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Latinos and HIV epidemic

[Editor's note: This is the first in a two-part series that examines the HIV/AIDS epidemic among Latinos in the United States. In this issue are stories about the extent of the problem and about an effective intervention that is aimed at reducing HIV transmission among Latino youths. In the January 2008 issue of AIDS Alert, *there will be an article about an HIV intervention that spreads HIV education and condoms to Latino men in the rural, Southeastern United States.]*

CDC is working on action plan to target HIV epidemic among US Latino population

Recent MMWR highlights concern

Nationally, public health agencies are turning their focus to the HIV epidemic in the Latino community, but some say it's long overdue.

"We're 25 years into this epidemic, and very little has been done addressing the Latino communities directly," says **Jesus Ramirez-Valles**, PhD, MPH, an associate professor in the School of Public Health of the University of Illinois at Chicago.

There has been too little basic research done to understand the epidemic's impact on Hispanics, and there have been too few prevention interventions studied and developed, Ramirez-Valles says.

"We know little about how Latinos are doing with therapists, talking about adherence, and quality-of-life issues," he says. "We have limited data on what's happening in Latino communities."

Hispanics in the United States are second only to African Americans in being disproportionately affected by the HIV epidemic.

According to the latest data available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA, 18.9 percent of people who received an AIDS diagnosis in 2007 were Hispanic, while Hispanics were 14.4 percent of the U.S. population in 2005.[1]

Yet there are few prevention interventions and public campaigns aimed at reducing HIV transmission specifically in this population.

"The CDC doesn't have one intervention that's appropriate for

Latino men," says **Scott D. Rhodes**, PhD, MPH, an associate professor at Wake Forest University, division of public health sciences, in Winston-Salem, NC. **(Look for story about prevention intervention directed to Latino men in SE in the January 2008 issue of *AIDS Alert*.)**

The main reasons why the Latino community has been sidelined in HIV/AIDS research and public health focus are three-fold, Ramirez-Valles says.

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"First of all, although the Latino population is becoming a large size, Latinos still have a very limited voice in the political arena," he explains.

Secondly, when the gay white advocacy groups lobbied hard for more funding and action on the epidemic, the African American and Latino communities distanced themselves from the gay community's efforts, Ramirez-Valles says.

And lastly, there is a shortage of Latino researchers and public health officials who have the expertise to take public health leadership roles in fighting the epidemic among American Hispanics, he adds.

There have been some Latino advocacy groups working with the CDC and other government agencies to increase funding and programs directed at this population, but progress has been slow.

"I think it's terrible that in 25 years of the HIV epidemic there have been very few interventions targeting Latinos," says **Antonia M. Villarruel**, PhD, FAAN, a professor and the Nola J. Pender collegiate chair in health promotion and director of the Center for Health Promotion at the University of Michigan School of Nursing in Ann Arbor, MI.

For example, teenage Latinos largely have been ignored in HIV prevention research, Ramirez-Valles says.

This may change soon, however.

Villarruel and other investigators have developed a prevention intervention that is designed specifically for reducing HIV risk behaviors among Latino youths, ages 13 to 18. The CDC recently featured the intervention on its Web site as one of its examples under the Replicating Effective Programs. **(See Latino youth intervention, p. 136.)**

Also, the CDC is in the early stages of developing an enhanced CDC action plan to target and reduce HIV infection among Hispanics, says **Ken Dominguez**, MD, MPH, a medical epidemiologist in the division of HIV/AIDS prevention at the CDC.

The plan also aims to increase access to culturally-appropriate care and treatment, he adds.

As part of this focused attention on the epidemic's impact on Hispanics, Dominguez participated in October in a radio media campaign.

"I was on the radio from 8 a.m. to 2 p.m. on Oct. 13, talking with numerous radio stations across the country," Dominguez says. "I gave people information about the epidemic and answered questions from Hispanic radio listeners."

One of the problems public health officials have had in developing specific prevention messages for Hispanic communities is the diversity of these communities and the diversity in their modes of transmission.

A CDC chart shows that most of the Hispanics who have been diagnosed with HIV/AIDS were born in the United States, followed by Mexico, South America, Puerto Rico, Central America, and Cuba. Also, a high number who were diagnosed have an unknown place of birth.[1]

"Infection rates do vary greatly by place of birth," Dominguez says.

