NEWS BRIEFS

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CONFERENCE COVERAGE

The Conference on Retroviruses and Opportunistic Infections, which took place February 3–6, 2008, in Boston, is one of the major annual scientific meetings covering HIV/AIDS and its management. Highlights from the meeting are described below (with abstract numbers), along with recent news from medical journals and other sources.

ON THE WEB

15TH RETROVIRUS CONFERENCE
www.retroconference.org/2008

DOES ABACAVIR (ZIAGEN) RAISE HEART ATTACK RISK?

Researchers with the large D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study have raised concerns about a potential elevated risk of heart attacks in people taking abacavir (Ziagen; also a component of the Trizivir and Epzicom combination pills).

As initially reported at the Retrovirus conference (*abstract 957c*) and described in the April 26, 2008, issue of *The Lancet,* the D:A:D investigators compared myocardial infarction (MI) rates in more than 33,000 HIV positive people in Europe, North America, and Australia who had used different nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs).

Recent use of abacavir or ddI (didanosine; Videx) was associated with a significantly increased MI risk, primarily in people with other cardiovascular risk factors. This elevation was not seen in people who stopped taking these drugs more than six months ago, nor in patients exposed to AZT (zidovudine; Retrovir), 3TC (lamivudine; Epivir), or d4T (stavudine; Zerit); the newer NRTIs tenofovir (Viread) and emtricitabine (Emtriva) were not included in the analysis.

Putting their findings into perspective, the D:A:D Steering Committee released a statement noting that "the 1.9-fold (90%) increased risk associated with use of abacavir compares with a 2–3-fold increased risk of heart attack associated with current cigarette smoking."

These results were unexpected, since the investigators did not observe a hypothesized link between MIs and thymidine analog NRTIs (AZT and d4T), and because abacavir had not previously been associated with heart problems. In response, abacavir manufacturer GlaxoSmithKline (GSK) performed a retrospective review of 54 previous clinical trials and reported that they did not find an increased MI risk in study participants who took abacavir.

Following the D:A:D revelations, the U.S. Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents—which in January upgraded abacavir to a "preferred" first-line NRTI, while demoting AZT to an "alternative"—issued a statement that the preliminary findings did not warrant a change in the current recommendations since the overall MI risk remains small. Likewise, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) also said the data did not warrant changing abacavir prescribing recommendations at the present time.

On June 18, in consultation with Health Canada, GSK issued a letter to health care providers stating, "at this time, though the available data do not allow a definitive conclusion regarding the association between the use of abacavir and an increased risk of myocardial infarction, it is recommended that physicians discuss the potential benefits and risks of abacavir with their patients…. The overall benefit-risk profiles of abacavir-containing products should be considered, especially in patients with pre-existing serious cardiovascular diseases."

DARUNAVIR (PREZISTA) LIVER CAUTION

On March 11, Tibotec Therapeutics issued a letter to health care providers regarding drug-associated liver toxicity (hepatotoxicity) in people taking its protease inhibitor (PI), darunavir (Prezista), boosted with ritonavir (Norvir). Liver toxicity—which occurred in 0.5% of clinical trial participants—has mainly been reported in patients with advanced HIV disease taking multiple medications, some of whom had other liver conditions, such as chronic hepatitis B or C.

Tibotec, in consultation with the FDA, revised the darunavir prescribing information to include a stronger warning about the risk of hepatotoxicity and a recommendation that laboratory liver function tests be performed before starting darunavir/ritonavir and repeated during therapy. If there is evidence of new or worsening liver dysfunction, "interruption or discontinuation of treatment

must be considered." The full revised package insert is available at ***www.prezista.com.***

NEW GUIDELINES AND DRUG FORMULATIONS FOR CHILDREN

On February 29, the DHHS issued updated *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.* The recommendations now state that all HIV-infected infants should receive antiretroviral therapy, regardless of CD4 cell count or clinical symptoms. This recommendation is based on data from the CHER study, which showed that starting treatment immediately after birth—rather than waiting for signs of immune decline—led to a 75% reduction in infant mortality.

The new guidelines also include revised recommendations regarding CD4 cell thresholds for initiation of antiretroviral therapy in children age one year or older, timing of diagnostic tests for HIV-exposed infants, and information on pediatric use of the recently approved drugs maraviroc (Selzentry), raltegravir (Isentress), and etravirine (Intelence). The updated guidelines are available at ***www.aidsinfo.nih.gov/Guidelines.***

In related news, drug manufacturers and the FDA have recently announced new pediatric formulations and dosing recommendations for several antiretroviral agents.

In February, the FDA approved a new formulation of 3TC for use by HIV-infected children weighing at least 14 kg (about 30 lb). The new 150-mg scored tablets are designed to allow for easier dose adjustment for pediatric patients. Epivir is also available as an oral solution for children who are unable to swallow pills. Full prescribing information is available at ***http://us.gsk.com/products/assets/us_epivir.pdf.***

In March, the product label for atazanavir (Reyataz) capsules was updated to include weight-based dosing recommendations for treatment-naive and treatment-experienced children and adolescents aged 6 to 18 years; younger children should not use the drug due to the risk of brain damage caused by elevated bilirubin. The revised label can be viewed at ***www.reyataz.com.***

In June, the prescribing information for lopinavir/ritonavir (Kaletra) tablets and oral solution was updated to include dosing recommendations for infants aged 14 days to 6 months and adolescents aged 12 to 18 years. The revised product label is available at ***www.kaletra.com.***

The same month, the FDA approved a new oral solution of tipranavir (Aptivus) for treatment-experienced children and adolescents; the drug's product label was updated to include dosing recommendations for pediatric patients aged 2 to 18 years. According to Boehringer Ingelheim, the oral solution will be available in pharmacies by mid-September. Full prescribing information is available at ***www.aptivus.com.***

The FDA also approved labeling changes for nevirapine (Viramune) tablets and oral solution to reflect new dosing recommendations for infants aged 15 days to 2 months. Doses for all pediatric age groups are now based on body surface area rather than weight. For details, see ***www.viramune.com/viramuneus.html.***

NELFINAVIR (VIRACEPT) OK'D FOR CHILDREN AND PREGNANT WOMEN

As reported in the Summer 2007 issue of *BETA,* nelfinavir (Viracept) manufactured by Roche and marketed outside the U.S. was recalled in June 2007 due to an unacceptable level of the chemical contaminant ethyl methanesulfonate (EMS).

