Brenda J. Mooney
I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

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