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25TH ANNIVERSARY OF AIDS

In June, the world commemorated the 25th anniversary of the first published medical reports heralding the beginning of the HIV/AIDS epidemic. The June 5, 1981 issue of *Morbidity and Mortality Weekly Report*, published by the Centers for Disease Control and Prevention (CDC), featured an article about five cases of a rare type of pneumonia in gay men in Los Angeles. This was soon followed by reports out of New York City and California about clusters of gay men with Kaposi's sarcoma, an unusual form of skin cancer. According to the CDC, more than one million people are now living with HIV/AIDS in the United States, with some 40,000 new infections annually, increasingly concentrated among African Americans.

The quarter-century commemoration was marked by a flood of ink in the national and international press, a new Joint United Nations Programme on HIV/AIDS (UNAIDS) report on the state of the epidemic, and a United Nations (UN) special session to discuss prevention and treatment efforts. According to the *UNAIDS 2006 Report on the Global AIDS Epidemic*, an estimated 38.6 million people worldwide were living with HIV/AIDS and nearly three million died from the disease last year. Although the global rate of new infections appears to have leveled off somewhat—and UNAIDS director Peter Piot, MD, described 2005 as “the least bad year in the history of the AIDS epidemic”—the number remains staggering.

As the UN special session got underway at the end of May, hundreds of activists protested outside the meeting in New York City. HIV community advocates criticized the failure of wealthy nations to provide adequate funds for HIV/AIDS care in resource-poor countries—estimated at more than \$20 billion by 2010—as well as attempts by religious conservatives to limit science-based prevention efforts (such as provision of condoms and clean needles) and thwart initiatives to empower women and girls to have greater control over their own health.

Clearly, there have been dramatic advances in response to the disease over the past two and a half decades, notably the development of increasingly effective combination antiretroviral therapy and a reduction in the rate of mother-to-child HIV transmission to less than 2% in wealthy countries. A study by Rochelle Walensky, MD, of Harvard Medical School and colleagues, published in the July 1, 2006 *Journal of Infectious Diseases*, calculated that these and other improvements in care have saved approximately three million years of life in the U.S.

However, many challenges remain, including the need for new therapies for heavily treatment-experienced patients, an effective HIV vaccine, improved prevention and education efforts, increased voluntary testing and treatment of individuals who currently do not know they are infected, and expanded availability of antiretroviral therapy on a global scale. Indeed, Walensky and colleagues estimated that 740,000 additional years of life might have been saved in the U.S. if all patients had received appropriate therapy starting at the time of HIV/AIDS diagnosis; extending this level of care throughout the world “has the potential to save hundreds of millions of years of life.”

UPDATED HIV TREATMENT GUIDELINES

On May 4, the U.S. Department of Health and Human Services (DHHS) once again updated its “Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.” The new guidelines incorporate the latest data about antiretroviral agents—including the new formulation of lopinavir/ritonavir (Kaletra)—and treatment strategies. Among the major changes, the revised guidelines include new information about short- and long-term treatment interruptions (see “Structured Treatment Interruptions: After SMART” on page 30), drug interactions, and coinfection with hepatitis B. No changes were made at this time to recommendations about which preferred or alternative antiretroviral agents to include in a first-line regimen.

The guidelines also recommend that all individuals newly diagnosed with HIV infection should receive genotypic drug-resistance testing before starting antiretroviral therapy to help select appropriate medications; the previous version recommended resistance testing only for treatment-experienced patients. In July, the “Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States” were also updated with recommendations concerning drug-resistance testing in pregnant women. A German study published in the April 15, 2006 *Journal of Acquired Immune Deficiency Syndromes* found that some 16% of individuals newly diagnosed with HIV in 2002–2003 already harbored drug-resistant virus, and that such patients could benefit from resistance testing.

For the latest updated guidelines for HIV treatment in adults, adolescents, children, and pregnant women; post-

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exposure prophylaxis (PEP) for occupational and nonoccupational exposure; and opportunistic illness prevention, see www.aidsinfo.nih.gov.