The CDC noted a pattern in which HIV transmission via the men who have sex with men (MSM) route was more common among Hispanics who were born in the United States, South America, Cuba, and Mexico, he notes.

"Heterosexual transmission was more common among those born in Central America and the Dominican Republic, and injection drug use was more common among those born in Puerto Rico," Dominguez adds.

Another challenge involves developing Spanish-language materials, Dominguez says.

"Cuban Spanish is different from Mexican Spanish, which is a little different from Puerto Rican Spanish," he explains. "So when you develop messages you have to put them in the correct language."

These differences make it difficult to find one intervention in which culturally appropriate materials will stay appropriate for all Latino communities.

Immigration is itself a risk factor for HIV infection, especially when only the men immigrate to the United States to find jobs.

"There's loneliness when you're on your own and traveling, and there's isolation," Dominguez says. "You're separated from your partner, and this by itself makes you more likely to develop new relationships with new partners."

A further challenge is that in the past decade, Hispanic immigrants have changed patterns and moved toward smaller towns, Midwestern and Southeastern cities, and even rural areas that previously were not destinations. This makes intervention designs more complex since the health care infrastructure that's available to Latino laborers in California is entirely different from the infrastructure that's available to Latino laborers in North Carolina, for example.

"I think it's an important issue that the history of immigration from Mexico and, especially, Central America has been longstanding in California, Texas, and the Northeast," Rhodes says. "But the trends of immigration now in the United States are very different, and the Southeast's Hispanic population is growing very rapidly."

Developing HIV prevention interventions for the various Latino populations, divided culturally by nation of birth, geographically, and divided also by risk behaviors, is challenging, the experts say.

And there is very little research available to provide the basic groundwork for intervention study.

"We have a National Institutes of Health (NIH)-funded study to look at what's going on with gay Latinos in rural North Carolina," Rhodes says. "We don't know anything about what their lives are like, and so we're exploring that right now."

For example, investigators do not even have the basic information about how to reach out to rural Latino MSM, Rhodes notes.

"It's horrible that we don't know more," he adds. "Even the little we do know is based on early experiences in more urban environments, and now that the epidemic has evolved, some of that knowledge isn't applicable."

What compounds this problem is that some existing interventions targeting Latinos, and even some research, have been lost or ignored by federal funders because the research didn't meet the gold standard of having randomized, controlled trials, Ramirez-Valles says.

"I was one of the first researchers to publish an intervention for Latino gay men, but I didn't do a randomized, controlled trial, so when I asked the CDC to look at it, they wouldn't because it wasn't a randomized, controlled trial," he says.

"But there was some information you could learn from this research," Ramirez-Valles says. "By having this gold standard it eliminates a lot of knowledge we have about interventions, and it prevents us from moving forward."

The CDC recognizes that its standards for recognizing interventions poses challenges to researchers and community-based organizations, Dominguez says.

"We're in the process of bringing more of those interventions out into public use," Dominguez says. "They take a while to study and evaluate and see that they're truly effective." ■

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Latinos and HIV epidemic

Intervention "effective program" for Latino youth

Intervention works equally well with boys and girls

Too few scientifically tested HIV prevention interventions target Latino men and women, and even fewer are specifically designed for Latino youth, an expert says.

So it should interest HIV providers and service organizations that there is a new intervention that targets precisely that population, and it recently has been designated as a part of the effective programs for replication by the Centers for Disease Control and Prevention (CDC) of Atlanta, GA.

Called Cuidate! A culturally-based program to reduce HIV sexual risk behavior among Latino youth, the intervention is based on social cognitive theory and the theories of reasoned action and planned behavior.[1]

The intervention is a replication project itself, since researchers built on the work of the "Be Proud, Be Responsible" intervention that is designed for African American adolescents, says **Antonia M. Villarruel**, PhD, FAAN, professor and the Nola J. Pender Collegiate Chair in Health Promotion and director of the Center for Health Promotion at the University of Michigan's School of Nursing in Ann Arbor, MI.

Villarruel researched the cultural influences among Latinos in the United States, to understand how they influence safer sex behavior.

