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C O N F E R E N C E C O V E R A G E

Three major scientific meetings on HIV/AIDS have taken place since the last issue of *BETA*: the 4th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment, and Prevention, held in Sydney, Australia, in July; the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held in Chicago in September; and the 11th European AIDS Conference (EACS), held in Madrid, Spain, in October.

Highlights from these meetings are described below, along with recent news from medical journals and other sources.

O N T H E W E B

IAS

www.ias2007.org

ICAAC

www.icaac.org

EACS

www.eacs-conference2007.com

UPDATED TREATMENT GUIDELINES

U.S. and European experts have released revised guidelines for the clinical management of HIV/AIDS, reflecting an evolving understanding of the disease, its treatment, and related complications.

U.S. HIV TREATMENT GUIDELINES

The U.S. Department of Health and Human Services (DHHS) issued an updated version of its *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* on December 1, 2007. Among the major changes, the guidelines now recommend that antiretroviral therapy should be started when an individual's CD4 cell count falls below 350 cells/mm³. This shift from the previous version—which recommended considering therapy when the CD4 count was in the 200–350 cells/mm³ range—was prompted by recent research showing that people who start treatment sooner, while immune function is still relatively well preserved, have better treatment outcomes (see “News Briefs: Benefits of Early Treatment” in the Summer 2007 issue of *BETA*).

In addition, the DHHS panel now recommends treatment, regardless of CD4 cell count, for all pregnant women, people with HIV-associated nephropathy (kidney disease), and HIV positive patients who require treatment for hepatitis B virus (HBV) coinfection.

The guidelines recommend that all treatment-naïve individuals entering clinical care receive genotypic HIV resistance testing, whether or not they plan to immediately start antiretroviral therapy. In addition, a viral tropism assay is recommended if considering the use of coreceptor-blocking agents, and HLA-B*5701 testing is advised prior to starting abacavir (Ziagen) to reduce the risk of hypersensitivity reactions (see news item below).

For treatment-experienced individuals, the new guidelines include information on two recently approved antiretroviral agents from novel classes, the CCR5 antagonist maraviroc (Selzentry) and the integrase inhibitor raltegravir (Isentress). (See news items below.)

The complete revised DHHS guidelines are available at www.aidsinfo.nih.gov.

EUROPEAN GUIDELINES

On October 26, coinciding with its conference in Madrid, the European AIDS Clinical Society issued new guidelines for HIV treatment in adults, as well as for the management of HIV/HBV and HIV/hepatitis C virus (HCV) coinfection and HIV-related metabolic complications. The drafts will be finalized after a public comment period.

Overall, the updated guidelines reflect a more aggressive approach to antiretroviral therapy and, like the new U.S. guidelines, now recommend treatment for individuals

with a CD4 count between 200 and 350 cells/mm³. Treatment may be offered to patients with a CD4 count of 350–500 cells/mm³, depending on factors such as HIV viral load, rate of immune decline, HIV/HCV coinfection, and older age. For both treatment-naïve and treatment-experienced individuals, the goal should be viral suppression below 50 copies/mL.

EACS also recommends genotypic resistance testing and HLA-B*5701 testing for abacavir hypersensitivity, as well as HIV subtype determination. With the availability of the HLA-B*5701 assay, abacavir plus 3TC (lamivudine; Epivir) has been upgraded to a “recommended” nucleoside reverse transcriptase inhibitor (NRTI) backbone, while AZT (zidovudine; Retrovir) plus 3TC has been downgraded to “alternative” status due to toxicity concerns.

The EACS hepatitis B and C coinfection guidelines were issued for the first time, and are based on European and international consensus recommendations (see “News Briefs: New HIV/HCV Coinfection Guidelines” in the Summer 2007 issue of *BETA*). Hepatitis A and B vaccination is recommended for all HIV positive people. Condom use is advised, due to growing evidence of sexual transmission of HCV, especially among HIV positive gay and bisexual men.

Hepatitis B treatment in HIV positive patients may include interferon, 3TC, adefovir (Hepsera), tenofovir (Viread), telbivudine (Tyzeka), and/or entecavir (Baraclude); combination therapy is most effective, and agents that are also active against HIV should never be used without other antiretroviral drugs. Hepatitis C treatment may be started without a liver biopsy under certain conditions. Anti-HCV therapy is especially recommended for coinfecting people with a high likelihood of achieving sustained virological response. Standard treatment is pegylated interferon (Pegasys or PegIntron) plus ribavirin; patients taking ribavirin should avoid AZT, ddI (didanosine; Videx), and d4T (stavudine; Zerit) due to additive toxicities.

