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First once-daily drug simplifies dosing, offers new options in HIV-1 treatment

Side effects, risks of cross-resistance remain, as with other therapies

The U.S. Food and Drug Administration has approved the first once-daily antiretroviral drug — efavirenz (Sustiva), a non-nucleoside reverse transcriptase inhibitor (NNRTI) — to treat HIV-1 infection in adults and children. Although the drug is being touted as highly potent and more convenient than other therapies, it is not without side effects or risk of cross-resistance, like other anti-HIV drugs.

"We . . . welcome the introduction of this much-needed once-daily anti-HIV drug," says **A. Cornelius Baker**, executive director of the National Association of People with AIDS in Washington, DC. "The clinical trial results suggest that [efavirenz], when used in combination with other antiretroviral agents, may not only simplify dosing and reduce patients' pill burden, but its potency and tolerability may also offer physicians and patients, including children, new treatment options."

At the 12th World AIDS Conference in Geneva earlier this year, investigators presented data that compared various combinations of efavirenz, zidovudine (AZT, Retrovir), lamivudine (3TC, Epivir), and indinavir (Crixivan) in patients with asymptomatic or minimally symptomatic HIV disease who hadn't received lamivudine, any of the NNRTIs, or protease inhibitors. Data from 450 patients studied over 24 weeks were presented. Patients on the efavirenz/lamivudine/zidovudine regimens performed statistically significantly better than patients on regimens containing indinavir/zidovudine/lamivudine or indinavir plus efavirenz. HIV-1 RNA levels were below 400 copies in 74.7% of patients on efavirenz/lamivudine/zidovudine, compared to 56.2% of patients on indinavir/lamivudine/zidovudine.

Adverse events vary among study groups

In addition, patients on efavirenz had fewer side effects than patients on the other triple-therapy regimen. Patients on indinavir/zidovudine/lamivudine were most likely to experience adverse events (26 of 148 patients), compared to 10 of 154 patients on efavirenz/zidovudine/lamivudine and seven of 148 patients on efavirenz and lamivudine.

"That trial has been criticized because the superiority of Sustiva can probably be attributed to patients stopping their indinavir because of side effects," says **David Margolis**, MD, assistant professor at the Institute for Human Virology at the University of Maryland in Baltimore. "So it can't be definitely said that Sustiva triple-combination is better or more potent than the indinavir triple combination or a protease inhibitor triple combination. But it certainly is potent, it certainly has good effect, and it certainly is well tolerated. So I think it presents a very exciting new alternative for potent triple therapy for patients."

However, Margolis says it remains to be seen whether the triple combination therapy with efavirenz will be used as first-line therapy. One problem is that patients who are on any type of drug that affects the central nervous system (CNS), such as methadone or anxiolytics, may have more CNS side effects from efavirenz, such as irritability or sleepiness.

"There are some reports of patients with underlying psychiatric disorders that may be occasionally exacerbated by exposure to Sustiva," Margolis notes. "But the bottom line is, there is some reason to be a little cautious in people whose thinking is challenged in some way."

He says he has only been using efavirenz as second-line therapy because of his involvement in the expanded access program for the drug at the University of Maryland.

"I've only [used] it so far in patients who have failed or can't tolerate other potent therapy, and I've used it in some of my protease inhibitor patients who have gotten the 'belly' or other protease side effects," Margolis says. "Over the short term, their clinical effect has been maintained, so that's been encouraging." **(For more information on problems with body fat redistribution in patients taking protease inhibitors, see *AIDS Alert*, September 1998, p. 101.)**

Watch out for cross-resistance

Margolis warns of cross-resistance between efavirenz and the two other available NNRTIs, nevirapine (Viramune) and delavirdine (Rescriptor).

"[Cross-resistance] is not all across the class," he says. "Some viruses will be resistant to all three drugs. Some viruses, from people who have been exposed to either Rescriptor or Viramune, will not be completely resistant to Sustiva, although just like the protease inhibitors, I think you need to be concerned that the first time you're exposed to a drug of a certain class, it's going to be your best response."

However, it appears that resistance with efavirenz may take longer to develop.

"So I think for a lot of reasons, most of the market for non-nucleoside reverse transcriptase inhibitors will go to Sustiva," Margolis adds.

Also, there are "very limited data" on efavirenz and fetal toxicity, so women of childbearing age should be counseled carefully before they take the drug, he says.

In patients with low CD4 counts and high viral loads, Margolis says he would use efavirenz "cautiously" in certain circumstances.

"I would have some concern using simply Sustiva and two nucleosides at this point," he notes. "I might use it cautiously in them if I thought they would have trouble taking two protease inhibitors, for example. I would want to follow them closely to see whether or not [the drugs] are working."

