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IN THIS ISSUE

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MARCH 2010
VOL. 25, NO. 3 • (pages 25-36)

Graying plague: By 2015 over half of HIV in U.S. will be in those over 50

Late diagnoses contribute to problem

Contrary to stereotypes, HIV in America is showing more than a touch of gray.

Researchers are studying the impact of HIV on the aging process as HIV demographics show the disease's impact on people ages 50 years and older is on a sharp rise. This demographic uptick is coupled with increasing evidence that HIV infection ravages the body, adding years and decades to one's actual age health-wise — even with treatment.

Together, the two trends make it increasingly important that HIV clinicians focus on both comorbidity prevention and early detection and treatment with their older patients.

Nearly one-quarter of Americans with HIV infection are 50 years or older, according to the most recent Center for Disease Control and Prevention surveillance data from 33 states with HIV reporting.[1,2]

Also, older Americans account for 15% of new HIV/AIDS diagnoses, 29% of persons living with AIDS, and 35% of all deaths of people with AIDS.

Projections show this trend could increase until people over age 50 account for half of HIV infections in the United States by 2015.

From 14 to 19 years ago, the CDC reported that 11% of all AIDS cases were among people ages 50 and up. While successful antiretroviral therapy (ART) has contributed to people living into middle-and-older age with HIV, there also is an increasing trend of older people becoming infected through the same high-risk behaviors that impact younger Americans.

Studies also show that older Americans often are sicker when they are first diagnosed with HIV infection, and their immune system's ability to bounce back is limited once they are treated with ART.

"At least once a month I have a patient who is 50 or above and being diagnosed with HIV infection," says **Beau Ances**, MD, PhD, assistant professor of neurology at Washington University in St. Louis.

"It's becoming more of a norm," he says. "Usually these people have had the infection for a longer period of time and have not gone into care, so they have two knocks against them."

Their virus is not well controlled, their CD4 cell counts are low, and their ability to fight infection is not as good, Ances adds.

AIDS Alert® (ISSN 0887-0292), including **AIDS Guide for Health Care Workers**®, **AIDS Alert International**®, and **Common Sense About AIDS**®, is published monthly by AHC Media LLC, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to *AIDS Alert*®, P.O. Box 740059, Atlanta, GA 30374.

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Societal, individual misperceptions

Both societal and individual misperceptions contribute to a later diagnosis among older people, clinicians say.

"There's still a stereotype of youth developing HIV infections," says **Nur Onen**, MBChB, an instructor in internal medicine in the infectious diseases division of Washington University School of Medicine in St. Louis, MO.

"People think of drug users or men who have sex with men (MSM)," she adds. "Also, younger people are more inclined to do HIV testing, so we are increasingly seeing older people who are diagnosed after considerable delay."

Delayed diagnosis is particularly troubling for older HIV patients, she says.

"We see symptoms occurring in the older population because they are tested much later in illness, and some have very severe immunosuppression, and they either have an AIDS-defining moment or a very low CD4 cell count," Onen explains. "This poses another problem because we have to get their CD4 count up as high as we can, and it's harder for the older population to get the CD4 count up to a normal range."

Also, older HIV patients have a higher prevalence of frailty, even if they're under age 65, Onen says. **(See story on HIV and frailty, p. 28.)**

"Once they enter the frailty state, it's very hard to reverse and has a lot of negative implications on morbidity and mortality outcomes, including deaths, falls, etc.," Onen says.

The key is to identify older HIV-infected individuals earlier in their disease, and this means educating the public about the risk older, sexually-active adults face.

As older Americans divorce or lose their partners, they become engaged in sexual relationships, sometimes for the first time in decades, and they often are unaware that some things have changed, notes **Diane Zablotsky**, PhD, an associate professor of sociology at the University of North Carolina at Charlotte.

An expert and researcher on aging and HIV, Zablotsky has found that older women, in particular, might not know how to negotiate condom use. Perhaps they became sexually active in the years after oral contraceptives first were introduced, and then were married when HIV was identified. So they have never used condoms and need help in improving their comfort level with discussing condom use with partners, she explains.

Also, HIV prevention campaigns need to include older faces in posters, brochures, and advertisements.

"Don't let information campaigns reinforce the stereotype that sexual risk and sexual behavior end at mid-life," Zablotsky says. "We should broaden [older] people's knowledge and open them to the idea of risk prevention."