The new guidelines for the management of metabolic complications are particularly relevant as HIV positive people live longer due to effective antiretroviral therapy. They include recommendations for assessing cardiovascular risk, monitoring metabolic parameters, managing abnormal blood lipid levels with lifestyle changes and medication, preventing and/or reversing lipoatrophy and body fat accumulation, and treating blood glucose abnormalities and high blood pressure. At the same time, they acknowledge that much remains to be learned about metabolic abnormalities in people with HIV.

The new EACS guidelines are available at www.eacs.eu/guide/index.html.

GUIDELINES FOR PREGNANT WOMEN

On November 2, the Perinatal HIV Guidelines Working Group of the U.S. Public Health Service issued updated *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*.

The panel confirmed that HIV positive pregnant women—regardless of CD4 cell count—should receive antiretroviral drugs during pregnancy and delivery, and the infant after birth, to prevent HIV transmission. For this purpose, combination regimens are more effective than monotherapy.

The revised guidelines include new information about treatment for pregnant women with prior antiretroviral exposure, those with hepatitis B or C coinfection, and those who do not achieve full viral suppression. The panel reaffirmed its recommendation that women with an HIV RNA level above 1,000 copies/mL near the time of delivery should undergo scheduled cesarean section, and that HIV positive women, regardless of viral load, should not breast-feed their infants. The panel emphasized that these recommendations are intended for the U.S., and that different strategies may be more appropriate in other regions.

The updated guidelines no longer recommend nelfinavir (Viracept) for pregnant women or children due to concern about a chemical impurity in the drug (see news item below).

The updated U.S. pregnancy and perinatal guidelines are available at www.aidsinfo.nih.gov.

The updated European HIV treatment guidelines also include recommendations for pregnant women. The latest recommendations are similar to the U.S. guidelines, but include a stronger caution against use of tenofovir during pregnancy. Single-dose nevirapine (Viramune) monotherapy—often used to prevent perinatal HIV transmission in resource-limited settings—is not recommended since it can lead to drug resistance.

NEW ANTIRETROVIRAL DRUGS APPROVED

The past year witnessed a breakthrough in the evolution of antiretroviral therapy, as two new drugs with novel mechanisms of action against HIV, plus a new non-nucleoside reverse transcriptase inhibitor (NNRTI), were approved by the U.S. Food and Drug Administration (FDA).

ETRAVIRINE

On January 18, the FDA approved Tibotec’s next-generation NNRTI etravirine (Intelence; formerly TMC125) for use as part of combination therapy in treatment-experienced

Etravirine, maraviroc, and raltegravir were recently approved for treatment-experienced adults with multidrug-resistant HIV.

adults. For more information, including study data, see “Drug Watch,” page 11.

MARAVIROC

Maraviroc (Selzentry in the U.S.; Celsentri in Europe), the first CCR5 antagonist to reach the market, received FDA accelerated approval on August 6. The drug, developed by Pfizer, was approved by the European Medicines Agency (EMA) on September 24.

Maraviroc prevents HIV from attaching to CCR5, one of the coreceptors the virus uses to enter cells. Importantly, the drug is only beneficial for individuals with exclusively CCR5-tropic (as opposed to CXCR4-tropic or dual/mixed-tropic) virus, as determined by a tropism test such as the Monogram Biosciences Trofile assay. (For an explanation of HIV coreceptor tropism, see “Drug Watch” in the Winter 2007 issue of *BETA*.)

Approval was based on data from the Phase IIb/III MOTIVATE-1 and MOTIVATE-2 trials, which compared once- or twice-daily oral maraviroc versus placebo plus optimized background therapy in more than 1,000 highly treatment-experienced patients with drug-resistant virus. After 24 weeks, virological response rates (HIV RNA < 50 copies/mL) were about twice as high in the maraviroc arms compared with the placebo arms (about 45% vs about 23%). At 48 weeks, according to data presented at ICAAC, response rates remained similar in the maraviroc arms, but declined in the placebo arms.