Margolis checks viral load within two to three weeks after starting a regimen, then one month later, and finally monthly for two months until patients are stable.

Potency similar to protease inhibitors

Steven Johnson, MD, associate professor of medicine and director of the HIV/AIDS Clinical Program at University Hospital in Denver, says efavirenz is as potent as a protease inhibitor.

"This is an exciting new drug," he notes. "Even removing some of the company-sponsored activism about the drug, we're really very excited to be able to have it."

Typically, efavirenz is used as part of a three-drug regimen, says Johnson. Although it was studied in premarketing trials with zidovudine and lamivudine and was found to be highly effective, it also has been found effective in combination with protease inhibitors.

"So I think one of the open questions with its licensure is what precisely is the best combination to use in terms of effectiveness and tolerability," Johnson says. "It's a consequence of our rapid licensure of medications that the first four [anti-HIV] drugs that were licensed were licensed over about eight years, and now the last eight drugs have been [licensed] over the

last three years. So we've rapidly licensed new drugs, and obviously have had great effects with them, but what has happened is that these drugs have emerged so rapidly that we don't precisely know the comparability of every different combination of these medications. There are literally thousands of combinations at this point."

He estimates that 10% of patients at the clinic have been on efavirenz as part of clinical trials and the expanded access program. Although he says there is no "cookbook approach" to antiretroviral drug therapy, patients generally receive three or more drugs.

"We usually base decisions on prior drug experience, so [with] people who have been on drugs before, our concern might be resistance to therapy, [so] we may choose drugs they haven't been on before," Johnson explains. "That's certainly an important role for efavirenz. For people who have some degree of resistance to the licensed drugs, Sustiva can be part of the new regimen that would hopefully be effective against resistant virus."

What about compliance?

With current regimens requiring patients to take many pills, compliance with drug therapy isn't always optimal. Efavirenz should help that problem somewhat, says Johnson, because it lowers the number of pills patients must take.

"We think the less frequently you dose a drug during the day, the more likely it is to lead to adherence," Johnson says. "A three-times-a-day drug is taken less consistently than a two-times-a-day drug. So a once-a-day drug is probably going to be easier to take than a three-times-a-day drug."

Another advantage of efavirenz is that there are no dietary restrictions associated with it. For example, indinavir should be taken on an empty stomach.

"The simpler the better, because the more adherent people are, the more likely that the virus will be suppressed and the immune system will recover to the greatest extent possible," Johnson says.

The regimen found to be most effective in premarketing trials — efavirenz, zidovudine, and lamivudine — will be five pills daily, he adds. Zidovudine and lamivudine must be taken as a combination pill twice daily, and three efavirenz pills are taken at bedtime. Another regimen that requires fewer pills is indinavir, zidovudine, and lamivudine, which requires eight pills daily. But some regimens require 20 or more pills daily.

James Hellinger, MD, associate research director of Community Research Initiative of New England in Boston, agrees that having to take fewer pills means efavirenz may increase compliance.

"The most important thing is that the medication combinations that work best are the ones patients can take," he notes. "A drug can be unbelievably potent, but if it's got intolerable short-term effects that develop immediately or side effects that accumulate and develop over a longer term, that can create problems resulting in people not wanting to take their meds. So far, the studies suggest that combinations including Sustiva look to be very potent and very tolerable in both the short term and the long term. So people who start them stay on them."

Efavirenz can be used in many combinations of other drugs. "There's enough background for the use of medications of this class together with nucleosides — for example, the class of nucleosides that includes Retrovir and Epivir," says Hellinger.

"There's enough background that the overwhelming likelihood is that one could probably combine Sustiva with nucleosides and achieve a comparable effect, but those studies are in progress and haven't yet been reported. Sustiva also has been studied with single protease inhibitors such as nelfinavir together with nucleosides. [It also has been studied] with nelfinavir alone or indinavir alone. It looks like Sustiva will be a valuable agent when combined with all of those other classes," he says.

Nevirapine works well in combinations

Another NNRTI, nevirapine (Viramune), also is highly effective in three- or four-drug combinations, says Hellinger. He says it has been "underutilized" because it was studied as a single-drug therapy in preclinical trials.

"But when it has been combined with three- and four-drug combinations, it's been extremely active," he says. "One of the key differences, though, is that Viramune has a somewhat higher — at least twofold — rate of developing rash. So it can be harder to start that medication. In contrast, Sustiva has about half the incidence of rash [of Viramune], but a much higher

rate of CNS side effects such as dizziness or grogginess."

With nucleosides, it appears that patients can start on one agent in the class and follow with one or two different agents in the class and still have an effect, says Hellinger.