ATRIPLA APPROVED: FIRST ONE-PILL, ONCE-DAILY HAART REGIMEN

On July 12, the Food and Drug Administration (FDA) announced the approval of Atripla, a fixed-dose coformulated tablet containing Gilead Science's tenofovir disoproxil fumarate (Viread; 300 mg) and emtricitabine (Emtriva; 200 mg)—already available together in the Truvada combination pill—plus Bristol-Myers Squibb's efavirenz (Sustiva; 600 mg). Atripla is the first-ever one-pill, once-daily complete HAART regimen. It is also the first cooperative venture by two pharmaceutical companies in the HIV field to combine their patented drugs into a single product, and the first multiclass antiretroviral coformulation available in the U.S.

Atripla was approved in less than three months under the FDA's "fast track" expedited review process. Data presented at the 7th Workshop on Clinical Pharmacology of HIV Therapy in April showed that the coformulation is bioequivalent to the three separate drugs used together; that is, it is processed the same in the body and works equally well.

Atripla was approved for treatment-naïve and treatment-experienced adults; it may be taken as a stand-alone regimen or in combination with other antiretrovirals. The coformulation will cost \$1150 per month—the same as Truvada and efavirenz purchased separately—but patients may save money because insurance companies are likely to consider it a single drug requiring one copayment.

Cautions regarding Atripla are the same as for its component agents: lactic acidosis associated with nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), kidney impairment due to tenofovir (see conference coverage on page 10), and central nervous system side effects related to efavirenz (see news item on page 7); pregnant women should not use Atripla because efavirenz may cause birth defects. Discontinuation of Atripla may cause liver inflammation "flares" in people coinfecting with hepatitis B. Complete prescribing information is available at www.atripla.com.

In related news, Gilead announced in March that both tenofovir and Truvada had been granted full traditional FDA approval, following earlier conditional accelerated approval in October 2001 and August 2004, respectively. Results from Gilead's Study 934, which showed that Truvada was more effective and better tolerated than Combivir (AZT/3TC) when used with efavirenz, were reported in the January 19, 2006 *New England Journal of Medicine*.

DARUNAVIR APPROVED FOR TREATMENT-EXPERIENCED PATIENTS

On June 23, the FDA announced the accelerated approval of Tibotec's new nonpeptide protease inhibitor (PI), darunavir, formerly known as TMC114; the drug will be marketed under the brand name Prezista. Darunavir was approved for treatment-experienced adults who do not respond to other potent antiretroviral regimens. To achieve adequate concentrations, darunavir must be coadministered with a boosting dose of ritonavir (Norvir).

The approval was based on evidence from two randomized controlled trials, POWER 1 and 2, showing that boosted darunavir produced superior virological suppression and greater CD4 cell recovery compared with other boosted PIs in treatment-experienced patients with PI-resistant HIV. At this year's Conference on Retroviruses and Opportunistic Infections in February, researchers reported that 70% of patients taking darunavir experienced at least a 1-log reduction in HIV RNA and 45% achieved undetectable viral load (below 50 copies/mL) after 24 weeks, compared with 16%–32% and 7%–24%, respectively, in the comparator PI arms (*abstract 157*). Darunavir appears to work best when used in conjunction with T-20 (enfuvirtide, Fuzeon).

The most common side effects of darunavir were nausea, diarrhea, and headaches, and about 7% of study subjects developed skin rashes of varying severity; it is too soon to know whether darunavir will cause long-term metabolic manifestations (e.g., lipodystrophy) as seen with other PIs. As a condition of the accelerated approval, Tibotec (owned by Johnson & Johnson) must conduct post-marketing trials to assess how well the drug works in children and people with pre-existing liver impairment, as well as drug interaction studies. Complete prescribing information for darunavir is available at www.prezista.com.

"BLACK BOX" WARNING ABOUT BRAIN HEMORRHAGE WITH RITONAVIR-BOOSTED TIPRANAVIR

On June 30, the FDA and manufacturer Boehringer Ingelheim announced that patients taking the PI tipranavir (Aptivus) boosted with ritonavir appear to be at greater risk of developing intracranial hemorrhage (bleeding within the skull). The recent warning follows an analysis of data showing that 13 out of 6840 patients taking ritonavir-boosted tipranavir in clinical trials developed intracranial hemorrhage; one patient experienced two hemorrhages and eight died. Tipranavir was approved in June 2005 for treatment-experienced individuals with multidrug-resistant HIV. In preclinical studies, the drug inhibited

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human platelet aggregation (clotting) *in vitro* and caused impaired coagulation and fatal bleeding in mice, but this was not observed in dogs; in clinical trials, the rate of intracranial hemorrhage among subjects taking tipranavir was 0.2 per 100 person-years (PY) of exposure.