Nelfinavir produced by Pfizer for sale in the U.S. did not contain significant amounts of EMS and was not recalled, but the FDA asked the company to limit levels of the chemical, which can potentially cause genetic damage, birth defects, and cancer. Based on this concern, Pfizer, the FDA, and the DHHS guidelines panel recommended last year that children and pregnant women starting antiretroviral therapy should not receive nelfinavir; children already taking nelfinavir could continue, but pregnant women were advised to switch to an alternative drug.

This spring, Pfizer and the FDA agreed on a specification for levels of EMS in nelfinavir, and the restrictions on its use were lifted. Effective March 31, all nelfinavir manufactured by Pfizer meets the new final limits, and the drug may again be prescribed for all patient populations, including children and pregnant women with HIV. For full updated prescribing information, see ***www.viracept.com.***

UPDATED OPPORTUNISTIC INFECTION GUIDELINES

In mid-June, the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Diseases Society of America released updated guidelines for the prevention and treatment of opportunistic infections (OIs) in children, adolescents, and adults with HIV.

Major changes to the adolescent and adult guidelines include a greater emphasis on the importance of antiretroviral therapy for prevention and treatment of OIs. This was illustrated by a study presented at the Retrovirus conference (*abstract 142*) which showed that delaying antiretroviral therapy even for several weeks while starting OI treatment was associated with a higher risk of AIDS progression or death compared with immediate HAART.

The revised guidelines also include added information on diagnosis and management of immune reconstitution inflammatory syndrome (IRIS), detection and treatment of tuberculosis, and new sections on hepatitis B virus infection and malaria.

The documents are available at ***www.aidsinfo.nih.gov/Guidelines*** and are being reviewed for publication in the CDC's *Morbidity and Mortality Weekly Report.*

MORE SENSITIVE TROFILE TEST AVAILABLE

In early June, Monogram Biosciences announced the immediate availability of a new, more sensitive Trofile assay for measuring HIV tropism. Tropism tests are used to determine whether HIV uses the CCR5 or CXCR4 coreceptor, or both, to enter CD4 T-cells. Individuals who have exclusively CCR5-tropic virus (that is, not CXCR4-tropic or dual- or mixed-tropic strains) are potentially eligible to use the recently approved CCR5 antagonist maraviroc. The new Trofile assay can detect CXCR4-tropic or dual/mixed-tropic virus that composes as little as 0.3% of a person's total viral population; at that level of CXCR4-tropic virus, the assay is 100% sensitive, according to Monogram. For more information, see ***www.trofileassay.com.***

TWO ONCE-DAILY REGIMEN TRIALS MODIFIED

In March, the National Institutes of Allergy and Infectious Diseases (NIAID) modified its AIDS Clinical Trials Group (ACTG) 5202 study after interim results showed that abacavir plus 3TC (the two drugs in the Epzicom combination pill) combined with efavirenz (Sustiva) or ritonavir-boosted atazanavir did not suppress HIV as well as tenofovir/emtricitabine (the drugs in the Truvada pill) in treatment-naive patients with a high baseline viral load (above 100,000 copies/mL). In addition, the high viral load abacavir/3TC group was quicker to develop certain non-specific side effects and laboratory abnormalities. Participants in this group were informed of their blinded treatment assignment, but the other arms of the study are continuing.

These data conflict with findings from other studies. The recent HEAT trial, reported at the Retrovirus conference (*abstract 774*), showed that abacavir/3TC and tenofovir/emtricitabine in combination with once-daily lopinavir/ritonavir were both about 68% effective in suppressing HIV RNA below 50 copies/mL at 48 weeks. GSK issued a statement suggesting that the inferior results in ACTG 5202 might have been due to pre-existing drug resistance or to unrecognized abacavir hypersensitivity reactions, since the trial did not use the HLA-B*5701 genetic test to exclude susceptible individuals.

In related news, one arm of ACTG study 1571—which enrolled treatment-naive individuals in resource-limited settings—was halted in May after interim results showed that once-daily atazanavir plus emtricitabine plus enteric-coated ddI was less likely to produce undetectable viral load than efavirenz plus either twice-daily AZT/3TC (the two drugs in the Combivir pill) or once-daily tenofovir/emtricitabine. Participants assigned to the atazanavir/emtricitabine/ddI arm were advised to switch to another regimen and follow-up is continuing.

DECREASED HOSPITALIZATION OF PEOPLE WITH HIV

Long-term studies continue to confirm the benefits of combination antiretroviral therapy. In the July 11, 2008, issue of *AIDS,* Kate Buchacz of the CDC and colleagues reported that hospitalizations of HIV positive people fell by more than half between 1994—as the first protease inhibitors were coming online in clinical trials—and 2005. Declines were similar for men and women, and for all racial/ethnic groups.