"But with the non-nucleoside that Sustiva is a part of, it looks like that doesn't work," he notes. "There's no class-bearing benefit. If you started with something in the class, nothing else is going to work. But with the other classes, you might be able to do a sequencing approach where you start with something and switch to alternatives in the class and still have some benefit."

Side effects lessened at bedtime

Johnson says some of his patients complain of dizziness or lightheadness with efavirenz, but because it is taken at bedtime, symptoms are less noticeable because patients go to sleep and the effects of the drug wear off after about two hours.

Efavirenz also can lower the plasma level of other drugs such as saquinavir (Invirase) and indinavir.

"So what that means is that in regimens that combine those, the physician may increase the dose of the protease inhibitor to compensate for it," Johnson explains.

He says he is optimistic about the approval of efavirenz.

"This field is more complex now than it's ever been," Johnson notes. "So an important part of the success of this drug is that it be in the hands of people who understand its limitations, its effectiveness, its drug interactions, and its side effects."

Hellinger says efavirenz is appropriate for patients who have been in long-term drug therapy or for those who are just starting it.

"I think it's likely to be extremely useful for people who have never had medication, whether they have high or low CD4 counts," he notes. "It's likely to have an important role in people who have had medications, have had partial or no effect, and then have had an adjustment and a Sustiva combination added. So it's likely to be useful at all points along the spectrum of HIV infection."

(Editor's note: To obtain more information about efavirenz, including product labeling, visit the Web site maintained by the drug's manufacturer, DuPont Pharmaceuticals in Wilmington, DE. Address: www.sustiva.com.) ■

New CMV drug won't replace other therapies

Cost, compliance issues may influence treatment

A newly approved drug for treating cytomegalovirus (CMV) retinitis, injectable fomivirsen (Vitravene), has shown promise in premarketing clinical trials in AIDS patients with advanced CMV disease. According to the drug's manufacturer, Isis Pharmaceuticals in Carlsbad, CA, fomivirsen belongs to a new class of drugs called "antisense technology," which work at the genetic level to interrupt the process by which proteins involved in human disease are produced.

"Traditional drugs are designed to interact with protein molecules that support or cause diseases throughout the body," according to **Karen Handel**, director of corporate communications at Isis. "Antisense drugs are designed to inhibit the production of disease-related proteins" by inhibiting the production of the protein encoded by the target RNA, she says.

Fomivirsen inhibits the production of viral proteins that are critical to the virus life cycle, thus delaying disease progression.

Data were presented earlier this year in Chicago at the Fifth Conference on Retroviruses and Opportunistic Infections on a multicenter phase-three study of previously untreated patients with greater than 25% retinal involvement. Eighteen patients received 0.05 ml fomivirsen (3.0 mg / ml) by intravitreal injection for three weekly doses followed by bimonthly maintenance doses of the drug. Ten additional patients were assigned to a deferred treatment group and were followed to progression before being given fomivirsen. All patients were followed for time to progression for CMV retinitis, which was determined using clinical criteria and with masked reading of fundus photographs. Ocular adverse events were assessed using complete bilateral ophthalmic exams. CD4 counts also were measured at baseline and throughout the study.

There was a median time to observed progression of 71 days for patients in the immediate treatment group vs. 13 days for patients in the deferred treatment group. CD4 counts were not significantly different between the two treatment groups. The most frequently reported side effects were transient increased intraocular pressure (18.5%), anterior chamber inflammation (15%), and vitritis (7%).

In other data provided by Isis Pharmaceuticals, an open-label study indicated that fomivirsen delayed progression of CMV retinitis for as long as 600 days.

Debra A. Goldstein, MD, assistant professor of ophthalmology and director of the Ocular HIV / AIDS Service at the University of Illinois in Chicago, was one of the investigators of fomivirsen for premarketing trials. She also is conducting current studies of the drug.

"It's not effective in 100% of patients, but neither are any of the other therapies," she notes. "Ganciclovir is only effective in probably 90% of the people who are treated for the first time."

Goldstein uses the drug as first-line therapy in patients who have recently started highly active antiretroviral therapy (HAART) in hopes that there will be an immune response.

"That person would be a great [candidate] to put on this first-line rather than an acyclovir implant," she says. "My usual first-line is an acyclovir [Zovirax] implant."

In addition, patients who are resistant to ganciclovir (Cytovene) are appropriate candidates for fomivirsen therapy.

"The drug is being approved for use for maintenance of a once-a-month injection," Goldstein explains. "That's a very reasonable thing."

The advantage of local fomivirsen therapy is that there are high concentrations of the drug where it is needed without systemic side effects.

"Ganciclovir [given] intravenously has a lot of side effects; the most prominent is [the effect] on the bone marrow," Goldstein says. "Foscarnet [Foscavir] has side effects on the kidneys."