The CDC's four-year-old guidelines for providers to offer opt-out HIV testing for everyone between ages 13 and 64 might have a positive impact, but some pressures fueled by stigma and lack of knowledge continue to hinder the older set from receiving optimal screening and treatment, experts say.

"The main gist of the CDC's recommendations is to stop people from being driven by stereotype beliefs and to test no matter how old you are," Onen says.

Compounding factors

There are other issues HIV clinicians need to consider when dealing with older patients, and one has to do with the disease's impact on cardiovascular, neurological, and other diseases.

For instance, a new study on HIV and its impact on the brain has found that HIV-positive patients have functional brain demands that are equivalent to those of HIV-negative people who are 15 to 20 years older.[3]

"If you're HIV positive, and you're older, you are really taxing your system," Ances says.

A 50-year-old who is HIV positive has similar cerebral blood flow as a 75-year-old who is not infected with HIV, Ances says.

"So they're aging, and the virus also is aging them, and the question is 'Why?'" he adds. "We really don't know the answer."

Ances and co-investigators used functional imaging measures as possible biomarkers of disease. The technique measured blood flow in the brain, and the study compared an HIV cohort with a non-infected cohort, finding that HIV infected persons consistently had lower blood flow than their same-age, non-infected peers.[3]
(See story about HIV and premature aging, p. 29.)

Older people diagnosed with HIV also are at greater risk for cardiovascular disease and mortality, another new study shows.[4]

The study found that people of all ages who were infected with HIV had a mortality risk that was three-fold higher during a five-year period than the mortality risk of non-HIV infected people of similar demographics and cardiovascular factors. This included people who were taking antiretroviral medications.

"We mainly looked at demographic risk factors, including age, race, and cardiovascular risk factors, including cholesterol, smoking, and blood pressure," says **Leslie Cockerham**, MD, an internal medicine resident physician at the University of California - San Francisco (UCSF).

"The main thing that came out was how older age impacted mortality," Cockerham says. "We looked at all of these factors among HIV-infected participants, who were a wide range of ages from 19 to 76 years, and when we looked at risk of death, the risk increased 60% with each decade of aging."

Mortality rates increased among HIV-infected people with lower CD4 cell counts, as anticipated, Cockerham says.

But there also was an increased risk of death due to non-HIV causes, including malignancy and cardiovascular disease, she notes.

"HIV is not only a disease of immunosuppression, but also of inflammation," Cockerham says. "It could be that some of the risk is due to chronic inflammatory diseases."

Cockerham's co-investigators have worked on another study that looks at how inflammation might be impacting mortality among HIV patients.

"It's still under investigation, but their speculation is that perhaps viremia has led to inflammatory changes, and these are contributing to mortality," Cockerham says. "There are increased rates of arteriosclerosis and cardiovascular disease."

HIV-infected people also have a higher rate of lung cancer, she notes.

"Whether it's due to inflammation or other factors, it's hard to know," Cockerham says. "Our study group has done a follow-up paper that looks at the roles of mortality risk in the same cohort — this definitely needs to be studied more."

Increased risk of comorbidities

Other new research has found these increased health risks in older HIV-infected populations:

- Investigators found that stavudine neuropathy risk increases with patient age and height, so clinicians should prioritize these patients for alternative agents.[5]

• HIV infection was associated with increased risk for some types of skin cancer among elderly adults.[6]

• Older HIV-1 infection in patients older than 70 years is associated with lower CD4 counts, comorbidities, and co-medication, and is suggestive of a late diagnosis.[7]

• Older HIV patients have more comorbidities than younger patients, and their disease is compounded by the incidence of cardiovascular disease, malignancies, depression, cognitive impairment, frailty, and depression.[8]

When HIV clinicians work with older patients they often find it is difficult to determine which symptoms and comorbidities are due to the disease or natural aging, Onen notes. **(See study on treatment of aging HIV patient, p. right.)**

"You're dealing with a person who has lived a lifetime, and we're seeing an impact on their lifestyle choices, including tobacco use, drug use, and dietary behaviors," Onen says. "We often have to deal with their HIV infection and a lot of other comorbidities as well, and you can't always tease out which is the result of HIV-uncontrolled viremia for years and low CD4 cell counts and immune dysfunction with aging."