A June 30 “Dear Healthcare Professional” letter from Boehringer Ingelheim urged providers to exercise caution when prescribing tipranavir/ritonavir to patients who may be at risk for bleeding due to head trauma or surgery, who have medical conditions such as hypertension (high blood pressure) or coagulopathy (blood clotting problems), or who are taking drugs such as antiplatelet agents or anticoagulants (“blood thinners”) that may increase the risk of bleeding. The revised tipranavir label information advises patients to report any unusual or unexplained bleeding to their physician. Complete, revised tipranavir prescribing information is available at www.aptivus.com.

In related news, Boehringer Ingelheim announced earlier in June that it was discontinuing a study of ritonavir-boosted tipranavir in treatment-naïve individuals (Study 1182.33) because patients receiving tipranavir plus 200 mg ritonavir (the dose currently approved for treatment-experienced individuals) were more likely to develop elevated liver enzymes compared with patients taking lopinavir/ritonavir (Kaletra), and those taking tipranavir plus 100 mg ritonavir were less likely to achieve undetectable HIV viral load after 60 weeks.

TRIPLE-NRTI REGIMEN ASSOCIATED WITH VIROLOGICAL BREAKTHROUGH

Several studies in recent years have shown that while triple-NRTI regimens are less potent than those containing PIs or non-nucleoside reverse transcriptase inhibitors (NNRTIs), they may be appropriate for some patients, especially those with low HIV viral loads and those starting treatment for the first time. However, a study reported in the July 1, 2006 *Journal of Infectious Diseases* found that triple-NRTI combinations containing abacavir (Ziagen) were more likely to lead to eventual loss of virological control than efavirenz-based regimens. Alessandro Cozzi-Lepri and colleagues conducted an observational analysis of data from 744 patients who achieved HIV viral loads of 80 copies/mL or less while taking first-line antiretroviral regimens containing either abacavir or efavirenz plus two other NRTIs (most often AZT/3TC, d4T/3TC, or d4T/ddI). Among individuals taking triple-NRTI regimens, the rates of virological breakthrough and treatment failure were significantly higher than those seen in patients taking efavirenz. The authors concluded that patients who achieved virological suppression while taking triple-NRTI abacavir regimens were more likely to experience eventual virological break-

through, and should perhaps consider switching to a more potent regimen before treatment failure occurs.

EVEN “FAILING” HAART REDUCES ILLNESS

HAART may reduce the risk of disease progression and the incidence of AIDS-related illnesses even if it fails to suppress HIV, according to a study published in the March 15, 2006 issue of *Clinical Infectious Diseases*. Tejal Gandhi, MD, and colleagues from the University of Michigan conducted an analysis of the medical records of 302 patients who had CD4 cell nadirs (lowest-ever levels) below 200 cells/mm³, one of the criteria for an AIDS diagnosis. The researchers found that even patients with HIV viral loads above 100,000 copies/mL and CD4 cell counts below 50 cells/mm³ still had lower rates of opportunistic illnesses (OIs)—including *Mycobacterium avium* complex, *Pneumocystis pneumonia*, and esophageal candidiasis—compared with individuals who had similar CD4 counts in the pre-HAART era (39 per 100 PY vs 76 per 100 PY). Among patients with CD4 counts below 100 cells/mm³, again there were fewer AIDS-related events after the advent of HAART (18 per 100 PY vs 65 per 100 PY); among subjects with CD4 counts of 200 cells/mm³ or less, the corresponding figures were 8 per 100 PY vs 35 per 100 PY. “Even in patients with advanced immunosuppression and inadequate CD4 cell count and viral load responses to HIV therapy,” the authors concluded, “continuing HAART may reduce the incidence of new AIDS-related events.” They suggested that patients on “failing” antiretroviral therapy may harbor less virulent drug-resistant strains of HIV, or that HAART-treated individuals may have higher numbers of memory CD4 cells that attack specific pathogens, even if the overall CD4 count remains low.