For example, studies have shown that Latino youth are more likely to delay sexual intercourse than are their non-Latino peers, Villarruel notes.

"But when Latino adolescents do have sex, they are less likely to use contraception or condoms, and that's the behavior we have to change," she says. "We need to support what is their strength and teach them other skills to use when they are sexually active."

A randomized, controlled trial involving more than 600 youths found that the HIV risk-reduction intervention had significant effects on reducing sexual intercourse among youths than did the health-promotion intervention, which was the comparison intervention.[1]

Also, the HIV risk-reduction intervention resulted in adolescents reporting having fewer multiple partners, and they reported more consistent condom use.[1]

These positive findings were true for both male and female youths, Villarruel says.

Some people would be surprised that there was no difference between boys and girls because they advocate for separate HIV prevention programs for girls, she notes.

But with this six-module group session intervention, the inclusion of both genders appeared to have a positive impact on the youths.

"I think it was powerful having both genders there, and that's what the kids said," Villarruel says. "They said they preferred having mixed groups."

For example, in one session, the discussion centered on condom use, which is always a difficult topic for young women to discuss with their partners. In this session, a very attractive teenage boy told the group that he would respect a girl who asked him to use a condom because it would mean the girl was looking out for him, Villarruel recalls.

Hearing from a male peer that condom discussions are okay made it far more likely that the girls would initiate condom discussions with their partners in the future than if the girls were simply told by an adult that it was okay to ask boyfriends to use condoms, she adds.

Investigators are working on developing a training manual, facilitator curriculum, technical assistance, and other material that can be shared with other organizations or clinics that would like to use this intervention, Villarruel says.

The intervention is geared toward youths, ages 13 to 18, and the community workers who served as facilitators were trained to follow the curriculum in providing the six, 50-minute modules to mixed gender groups. The modules were provided in either Spanish or English.[1]

The facilitators did not need more than a high school education, but they had to have basic skills in communicating with teenagers about sexual behavior and condom use, Villarruel says.

Facilitators received 2.5 days of training, which included building skills in providing a supportive and open environment, Villarruel says.

"We taught them how to deal with adolescents; how to be concrete, and to understand

why we're repetitive throughout the curriculum," she says. "We taught them how to provide an open environment in which youths can ask questions and are not attacked within the group."

"Using the program is low-cost, with expenses being investments in training and time for persons to deliver the program," she notes. "I think the training is very effective as well, and we've had a good deal of fidelity to the intervention."

Researchers recruited youths, mainly of Puerto Rican descent, from Philadelphia high schools and community-based organizations, and eligibility was based on their being self-identified as Latino, ages 13 to 18, and having provided assent and parental consent.[1]

The health-promotion intervention focused on diet, exercise, and physical activity, as well as cigarette, alcohol, and drug use.[1]

The HIV prevention intervention focused on HIV transmission and behaviors that could prevent infection, Villarruel says.

"We share the story of the epidemic and focus on the transmission of HIV and building skills to protect themselves," she says. ■

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IDU researchers face myriad of ethical dilemmas

IRBs may raise the wrong concerns

HIV researchers who work with study participants who are injection drug users (IDUs) sometimes find themselves facing challenges that wouldn't be issues in the typical HIV trial.

For example, research has overwhelmingly shown that the most effective prevention method for IDUs is a needle exchange program, and yet investigators are prohibited from spending federal research funds on needle exchange.

"It's sad that despite overwhelming evidence that these programs reduce HIV, there's still a federal ban," says **Kaveh Khoshnood**, PhD, an assistant professor of epidemiology and public health in the Yale School of Public Health in New Haven, CT.

This prohibition posed a major ethical problem during a study protocol in which investigators were collecting used syringes and testing them for HIV and hepatitis infection, Khoshnood notes.

When the study subjects turned in their used syringes, they asked researchers, "I'm giving you my syringe, so what am I going to do?" Khoshnood recalls.

This was an unanticipated ethical dilemma that arose, and investigators were put in a bind; the study was federally funded, so they couldn't use the research grant to fund clean needles that would be given back to the study participants.

"If we left them in a situation where for their next drug injection, they're without a syringe, then they'd borrow one from someone else," Knoshnood explains. "That's a tricky issue."