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Rapid aging, frailty common in older HIV

Prevalence is 9% in one study

Frailty is not a diagnosis that typically comes to mind when clinicians examine HIV patients, but with increasing numbers of older people being diagnosed or younger patients growing old with the disease, it should be on HIV clinicians' radar.

"HIV infection is really a disease of accelerated aging," says **Nur Onen**, MBChB, an instructor in internal medicine in the infectious diseases division of Washington University School of Medicine in St. Louis, MO.

"A new concept we're looking at is the concept of frailty in HIV-infected individuals, and this is occurring in individuals who are under 50 years of age," Onen says.

Onen's research reported a frailty prevalence of 9% among 445 persons attending Washington University HIV Clinics between June and December, 2008.[1]

The study identified these independent predictors of frailty: unemployment, higher number of comorbid conditions, past opportunistic infections (OIs), higher depression severity score, receipt of antidepressants, and lower serum albumin.

Interestingly, the study did not find that age was an independent predictor.

"Our HIV outpatient population had a mean age of 42 years," Onen says. "Patients became prematurely frail."

Clinicians who observe frailty in HIV patients should be on the look out for higher blood pressure and bone density loss, she notes.

In fact, bone density screening should be routine for HIV patients older than 50 years of age, as recommended by the National Osteoporosis Foundation of Washington, DC, Onen says.

Patients can be screened for frailty with the Health Status Form (HSF), which notes four variables that best predict elderly members of

the general population who are most at risk of frailty. These variables are age, indicating that health conditions interfered with daily activities, needing assistance for bathing, and needing assistance for taking medications.[2]

Onen also suggests clinicians use criteria for physical frailty diagnosis published by researcher **Linda Fried**, MD, who looked at weight loss, low physical activity, and exhaustion as signs of frailty.

Fried's work, published in the Cardiovascular Health Study, has associated frailty with these characteristics: diminished energy, systems dysfunction, such as diminished heart rate variability and immune function, low testosterone and IGF-1 levels, elevated cortisol, insulin, and glucose levels, and multisystem dysregulation.[3]

"What we have done is look at her criteria in HIV-infected population, and, yes, typically these patients don't have a lot of muscle mass, are thinner, and look frail," Onen says.

"We looked at a mixture of people and found that these characteristics predict frailty: a greater number of premorbid conditions, distinct from comorbidity, a history of OIs, higher depression scores, being on an antidepressant, and higher unemployment."

Onen's frailty and HIV patients study also found a high prevalence of neuropsychiatric comorbidity among frail patients and the suggestion that these increase with age.

Frailty also was associated with adverse socioeconomic and clinical outcomes. The study concludes that HIV clinicians likely will see increasing numbers of frail patients in coming years as the nation's HIV patient population ages.[1]

Frail patients cost more to treat, Onen says. "They have greater hospitalization rates for nonelective admissions, and five-fold longer inpatient stays."

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Research takes close look at HIV's impact on brain of aging patients

Imaging shows reduced blood flow

Research consistently has shown that HIV-positive patients perform cognitively at lower levels than their uninfected peers, an expert says.

"Some studies have looked at aging and cognitive performance and found that when compared with other patients, a 55-year-old HIV positive person with zero to four years of infection was equal to a 65-year-old HIV negative person," says **Beau Ances**, MD, PhD, assistant professor of neurology at Washington University in St. Louis.

However, the physiology of this difference has been less studied. Ances and co-investigators sought to find a noninvasive way to compare brain function in HIV positive people to HIV negative people.

The research led to the finding that at any given age the baseline cerebral blood flow value for HIV-positive subjects were equivalent to those for HIV-negative subjects who were 15 years older.[1]

"I was very interested in a technique I've been working on to measure blood flow in the brain," Ances says. "We tag red blood cells in the neck and wait a period of time and then measure how many tagged at the neck reached a certain slab of the brain."

This process can be done without an injection, he says.

The study performed imaging on a 3 Tesla whole-body system using an 8-channel receive head coil. Then researchers used an inversion recovery prepared 3-dimensional fast spoiled pulse sequence to obtain high-resolution structural images.[1]

"We excited the molecules in the neck and waited for them to get to the brain," Ances explained. "Then we measured how much blood flow is going to the brain."