RACIAL IMPACT ON LIPODYSTROPHY

The risk of developing elevated blood fat levels after starting HAART is influenced by race/ethnicity, according to a study in the March 2006 issue of the open-access journal *PLoS Medicine*. Andrea Foulkes, ScD, from the University of Massachusetts at Amherst and colleagues conducted a cross-sectional analysis of data from 626 HIV positive individuals taking part in various AIDS Clinical Trials Group (ACTG) studies of antiretroviral therapy. After controlling for other factors, race/ethnicity had a significant impact on the likelihood of blood lipid elevation. On the whole, compared with whites and Latinos, African Americans receiving HAART had lower levels of triglycerides and LDL (“bad”) cholesterol, but higher levels of HDL (“good”) cholesterol. As expected, PIs as a class—and in particular, those boosted with ritonavir—were associated with elevated blood fats. But this also differed based

on race/ethnicity: African Americans experienced the greatest triglyceride increases after starting PI-based regimens and—unlike whites and Latinos—even after starting unboosted PIs.

The authors further reported that lipid elevations were associated with variant forms of the gene for apolipoprotein C-III (apoC-III), a protein that plays a role in the transport and processing of fats. In Latino patients—but not whites or African Americans—certain apoC-III variations were associated with smaller triglyceride increases after starting HAART. The authors emphasized that long-term prospective studies are needed to confirm these observations, tease out the genetic or environmental factors involved, and determine their implications for therapy.

DEPRESSION NOT LINKED TO EFAVIRENZ

Efavirenz can cause a variety of central nervous system side effects, including unusual dreams and impaired concentration; some past studies have shown an association with anxiety and depression, and many providers therefore recommend that patients with a history of psychiatric conditions should not receive the drug. A recent study, however, did not find an increased rate of depressive illness among patients taking efavirenz. As reported in the June 15, 2006 issue of *Clinical Infectious Diseases*, Valerie Journot, PhD, and colleagues analyzed data from the French ALIZE-ANRS 099 study, in which 355 HIV positive patients with undetectable HIV viral load were randomly assigned to either continue their current PI-based regimen or switch to a simplified once-daily regimen of efavirenz/ddI/emtricitabine. After 48 weeks, rates of depressive disorders (e.g., depression, suicidal thoughts, suicide attempts) were similar in the efavirenz and PI arms (8% vs 7%), and no patients discontinued therapy due to depression. Over three years of follow-up, similar numbers in both arms were prescribed antidepressants (7% vs 4%). The only factors associated with a higher risk of depressive disorders were younger age and a prior history of depression. “Contrary to the idea widely held among HIV-infected patients, physicians, and researchers,” the authors concluded, “our data showed no evidence of efavirenz having an effect on the risk of depression or suicide in the first 48 weeks of use—or even up to 36 months of use.” While this study suggests that most patients can safely use efavirenz, caution is still warranted for patients with prior depression, since they are more likely to experience depressive symptoms again.

SMOKING WORSENS HIV PROGRESSION IN WOMEN

Tobacco smoking is associated with poorer response to antiretroviral therapy and worse disease progression in

women with HIV, according to a report published in the June 2006 *American Journal of Public Health*. Joseph Feldman, MD, and colleagues analyzed data from 924 participants starting HAART in the Women’s Interagency HIV Study; subjects were followed for periods of up to nearly eight years. After controlling for potentially confounding factors such as age, race, illegal drug use, hepatitis C coinfection, and past AIDS diagnosis, the researchers found that women who smoked cigarettes had poorer virological and immunological response to HAART, lower CD4 cell counts, higher HIV viral loads, a 36% greater likelihood of developing AIDS-defining illnesses, and a 53% higher risk of death compared with nonsmokers; however, the rate of specifically AIDS-related death was similar. The authors concluded that “[s]ome of the benefits provided by HAART are negated in cigarette smokers,” and emphasized the need for smoking cessation efforts targeting HIV positive women.