Ethically, once they were aware of the fact that the research study could be placing trial subjects at a greater risk of becoming infected with HIV or hepatitis, investigators were ethically bound to do something about it. Yet, their most logical course of action was prohibited by the study sponsor.

So they found a way around the federal ban by using both personal and, where it was available, state and local funds to buy clean needles for an exchange, Khoshnood says.

"In some site there were needle exchange programs offered by the state," he adds. "In one location, needle exchange was not allowed, so investigators decided to use their personal funds to make sure drug users have access to clean syringes."

This was the only way they could make sure they didn't break the law or endanger the life of their study subjects, he says.

Khoshnood first became interested in the ethical issues surrounding studies with IDU populations after years of HIV prevention research.

"I've been doing HIV prevention research for about 15 years, and to be honest, in the beginning I wasn't really thinking about ethical issues because we felt the research was so important," Khoshnood says.

"Then I began noticing ethical issues and feeling frustrated that I didn't have answers to questions and couldn't identify in the literature discussions about these issues," Khoshnood says. "A lot of ethical issues that came up with this population is because they're involved in illegal behavior."

There are less dramatic concerns when dealing with an IDU study population, as well.

For instance, any breach of confidentiality has greater implications among IDUs than it does for most other potential research participants.

If a drug user's family finds out about his or her IDU status, then it could have severe economic and emotional repercussions. Or if an injection drug using woman participates in a study and becomes pregnant, any disclosure of her pregnancy and drug use could result in her being arrested and charged with endangering her unborn child in some states, Khoshnood says.

IRBs sometimes fail to anticipate those examples of ethical concerns, but they likely will ask researchers about others, including the informed consent process and the payment of subjects for their participation.

Research subjects who are obviously high from a drug or are going through withdrawal symptoms may have an impaired ability to consent to a study, Khoshnood says.

But if the subject's drug use does not impair his or her ability to think and function, then the ability to provide informed consent may not be compromised, he adds.

"The way we deal with this is pragmatic," Khoshnood says. "If someone is so high they can't think straight, we say, 'Thanks for coming today, but today is not a good day for us to do this. Why don't you come back tomorrow?'"

An IRB might think that anyone who at any time is using an illegal substance is not able to provide acceptable informed consent, but Khoshnood disagrees with this philosophy.

"An IRB member's opinion about drug users' capacity to consent is not based on science," he says.

IRB members may put all illicit drugs into the same category when the pharmacology is quite varied, he adds.

Likewise, all drug users are not the same. Some have fulltime jobs and homes and families, Khoshnood says.

"Clearly, they're making decisions every day," he adds. "They're driving buses and taking care of us in hospitals, educating our kids, and they're everywhere."

When Khoshnood has asked IRB members whether they have any experience with protocols that enroll drug users, they typically say they don't receive these protocols very often.

"What they fail to recognize is that if they're looking at a chronic pain protocol, they will be enrolling drug users in that study whether it's explicitly stated or not," Khoshnood says. "Many of the research protocols submitted to the IRB may not have drug use in the title or in the protocol, but our experience is that drug users end up in all kinds of studies."

IRBs also may have some preconceived opinions about how IDUs are compensated for their study participation.

Many IRBs express discomfort with an investigator making cash payments to IDU subjects, even when the amount is minimal, Khoshnood says.

Since they often don't express the same discomfort with paying college students cash, even when the money could be used to buy beer on the weekend, this would seem to be part of the stigma or prejudice against IDU populations.

"If you offer someone hundreds of dollars to do a research interview, then, yes, it could be undue inducement," Khoshnood says. "The main concern is when individuals may offer to participate in a study that involves significant risk against their better judgment because of the cash payment."

But this is not a problem unique to drug users, he notes.

"I feel like this statement about drug users being desperate and shouldn't participate in a study that pays cash speaks more to the discomfort of IRB members," Khoshnood says.

It's also unrealistic of IRB members to think they can control a drug user's motivations by having the researcher offer gift certificates instead of cash for participation, he adds.

"They can exchange gift certificates for money, but only 60-70 percent of the value, so you're short-changing them," Khoshnood says.

"I have no problem with giving cash payments to people with drug abuse issues," he adds. "I do have problems if it's an excessive amount and if the protocol is more than minimal risk."