It's known that as people age their blood flow decreases, partially due to arteriosclerosis, vessels that are less spongy, strokes, and other factors, he notes.

Comparing HIV-positive to HIV-negative subjects, the study found that HIV-positive people had the blood flow of HIV-negative people years and sometimes decades older.

Study inclusion/exclusion criteria had people screened for a clear-cut medication use status. That is, subjects either had not been taking medications for at least a few months, or they had been on medication for at least three months, Ances says.

Their findings suggested that antiretroviral therapy helps to restore blood flow, but not to the extent of people who are HIV negative, he says.

"It could mean that medications give them a boost and make things better, but after time they go down again," Ances explains. "You don't get back to your baseline of what a person should be for that age."

This research suggests that HIV clinicians have yet another reason to start HIV positive patients earlier on their medication therapy, particularly if they already are middle-aged or older.

"We make the decision about when to start therapy dependent on patients' CD4 cell count and viral load, and we don't look at what happens in the brain," Ances says. "But within days of infection the virus already is in the brain, and it stays in the brain for the rest of that person's life."

The study shows that even a 20-year-old with HIV infection already has an impact on blood flow to the brain, so maybe this issue should be a consideration in therapy decisions, he suggests.

"What these results are suggesting is we have a marker here to evaluate patients," Ances says.

If HIV-positive patients have signs of cognitive decline then clinicians should ask whether they will need to be treated with neuroprotective medications or start on ARTs sooner, he says.

There are no definitive answers, but these questions need to be investigated, he adds.

At the very least, HIV clinicians should acknowledge their patients' cognitive complaints and let them know that this is an impact of the disease, Ances says.

"I have a large number of older patients who say, 'My thinking is not right. What's going on with me?'" he says. "The answer is, 'Yes, your brain is not right. We may need to consider other medication.'"

Expert tips for treating older HIV patients

Look for comorbities, depression

AIDS-defining conditions and risks are different for HIV-positive patients who are older, usually defined as age 50 and above, experts say.

Older HIV patients often have higher risks of CMV disease, Kaposi sarcoma, oral candidiasis, wasting syndrome, HIV encephalopathy, and AIDS dementia complex.[1]

Also, older patients typically underreport symptoms such as diarrhea, pain, and depression, but will focus on weight loss, hair loss, and peripheral neuropathy.

"We found that patients who are older and have HIV infection have a higher prevalence of hypertension, hypertriglyceridemia, and low bone mineral density, suggestive of osteoporosis and abnormalities in distribution of body fat," says Nur Onen, MBChB, an instructor in internal medicine in the infectious diseases division of Washington University School of Medicine in St. Louis, MO.

"This problem of accelerated bone loss has been defined in younger HIV patients, as well," Onen notes. "Just when antiretroviral therapy (ART) first is started patients' bone density goes down, and then it stabilizes, so we think it's caused predominantly by HIV infection."

The changes in body fat put HIV patients at greater risk of diabetes, she says.

Since HIV physicians also are often their patients' primary care doctors, they should screen patients for clinical depression, which also is common in older patients, Onen suggests.

"We should talk with them about it and have colleagues who are counselors meet with them," she says.

Another issue concerns the compounding of HIV and lifestyle choices, including smoking, substance abuse, and exposure to other viral infections.

"We have to be very aggressive with our older HIV population and tell them to stop smoking and try our best to address any alcohol and substance use issues that may impact their health and their ability to stay on their HIV medications," Onen says. "We should be aggressive in recognizing and treating depression because it also can impact their medication use."

Clinicians also should encourage patients to maintain good diabetic control, when this is an issue, and check for malignancies, she adds.

"We need to keep HIV patients as healthy as possible for as long as possible," she says.

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With the nation's aging population of HIV patients, clinicians might find that it is difficult to identify whether cognitive decline is due to their HIV infection or Alzheimer's disease or some other forms of dementia.

But there is some pathological research that suggests some of the factors leading to cognitive decline are similar between Alzheimer's disease and the way the brain is impacted by HIV infection, Ances says.

"There might be a common mechanism of aging the brain," he says.

There are no medical solutions to these kinds of cognitive decline, but HIV clinicians can give their patients general advice that will improve their overall health, including mental health.

"I tell patients, 'If you don't use it, you'll lose it,'" Ances says.