Overall, adverse events occurred with similar frequency in the maraviroc and placebo arms, with about 5% discontinuing therapy for this reason. The most common side effects in the maraviroc arms were fever, cough, upper respiratory tract infections, skin rash, muscle aches, abdominal pain, and dizziness. There were no cases of severe (grade 3–4) liver toxicity, which led to the abandonment of another CCR5 inhibitor candidate, aplaviroc. Nevertheless, the maraviroc package insert includes a warning about possible hepatotoxicity, as well as a potential increased risk of cardiovascular events. As a condition of approval, the FDA required Pfizer to conduct further studies of long-term side effects.

Maraviroc was approved for treatment-experienced patients with persistent HIV replication and resistance to other drugs. At the July IAS conference, researchers presented promising data from a study of maraviroc in previously untreated individuals. In the Phase III MERIT study, 721 participants were randomly assigned to receive maraviroc twice daily or efavirenz (Sustiva) once daily, plus AZT/3TC. Overall, patients in the maraviroc and efavirenz arms were about equally likely to achieve HIV RNA below 400 copies/mL (71% vs 73%), but those taking maraviroc were slightly less likely to achieve a viral load below 50

copies/mL if they had more than 100,000 copies/mL at baseline (60% vs 67%). At this time, U.S. and European regulators have not approved maraviroc for treatment-naïve patients. It has not been tested in pregnant women and is not approved for children.

Maraviroc must be used in combination with other antiretroviral drugs, and it works best if there are other active agents in the background regimen. The approved dose is 150, 300, or 600 mg twice daily, depending on which other medications are used, due to interactions that can raise or lower drug levels; it can be taken with or without food. The wholesale cost is about \$10,800 per year.

For further information on maraviroc, including full prescribing data, see www.selzentry.com.

RALTEGRAVIR

The third new drug, Merck’s raltegravir (Isentress; formerly MK-0518), received FDA accelerated approval on October 12. European approval was granted in December.

Raltegravir, the first integrase inhibitor, prevents HIV from inserting its genetic material into the DNA of a human cell, a necessary step in viral replication.

Approval was based in part on data from the Phase III BENCHMRK-1 and BENCHMRK-2 trials, in which 699 heavily treatment-experienced patients with drug-resistant virus were randomly assigned to receive 400 mg oral raltegravir or placebo twice daily plus optimized background therapy. After 24 weeks, 63% of people in the raltegravir arms achieved HIV suppression below 50 copies/mL, compared with 33% in the placebo arms. Longer-term, 48-week data from an earlier Phase II dose-ranging trial showed that raltegravir remained effective at 48 weeks, with 64% of patients taking the 400-mg dose maintaining a viral load below 50 copies/mL. Among a subset of patients followed for up to 72 weeks, about 70% still had a viral load below 400 copies/mL.

Raltegravir was well tolerated, with fewer than 2% of BENCHMRK participants discontinuing therapy due to adverse events. The most common side effects associated with raltegravir were nausea, diarrhea, headache, fever, and rash; some patients had elevated levels of creatine kinase, an enzyme associated with muscle damage. Although early data suggested that more people taking raltegravir developed cancer, the FDA determined that this was likely attributable to an unusually low malignancy rate in the placebo group.

Raltegravir was approved for treatment-experienced patients with prior treatment failure and evidence of resistance to other antiretroviral drugs. Like maraviroc, it has been studied in previously untreated individuals. As reported at the IAS meeting (and in the October 1, 2007, *Journal*

Trials of the HIV vaccine candidate V520 were halted in September; V520 did not appear to protect against HIV infection or disease progression.

of *Acquired Immune Deficiency Syndromes*), researchers randomly assigned 198 participants to receive twice-daily raltegravir at doses ranging from 100 to 600 mg or once-daily efavirenz, plus tenofovir/3TC. At 48 weeks, outcomes were similar across treatment arms, with about 85% achieving a viral load below 50 copies/mL. However, the FDA has not yet approved raltegravir for treatment-naïve patients. It has not been tested in pregnant women, but Merck is conducting a study in children.

Raltegravir must be used as part of a combination antiretroviral regimen, and works best with other active drugs. The standard dose is 400 mg twice daily, either with food or on an empty stomach. It will cost about \$9,800 per year.