Also, it's not a fair assumption that all drug users will enroll in research solely for the compensation, Khoshnood says.

One study in Australia found that drug users provided varied reasons for participating in research, he says.

While some said the money was a significant factor, others said they would participate because they wanted to give something back to society, and still others cited a desire to have access to medical care, Khoshnood says. ■

Resource:
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Effects of Antiretroviral Agents on Lipid Panels

Special Report

***By Jessica C. Song**, MA, Pharm D*
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HIV-infected patients have been shown to experience hypertriglyceridemia and/or hypercholesterolemia as a result of their highly active antiretroviral therapy (HAART), along with natural disease progression.[1,2] In particular, dyslipidemia associated with HAART therapy has been reported in up to 70-80 percent of HIV-infected individuals. Hypertriglyceridemia appears to be especially problematic in patients receiving protease-inhibitor-based regimens, with the highest frequencies seen in patients treated with ritonavir-based HAART regimens.[1] Because of the potential pharmacological interactions with certain antiretroviral agents, many clinicians tend to under-treat HAART-associated dyslipidemias. However, recent literature reports have shown that young HIV-positive individuals receiving protease inhibitors may be at increased risk of experiencing premature coronary artery disease.[1] At present, despite the relative lack of treatment recommendations for dyslipidemic HIV-infected patients, most HIV specialists are of the opinion that the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) guidelines could be applicable to their patient population.[2]

The updated NCEP ATP III guidelines highlighted significant changes in the treatment of high-risk patients, as the panel recommended more intensive LDL-C lowering in very high-risk patients to a goal of less than 70 mg/dL.[3] Patients who are classified as very high-risk have established CVD plus one of the following: multiple major risk factors, especially diabetes; severe and poorly controlled risk factors, especially cigarette smoking; multiple risk factors of the metabolic syndrome, especially TG (triglyceride) 200 mg/dL, non-HDL-C 160 mg/dl, and HDL-C (high-density lipoprotein cholesterol) < 40 mg/dL; or acute coronary syndrome (ACS).

Lipid-lowering treatment options for HIV-infected patients include certain hydroxymethyl-coenzyme A reductase inhibitors (statins), fibric acid derivatives, niacin, ezetimibe, and fish-oil supplements, either provided as monotherapy, or in combination, depending on the specific lipid disorder.[2] Bile acid-binding resins (cholestyramine, colestipol, colesevelam) should not be used by HIV-infected patients, as absorption of antiretrovirals may be impaired, and these agents have the potential to increase serum triglyceride levels.[2]

Statins are commonly used antihyperlipidemic agents that are well tolerated and relatively safe. The most common adverse effects are headache and gastrointestinal-related (i.e., abdominal pain, dyspepsia, nausea), but myopathy and hepatotoxicity have also been of some concern.[4] Statin-induced myotoxicities are dose-related and related to the lipophilicity of the drug.[5,6] Other drug-related properties that may increase risk of myopathy are high systemic exposure, high bioavailability, limited protein binding, and potential for drug-drug interactions metabolized by cytochrome p450 (CYP) pathways (particularly CYP 3A4).[6] While myalgia represents the most common myotoxic event1, myositis and rhabdomyolysis have been reported to cause significant morbidity and mortality worldwide.[5,6]

Fibric acid derivatives represent the most potent triglyceride-lowering agents, but exert variable effects on LDL-C and modest effects in regards to increasing HDL-C. Unlike statins, fibric acid derivatives do not inhibit CYP3A4, but are more likely to inhibit CYP2C8/2C9.[7-10] Niacin derivatives have been shown to be the most potent HDL-raising agents, and also provide moderate reductions in LDL-C and serum triglyceride concentrations.[11-13] However, despite the availability of extended-release products that have improved side effect profiles, the initial flushing reaction associated

with niacin use has required the use of a gradual dose-titration process and the use of prophylactic aspirin. Furthermore, because of its potential to increase blood glucose concentrations during the initial stages of dose titration, healthcare providers may need to increase the doses of hypoglycemic agents in patients starting niacin therapy.[14-15] Ezetimibe has been shown to primarily decrease LDL-C, but to a lesser extent than statins and niacin, thereby limiting its use to providing additional LDL-C reductions in patients receiving other LDL-C-lowering agents.[16-17] Fish oil supplements are available as nonprescription products and as a prescription drug. Reductions in serum triglyceride concentrations with fish oil supplements have been shown to be comparable to the reductions associated with fibric acid derivative use, but some patients may experience increases in LDL-C concentrations.[18-19]