Looking at medical records from 7,155 participants in the HIV Outpatient Study, the researchers found that the overall hospitalization rate decreased from 24.6 to 11.8 per 100 person-years. The decline in hospitalizations due to opportunistic illness was especially dramatic, falling from 7.6 during 1994–1996 to 1.0 during 2003–2005. Nearly one-third of patients hospitalized during the early period had an OI, falling to about 10% during 2003–2005. Conversely, the number of patients hospitalized with chronic organ disease doubled, from 7% to 14%.

Individuals with lower current or nadir (lowest-ever) CD4 cell counts were more likely to be hospitalized, adding to the growing body of evidence favoring earlier treatment (see "When to Start Antiretroviral Treatment: A Changing Equation," page 17).

DEATH RATES ALSO DECLINE

Mortality rates of people with HIV in industrialized countries have also dipped dramatically, according to a study in the July 2, 2008, *Journal of the American Medical Association.* Krishnan Bhaskaran of the U.K. Medical Research Council and colleagues reported that among HIV positive individuals on HAART, the risk of death during the first five years after seroconversion was similar to that of the general population.

Looking at 16,534 mostly European participants in the CASCADE cohort, the "excess mortality rate"—or number of deaths above the expected rate in the general population—fell from 40.8 per 1,000 person-years in the pre-HAART era (1981–1995) to 6.1 during 2004–2006. In fact, by the latter period, there was no evidence of any excess mortality during the first five years after seroconversion among sexually infected individuals; injection drug users (IDUs), however, continued to have a higher risk of death.

The mortality rate rose with longer duration of infection, resulting in an excess risk of death after ten years of 4.8% for individuals who seroconverted between the ages of 15 and 24 years, and 4.3% for those who seroconverted at age 45 or older. The researchers concluded that overall excess mortality was 94% lower during 2004–2006 compared with the pre-1996 level.

In related research presented at the Retrovirus conference (*abstract 141*), investigators with the Study Group on Death Rates at High CD4 Counts in Antiretroviral-Naive Patients reported that among 46,400 study participants, HIV positive men who have sex with men had only a slightly higher mortality risk compared with the general

population. However, HIV positive heterosexual men and women had a three times higher risk of death compared with the population as a whole, while IDUs had a 10 times greater risk.

HIV ERADICATION IS NOT YET POSSIBLE

Studies continue to show that the ultimate goal of anti-HIV treatment—complete eradication of the virus—remains out of reach using currently available therapies. Preliminary findings from David Margolis of the University of North Carolina and colleagues previously showed that valproic acid (Depakote), a drug used to treat epilepsy and bipolar disorder, could "flush" HIV out of long-lived, latently infected CD4 T-cells, rendering it susceptible to antiretroviral therapy.

In the June 19, 2008, issue of *AIDS,* however, the researchers reported that adding 1,000 mg valproic acid to standard HAART did not decrease the reservoir of resting CD4 cells in seven of the 11 patients studied, despite stable undetectable viral load using a standard assay. In the same issue, Nathalie Sagot-Lerolle from the Université René Descartes in Paris and colleagues similarly reported that 11 HIV positive individuals who maintained undetectable viral load while treated with HAART plus valproic acid for at least two years did not have fewer resting CD4 cells than did untreated patients.

As long as even a small number of such cells remain, they may later become activated, leading to resurgent HIV replication and infection of new cells. But Margolis' team found that three of the four individuals who experienced a decrease in resting CD4 cells had a plasma viral load less than 5 copies/mL using an ultra-sensitive assay that can measure down to a single copy of HIV RNA, while those with unchanged resting CD4 cell reservoirs had higher viral loads (up to 87 copies/mL). A recent analysis published in the March 11, 2008, *Proceedings of the National Academy of Sciences USA* found that more than three-quarters of people with "undetectable" viral load using a standard test had detectable virus using a single-copy assay. These results leave open the possibility that truly suppressive antiretroviral therapy that does not permit any residual viral replication might still allow for eventual HIV eradication.

HARMS OF TREATMENT INTERRUPTION

Evidence continues to accumulate showing that interruption of antiretroviral therapy has a variety of detrimental effects. Investigators with the large SMART (Strategies for Management of Anti-Retroviral Therapy) trial presented further data from their study of CD4-guided treatment interruption at the February Retrovirus conference (*abstract 36*).

SMART included 5,472 mostly treatment-experienced participants with CD4 cell counts above 350 cells/mm^3 at baseline who were randomly assigned either to remain on combination antiretroviral therapy throughout the study, or to stay off HAART while their CD4 count was above 350 cells/mm^3 and resume when it fell back to 250 cells/mm^3. The treatment interruption arm was halted in January 2006 after interim data showed that patients in this group had higher rates of illness (both AIDS-defining opportunistic conditions and major non-AIDS-related heart, liver, and kidney events) and death compared with those receiving continuous therapy.

SMART co-chair Wafaa El-Sadr reported final results from the trial, focusing on outcomes among patients in the treatment interruption arm who resumed therapy after the trial was modified. At that point, only 35% of patients in the treatment interruption arm had a viral load of 400 copies/mL or less, compared with 82% in the continuous therapy arm; median CD4 cell counts were 425 and 625 cells/mm^3, respectively. After resuming therapy, viral load decreased rapidly, but there was a delay in CD4 cell recovery.

After January 2006, rates of opportunistic disease, heart, liver, and kidney events, and death due to any cause declined in the former treatment interruption arm. However, patients who experienced a non-fatal opportunistic illness or a serious organ event during the treatment interruption phase continued to have a nearly six-fold higher risk of death after resuming therapy. (For more details on the detrimental impact of treatment interruption in SMART, including effects on cardiovascular risk factors, see "When to Start Antiretroviral Treatment: A Changing Equation," page 17).