For further information on raltegravir, including full prescribing data, see www.isentress.com.

KALETRA FOR CHILDREN

In November, the FDA approved a lower-strength formulation of lopinavir/ritonavir (Kaletra in the U.S.; Aluvia in developing countries) for use by children who weigh at least 15 kg (about 33 pounds). Liquid lopinavir/ritonavir is also available, but the new pill—in a size that is easier for children to swallow—provides an additional option for pediatric patients. The new tablets contain 100 mg lopinavir plus 25 mg ritonavir, half the dosages in the original Kaletra pill. They do not require refrigeration and can be taken with or without food. European approval is pending, and manufacturer Abbott plans to offer the new pill at half the price of the original-strength tablet in resource-poor countries that are home to most of the world's HIV positive children.

For full lopinavir/ritonavir prescribing information, see www.kaletra.com.

NELFINAVIR WARNING FOR CHILDREN AND PREGNANT WOMEN

Pfizer issued a letter to health care providers on September 10, alerting them to the presence of ethyl methanesulfonate (EMS; also known as ethyl mesylate) in the protease inhibitor nelfinavir (Viracept); Pfizer manufactures nelfinavir for sale in the U.S. As previously reported (see “News Briefs: Nelfinavir Recalled Outside The U.S.” in the Summer 2007 issue of *BETA*), Roche—which manufactures nelfinavir sold throughout most of the rest of world—announced in June that it was recalling its entire stock of nelfinavir tablets in Europe due to the discovery of the chemical impurity in some batches of the drug.

A byproduct of the manufacturing process, EMS is usually present in nelfinavir in tiny quantities (less than three parts per million). The contamination of the Roche nelfinavir reached more than 2,000 parts per million. The

Pfizer version does not contain a large amount of EMS, but U.S. authorities asked Pfizer to limit EMS levels, since even a small quantity of the chemical—which has been shown to cause genetic mutations, birth defects, and cancer in animals—is a potential concern for young children and pregnant women.

Pfizer and the FDA recommended that children starting antiretroviral therapy should not receive nelfinavir, although those already taking the drug may continue. Pregnant women should not start taking nelfinavir, and those already doing so should in most cases switch to a different drug. However, if a pregnant woman has no good alternatives, the risk-benefit ratio favors continued use of nelfinavir. DHHS and U.S. Public Health Service guidelines were revised to reflect these changes (see previous news item). The protease inhibitor now recommended for pregnant women is lopinavir/ritonavir; alternatives are boosted indinavir (Crixivan) or boosted saquinavir (Invirase). The EMS in nelfinavir is thought to be a minimal risk for non-pregnant adults, and recommendations for this group have not changed.

AMPRENAVIR DISCONTINUED

GlaxoSmithKline announced in November that it would discontinue production and marketing of its original protease inhibitor, amprenavir (Agenerase). Since its approval in 1999, demand for the amprenavir pill has fallen dramatically, due to the introduction of new drugs in the same class and the greater bioavailability and efficacy of its pro-drug, fosamprenavir (Lexiva). Liquid amprenavir continued to be used in some circumstances, including treatment of children; however, the company recently introduced an oral suspension of fosamprenavir that is expected to replace the older drug. Accordingly, GlaxoSmithKline will discontinue both the oral solution and 50-mg capsule formulations of amprenavir. People who are currently taking amprenavir should consult their clinician about changing to fosamprenavir or another appropriate drug. To facilitate the switch, GlaxoSmithKline will cover fosamprenavir under the same patient assistance program.

HIV VACCINE TRIALS HALTED

On September 21, the HIV Vaccine Trials Network (HVTN) of the National Institutes of Allergy and Infectious Diseases (NIAID) and Merck announced that they were halting development of the HIV vaccine candidate V520 (also known as MRKAΔ5) due to interim data showing that it did not lower the risk of infection or disease progression. HVTN and Merck ended enrollment and vaccine dosing in the international Phase II STEP study—which included 3,000 “high-risk” volunteers, including gay and bisexual men, fe-

male sex workers, and injection drug users—and a similar trial in South Africa was also stopped.

V520, a trivalent vaccine that contains three recombinant HIV-1 subtype B genes (*gag*, *nef*, and *pol*) carried by a weakened adenovirus type 5 vector, was one of the furthest along in clinical development. Designed to stimulate a stronger killer T-cell immune response to HIV, researchers hoped it would both lower the risk of initial infection and slow disease progression in people who contracted the virus.