BONE LOSS AT MENOPAUSE

Bone loss, which can lead to disabling fractures, is a concern for all women as they age; a recent study published in the April 1, 2006 issue of *Clinical Infectious Diseases* suggests that the problem may be more common among women with HIV. Julia Arnsten, MD, and colleagues with the U.S. Menopause Study analyzed data from 263 HIV positive and 232 HIV negative middle-aged women; the average age was 44, and most were not yet menopausal. About three-quarters were taking HAART, most were current or former tobacco smokers, 75% had a history of opiate use, and a majority were overweight. The researchers found that, overall, the HIV positive women had lower bone mineral density (BMD) in their hips and lumbar spines than HIV negative women. Among the women with HIV, 27% had low BMD, compared with 19% of HIV negative women; most affected women had osteopenia, or mild bone loss, but a few had osteoporosis, or more severe bone atrophy. After stratifying participants by race (about half were black and half white), the association between HIV and lower BMD was observed among white women but not black women; in the general population, white women are about four times more likely than black women to develop osteoporosis. Past studies have reported decreased BMD in HIV positive individuals, but these included mostly men. Some previous research has also suggested that bone loss may be a side effect of HAART, but this study did not show a link between decreased BMD and use of antiretroviral therapy in general or any specific drugs. The authors recommended that HIV positive women should be screened for osteopenia as they approach menopause,

and should consider speaking with their health-care providers about taking calcium and vitamin D supplements.

CONFERENCE COVERAGE

Several recent conferences have featured reports related to HIV/AIDS, most prominently the 13th Conference on Retroviruses and Opportunistic Infections, held February 5–8 in Denver, the 7th International Workshop on Clinical Pharmacology of HIV Therapy, held April 20–22 in Lisbon, and the XV International HIV Drug Resistance Workshop, held June 13–17 in Sitges, Spain. Also in April, the Microbicides 2006 conference showcased the latest scientific and public policy information related to the development of microbicides to prevent sexual transmission of HIV; this meeting is covered on page 37. Two major liver disease conferences, the 41st European Association for the Study of the Liver (EASL) meeting in Vienna in April and the Digestive Disease Week 2006 conference in Los Angeles in May, covered hepatitis B and C, including some presentations on HIV/hepatitis coinfection.

Due to the large amount of information presented at these meetings, *BETA*'s news summaries are necessarily incomplete; for more in-depth conference coverage, see the Web sites listed below.

ON THE WEB

RETROVIRUS CONFERENCE:

www.retroconference.org/2006

DRUG RESISTANCE WORKSHOP:

www.informedhorizons.com/resistance2006

MICROBICIDES 2006:

www.microbicides2006.org

CONFERENCE COVERAGE:

www.aidsmap.org

www.hivandhepatitis.com

www.natap.org

www.thebody.com

HIGHLIGHTS FROM THE RETROVIRUS CONFERENCE

The Retrovirus conference featured numerous reports on advances in antiretroviral therapy, management of treatment-related side effects, and new drugs in development. One topic that generated considerable interest was data showing that CD4-guided strategic treatment interruptions do not appear to be beneficial, and may in fact be harmful. The treatment-interruption arms of three major trials

(SMART, DART, and Trivacan) were stopped early after it was observed that patients were more likely to experience serious illness or death; the risks and benefits of treatment interruption are discussed in an article on page 30.

BENEFITS OF EARLY HAART

Three studies presented at the conference found that early antiretroviral therapy appears to offer greater benefits with fewer side effects. Jonathan Sterne, MD, presented data on behalf of the international ART Cohort Collaboration (*abstract 525*), which followed 10,885 treatment-naive patients for a median of 2.7 years. After controlling for duration of therapy, patients who started with CD4 counts of 350–500 cells/mm³ were less likely to progress to AIDS or death than those who started with 200–350 cells/mm³, who in turn were less likely to progress than those starting with fewer than 200 cells/mm³.

In the Hopkins HIV Clinical Cohort (*abstract 529*), 262 patients who maintained virological suppression on HAART were followed for up to five years. Those who started therapy with higher CD4 cell counts were more likely to eventually achieve normal levels. Among those who started with CD4 counts below 200 cells/mm³, the mean CD4 count attained during follow-up was 423 cells/mm³, compared with 501 cells/mm³ for those starting treatment with 201–350 cells/mm³, and 681 cells/mm³—near the normal level—for those starting with more than 350 cells/mm³.