Education and exercise are neuroprotective, he says.

"I tell all my patients, 'Stop sitting in front of the TV; stay active and physically fit, and this is very important: try to walk and do things,'" he adds. "If they do this it will help their brain function, their heart function, bones, and everything."

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Perinatal HIV: Decline, but disparities persist

Rates still much higher in black, Hispanic children

Although the total number of annual perinatal HIV infections in the United States has decreased approximately 90% since 1991 — and continue to fall in the most recent data set from 2004-2007 — racial/ethnic disparities persist, the Centers for Disease Control and Prevention reports.

Racial/ethnic disparities in the incidence of HIV/AIDS among children have been documented since 1981-1986, when 78% of children with AIDS were black or Hispanic. These racial/ethnic disparities have been reflected in rates of perinatal HIV infection. Of all reported diagnoses of perinatal HIV infection during 2004-2007, 85% were in children who were black or Hispanic, and rates were several-fold higher among black and Hispanic children than among white children.[1]

"To eliminate perinatal transmission and racial/ethnic disparities, continued measures are needed, including primary HIV prevention for women, reproductive health and family planning for women with HIV infection, and prenatal care and early treatment with antiretroviral medications for pregnant women and their infants," the CDC states.

These disparities are directly related to the racial/ethnic distribution of women diagnosed with HIV infection. High-risk heterosexual transmission remains the principal source of exposure for HIV-infected women of all races/ethnicities, accounting for 80% of new infections among women. Recent studies also have suggested that the higher rates of HIV infection among blacks in the United States are related to a number of social factors, such as tight social networks, mixing, and poverty.[2] In addition, in a study of women enrolled in Medicaid during 1995-1997, black (71%) and Hispanic women (74%) were significantly less likely than non-Hispanic white women (81%) to initiate prenatal care in the first trimester and less likely (62% and 69% versus 72%, respectively) to make an adequate number of prenatal care visits, indicating that black women would have less opportunity for timely HIV testing and early initiation of antiretroviral prophylaxis to prevent perinatal transmission.[3]

Further reductions in perinatal HIV transmission are achievable, toward an elimination goal of <1% among infants born to HIV-infected women and <1 transmission per 100,000 live births. Primary HIV prevention in women is the best way to prevent HIV infection in children. All women with HIV infection should have reliable access to comprehensive HIV treatment and primary women's health care to optimize their health before pregnancy and receive effective contraception to avoid unintended pregnancy. To eliminate perinatal HIV transmission, all HIV-infected pregnant women must 1) receive a diagnosis of HIV infection before or early in pregnancy, 2) receive prenatal care, 3) adhere to an antiretroviral medication regimen during pregnancy, 4) have a scheduled cesarean delivery at 38 weeks' gestation if viral suppression has not been achieved, and 5) receive antiretroviral medication during labor and delivery. Antiretroviral medication also should be provided to HIV-exposed

newborns within the first hours after birth and for the first 6 weeks of life.

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'Persistent stigmas' fueling HIV in black community

Warning on National Black HIV/AIDS Awareness Day

"We have a national responsibility to alleviate the HIV/AIDS-related suffering of African-Americans by ensuring that they have full knowledge of—and access to—all proven forms of HIV prevention, treatment and care," **Anthony S. Fauci**, MD, director, National Institute of Allergy and Infectious Diseases said Feb. 7, 2010, commemorating the 10th annual National Black HIV/AIDS Awareness Day.

African-Americans continue to bear the largest and most disproportionate burden of HIV/AIDS of all racial and ethnic groups in the United States. While black men and women made up 13% of the U.S. population in 2007, they accounted for more than half of all new HIV/AIDS diagnoses that year and nearly half of all Americans living with HIV/AIDS. For black women ages 35 to 44, HIV was the third leading cause of death in 2006.

"As a nation, we must knock down the barriers that prevent many Americans, especially African-Americans, from receiving health care in general, and HIV testing, counseling and treatment in particular," he said. "An insidious component of this barrier is persistent stigma around homosexuality, HIV-positive status and injection drug use."

Fostering acceptance of all people, regardless of lifestyle, and encouraging discussions about the behaviors that increase risk for HIV infection will help create a positive climate for HIV prevention and treatment services in black communities, he said.