Researchers conducted a preliminary analysis after about one year that included 1,500 participants who had low pre-existing immunity to adenovirus type 5, a virus that causes the common cold. The data showed that volunteers who received the active vaccine were no less likely to become infected with HIV than those who received placebo injections: 24 of 741 subjects who received at least one dose of the vaccine contracted HIV, compared with 21 of 762 volunteers who received the placebo—about 3% in both groups. Protection did not improve among participants who received additional vaccine doses. Further, subjects who seroconverted despite the vaccine did not have lower viral loads. Based on these results, the study's data safety and monitoring board recommended that the trial end due to lack of efficacy.

But worse news came two months later, when a more complete analysis of data from all study participants revealed that vaccine recipients appeared to actually have an *increased* risk of HIV infection. Among men who have sex with men, 49 of 914 who received the active vaccine contracted HIV, compared with 33 of 922 who received the placebo (5.36% vs 3.85%). However, the increased risk of infection was limited to volunteers who already had immunity to the adenovirus vector.

Although researchers had suspected that people with pre-existing immunity to the vector virus might not respond as well to the vaccine, they could not explain how this could have increased the risk of HIV infection. One suggestion is that the adenovirus might have boosted immune activation in a way that increased susceptibility to HIV, perhaps by stimulating production of HIV-prone CD4 cells. Interestingly, while women made up more than one-third of study volunteers, only one was infected with HIV. Because the vaccine does not contain whole HIV, it could not have directly infected the recipients.

Following these findings, the STEP study was unblinded and recipients of the active vaccine were notified of the possible increased risk of infection. While the vaccine will not be administered to additional people, researchers hope to continue follow-up of currently enrolled participants. While investigators search for answers, several planned trials of similar vaccine candidates have been put on hold.

EARLY TREATMENT FOR HIV-INFECTED INFANTS

Several recent studies have indicated that starting antiretroviral therapy before severe immune system damage occurs leads to better outcomes in HIV positive adults. According to a study presented at the IAS meeting, earlier treatment is also beneficial for infants with HIV who were infected via mother-to-child transmission. In some parts of the world, especially where resources are limited, the standard of HIV care is to start babies on antiretroviral therapy only after they show symptoms of opportunistic illness or immune decline.

In a late-breaker session, Avy Violari of the University of the Witwatersrand in South Africa reported data from the NIAID-sponsored CHER (Children with HIV Early Antiretroviral Therapy) study, a Phase III trial that began in 2005. By 2007, a total of 377 HIV-infected infants aged 6 to 12 weeks without signs of immune suppression or severe clinical disease were randomly assigned to receive either immediate antiretroviral therapy for 40 weeks, immediate therapy for 96 weeks, or deferred treatment after they developed signs of clinical or immunological disease progression.

Although the trial was scheduled to continue through 2011, the study's data safety and monitoring board conducted a planned review of preliminary data this past June, and found that after a median follow-up period of about 30 weeks, infants who received immediate antiretroviral therapy had a significantly higher survival rate (96%) than those who delayed treatment (84%). The deferred therapy arm was halted, but the babies who started immediate treatment will continue to be followed for long-term outcomes.

NIAID's Edward Handelsman said that the CHER findings underline the need for timely diagnosis of pregnant women with HIV, so that their children may receive prompt treatment. However, because babies born to HIV positive women retain their mothers' antibodies for up to two years, earlier diagnosis would require more sophisticated and expensive testing to detect the virus itself, in order to avoid unnecessary exposure to antiretroviral drugs.

STRESS PROMOTES HIV DISEASE PROGRESSION

In accordance with popular wisdom, psychological stress really is detrimental to health and can promote progression of HIV and other diseases, according to a report in the October 10, 2007, *Journal of the American Medical Association*. Sheldon Cohen and colleagues conducted a review of previously published studies looking at the connection be-

A new genetic test can reliably predict which individuals are prone to abacavir hypersensitivity.

tween psychological stressors and progression of HIV/AIDS, clinical depression, cardiovascular disease, and cancer. They found that major stressful life events such as serious illness, divorce, or the death of a loved one could trigger clinical depression, but chronic stress associated with work and everyday annoyances played a greater role in cardiovascular conditions such as coronary heart disease. For cancer, studies yielded conflicting data.