Systemic therapy also requires long-term intravenous administration of drugs.

"On average, there is more than one episode of line sepsis per year per patient with a permanent indwelling [intravenous] catheter," Goldstein says. "When treating the patient locally, you avoid the [risk of] line sepsis."

Goldstein says she typically gives either 150 mcg or 330 mcg of fomivirsen every week (depending on the severity of disease) for three doses, with subsequent maintenance injections once every two or three weeks given indefinitely until the patient either has immune reconstitution or dies.

"In some patients, it causes some inflammation in the eye, and some patients will get [intraocular] pressure after the injection, but these are manageable side effects," Goldstein says.

Although she says fomivirsen is slightly more inflammatory than ganciclovir and foscarnet when given intravitreally, it is much less inflammatory than cidofovir (Vistide), another type of injection used to treat CMV retinitis.

Robert Nager, MD, a spokesman for the American Academy of Ophthalmology in San Francisco, is less enthusiastic about fomivirsen. He says it was approved based on studies with "very small numbers." But Goldstein says that because of newer effective systemic therapies, there are fewer and fewer patients with CMV retinitis to enroll in studies.

"With HAART therapy, the number of people with CMV has really gone down, so any trial of CMV is going to be small," she notes.

Nevertheless, Nager says he prefers the ganciclovir implant (Vitrasert) over fomivirsen. The implant is placed behind the lens of the eye and it releases the drug slowly for about eight months. To his knowledge, there are no studies comparing the two treatments.

Which is better: Implant or injection?

"I think the real issue would be, how does Vitravene work compared with Vitrasert?" Nager asks. "Vitrasert really keeps the eye inactive for about 220 days. If the [efficacy] is equal, then the argument could be made that fomivirsen [is better because] Vitrasert is more of a surgical procedure. But I have a patient who is very, very sick, and we're going to give him a Vitrasert so he doesn't have to deal with shots every week. Vitravene is more difficult for patients. Plus, you run the risk of having infections because you're putting shots in peoples' eyes more frequently than if they have a Vitrasert."

Although the implant has the drawback of requiring that the patient undergo major surgery every eight months for a new implant, Nager says he believes patients would rather undergo infrequent surgery than have an intravitreal injection on a regular basis.

"With the implant, you put it in once, and you follow patients, but you basically don't have to worry about them," he says. "I put an implant in and see them every month and I really almost never have to do anything. Vitravene involves injecting them every month."

Nager says he would use fomivirsen in patients who are "profoundly resistant" to ganciclovir. "One of the advantages of vitravene is there is no resistance known to this," he says. "I'd say if they couldn't have a Vitrasert because

they were profoundly resistant to ganciclovir, then it would be a good choice."

Ronni Lieberman, MD, associate professor of ophthalmology at Mount Sinai School of Medicine in New York City, has investigated fomivirsen. She says almost 100% of her practice consists of patients with CMV retinitis.

"No one is going to argue that Vitrasert is tremendous," she notes. "It's one operation, it works for eight months, and it's a fairly benign operation."

But there is a downside to the surgery, Lieberman adds.

"This is an operation," she says. "You can have complications with operations. What I say to every patient before I operate on them is that you have a 3% chance of getting an infection and a 3% chance of getting a hemorrhage and all of these things, but if it happens to you, it's 100%. So although the risk is small, if it happens, these are all devastating complications."

In addition, as patients continue to undergo repeated implant surgery, their risk for complications goes up as well.

What about the price tag?

"And the dirty little secret that nobody wants to talk about is that Vitrasert is not cheap," Lieberman says. "The Vitrasert costs $4,000 to buy from Chiron [the manufacturer]. Then the patients or their insurance have to pay the hospital for OR time, nurses' time, medications, a separate bill for anesthesia and preadmissions testing, and a separate bill for your medical doctor who has to give you clearance. This is a lot of money."

She estimates it may cost $10,000 or more to insert Vitrasert. Although fomivirsen probably won't be inexpensive, Lieberman estimates that in patients on HAART, fomivirsen may be the best therapy. (The cost of fomivirsen was unavailable from Isis.)

"If you put Vitrasert in a patient on HAART therapy, you will have spent that $10,000," she says. "You've given them that eight months of treatment. You've spent that $10,000. If somebody comes on day one and you decide to give them Vitravene, you inject them, that's $100 for the doctor's fee. They then continue on their Vitravene for three to four months, and we'll see what their viral load and [CD4] cell count is. And if indeed their eye looks lovely and their [CD4] cells have come up and their viral load has come down, you may very well just decide to skip the injection and wean them off the Vitravene. I've done that with a lot of patients. You haven't guaranteed buying eight months of treatment. From a medical-economic point of view, you've spent all your money up front with the Vitrasert."