Kenneth Lichtenstein, MD, of the University of Colorado Health Sciences Center and colleagues (*abstract 769*) conducted a retrospective analysis of medical records collected between 1996 and 2005 from more than 2300 patients in the HIV Outpatient Study (HOPS). Treatment-naive individuals who started therapy with CD4 cell counts above 350 cells/mm³ were significantly less likely to experience peripheral neuropathy, lipoatrophy (fat loss in the face and limbs), or kidney failure compared with patients who started at lower baseline levels; the authors suggested that the higher rate of toxicity in patients with lower baseline CD4 cell counts may be due to a chronic state of inflammation. In this study, starting treatment with higher CD4 counts, staying on therapy continuously, and achieving at least 95% adherence were associated with better outcomes in terms of both reduced toxicity and lower risk of AIDS-defining illness and death.

Current U.S. federal HIV treatment guidelines recommend that people start HAART when their CD4 counts fall below 350 cells/mm³. Taken together, these studies suggest there may be reason to shift back toward the “hit early” treatment philosophy, which fell out of favor due to the unexpected long-term toxicities associated with antiretroviral therapy.

HAART-RELATED TOXICITIES

Numerous presentations at the Retrovirus conference covered HAART-related toxicities and their management.

Cardiovascular Risk

Data from the large international D:A:D study, following more than 23,000 HIV positive individuals, have shown that antiretroviral therapy is associated with an increased risk of heart attacks and strokes. In 2003, researchers reported that the risk of myocardial infarction increased by 26% per year on HAART; at the 2005 Retrovirus conference, they reported that the rate appeared to have leveled off, to 17%. This year, Nina Friis-Møller, MD (*abstract 144*) presented the latest data showing that the increase in risk per year has fallen further, to 16%, representing 3.65 heart attacks per 1000 PY of treatment. She also reported that the elevated risk of cardiovascular events was associated with use of PIs, but not NNRTIs; the increased risk associated with PIs was attributable in part to increases in blood lipid (fat) levels.

Lichtenstein (*abstract 735*) reported that among 1744 HOPS participants seen between 1989 and 2005, 2.8% developed cardiovascular disease; however, as with D:A:D, the incidence of myocardial infarctions decreased in recent years, after peaking in 2000–2001. In this cohort, cardiovascular disease was associated with traditional risk factors, including age over 40 years, elevated blood fats, hypertension, and diabetes. Use of lipid-lowering medications reduced the risk of cardiovascular disease by two-thirds, but—in contrast to other studies—switching to a PI-sparing regimen or to atazanavir (Reyataz) did not decrease the risk.

Among the more than 5400 HIV positive patients treated at Kaiser Permanente of Northern California (*abstract 737*), the rate of cardiovascular events was twice that seen among the health plan's HIV negative members (2.9 vs 6.0 cases of cardiovascular disease per 1000 PY; 2.2 vs 3.6 heart attacks per 1000 PY). Like D:A:D, this study also found a 16% increase in cardiovascular risk per year of HAART use; here, too, the annual rate leveled off, after peaking at 4–6 years' use of antiretroviral therapy. Unlike D:A:D, however, the risk of cardiovascular events did not differ significantly between patients taking PIs or NNRTIs (though there was a trend toward higher rates with PIs).

The recent decrease in cardiovascular events in these studies may be in part due to more aggressive use of adjunct medications to manage elevated blood lipids (increasing from 1% in 2001 to 27% in 2005 in the Kaiser study), hypertension, and blood glucose abnormalities, as well as wider use of the newer PI, atazanavir (increasing from 6% to 35% at Kaiser), which is less likely to cause blood-lipid elevation.

Managing Metabolic Manifestations

Several presentations covered strategies for managing HAART-related metabolic manifestations, including peripheral fat loss, central fat accumulation, and elevated blood lipids. One study looked at whether pioglitazone (Actos), a medication used to manage type 2 diabetes, can help restore lost limb fat. A related agent, rosiglitazone (Avandia), offers minimal or no benefit, according to several past studies. In this double-blind, placebo-controlled study of 130 heavily treatment-experienced participants with lipoatrophy (*abstract 151LB*), patients in the pioglitazone arm experienced a significant increase in limb fat as assessed by DEXA scans—unless they were taking d4T (stavudine, Zerit)—but the improvement was too subtle for patients to notice.