In the case of HIV/AIDS, studies done since the advent of highly active antiretroviral therapy (HAART) consistently demonstrated a link between stress and disease progression. The authors suggested that stress—which may be exacerbated by dealing with complex treatment regimens—might help explain some of the individual variation in rates of HIV disease progression. In particular, hormonal and nervous system changes due to stress may interfere with proper immune function and promote chronic inflammation. Further, they added, stress may lead to unhealthy behaviors such as drinking, smoking, illicit drug use, poor eating habits, lack of exercise, and inadequate sleep.

HLA-B*5701 GENETIC TESTING

Many people with HIV and their clinicians have been reluctant to use the NRTI abacavir (a component of the Trizivir and Epzicom fixed-dose combination pills) due to the risk of hypersensitivity reactions. This type of reaction has been reported in about 3%–8% of patients starting the drug, and may be characterized by skin rash, fever, gastrointestinal upset, and respiratory symptoms.

People who experience such symptoms are advised to stop taking abacavir and never take it again, since doing so may be life-threatening. As a result, some patients discontinue the drug unnecessarily, since these common symptoms may have other causes and not truly indicate hypersensitivity.

But a new genetic test can reliably predict which individuals are prone to abacavir hypersensitivity, according to research presented in Sydney. Simon Mallal of Royal Perth Hospital in Australia and colleagues previously demonstrated that a specific human genetic variation, known as HLA-B*5701, is associated with susceptibility to abacavir hypersensitivity. In the PREDICT-1 study, 1,650 patients at more than 300 sites in Europe and Australia started abacavir-containing antiretroviral regimens; 84% were Caucasian and 12% were of African descent (an important consideration, since HLA-B*5701 occurs with different frequencies in various populations, being less common among blacks than among whites).

All participants received genetic screening for HLA-B*5701; however, while half used the test results to determine whether they should receive abacavir, the others had their results stored for later analysis. Any individual who

experienced a suspected hypersensitivity reaction stopped abacavir and received a skin patch test to confirm that the reaction really was related to the drug.

Patients who used the genetic test results to guide treatment were about half as likely to experience hypersensitivity reactions (3.4% vs 7.8%). While 2.7% of subjects in the arm without test guidance had confirmed hypersensitivity reactions, there were none in the guided treatment arm, yielding a negative predictive value of 100%. However, some people who tested positive for HLA-B*5701 did not develop hypersensitivity reactions, so the positive predictive value was only 48%. Conversely, in the arm without test guidance, fewer than half the participants with suggestive symptoms had immunologically confirmed abacavir hypersensitivity reactions; in some cases, the symptoms were due to hypersensitivity to an NNRTI drug started at the same time.

The researchers concluded that the study findings “demonstrate that prospective HLA-B*5701 screening results in a dramatic, clinically relevant and statistically significant reduction in abacavir hypersensitivity reactions.” These findings have already been incorporated into clinical practice, with the latest U.S. and European treatment guidelines recommending routine use of the test (see previous news item). The genetic test cannot predict every reaction, however, and the researchers urged clinicians to remain vigilant for signs of hypersensitivity.

GLOBAL HIV ESTIMATES REVISED DOWNWARD

To mark World AIDS Day on December 1, the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) released updated statistics on the number of people worldwide estimated to be living with HIV.

In contrast with past years, which saw steady increases, the figures for 2007 fell sharply, from 39.5 million in 2006 to 33.2 million. According to the latest UNAIDS/WHO report, about two-thirds of all people with HIV (22.5 million) are in sub-Saharan Africa, while Asia (including India) accounts for about 4.8 million cases. In addition, the agencies estimated that about 2.5 million people were newly infected in 2007 and about 2.1 million died of HIV/AIDS-related causes.

About 70% of the total decrease was due to lower estimates for five African countries (Angola, Kenya, Mozambique, Nigeria, and Zimbabwe) and India, the latter of which alone accounted for about half the downward revision (from 5.7 million to 2.5 million people).

While the incidence of new HIV infections appears to have peaked in the late 1990s and then slowly declined

(due to factors such as effective prevention and natural trends in the epidemic), the dramatic decline in the past year was mainly attributable to more accurate estimation methods.