"I am gratified that Congress and President Obama recently lifted the 21-year-old ban on federal funding for needle exchange programs, which have been scientifically proven to reduce HIV transmission among injection drug users and serve as a gateway to treatment for drug addiction, HIV and other diseases," Fauci said.

One of the fundamental ways black men and women can reduce the spread of HIV in their communities and preserve their health is by getting tested for the virus during routine medical care, as recommended by the Centers for Disease Control and Prevention and the American College of Physicians, Fauci said. Identifying HIV infection early in its course is critical. A growing number of studies have shown that starting treatment early, while the immune system is still intact, is more beneficial to HIV-infected patients than initiating therapy later in the course of disease.

Another barrier to HIV care in black communities may be a reported reluctance among some individuals to start treatment for HIV infection before they feel sick. Research tells tell us that HIV-infected individuals are more likely to remain alive and healthy if they start treatment early—even if they feel well. Treatment for HIV may benefit not only the infected person who is receiving antiretroviral therapy, but also his or her sexual partner. Treatment with antiretroviral drugs lowers the amount of virus in bodily fluids, potentially decreasing the risk of HIV transmission. NIAID is conducting a clinical trial to test this hypothesis in collaboration with the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Institute on Drug Abuse and the National Institute of Mental Health, all part of the National Institutes of Health, he said. **(See related story, below.)** ■

PROMISE targets maternal transmission

Ambitious clinical trial now under way

An estimated 430,000 children worldwide became infected with HIV in 2008, mostly through birth or breastfeeding from an HIV-

infected mother. Many regions of the world are gaining increased access to complex antiretroviral drug regimens for preventing HIV transmission from a mother to her child. However, these strategies have not yet been directly compared with simpler antiretroviral drug regimens in terms of their safety, efficacy, feasibility and cost-effectiveness, the National Institute of Allergy and Infectious Diseases (NIAID) reports.

On January 15, 2010 a large, multinational clinical trial began to determine how best to reduce the risk of HIV transmission from infected pregnant women to their babies during pregnancy and breastfeeding while preserving the health of these children and their mothers. The PROMISE ("Promoting Maternal-Infant Survival Everywhere") study aims to enroll 7,950 HIV-infected women who are pregnant or have recently given birth and 5,950 HIV-exposed infants of these women. The participants will come from as many as 18 countries whose levels of resources range from high to low.

The International Maternal Pediatric Adolescent AIDS Clinical Trials network is conducting the study with funding from the National Institute of Allergy and Infectious Diseases and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, both part of the National Institutes of Health. Led by protocol chair **Mary Glenn Fowler**, MD, MPH., of the Makerere University–Johns Hopkins University Research Collaboration in Kampala, Uganda, the study team expects results in five to six years.

The HIV-infected women eligible to participate in PROMISE do not yet qualify for treatment—that is, their CD4+ T cell count, a measure of immune health, exceeds the level (350 cells per cubic millimeter of blood) at which highly active antiretroviral therapy (HAART) generally is recommended. HAART consists of a potent combination of three or more antiretroviral drugs.

The study addresses four distinct research questions. Most volunteers will participate in multiple components of the study to answer these questions. The first component will examine which of two proven strategies is safer and more effective at preventing mother-to-child HIV transmission before and during delivery: giving HIV-infected pregnant women a three-antiretroviral-drug regimen beginning as early as 14 weeks of gestation, or giving them the antiretroviral drug zidovudine beginning as early as 14 weeks of pregnancy and a single dose of the antiretroviral drug nevirapine during labor. The regimen of zidovudine and nevirapine is the standard of care in many countries for women who do not yet require treatment for their HIV infection. Some 4,400 women will be assigned at random to receive either one of these two interventions.

The second component of the PROMISE study will compare the safety and efficacy of two methods of preventing mother-to-child HIV transmission during breastfeeding. The study team will assign 4,650 mother-infant pairs at random either to receive a daily dose of infant nevirapine or to have the mothers take a three-antiretroviral-drug regimen throughout breastfeeding.

The third component of the PROMISE study will examine the effects of short-term use of a three-antiretroviral-drug regimen during pregnancy and breastfeeding to prevent mother-to-child HIV transmission on the health of HIV-infected mothers who do not yet need treatment. For such women, it remains unclear whether stopping the three-drug regimen after giving birth or ceasing to breastfeed would compromise their health. Although past studies have shown that interrupting treatment with antiretroviral drugs has a negative effect, the conditions in those studies are different enough from the conditions of the PROMISE study to make extrapolating the results difficult, according to the study investigators.