The purpose of this two-part review is to 1) review the drug-interaction potential between antiretroviral agents and lipid-lowering agents, 2) review the propensity of antiretroviral agents to cause hyperlipidemia disorders, 3) review the efficacy and safety profiles of lipid-lowering agents, and 4) develop an algorithm for the treatment of various HAART-associated hyperlipidemia disorders. The review featured in this issue will focus on the first 2 objectives. ■

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Screening for Abacavir Hypersensitivity

***By Stan Deresinski**, MD, FACP*
Clinical Professor of Medicine, Stanford, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, is Editor for Infectious Disease Alert.

***Source:** Chui CK, et al. Simple screening approach to reduce B*5701-associated abacavir hypersensitivity on the basis of sequence variation in HIV reverse transcriptase. Clin Infect Dis 2007; 44:1503-1508.*

***Synopsis:** A major drawback to the routine use of abacavir in the treatment of HIV-1 infection is the occurrence of a hypersensitivity reaction in as many of 8% of recipients of this nucleoside analog reverse transcriptase inhibitor. Individuals carrying the HLA class I allele B*5701 have a >100-fold increased risk of such hypersensitivity reactions. T Direct screening for the presence of HLA-B*5701 is an alternative but*

expensive. The authors describe an alternative, relatively inexpensive screening method.

The immune response to HIV exerts a selective pressure, just as do antiretroviral drugs. Cytotoxic T lymphocytes (CTL) that recognize HLA class I-restricted viral epitopes expressed on the surface of infected cells exert a pressure on these epitopes. Mutation in these viral epitopes may allow escape of HIV-1 from the CTL immune response. Just as viral mutations allowing escape from the action of antiretroviral drugs often follow a predictable path, similar predictable sequences of HLA-restricted epitope mutations may also occur so that this aspect of viral evolution may potentially be predictable on the basis of the HLA profile of the infected host.

As a consequence of the above, Chui and colleagues have examined the hypothesis that identification of a signature CTL-driven immune escape that resides within the viral reverse transcriptase (RT) may represent a simple means, available by routine HIV-1 genotypic assays used to screen for antiretroviral associated resistance mutations, capable of abacavir hypersensitivity risk screening. They set out to demonstrate that detection of a HLA-B*5701 amino acid change at HIV-1 RT codon 245, which is known to lie within the epitopes restricted to this HLA allele, predicts the presence of HLA-B*5701 and, therefore, an increased risk of hypersensitivity to abacavir.

The relationship between codon 245 variation, the presence of HLA-B*5701, and premature abacavir discontinuation was investigated in 392 HIV infected adults receiving their initial antiretroviral therapy. The sensitivity of codon 245 mutations in predicting the presence of HLA-B*5701 was 96% and its specificity was 75%, while the positive and negative predictive values were 20% and 99.6%, respectively. This association remained strong even after the patients had received antiretroviral therapy. The presence of codon 245 substitutions was significantly associated with premature discontinuation of abacavir therapy.

Thus, the inclusion of RT codon 245 in genotypic assays meant to assess antiretroviral resistance could provide an effective means, without significant added cost, of screening for risk of hypersensitivity to abacavir in North America and Europe where clade B virus are prevalent and HLA-B*5701 is present in up to 10% of whites. ■

FDA Notifications

Revised guidelines for pregnant women

The Public Health Service Task Force 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 have undergone a complete revision and reorganization to reflect important new information, and to make them more user-friendly. The guidelines have been restructured into principles for medical management of the woman and her infant during the antepartum, intrapartum, and postpartum period, including panel recommendations for each section.