Many earlier HIV prevalence estimates from developing countries were extrapolated from infection rates observed among women receiving prenatal care at urban clinics—a group that now appears to have a higher likelihood of infection than the population as a whole. The lower estimates came in part from representative household surveys in both urban and rural areas of developing countries.

While any decline in the prevalence and incidence of HIV infection is welcome news, advocates emphasized that the AIDS pandemic remains a pressing concern—affecting more than 30 million people worldwide—and that more resources are still urgently needed to expand prevention programs and provide universal antiretroviral treatment.

The complete *2007 AIDS Epidemic Update* is available at www.unaids.org/en/HIV_data/2007EpiUpdate/default.asp.

HIV AMONG U.S. HISPANICS

Routes of HIV transmission among Hispanic men and women living in the U.S. differ depending on where they were born, CDC researchers reported in the October 12, 2007, issue of *Morbidity and Mortality Weekly Report*.

Lorena Espinoza and colleagues analyzed data on Hispanic adults (age 13 or older) living with HIV/AIDS. The analysis included figures from 2001 through 2005 for 33 states that consistently reported HIV and AIDS by name or unique identifier, and from all 50 states in 2005, when the remaining states began using this reporting method. This is a limitation, since it excludes early data from some states—including California and New York—with high HIV/AIDS case loads and large Latino populations. About half of all Hispanics living in the U.S. were born elsewhere, and undocumented immigrants may have been underrepresented in the analysis.

During the 2001–2005 period, a total of 184,167 adults and adolescents from all racial/ethnic groups in the 33 states had an HIV/AIDS diagnosis. Of these, 33,398 (18%) were Hispanic, compared with 51% non-Hispanic blacks, 29% non-Hispanic whites, and 1% or fewer Asian/Pacific Islanders and Native Americans.

For both Hispanic men and women, rates were significantly higher than those for whites, but much lower than those for blacks. Among men, the rates for whites, Hispanics, and blacks were 18.2, 56.2, and 124.8 cases per 100,000 people, respectively; for women, the corresponding rates were 3.0, 15.8, and 60.2 cases per 100,000 people. Between 2001 and 2004, the HIV diagnosis rate fell by about 5% for Hispanic men and by 13% for women.

Among Hispanic men, HIV diagnosis occurred most often in the 30–39 age group, and the main transmission routes were male-to-male sex (61%), heterosexual sex (17%), and injection drug use (17%). Among Hispanic women, the highest HIV rate was seen in the 40–49 age group, and the main risk factors were heterosexual sex (76%) and injection drug use (23%).

However, these percentages varied depending on where an individual was born. About two-thirds (65%) of Hispanic men born in South America and 62% of those born in Cuba contracted HIV through male-to-male sex, compared with 54% of those born in Mexico and 46% of those born in the U.S. While 45%–47% of HIV positive Hispanics born in the Dominican Republic or Central America contracted the virus through heterosexual sex, the figure was 28% for U.S.-born Hispanics. And one-third (33%) of Hispanics born in Puerto Rico contracted HIV through injection drug use, compared with 22% of those born in the U.S.

These findings, the researchers concluded, indicate that prevention messages should be tailored to specific sub-populations, rather than regarding Hispanics/Latinos as a single group.

HIV ON THE RISE AMONG MEN WHO HAVE SEX WITH MEN

While the relative HIV prevalence and incidence rates among women and heterosexuals have risen since the early 1980s, men who have sex with men (MSM) continue to bear the brunt of the epidemic in the U.S., according to Kevin Fenton, director of the CDC's National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, speaking as part of a World AIDS Day webcast.

Fenton added that some two-thirds of new HIV/AIDS diagnoses are occurring among gay and bisexual men. However, he declined to release updated overall national HIV incidence figures, which are widely expected to be perhaps 50% higher than the 40,000 annual new cases the CDC has estimated for the past decade.

In an overview of the “re-emerging” epidemic among MSM published in the November 28, 2007, *Journal of the American Medical Association*, Harold Jaffe (who formerly held Fenton's position), Ronald Valdiserri of the Department of Veterans Affairs, and WHO Director of HIV/AIDS Kevin De Cock wrote that the number of HIV/AIDS cases among MSM increased by 13% in the U.S. between 2001 and 2006, and by 55% in Europe between 1998 and 2005.