The 4,675 women participating in this third component of PROMISE will be assigned at random either to stop the three-antiretroviral-drug regimen after giving birth or weaning, or to continue the drug regimen indefinitely. The health of these two groups will be compared. In addition, the women who receive the time-limited three-drug regimen will be compared with the women who participated in the first component of PROMISE and did not receive the three-drug regimen, but rather took zidovudine during pregnancy and single-dose nevirapine during labor.

The last component of the PROMISE study involves protecting the health of HIV-exposed but uninfected infants. In resource-limited settings, it is standard to give the antibiotic cotrimoxazole once daily to infants exposed to HIV at birth until the infant has stopped breastfeeding and is known to be HIV-uninfected. While cotrimoxazole prophylaxis improves the survival rate of HIV-infected infants, it is not known whether continuing to administer the drug after weaning similarly would benefit HIV-exposed but unin-

fected children.

In this fourth component of the PROMISE study, nearly 2,290 HIV-exposed but uninfected, weaned infants under one year old will be assigned at random either to continue receiving cotrimoxazole or to receive a placebo through age 18 months. Neither the mothers of the infants nor the study team will know which infants are in which group. The study will determine whether continuing cotrimoxazole prophylaxis in HIV-exposed, uninfected infants from the time they stop breastfeeding through age 18 months decreases their risk of illness and death without causing side effects or generating bacterial resistance to cotrimoxazole. ■

FDA Notifications

Kaletra revisions to packaging approved

On Jan. 29, 2009, the Food and Drug Administration (FDA) approved revisions to the lopinavir/ritonavir (Kaletra®) package insert to include drug-drug interaction information for concurrent lopinavir/ritonavir administration with inhaled medicines such as salmeterol or salmeterol in combination with fluticasone propionate (Serevent®, Advair®) and sildenafil (Revatio®).

Specifically, sildenafil — when used for the treatment of pulmonary arterial hypertension is listed under Contraindications (Section 4, Table 3) because a safe and effective dose has not been established when used with lopinavir/ritonavir. There is an increased potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erections and syncope. Additionally, in Section 7 Drug Interactions, Table 9 was revised to include this information and differentiate use of PDE5 inhibitors for pulmonary arterial hypertension and for erectile dysfunction.

Section 7 Drug Interactions Table 9 was revised to include the following information on salmeterol:

• Concurrent administration of salmeterol and Kaletra is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.

Section 17 Patient Counseling Information was revised to state:

• If they are receiving sildenafil, tadalafil, or vardenafil they may be at increased risk of associated adverse reactions including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor.

• If they are taking or before they begin using Serevent (salmeterol) and Kaletra, they should talk with their doctor about problems these two medicines may cause when taken together. The doctor may choose not to keep someone on Serevent (salmeterol).

• If they are taking or before they begin using Advair (salmeterol in combination with fluticasone propionate) and Kaletra, they should talk to their doctor about problems these two medicines may cause when taken together. The doctor may choose not to keep someone on Advair (salmeterol in combination with fluticasone propionate).

Similar changes were made to the Medication Guide. Kaletra is a product of Abbott Laboratories. ■

Labeling changed on Prezista

On Jan. 27, 2010, the FDA approved revisions to the darunavir (Prezista®) product labeling to include the 96 week data from two trials; one trial in treatment-experienced patients (TMC114-C214) and one trial in treatment-naïve patients (TMC114-C211).

Section 6: Adverse Reactions and Section 14 Clinical Studies were updated to reflect the updated 96 week efficacy and safety data. The 96 week efficacy results are summarized briefly below:

• Study TMC114-C211 is a randomized, controlled, open-label Phase 3 trial comparing PREZISTA/ritonavir 800/100 mg once daily versus lopinavir/ritonavir 800/200 mg per day

(given as a twice daily or as a once daily regimen) in antiretroviral treatment-naïve HIV-1 infected adult subjects. All patients received a fixed background regimen consisting of tenofovir disoproxil fumarate (TDF) 300 mg once daily and emtricitabine 200 mg once daily (FTC). At Week 96, 78% of patients randomized to PREZISTA/ritonavir were virologic successes (HIV RNA < 50 copies/mL) compared to 74% of patients randomized to lopinavir/ritonavir.