Lieberman says she places patients on many different regimens for CMV retinitis, from local to intravenous therapy to implants. "The bottom line is that every patient is different," she says. "They have different immune systems, they have different kidney function, they are on different HAART therapy, they're in a different course of the illness, and they've got different psychosocial factors."

In patients who are noncompliant, she may consider Vitrasert, because she is concerned that they may not show up for follow-up appointments for weekly or monthly therapies. For a single mother with no health insurance who can't afford Vitrasert, intravitreal injections with fomivirsen or other drugs may be the best therapy.

"Vitravene is an excellent drug that has had excellent results in many patients," Lieberman explains. "It is certainly my choice for first- or second-line therapy in some patients. But there is no drug I would say I'd use unequivocally ahead of other drugs. Every patient is different. You have to weigh the pros and cons of every drug with every patient." ■

New HIV strain could pose public-health concerns

Can current blood bank tests detect new viruses?

A new strain of HIV detected in a woman in the central African country of Cameroon does not have immediate public-health consequences, experts say, but it does provide more information about the origins of HIV.[1]

The new HIV-1 isolate (called "YBF 30" as well as HIV-1, group N) was obtained in 1995 from a 40-year-old Cameroonian woman with AIDS. The isolate appeared to have characteristics of both SIV and HIV-1 group M, but because it is distinct from both SIV and HIV-1, it is considered a new strain.

"This strain is exactly between SIVcpz Gab, which was isolated from a chimp from Gabon

seven years ago, and HIV-1 group M," says **Francois Simon**, MD, a virologist at Laboratoire de Virologie at Bichat-Claude Bernard Hospital in Paris, and lead author of the report on the new virus. (Gabon is a country immediately south of Cameroon.) "Some parts [of the new virus] are closer to the chimp [SIV] in the envelope" of the virus, he says.

Simon says Cameroon has many simian and prosimian primate species, which may have facilitated the spread of the virus to the Cameroonian woman.

"This may have increased the probability of cross-species transmission during casual contact — because there are a high number of [primate] pets — or by hunters," Simon explains. "Many people eat monkeys in central Africa. [Cross-transmission] is clear for HIV-2, which shares the same identity as SIV from mangabey monkeys. This could be true with HIV-1 and SIVcpz, which is not yet identified [in humans]."

Can blood banks detect virus?

The most common strain of HIV worldwide is called group M for major. Group O (for outlier) is far less common and occurs most often in Cameroon. **Harold W. Jaffe**, MD, associate director for HIV / AIDS in the National Center for Infectious Diseases at the Centers for Disease Control and Prevention in Atlanta, says the main public-health concern regarding the new HIV strain is similar to concerns about group O viruses: Will current tests used in blood-bank screening detect those viruses reliably?

"We have more experience looking at the group O viruses that were first found in Cameroon," he says. "We know that some but not all of the tests that are used to screen blood will detect group O. Manufacturers have been working to modify their tests to allow group O to be detected. It appears that with group N, there may also be a problem with reliable detection."

Simon says the "first evaluation" of the current blood test indicates that it "recognized this strain."

"Of course, further studies are needed on a large group N panel," he adds.

Jaffe says the U.S. Food and Drug Administration now requires that any newly licensed tests for blood-bank screening be able to detect group O reliably, even though only two group O infections have been detected in the United States to date. Those two cases occurred in people thought to have been infected in Africa, he adds.

"But on the group N, we just don't have any information at all," Jaffe says. "It's probably appropriate to be concerned to the extent of looking at how well our tests detect these variants. I don't know whether the FDA would require that new tests detect group N."

Viral-load test reliability uncertain

Another unknown factor about the new strain is whether current viral-load tests are reliable for group N. "With group O, they are not reliable, and there have to be specific modifications with these tests to detect group O," Jaffe says.

"That's less of a public-health question," he adds. "That's more a question of individual patient management. If it turned out you were taking care of a person infected with one of these [new] strains and you wanted to be able to measure their viral load, you'd have a problem, because current tests don't do that reliably."

Group O HIV strains appear not to be spreading as far as M strains. "It's still concentrated largely in Cameroon and adjacent countries," Jaffe says. "It's not common in other parts of Africa. Where it's been looked for in Europe, it's been seen mainly in people originally from Africa. So that strain has not spread rapidly. We don't know yet about group N."

He adds that for now, at least, the new HIV strain does not appear to pose an immediate public-health threat.