Changes to the report include the following:

- Due to contamination with ethyl methane sulfonate (EMS), nelfinavir is no longer recommended for use in pregnant HIV-infected women.
- New sections on antepartum management of HIV-infected pregnant women in special situations, including HBV and HCV co-infection.
- New information on ARV drug choice and continuation during labor, and management of women not receiving antepartum ARVs.
- New sections on choice and management of infant ARV prophylaxis.
- Two new tables: "Results of Major Studies on ARV Prophylaxis to Prevent Mother-to-Child HIV Transmission" and "Clinical Scenario Summary Recommendations for ARV Use by Pregnant HIV-Infected Women and Prevention of Perinatal HIV-1 Transmission in the U.S."
- Updated information for emtricitabine, tenofovir, amprenavir, atazanavir, lopinavir/ritonavir, nelfinavir, maraviroc, and raltegravir.
- Updated information for tenofovir, saquinavir-HGC, atazanavir, nelfinavir, maraviroc, and raltegravir.
- The updated guidelines are available in the "Guidelines" section of the AIDS info Web site under " Perinatal Guidelines." You can download the guidelines or can request to receive them by e-mail or regular mail on the AIDSinfo Web site.

FDA draft guidance is\about new drug development

On Oct. 25, 2007, the FDA published draft guidance intended to assist the pharmaceutical industry and other investigators who are conducting new drug development in assessing the potential for a drug to cause severe liver injury (i.e., fatal, or requiring liver transplantation). The document may be of interest to those involved in drug development related to HIV/AIDS, although the guidance is broader in scope.

In particular, the guidance addresses how laboratory measurements that signal the potential for such drug-induced liver injury (DILI) can be obtained and evaluated during drug development. This evaluation is important because most drugs that cause severe DILI do so infrequently; typical drug development databases with up to a few thousand subjects exposed to a new drug may not show any cases. Databases do, however, often show evidence of a drug's potential for severe DILI if the clinical and laboratory data are properly evaluated for evidence of lesser injury that may not be severe, but may predict the ability to cause more severe injuries.

The guidance describes an approach that can be used to distinguish signals of DILI that identify drugs likely to cause significant hepatotoxicity from signals that do not suggest such a potential. The guidance does not address issues of preclinical evaluation for potential DILI, nor the detection and assessment of DILI after drug approval and marketing.

FDA is soliciting comments on the proposed guidance during the next 60 days. Comments and suggestions regarding this draft document should be submitted before Dec. 24, 2007, to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, room 1061, Rockville, MD 20852. Comments should be identified with docket number 2007D-0396.

You can view the draft guidance on the FDA web site at http://www.fda.gov/cder/guidance/7507dft.htm. The Federal Register Notice can be found at http://www.fda.gov/OHRMS/DOCKETS/98fr/E7-21060.htm.

Tentative approval for generic stavudine, oral solution

On Oct. 29, 2007, FDA granted tentative approval for a generic formulation of stavudine for oral solution, manufactured by Cipla, Limited, of Mumbai, India.

Stavudine is a Nucleoside Reverse Transcriptase Inhibitors (NRTI) indicated for used in combination with other antiretroviral agents in the treatment of HIV infection. This is the second tentatively approved generic version of the approved product, Zerit for oral solution, manufactured by Bristol-Myers Squibb. This child-friendly product is indicated for use in pediatric patients with HIV from birth through adolescence.

"Tentative Approval" means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, even though it may not yet be marketed in the U.S. because of existing patents and/or exclusivity rights. However, tentative approval does make the product eligible for consideration for purchase under the President's Emergency Fund for AIDS Relief, commonly referred to as the PEPFAR program.

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

FDA approves NDA for Lexiva

On Oct. 12, 2007, the Food and Drug Administration (FDA) approved a supplemental new drug application for Lexiva (fosamprenavir calcium; FPV) Oral Tablets, adding a new indication for once-daily dosing of 1400 mg of Lexiva with 100 mg ritonavir for the treatment of HIV infection in therapy-naïve adults. The approval was based on a bioavailability study demonstrating that this dosing regimen produced drug levels bracketed within those of the already approved 1400 mg once daily plus ritonavir 200 mg once daily regimen, and the Lexiva1400 mg twice daily dosing regimen.

Lexiva is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection, and is distributed by GlaxoSmithKline, Research Triangle Park, NC.