• Study TMC114-C214 is a randomized, controlled, open-label Phase 3 trial comparing PREZISTA/ritonavir 600/100 mg twice daily versus lopinavir/ritonavir 400/100 mg twice daily in antiretroviral treatment-experienced, lopinavir/ritonavir-naïve HIV-1 infected adult subjects. Both arms used an optimized background regimen consisting of at least 2 antiretrovirals (nucleoside reverse transcriptase inhibitors with or without non-nucleoside reverse transcriptase inhibitors). At Week 96, 58% of patients randomized to PREZISTA/ritonavir were virologic successes (HIV RNA < 50 copies/mL) compared to 52% of patients randomized to lopinavir/ritonavir.

Additional revisions were made to the label and include the following:

• The Contraindications section (Section 4) is updated for alfuzosin (Table 2) in order to maintain consistency with the list of contraindicated medications in the ritonavir label:

In Section 6.1 Clinical Trials Experience: Treatment-Naïve Adults, under Less Common Adverse Reactions: drug hypersensitivity, angioedema and urticaria were added.

In Section 6.2 Clinical Trials Experience: Treatment-Experienced Adults, under Less Common Adverse Reactions: urticaria was added.

A new section was added to identify osteonecrosis as an Adverse Drug Reaction (ADR).

Section 6.4 Additional ADRs to PREZISTA/ritonavir identified in adult subjects in other clinical trials.

The additional ADR of interest identified from other clinical trials was osteonecrosis.

The Postmarketing Experience Section (Section 6.7) was updated to include: redistribution of body fat and toxic epidermal necrolysis.

Drug Interactions (Section 7), Table 7 was updated with the maraviroc drug interaction data. In summary maraviroc concentrations are increased when co-administered with PREZISTA/ritonavir. When used in combination with PREZISTA/ritonavir, the dose of maraviroc should be 150 mg twice daily.

The Microbiology section (Section 12.4) is updated with additional resistance data and baseline genotype and phenotype virologic

CNE/CME *questions*

7. Centers for Disease Control and Prevention (CDC) data show that what proportion of people who are 50 years or older in the United States are infected with HIV?
   A. 15%
   B. nearly one-quarter
   C. 33%
   D. 9%

8. A new study identified which of these independent predictors of frailty among HIV patients?
   A. unemployment
   B. past opportunistic infections
   C. higher depression severity score
   D. All of the above

9. New research into cerebral blood flow comparing HIV positive patients to HIV negative people found that those infected with HIV had equivalent blood flow to their uninfected peers who were how much older?
   A. 4 years
   B. 9 years
   C. 15 years
   D. 18 years

Answers: 7. B; 8. D; 9. C

COMING IN FUTURE MONTHS

- Experts discuss revised ART guidelines
- Key HIV enzyme breakthrough could lead to new treatments
- More than one-fifth of HIV infections in U.S. are undiagnosed, study finds
- Inpatient care for HIV patients decreased in past decade

analyses and cross-resistance data.

The updated labeling will be posted soon at Drugs@FDA. Darunavir (Prezista) is a protease inhibitor made by Tibotec, Inc. ■

Updated Atripla label approved

On Jan. 7, 2010, the FDA approved an updated efavirenz/emtricitabine/tenofovir (Atripla®) label.

It includes new efficacy, safety and resistance data in treatment experienced patients from a trial (Study 073) in which HIV-1 infected adults on a stable antiretroviral regimen were either switched to Atripla or remained on their background regimen to compare the effectiveness (efficacy, safety, and tolerability) of Atripla to that of subjects continuing unmodified HAART as measured by the proportion of subjects who maintain HIV-1 RNA <200 copies/mL on their original assigned regimen at Week 48 based on the time-to-loss of virologic response (TLOVR) analysis. ■

CNE/CME objectives

The CE/CME objectives for *AIDS Alert*, are to help physicians and nurses be able to:
• Identify the particular clinical, legal, or scientific issues related to AIDS patient care;
• Describe how those issues affect nurses, physicians, hospitals, and clinics;
• Cite practical solutions to the problems associated with those issues.

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