The investigators concluded that while the risk of disease or death was significantly reduced among participants who reverted to continuous therapy after the study was modified, the decrease was "less than complete," and never reached the level of individuals who had been on continuous therapy all along. "Antiretroviral therapy interruption is associated with long-term consequences beyond the period of treatment interruption," they wrote.

Adding a further note of caution, researchers with the UK Collaborative HIV Cohort (UK CHIC) reported in the January 30 issue of *AIDS* that patients who previously underwent a structured treatment interruption with a detectable viral load remained at higher risk for virological rebound after resuming therapy and achieving HIV suppression below 50 copies/mL, as compared with individuals who never interrupted treatment.

CARDIOVASCULAR RISK IN ADULTS AND CHILDREN

Studies of cardiovascular risk factors and clinical outcomes in people with HIV continue to yield conflicting results. A previous analysis of the large D:A:D cohort, published in 2007,

showed that patients taking HAART—especially regimens containing a PI—had an increased myocardial infarction risk, which was largely attributable to elevated blood lipid levels.

A new analysis, however, suggests that this worsening cardiovascular risk profile has not led to an actual increase in the rate of heart attacks. As reported in the April 1, 2008, issue of *Clinical Infectious Diseases,* Carolyn Sabin and colleagues analyzed data collected from more than 33,000 D:A:D participants between December 1999 and February 2006. The proportion of patients at high risk for cardiovascular disease increased from 35% during 1999–2000 to 41% during 2005–2006. More participants had older age as a risk factor during the latter period (rising to 37% from 25%), but the proportion of smokers decreased (from 38% to 47%) and use of lipid-lowering drugs became more common (from 6% to 15%).

A total of 445 MIs were reported, for an incidence rate of 0.32 cases per 100 person-years, which remained stable over the follow-up period. After controlling for changes in cardiovascular risk factors, however, the MI incidence rate actually decreased over time. The investigators suggested that these findings might be attributable to "a more aggressive targeted approach to managing the risk of cardiovascular disease."

In the March 1, 2008, *Journal of Acquired Immune Deficiency Syndromes,* Samuel Bozzette and colleagues again reported no elevated risk of major cardiovascular events among U.S. veterans. Their latest analysis included 41,213 HIV positive patients (mostly men) receiving care within the Veterans Affairs health system between January 1993 and December 2003. Not surprisingly, the rate of death due to all causes fell dramatically after the introduction of HAART, but rates of serious cardiovascular events, such as heart attack or stroke, remained stable over time. Furthermore, cardiovascular events did not increase with exposure to HAART in general, duration of therapy, or use of specific antiretroviral drug classes. The researchers concluded that while cardiovascular risk in people on HAART "should be factored into individual patient management," it "does not pose an important public health risk."

More disturbing news came from a study of cardiovascular risk in HIV positive children, published in the June 6, 2008, advance online edition of the *Journal of Pediatrics.* Tracie Miller of the University of Miami and colleagues compared cardiovascular risk factors in 42 perinatally infected children and adolescents with those of matched control subjects in the general population National Health and Nutrition Examination Survey. The average age of the HIV positive children was 10 years and 76% were on HAART.

Compared with age- and sex-matched control subjects, the HIV positive children had lower body weight and lower body mass index. But they had significantly higher triglycerides, slightly elevated total and low-density lipoprotein (LDL or "bad") cholesterol, and lower high-density lipoprotein (HDL or "good") cholesterol, all of which are predictive of cardiovascular disease. PI use, in particular, was associated with abnormal lipid levels.

The researchers concluded that "children infected with HIV have adverse cardiac risk profiles" and that "antiretroviral therapy has a significant influence on these factors." Dr. Miller noted in an interview that it will take decades to determine whether these risk factors will translate into a higher rate of heart attacks and other cardiovascular events in this group, but that HIV positive children and adolescents—like adults—should eat a healthy diet, get adequate exercise, and avoid smoking.

MANAGING CARDIOVASCULAR RISK

People with HIV should take cardiovascular disease risk factors into consideration and undergo regular screening, according to recent recommendations by a group of HIV and heart disease experts. In June, the group met for a state of the science conference on an "Initiative to Decrease Cardiovascular Risk and Increase Quality of Care for Patients Living with HIV/AIDS," a joint effort of the American Heart Association (AHA) and the American Academy of HIV Medicine. Findings from the meeting will be published jointly in the *Journal of Acquired Immune Deficiency Syndromes* and the AHA journal *Circulation.*

The experts reviewed existing studies and clinical experience related to cardiovascular disease in people with HIV, in particular its association with HIV infection itself and antiretroviral therapy. They agreed that cardiovascular risk is an important concern given that HIV positive people have approximately a 70% to 80% higher risk of heart attack, though the risk remains low for younger individuals. HIV infection and its treatment can both contribute to worsening cardiovascular risk profiles, including abnormal blood lipids, in children as well as adults; furthermore, traditional risk factors such as diabetes, excess abdominal fat, and tobacco smoking are common in this group.

"It is important to stress that this report by no means diminishes the importance of antiretroviral therapy," meeting co-chair Steven Grinspoon of Harvard Medical School stated in a press release issued by the AHA. "Rather, it is a call to physicians and others who care for people with HIV to carefully evaluate them for cardiovascular risk because the literature shows that cardiovascular disease now accounts for a higher proportion of the deaths among HIV patients in this era of highly active antiretroviral therapy."