They attributed the jump to an increase in unprotected sex, lack of awareness of HIV status, and a feeling that “AIDS is simply not as frightening” as it was before

In a recent study, circumcision status was not significantly associated with either a higher or lower HIV prevalence among black or Latino MSM.

HAART became available. Inaccurate perception of current HIV status, they added, would “weaken the risk-reduction strategy of serosorting, in which partners who believe they have the same serostatus engage in unprotected sex.”

Indeed, as reported in the December 2007 *American Journal of Preventive Medicine*, about one-third of 628 self-identified HIV negative MSM surveyed at gay pride events in June 2006 reported that they engaged in serosorting. But more than half said they took an HIV test once per year or less, and the testing frequency was no higher among the serosorters.

HIV RISK AMONG BLACK MSM

Researchers at the 2007 National HIV Prevention Conference, which took place in Atlanta in early December, reported that young black MSM have experienced the largest recent increase in new HIV diagnoses. In an analysis of data from the national HIV/AIDS reporting system (limited to the 33 states with long-term name-based HIV reporting), Joseph Prejean and colleagues from the CDC found that black MSM born in 1965–1969 had a high but stable HIV incidence, while those born in 1975–1979 or 1980–1984 experienced an increase between 2000 and 2005. Other studies indicate that black MSM are about twice as likely as white MSM to be HIV positive.

But the reasons for this discrepancy are not clear, since black MSM do not appear to engage in more high-risk behavior. Gregorio Millett and colleagues, also from the CDC, performed a systematic review of 53 epidemiology studies published between 1980 and 2006, with a total of more than 60,000 MSM. Overall, the studies showed that black MSM were not more likely than their white counterparts to engage in unprotected receptive sex or to use drugs such as marijuana, methamphetamine, cocaine, or opiates. Indeed, young black MSM were less likely to do so than white MSM of the same age.

Analyzing the data by time period provided a possible explanation. In the early years of the epidemic (1980–1990), black MSM seemingly were more likely to engage in high-risk sexual behavior, though this was no longer the case by the middle (1991–2000) and late (2001–2006) periods. A higher rate of early HIV infection could continue to fuel higher prevalence and incidence rates in the ensuing years, since many black MSM have sex mainly with others in the same group. Under this scenario, a black man having sex with other black men would be more likely to encounter HIV positive partners than a white man having sex with other white men, and thus would be at greater risk of infection even if behaviors were the same.

In addition, studies indicate that black MSM may be less likely to know their HIV status, less likely to be tak-

ing antiretroviral therapy (thus potentially having higher viral loads), and more likely to have concurrent sexually transmitted diseases—all of which can facilitate HIV transmission.

CIRCUMCISION IN THE U.S.

Recent studies in sub-Saharan Africa have shown that adult male circumcision can reduce the risk of HIV infection by as much as 60% among heterosexual men, leading many to wonder whether this might also be the case in areas such as the U.S. and Europe with a much lower overall HIV prevalence. Worldwide, circumcision rates vary greatly across racial/ethnic, religious, and cultural groups, making it difficult to determine whether HIV rates in a population are associated with circumcision or other factors. (For an overview of circumcision and other biomedical prevention strategies, see “New Approaches to HIV Prevention” in the Winter 2007 issue of *BETA*.)

At the December prevention conference, the CDC’s Millett reported on a study assessing the relationship between circumcision status and HIV infection among black and Latino MSM; results were also published in the December 15, 2007, *Journal of Acquired Immune Deficiency Syndromes*.

Researchers recruited 1,154 black and 1,091 Latino MSM in Los Angeles, New York City, and Philadelphia. Study participants completed a computer-assisted interview and received a rapid oral HIV antibody test. The black men were more than twice as likely as the Latino men to report that they were circumcised (74% vs 33%). In both groups, circumcised men were more likely to have been born in the U.S. or to have a U.S.-born parent; the practice is uncommon in the Latin American countries where many U.S. Latinos originated.

Circumcision status was not significantly associated with either a higher or lower HIV prevalence rate among black or Latino MSM overall, or among men who said they were HIV negative on the basis of their last test. Nor was circumcision associated with decreased HIV risk among black MSM who recently had sex with a woman or those who reported only unprotected insertive but not receptive anal intercourse (the group most likely to derive a protective effect from circumcision).

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