"I think it's important to separate the more academic issues from the more public-health issues," Jaffe adds. "Academically, I think this is very interesting, because it supports the idea that these viruses are probably originating from nonhuman primates, and that there may have been multiple introductions of these viruses into humans over time. And it may be continuing. In parts of the world where there is ongoing contact between humans and nonhuman primates, this may continue to go on. That's an important academic concept. For public health, the issues are different, and so far at least, these other subtypes — subtype O and maybe subtype N — have not turned out to be really important public-health issues, but they certainly bear watching."

Reference

1. Simon F, Mauclere P, Roques P, et al. Identification of a new human immunodeficiency virus type 1 distinct from group M and group O. *Nat Med* 1998; 4:1,032-1,037. ■

Study: Candida vaginitis not a sign of early HIV

Reducing sugar in the diet may help prevent CV

A new study indicates that candida vaginitis (CV) is not an early marker for HIV infection among women, but it is an indication that an HIV-infected woman's immune system is declining.[1]

Ann B. Williams, EdD, RN-C, professor at Yale University School of Nursing in New Haven, CT, and colleagues conducted a cross-sectional analysis of the factors associated with the isolation of yeast from vaginal swabs and a clinical diagnosis of CV among 184 women with HIV. The study was conducted in 1995 and 1996.

Only 52% of the women were taking antiretroviral therapy. Williams says she and her co-investigators referred women who were not on antiretroviral therapy to area AIDS providers. Sixty-four (35%) of the women had positive vaginal swabs for yeast, and 19 (10%) met all of the following criteria for the case definition for CV:

- presence of vaginal pruritis or discharge reported by the patient or discharge observed by the examining clinician;
- observation of spores or hyphae on a potassium hydroxide or saline microscopic preparation of vaginal discharge;
- the presence of candida species cultured from a vaginal swab.

Of 107 women who were asked at the beginning of the study whether they currently had a yeast infection, 34 answered yes, although only four of these women met the criteria for clinical diagnosis of CV. Conversely, 15 women who did not believe they had a yeast infection when they were examined actually did have CV.

Ten percent of all the women (19) in the study were diagnosed with CV, compared to 20% of women with low CD4 counts (100 cells / mm^3).

Williams says it is particularly important to advise women with HIV to take steps to prevent CV, such as not wearing tight-fitting pants or underwear, only wearing cotton underwear, wiping from front to back after using the bathroom, avoiding douching, and using only unscented tampons or pads. There is some evidence that reducing the amount of sugar in the diet may help prevent CV as well, she adds.

She also advises HIV-infected women to receive regular gynecologic evaluations at least once a year. They should be instructed that if they develop symptoms of CV and decide to treat it with over-the-counter products, they should contact their clinician if their symptoms do not resolve quickly. A systemic medication such as fluconazole (Diflucan) may be necessary.

"There's no reason to believe candida should be treated any differently between HIV-positive and HIV-negative women," Williams says. "However, when women have very advanced HIV disease with very low CD4 counts, it is possible that the candida will be more difficult to treat or more recurrent. But generally speaking, when people have CD4 counts under 100, you're going to be looking at a variety of ways to deal with their vulnerability to opportunistic infections and fungal infections as well. At that point, you're thinking not only about candida vaginitis, but also esophagitis and other candidal [infections]."

Reference

1. Williams AB, Andrews S, Tashima K, et al. Factors associated with vaginal yeast infections in HIV-positive women. *J Assoc Nurses AIDS Care* 1998; 9:47-52. ■

OSHA targets reducing needlesticks among HCWs

Agency trails California on safer needle devices

The U.S. Occupational Safety and Health Administration (OSHA) has set a Dec. 8 deadline for responses to its request for information (RFI) on engineering and work practice controls that successfully reduce sharps injuries that could transmit HIV and other bloodborne pathogens to health care workers (HCWs).

However, while OSHA touts the RFI as a first step in directly addressing the problem of disease-transmitting needlesticks among workers, other advocates for HCW safety say OSHA already has the information it needs to protect workers from percutaneous injuries (PIs). They also point out that the federal agency lags behind California OSHA, which has taken the lead in revising its state bloodborne pathogens standard to require the use of safer needle devices whenever possible.

Federal OSHA's RFI, published recently in the *Federal Register*, states that "percutaneous injuries

continue to be a concern in work settings where employees are exposed to bloodborne pathogens. [OSHA] is considering possible actions that it can undertake to assist in addressing this issue. . . . The information received in response to this notice will be carefully reviewed and will assist OSHA in determining effective approaches to reducing percutaneous injury rates and what role the agency may have in these approaches."[1]

OSHA estimates the number of sharps injuries incurred by U.S. HCWs at 600,000 annually, but occupational health experts generally recognize that those numbers are vastly underreported. PIs can cause serious illness or death from bloodborne pathogens such as HIV and hepatitis B and C. Since promulgation of the federal bloodborne pathogens standard in 1991, which requires hospitals and other health care facilities to offer hepatitis B vaccine to employees, HBV infections among HCWs declined from about 5,000 new cases that year to about 800 new infections in 1995, according to OSHA. The incidence rate of hepatitis B infections among HCWs is now lower than the incidence rate for the general U.S. population.