Grinspoon also cautioned against treatment interruption, noting, "we think that going on and off these medications may cause more harm than good." (Recent data on

cardiovascular outcomes in the SMART treatment interruption study are reviewed in "When to Start Antiretroviral Treatment: A Changing Equation," page 17.)

In related news, two recent studies looked at management of cardiovascular risk factors in people with HIV. In the April 1, 2008, *Journal of Acquired Immune Deficiency Syndromes,* investigators with ACTG study A5186 reported on a study of 100 HAART-treated individuals (mostly men) with elevated serum triglycerides and LDL cholesterol who were randomly assigned to take fish oil or the drug fenofibrate for eight weeks. Those who failed to achieve a target triglyceride level of 200 mg/dL or lower using either agent alone took both therapies for an additional eight weeks. After the first eight weeks, 8.5% in the fish oil group and 16.7% in the fenofibrate group achieved the triglyceride target level. But 22.7% in the combination therapy arm reached the target level, representing a reduction of 65.5%.

In the second study, published in the June 2008 edition of *AIDS Patient Care and STDs,* researchers at Temple University School of Medicine conducted an uncontrolled prospective pilot study to explore whether adding ezetimibe (Zetia) would reduce LDL cholesterol in 20 HIV positive adults on PI–based HAART (85% using a ritonavir-boosted PI) who had continued elevated LDL despite using a statin drug. Unlike statins, ezetimibe lowers blood cholesterol by blocking cholesterol absorption in the intestines. After 18 weeks, LDL decreased by a mean 12.4%, while total cholesterol fell by 9.1%. The investigators concluded that "addition of ezetimibe to [a] low-dose statin effectively lowers LDL and total cholesterol and appears to be safe and well tolerated."

PEOPLE WITH HIV HAVE HIGHER CANCER RISK

A large study published in the May 20, 2008, *Annals of Internal Medicine* adds to the mixed evidence that people with HIV are at higher risk for non-AIDS-defining cancers. Pragna Patel from the CDC and colleagues performed a prospective analysis of cancer rates among 47,832 HIV positive participants in the Adult and Adolescent Spectrum of Disease Project and 6,948 participants in the HIV Outpatient Study; these were compared with nearly 335,000,000 general population records from the National Cancer Institute's SEER surveillance program.

Over a median follow-up period of about two years, 3,550 total new cancer cases were reported in the HIV positive cohorts, of which 80% were AIDS-defining malignancies (Kaposi's sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer) and 20% were non-AIDS-defining cancers. Incidence of several non-AIDS defining cancers was significantly higher in the HIV positive group, including anal cancer (59 times more common), vaginal cancer (20 times), Hodgkin's lymphoma (18 times), liver cancer (about 7 times), lung cancer (nearly 4 times), melanoma skin cancer and oropharyngeal cancer (both 3 times), and leukemia, colorectal cancer, and kidney cancer (all about twice as common). Prostate cancer, in contrast, was significantly less common among HIV positive men, while other cancers occurred at similar rates regardless of HIV status.

As expected, incidence of AIDS-defining cancers has fallen since the introduction of HAART, although they remain more common among people with HIV compared with the general population. Relative rates of non-AIDS-defining malignancies, on the other hand, have risen as HIV positive people survive longer and have more time to develop cancer. Anal cancer increased both in absolute incidence among HIV positive people and in relative incidence compared with the general population over time.

A related study, published in the June 2008 issue of *AIDS,* likewise found a marked increase in invasive anal cancer among HIV positive individuals. Christophe Piketty and colleagues examined the incidence of anal cancer between 1992 and 2004 among 86,322 patients in the French Hospital Database on HIV. They found 132 cases of anal cancer, mostly among men who have sex with men, of whom 78% were on HAART. The incidence rate rose from 11 per 100,000 person-years during 1992–1996 to 40 per 100,000 person-years during 1999–2004.

Though not classified as AIDS-defining malignancies, anal and vaginal cancer are caused by the same human papillomavirus strains as cervical cancer. Given the data showing that HAART does not prevent anal cancer in people with HIV, the French researchers concluded that their research "supports the urgent need for developing anal cancer screening programs for HIV-infected men who have sex with men."

GENETIC VARIATION MAY RAISE RISK OF HIV INFECTION IN PEOPLE OF AFRICAN DESCENT

In the U.S., African-American men and women have a disproportionately high rate of HIV infection, despite studies showing that they are no more likely to engage in high-risk sexual or drug injection activity; worldwide, Africa accounts for by far the largest number of HIV/AIDS cases. A study published in the July 17, 2008, issue of *Cell Host and Microbe* suggests a genetic mechanism that makes people of African descent more susceptible to HIV infection might help explain this disparity.

An international team of investigators studied a protein known as Duffy antigen receptor for chemokines (DARC) expressed on the surface of red blood cells (RBCs). DARC acts as the receptor for the *Plasmodium vivax* parasite that causes a form of malaria. Individuals who carry

the DARC –46C/C genotype and do not express the antigen on their RBCs are resistant to malaria. Due to natural selection, this genetic variation became more prevalent in Africa, and is found in about 90% of Africans and two-thirds of African Americans.

In individuals who express DARC, HIV uses the antigen to attach to RBCs; as the RBCs collect viral particles, they are unavailable to attack CD4 cells. DARC also influences levels of HIV-suppressive and pro-inflammatory chemokines such as CCL5 (RANTES). Conversely, individuals who do not express DARC lack this protective mechanism. Analyzing nearly 1,300 African-American military personnel, the researchers found that those with the DARC –46C/C genotype had about a 40% greater risk of HIV infection. Extrapolating to the African population, they calculated that approximately 11% of HIV infections on that continent might be attributable to this genetic variant.