Accelerated approval for raltegravir tablets

The Food and Drug Administration (FDA), on Oct. 12, 2007, granted accelerated approval for raltegravir tablets (400 mg) for treatment of Human Immunodeficiency Virus (HIV)-1 infection in combination with other antiretroviral agents. Raltegravir, sold under the trade name Isentress, is the first agent of the pharmacological class of antiretroviral agents known as HIV integrase strand transfer inhibitors, commonly referred to as integrase inhibitors. They are designed to slow the advancement of HIV-1 infection by blocking the HIV integrase enzyme that the virus needs in order to multiply.

When used with other anti-HIV medicines, raltegravir may reduce the amount of HIV in the blood and may increase white blood cells, called CD4+ (T) cells, that help fight other infections.

Raltegravir received a priority review by the FDA. The review and approval of the New Drug Application was completed in within six months.

FDA's approval of raltegravir is based on efficacy and safety data from two double-blind, placebo-controlled studies (BENCHMRK 1 and BENCHMRK 2) in 699 highly antiretroviral treatment-experienced HIV-1 infected adult patients (16 years or older, with documented resistance to at least 1 drug in each of 3 Classes (NNRTIs, NRTIs, PIs) of antiretroviral therapies). Four hundred sixty-two patients used the recommended 400 mg dose twice daily in combination with other currently available HIV medications; 237 patients received a placebo in combination with other currently available HIV medications. The mean changes in plasma HIV-1 RNA from baseline were -1.85 $\log_{10}$ copies/mL in the raltegravir 400 mg twice daily arm and -0.84 $\log_{10}$ copies/mL for the control arm. The mean increase from baseline in CD4+ cell counts was higher in the arm receiving raltegravir 400

CE/CME *questions*

35. In the United States in 2007, what percentage of people who received an AIDS diagnosis were Hispanics?
A. 12.7 percent
B. 14.4 percent
C. 18.9 percent
D. 22.1 percent

36. Which of the following is true about Latino youth in the United States?
A. Latino youth are more likely than non-Latino peers to delay sexual intercourse.
B. Latino youth are less likely than non-Latino peers to use contraception or condoms.
C. Both A & B are true
D. None of the above is true

37. Which of the following is an ethical dilemma sometimes faced by researchers dealing with injection drug using (IDU) study subjects?
A. If investigators take the subjects' used needles and do not replace them due to a federal ban on needle exchange, then they may be placing subjects' lives at risk of HIV infection.
B. If IDU subjects are paid a large sum of cash for participating in a high-risk study, it might constitute an undue inducement.
C. If IDU subjects are actively using and noticeably high when being informed about the study, it might mean they are not capable of informed consent.
D. All of the above is true

Answers: 35. (c); 36. (c); 37. (d)

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mg twice daily (89 cells/mm^3) than in the control arm (35 cells/mm^3).

The most common adverse events reported with raltegravir were diarrhea, nausea, and headache. Blood tests showed abnormal elevated levels of a muscle enzyme in some patients receiving raltegravir. Caution is advised when using raltegravir in patients at increased risk for certain types of muscle problems, such as patients taking other medications that can cause muscle problems.

Raltegravir has not been studied in pregnant women. Women who are taking HIV medications when they get pregnant are advised to ask their physician about registering with the Antiretroviral Pregnancy Registry.

As with other treatments for HIV, patients taking raltegravir may still develop infections, including opportunistic infections or other conditions that may develop in patients living with HIV-1 infection, and can still pass the virus on to others through sexual contact, sharing needles, or being exposed to blood.

The long-term effects of raltegravir are not known at this time, and its safety and effectiveness in children less than 16 years of age has not been studied.

Raltegravir is distributed by New Jersey-based Merck & Co., Inc.

Tentative approval to Aptivus for combination ART

On Oct. 4, 2007, FDA granted traditional approval to Aptivus (tipranavir), for combination antiretroviral treatment of HIV-1 infected adults with evidence of viral replication, who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor. Aptivus was granted accelerated approval on June 22, 2005, based on analysis of plasma HIV-1 RNA levels in two controlled phase 3 studies, of 24 weeks duration, of Aptivus/ritonavir. The traditional approval is based on continuation of the RESIST trials through 48 weeks and beyond, confirming durability of the virologic response. Aptivus is a product of Boehringer Ingelheim. ■

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.

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