However, PIs continue to be a major occupational health concern. The rapid development of safer needle devices that could prevent or minimize bloodborne pathogen exposures has spurred HCW unions and other concerned groups and individuals to call for a change in the bloodborne pathogens standard that would require health care facilities to purchase, evaluate, and use the new technologies.

'Systematic' approach planned

Whether the RFI will lead to a revised standard depends upon information submitted to the agency, OSHA officials say. At a recent HCW safety conference focusing on bloodborne pathogen exposures, **Charles N. Jeffress**, OSHA's assistant secretary of labor for occupational safety and health, announced the agency's commitment to reducing needlesticks. **(See related story, *AIDS Alert*, October 1998, pp. 113-115.)** The RFI is the first step in OSHA's plan to address the problem systematically, he said.

In releasing the request, Jeffress notes that OSHA has received numerous suggestions for reducing needlestick injuries. "To determine the best strategies, we must begin by gathering information systematically to find out what measures are effective in the workplace," he says.

The RFI specifically seeks information on strategies for eliminating or minimizing contaminated sharps injuries in the work environment that have been implemented successfully, and particularly on the use of safer medical devices designed to limit injury risks. The term "safer medical devices" refers to "the wide variety of implements designed to reduce the risk of needlesticks and other percutaneous injuries through such measures as substitution (as in the use of a blunt cannula with a prepierced septum for intravenous administration of medication), modification of the device to reduce the hazard (as with a blunt suture needle), or incorporation of safety features (as with a retractable-needle syringe)," the RFI states.

OSHA also is interested in successful PI prevention programs that integrate the use of safer medical devices, safer work practices, elimination of needles and other sharps in certain instances and procedures, focused intervention in high-injury areas, specialized training, and other elements.

Elise Handelman, RN, MEd, COHN-S, director of OSHA's office of occupational health nursing, says the agency is trying to ascertain the prevalence of needlesticks. "One of the big problems is underreporting," she says. "We believe needlesticks are widespread, and we're trying to get data on that."

In requesting information on preventing PIs, OSHA is "casting a wide net," Handelman explains. "We want to know what works. The question we're asking is, 'What's the best way to approach reducing needlesticks? Is it [safer] devices? Is it getting employee input? Is it making sure employees are trained properly? Is it redesigning work processes to eliminate the need for needles?' This is not an issue for which we have a lot of hard research, so we're trying to get more data on what works."

However, international sharps safety expert **Janine Jagger**, PhD, MPH, says OSHA already has all the information it needs to take action on promoting safer device technologies to prevent needlesticks, but thus far has failed to do so.

"I've already said a thousand times what I've had to say," says Jagger, director of the International Health Care Worker Safety Research and Resource Center at the University of Virginia in Charlottesville. Jagger founded and coordinates the Exposure Prevention and Information Network (EPINet) data collection system for identifying and assessing injury-causing needle

and sharps devices. "I don't have anything new to provide to OSHA that's not available to them already. I don't think anyone will have anything to say that OSHA hasn't heard already."

OSHA could have a significant impact on the rapid implementation of safety devices in health care facilities by looking for those devices during inspections, but "so far they haven't done it," she states. A change in the agency's inspection criteria would go a long way toward getting hospitals to recognize that implementation of safety devices "is not just a mere product choice like any other."

If the agency's RFI leads to incorporating additional inspection criteria aimed specifically at safer devices, then the effort will be worthwhile, she adds.

"Asking for information is one thing, but doing something with it is entirely different," Jagger says. "OSHA has done good things for health care worker safety in general, but has done very little in terms of promoting safer technologies to prevent needlesticks. They can make a big difference here, and I view this announcement as positive. But I won't view it optimistically until the first sign of turning information into action."

Handelman says OSHA could take any one of several actions, including changes in the bloodborne pathogens standard, changes in enforcement, changes in outreach, or changes in training for compliance officers.

"The plan will be based on the information we get," she says.

California to require safer needle devices

Whatever course of action OSHA eventually chooses, the federal agency will be lagging behind California OSHA (CalOSHA), which presently is in the final stages of revising its state bloodborne pathogens standard to mandate the use of new technology designed to prevent sharps injuries.

CalOSHA's actions have been motivated by passage of a state bill last August — the first such state law in the nation — that requires health care employers to make safer needle devices available to HCWs. At press time for this issue of *AIDS Alert*, it was not known whether California Gov. Pete Wilson would sign the bill or veto it.