But after HIV infection occurs, DARC-negative individuals experience slower disease progression and longer survival. The investigators suggested that HIV particles carried on RBCs might remain available as a reservoir of virus that can be transferred to CD4 cells in people who express the antigen. Furthermore, individuals who do not express DARC are not susceptible to certain disease-accelerating chemokine effects, but may benefit from HIV-suppressive chemokines. DARC is also expressed on some neurons and on endothelial cells at the blood-brain barrier, and people with the –46C/C genotype were less likely to develop HIV-associated dementia.

"Although the precise mechanisms by which DARC imparts its effects on HIV-AIDS pathogenesis are unclear," the researchers concluded, "our findings indicate that the triangular relationship between this chemokine-binding protein, its natural ligands (chemokines), and pathogen (HIV) is likely to lead to biologically complex and seemingly contrasting outcomes." Corroboration by additional studies is needed, but these findings might ultimately contribute to the refinement and selective targeting of HIV vaccine candidates.

HERPES TREATMENT MAY NOT PREVENT HIV INFECTION

Despite promising preliminary findings to the contrary, treatment of herpes simplex virus type 2 (HSV-2) does not appear to lower the risk of HIV infection.

Because the presence of sexually transmitted infections (STIs) has been shown in observational studies to facilitate HIV transmission, the HIV Prevention Trials Network (HPTN) 039 Protocol Team designed a placebo-controlled Phase III study to assess whether HSV-2 suppression would reduce the rate of new HIV infections.

The analysis included 1,358 heterosexual women from South Africa, Zambia, and Zimbabwe, and 1,814 men who have sex with men from the U.S. and Peru. At enrollment, all were HIV negative and HSV-2 positive, and reported high-risk sexual activity. They were randomized to receive 400 mg twice-daily oral acyclovir (Zovirax) or placebo, and were followed for up to 18 months. Results were reported at the Retrovirus conference (*abstract 32*) and in the June 21, 2008, issue of *The Lancet*.

During follow-up, retention in the study and acyclovir adherence (by self-report and pill counts) was good, and the presence of genital ulcers was reduced by about half in the acyclovir arm. HIV incidence, however, did not differ significantly in the acyclovir and placebo arms (75 vs 64 new infections, respectively, or 3.9 vs 3.3 cases per 100 person-years). Furthermore, no significant differences were observed when participants were stratified by sex, reported adherence, or history of genital ulcer disease. Lead investigator Connie Celum of the University of Washington at Seattle said the findings were "surprising and disappointing," given earlier data showing that acyclovir was associated with decreased plasma and genital HIV levels.

The HTPN 039 results were supported by another study published in the April 10, 2008, *New England Journal of Medicine* (*NEJM*). Deborah Watson-Jones and colleagues enrolled more than 800 women working at recreational facilities in Tanzania. Here, too, women who were HIV negative and HSV-2 positive were randomly assigned to receive 400 mg twice-daily acyclovir or placebo. After 12–30 months of follow-up—again, despite good reported adherence—HIV incidence was similar in the acyclovir and placebo arms (27 vs 28 new infections, respectively, for an overall incidence rate of 4.27 per 100 person-years).

The investigators concluded that "these data show no evidence that acyclovir (400 mg twice daily) as HSV suppressive therapy decreases the incidence of infection with HIV." However, they noted that urine tests showed that many of the women were not taking acyclovir as directed and some had undetectable drug levels, leading them to suggest that higher acyclovir doses and better adherence might offer more protection against HIV.

Dr. Celum likewise suggested that controlling sexually transmitted infections as a method of HIV prevention may still be a viable approach, possibly using more potent therapies. In a small pilot study of 20 HIV positive Peruvian women with HSV-2 presented at the Retrovirus meeting (*abstract 676*), researchers found that the acyclovir prodrug valacyclovir (Valtrex) reduced plasma and cervical HIV viral load. But it remains to be seen whether valacyclovir will perform any better than acyclovir when it comes to actually reducing HIV transmission.

HIV VACCINE TRIALS FACE MORE SETBACKS

As reported in the Winter 2008 issue of *BETA,* NIAID's HIV Vaccine Trials Network and Merck last fall halted development of the vaccine candidate V520 (also known as MRKAd5) after interim data showed that it did not lower the risk of HIV infection or slow disease progression among 3,000 high-risk participants in the STEP trial.

A more complete data analysis revealed that vaccine recipients appeared to actually have an increased risk of HIV infection, although this was limited to male volunteers who had pre-existing immunity to adenovirus type 5, a common cold virus used to carry HIV proteins in the vaccine. (For more on HIV vaccines and how they work, see "New Approaches to HIV Prevention" in the Winter 2007 issue of *BETA*.)

At the February Retrovirus conference, researchers provided further data from the STEP trial in two late-breaker presentations (*abstracts 88LB* and *89LB*). Post hoc analysis revealed no obvious differences in immunological response that might explain the unexpected results. Among uncircumcised men, those who received the vaccine were four times more likely to become infected with HIV than were placebo recipients; among circumcised men, however, there was no significant difference between the vaccine and placebo arms. Study participants outside North America also had a higher risk of infection, but the researchers suggested this might be attributable to differences in circumcision practices. Circumcision status was not initially taken into account because the clear protective effect of circumcision had not yet been established when the STEP trial was designed.

Following these presentations, Ronald Desrosiers of Harvard Medical School and Neal Nathanson of the University of Pennsylvania reviewed data from laboratory, animal, and human vaccine studies to date, with both reaching pessimistic conclusions about the future of preventive vaccine research. According to Dr. Desrosiers, there is "no rational basis" for believing that any vaccine candidates in development "have any reasonable hope" of being effective. Dr. Nathanson urged researchers to "go back to the drawing board" of basic science to devise more promising approaches.

NIAID convened a meeting with researchers in March to re-evaluate the agency's $500 million HIV vaccine research program. NIAID director Anthony Fauci reassured participants that "under no circumstances" would the federal government completely abandon AIDS vaccine research.

On July 17, however, NIAID announced that it will not proceed with the PAVE 100 trial, which was designed to study a candidate developed by the Vaccine Research Center (VRC)—which employs a prime-boost strategy using an adenovirus type 5 vector like the one in the failed Merck product—in 8,500 volunteers in the U.S. and around the world. In the wake of the STEP findings, the PAVE 100 trial was first scaled down to include just 2,400 circumcised U.S. men without pre-existing adenovirus immunity, but then was completely cancelled. However, NIAID stated in a media release that the VRC candidate is "scientifically intriguing and sufficiently different from previously tested HIV vaccines" to consider testing it in a smaller, more focused trial to assess whether it might lower viral load in vaccinated individuals who nevertheless become infected with HIV.

ANTIRETROVIRAL THERAPY AS PREVENTION

Given recent setbacks with other prevention initiatives, some researchers have suggested that expanding access to antiretroviral therapy might help limit the epidemic. As reported in the July 1, 2008, *Journal of Infectious Diseases,* Julio Montaner and colleagues with the British Columbia Centre for Excellence in HIV/AIDS in Vancouver constructed a mathematical model to assess the potential effect of greater HAART coverage among individuals with a medical need for treatment on the number of new HIV infections in British Columbia over the next 25 years.

Looking at different scenarios involving varying degrees of drug resistance, adherence, HAART coverage, and timing, they calculated that wider HAART use could lead to "substantial reductions in the growth of the HIV epidemic and related costs." If all medically eligible individuals were to start HAART at the recommended threshold of 350 cells/mm^3 and maintain good adherence, the researchers suggested, nearly two-thirds of new infections might be averted by the year 2030. They also calculated that at today's prices, expanding treatment coverage to this extent would save about $95 million. These findings, they stated, "provide powerful additional motivation to accelerate the roll out of HAART programs aggressively targeting those in medical need, both for their own benefit and as a means of decreasing new HIV infections."

PREVENTION OF HIV TRANSMISSION DURING BREASTFEEDING

While antiretroviral prophylaxis during pregnancy and delivery has dramatically reduced the rate of mother-to-child HIV transmission, the World Health Organization estimates that upwards of 200,000 infants per year are still infected through breastfeeding, primarily in resource-limited settings where formula-feeding may not be safe or feasible. But researchers have recently demonstrated that longer antiretroviral therapy for infants and mothers can significantly reduce this risk.

As reported at the Retrovirus conference (*abstract 42LB*) and in the July 10, 2008, *NEJM,* Taha Taha and colleagues studied the benefits of extended nevirapine prophylaxis for infants. The researchers enrolled 3,016 babies born to HIV positive women in Blantyre, Malawi. Infants were randomly assigned to receive a standard control regimen of single-dose nevirapine during delivery plus one week of AZT after birth, or else the standard regimen plus extended daily nevirapine with or without AZT until the age of 14 weeks.

Infants receiving extended therapy had consistently lower rates of HIV infection from the age of six weeks through 18 months: 5.2% for extended nevirapine monotherapy, 6.4% for extended dual prophylaxis, and 10.6% for the short control regimen. However, the transmission rate more than doubled in the extended prophylaxis arms between nine and 24 months, after the infants had discontinued therapy, as 15%–20% continued to breastfeed. Thus, by 12–15 months, the advantage in HIV-free survival was no longer evident and overall mortality rates did not differ significantly across study arms.

In an accompanying editorial, Glenda Gray and Haroon Saloojee from the University of Witwatersrand in Johannesburg, South Africa, argued that "it stands to reason that in settings where breastfeeding must be the practice for socioeconomic reasons, antiretroviral prophylaxis for infants for the duration of breastfeeding may be the logical approach."

Another study presented at the Retrovirus conference (*abstract 45aLB*) showed that treating mothers longer can also reduce HIV transmission during breastfeeding. The Kisumu Breastfeeding Study looked at 502 infants born to HIV positive women in Kenya who took AZT/3TC plus nevirapine from 34 weeks of gestation through six months postpartum (partway through the study, nevirapine was replaced with nelfinavir if a woman's CD4 count was above 250 cells/mm^3). Infants received single-dose nevirapine at birth. Mothers were advised to breastfeed exclusively for six months, then wean rapidly to avoid mixed feeding of breast milk and other foods.

A total of 29 infants became HIV infected by 18 months of follow-up, with three infections occurring after six months, and two after one year. The cumulative infant infection rate at 12 months was 5.9%, which fell to 3.5% after excluding babies who were presumably infected during delivery. The infection rate was higher for boys compared with girls, but rates did not differ according to maternal CD4 count. The investigators concluded that "low 12-month infant HIV transmission rates were achieved using maternal HAART from late pregnancy through six months of breastfeeding."

Finally, a second study in the same issue of *NEJM* assessed the effects of early weaning on HIV transmission. The Zambia Exclusive Breastfeeding Study enrolled 958 HIV positive women and their infants in Lusaka, Zambia, who planned to breastfeed exclusively for the first four months. Half were randomly assigned to a counseling program that encouraged abrupt weaning at four months and provided free formula, while the rest were encouraged to continue breastfeeding as long as they wished. In practice, however, there was considerable overlap, since nearly one-third of women in the abrupt weaning group did not complete early weaning.