Nevertheless, **Len Welsh**, JD, MPH, special counsel to CalOSHA, tells *AIDS Alert* that the legislation "basically tells us to do what we're already doing, which is adopt a standard like the one we're already working on."

If the bill becomes law, it would set an Aug. 1, 1999, deadline for adoption of a revised standard, but Welsh says he's confident that CalOSHA will have a new standard on the books well before that date. Action on a revised standard was accelerated "due to a tremendous outpouring of interest in having this attended to expeditiously," he says.

A state advisory board of labor, management, and infection control professionals came to an "unusual consensus that enabled us to move forward a lot more rapidly than we usually manage to do," he explains. Similar to the federal standard after which it was modeled, the present California standard merely mentions self-sheathing needles as an example of an engineering control for preventing injuries.

"It leaves everyone in a quandary as to what they're supposed to do," Welsh says.

The final draft of a revised state standard includes a three-tiered requirement for the use of needleless systems where available, needle devices with engineered sharps injury protection, and a "catch-all" category for non-needle sharps, such as capillary tubes, with engineered protection.

Welsh says four exceptions to the requirements also are included, mainly to assuage industry concerns. The exceptions are: lack of market availability of devices; patient safety considerations; safety performance (when a device marketed for safety doesn't perform as expected); and circumstances in which it is not known

whether a device works better or worse at reducing exposure incidents.

In addition to the safer technology requirements, the revised standard will include more detailed criteria for recording percutaneous injury incidents and data about devices that were used.

Welsh says California is the first state to make substantial amendments to its bloodborne pathogens standard. He adds that federal OSHA appears to be headed in the same direction, "but they're going a lot more slowly."

Some activists wonder why CalOSHA is doing more than its federal counterpart to protect HCWs.

"I'm glad there is some life in these federal agencies when it comes to protecting workers, but why is California doing so much more?" asks **William K. Borwegen**, MPH, director of health and safety for the Washington, DC-based Service

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Employees International Union (SEIU), which represents about 600,000 HCWs nationwide. "The FDA [Food and Drug Administration] has approved some 250 safer products, and lives could be saved if employers bought this newer generation of devices."

For nearly a decade, SEIU has been pushing CalOSHA for stronger state regulations to protect HCWs. On the federal level, the union has lobbied OSHA to cite employers for failing to evaluate safer devices and would like to see changes in the federal bloodborne pathogens standard similar to those planned in California.

"We applaud [federal] OSHA's new leadership, but this is just a baby step in the right direction," Borwegen says. "Hopefully, OSHA is just setting the stage here so they have a legal basis for being more aggressive. Health care workers in the other 49 states face the same hazards health care workers in California face. Lives could be saved by buying these safer devices."

[Editor's note: Comments on the RFI should be submitted on or before Dec. 8 in quadruplicate or one original (hard copy) and one diskette in WordPerfect 5.0, 5.1, 6.0, 6.1, 7.0, 8.0, or ASCII to: Docket Officer, Docket No. H370A, Room N-2625, U.S. Department of Labor, 200 Constitution Ave. NW, Washington, DC 20210. Telephone: (202) 219-7894.

Comments of 10 pages or less may be transmitted by fax to (202) 219-5046, provided the original and three copies are sent to the Docket Office thereafter.

Comments also may be submitted electronically through OSHA's Internet site at: http://www.osha-slc.gov/html/needle-form.html. Information such as studies and journal articles cannot be attached to the electronic response and must be submitted in quadruplicate to the above address. Those attachments must clearly identify the respondent's electronic submission by name, date, and subject.

For further information, contact Bonnie Friedman, director, OSHA Office of Public Affairs, at (202) 219-8148.

In addition to the Federal Register*, the RFI may be accessed on the OSHA Internet site at: http://www.osha.gov. Click on "Federal Register," then "date of publication" (Sept. 9), then "1998."]*

Reference

1. Department of Labor, Occupational Safety and Health Administration. Occupational exposure to bloodborne pathogens: Request for information. 63 *Fed Reg* 48,250-48,252 (Sept. 9, 1998). ■

CE objectives

After reading the November issue of *AIDS Alert*, participants in the continuing education program should be able to:

- understand the basics regarding the new antiretroviral drug efavirenz (Sustiva);
- discuss the pros and cons of using the new drug fomivirsen (Vitravene) to treat cytomegalovirus (CMV) retinitis;
- cite the origins of the new strain of HIV-1, group N, discovered in an AIDS patient in the African country of Cameroon;
- explain the role candida vaginitis (CV) plays in women with HIV;
- identify information OSHA seeks to help reduce percutaneous injuries. ■