Between four and 24 months, 6.2% of the infants in the abrupt weaning group and 8.8% in the prolonged breastfeeding group became infected with HIV—not a statistically significant difference—and rates of HIV-free infant survival were similar (64.0%–68.4%). But among babies who were infected by four months, those who stopped breastfeeding early had a significantly higher risk of death by 24 months than those who breastfed longer (73.6% vs 54.8%). The researchers concluded that early, abrupt cessation of breastfeeding in a low-resource setting "does not improve the rate of HIV-free survival among children born to HIV-infected mothers and is harmful to HIV-infected infants."

HIV ON THE RISE AMONG YOUNG GAY MEN

The CDC recently reported new figures indicating that the rate of HIV infection is rising among young gay men.

In late March, the agency released updated estimates reflecting expanded name-based reporting of HIV cases, which many states had previously utilized only for AIDS diagnoses. The agency estimated that in 2006, there were 35,314 new cases of HIV/AIDS in adults, adolescents, and children in the 33 states with consistent name-based reporting. Adding areas that only recently began reporting by name (including such large states as California, Illinois, and Michigan) brought the estimate up to 52,878—well above the 40,000 figure the CDC has cited for several years as the annual number of new HIV infections.

The agency said that the updated numbers do not represent an increase in either new infections or new diagnoses, but rather reflect the larger total population in these additional areas, which together accounted for more than 18,000 of the 2006 cases. The CDC maintained that the estimated number of newly diagnosed HIV/AIDS cases in the 50 states and the District of Columbia remained stable between 2003 and 2006, while the overall prevalence (total existing cases) steadily increased.

Among adults and adolescents diagnosed with HIV/AIDS in 2006, nearly two-thirds were men, about half were black, 30% were white, and 18% were Hispanic/Latino.

By risk category, about half were men who have sex with men (MSM), one-third were infected through high-risk heterosexual contact, and 13% were IDUs. Among men, 67% were MSM, while among women, 80% were infected through heterosexual contact.

A report in the June 27, 2008, issue of the CDC's *Morbidity & Mortality Weekly Report* provided sobering details on the rise in HIV among MSM. According to the report, of the 214,379 total new HIV/AIDS diagnoses during 2001–2006 in the 33 states with consistent name-based reporting, just under half (46%) occurred in gay or bisexual men.

But during this period, MSM were the only risk category to show an increase. Among gay and bisexual men, the number of new diagnoses rose from 16,081 in 2001 to 17,465 in 2006—an increase of 1.5% per year. In contrast, rates declined among IDUs (by 4.4% annually) and people exposed through heterosexual contact (by 9.5% annually).

The rise in new diagnoses was particularly dramatic among young gay and bisexual men (age 13–24 years), at 12.4% per year; among MSM age 45 and older, the rate rose by a smaller 2.7%. However, new cases decreased by 1.1% annually among gay men aged 25–44 years, which is promising news since this age group accounted for 64% of all cases among MSM.

Within the youngest age group, African-American MSM saw an increase of 14.9%, while whites and Hispanics/Latinos were similar at 9.4% and 7.9%, respectively. In fact, about twice as many young black gay men were diagnosed during 2001–2006 compared with their white counterparts, despite the fact that studies have shown that black MSM do not engage in riskier sexual or drug-use practices. Young Asian/Pacific Islander MSM experienced an even larger percentage increase (30.8%), though they continue to account for a small proportion of total new HIV/AIDS cases.

While the report authors acknowledged that some of the recent increase might be attributable to more widespread testing, they said testing alone could not explain the findings. "To reduce transmission of HIV among MSM of all races/ethnicities, prevention strategies should be strengthened, improved and implemented more broadly," they concluded. "Strengthened collaborations between STD, HIV, viral hepatitis, and substance abuse programs should result in more effective HIV prevention efforts."

SENATE REAUTHORIZES PEPFAR, RESCINDS HIV TRAVEL BAN

On July 16, as *BETA* went to press, the U.S. Senate voted to reauthorize the President's Emergency Plan for AIDS Relief (PEPFAR), which provides funding for HIV/AIDS prevention, antiretroviral therapy, and other medical care in resource-limited countries. (See "HIV Prevention in Zambia: Dropping the 'C' from ABC" on page 50 for more about PEPFAR.)

The new Lantos/Hyde U.S. Global Leadership against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act will replace the current PEPFAR program, which is due to expire in September. The bill triples funding to $50 billion over the next five years (from the current $15 billion), of which $2 billion will go to support health and other social services for Native Americans in the U.S.

The 80-16 vote came after a long delay while conservative legislators, including Senator Tom Coburn (R-OK), demanded changes in the proportion of funding to be spent on HIV treatment and provisions regarding abstinence and fidelity promotion in prevention efforts. The Senate rejected amendments to reduce funding levels and add language related to abortion.

The bill also includes a measure introduced by Senators John Kerry (D-MA) and Gordon Smith (R-OR) to overturn a ban on HIV positive visitors and immigrants to the U.S. The ban, first instituted in 1987, explicitly and uniquely specified HIV as an excludable condition; typically, the DHHS determines what constitutes a "communicable disease of public health significance." Advocates have widely criticized the ban, and the International AIDS Society has refused to hold its annual AIDS conferences in the U.S. for more than a decade due to the exclusionary policy.

The House of Representatives passed its own PEPFAR reauthorization bill in April, which includes the same level of funding. The House and Senate are expected to reconcile the two versions with little debate, and President George W. Bush has said he is eager to sign the legislation.