Moving on to fat accumulation, Rakhi Kohli, MD, from Tufts University and colleagues (*abstract 148*) reported that in a placebo-controlled trial of 48 participants with normal glucose tolerance, another diabetes drug, metformin (Glucophage), did not significantly reduce visceral fat after 24 weeks (again, assessed by DEXA scans). Patients also experienced no improvement in blood lipid levels, but did show an overall reduction in body mass index (BMI). Kathleen Mulligan, PhD, of the University of California at San Francisco and colleagues (*abstract 147*) reported data from a study of 105 HIV positive individuals with insulin resistance randomly assigned to receive metformin alone or metformin plus rosiglitazone. After 16 weeks, no significant changes in either visceral abdominal fat or subcutaneous fat were observed in either arm.

Study ACTG 5079 (*abstract 149*) included 88 men with abdominal fat accumulation and moderate hypogonadism (low testosterone); half were randomly assigned to use a 1% testosterone gel, while the rest used an inactive placebo gel. After 24 weeks, no significant difference was observed in terms of visceral fat reduction (as measured by CT scans), although the men in the testosterone arm lost significantly more subcutaneous and total abdominal fat, as well as trunk, limb, and whole-body fat. These results suggest that testosterone replacement should be used with caution in patients with lipoatrophy.

Finally, another study showed that a combination of fish oil (which contains omega-3 fatty acids) plus fenofibrate reduced triglyceride levels more than either alone. In the ACTG 5186 study (*abstract 146*), 100 HIV positive individuals with triglyceride levels above 400 mg/dL were randomly assigned to receive either fish oil or fenofibrate; those who did not show improvement after eight weeks (about 90%) added the second therapy. After an additional 12 weeks, triglycerides decreased by 65%, although three-quarters of the patients still did not reach values below 200 mg/dL (150–200 mg/dL is considered “borderline high”).

Taken together, these studies produced disappointing results overall, pointing to the need for more potent adjunct therapies for managing lipodystrophy or—better yet—antiretroviral medications that cause less metabolic toxicity.

Tenofovir Kidney Toxicity

Kidney toxicity has long been a concern with tenofovir (and the combination pills that contain it, Truvada and Atripla), and various studies have produced conflicting data—including several presented at the Retrovirus conference. Mark Nelson, MD, and colleagues (*abstract 781*) analyzed data from 10,343 patients in the tenofovir expanded access programs (EAPs) and from post-marketing safety reports received through April 2005. In the EAPs, only 0.57% experienced serious kidney problems. In the post-marketing database (which included some patients with pre-existing kidney impairment), the rate of kidney failure was 43 per 100,000 PY.

The CDC's Adult/Adolescent Spectrum of Disease database (*abstract 779*) collected safety information on 11,362 HIV positive individuals without pre-existing kidney disease. Here, the rates of kidney impairment among patients taking tenofovir were 35.1%, 6.4%, and 2.6%, respectively, for mild, moderate, and severe dysfunction. Tenofovir use increased the overall risk of kidney impairment by 60%, although there was no significant association with severe impairment. Kidney problems were associated with older age (over 50 years), lower CD4 cell count, diabetes, high blood pressure, and anemia.

In the University of Washington HIV cohort (*abstract 780*), 17.5% of the nearly 500 patients taking tenofovir showed evidence of kidney impairment. Here, kidney problems were associated with age over 50 years, low body weight, and use of ddI (didanosine, Videx). Jodie Guest, PhD, of the Atlanta Veterans Administration Medical Center and colleagues (*abstract 778*) reported that in a group of 222 heavily treatment-experienced patients with advanced HIV disease, 17.1% developed nephrotoxicity (damage to the kidney tubules), 13% developed hypophosphatemia (low blood phosphate), and 4% had impaired creatinine clearance during the first year on tenofovir.

While interpretation of these studies is complicated by the varying measures of kidney impairment, the take-home message is that the overall rate of kidney toxicity is low among patients taking tenofovir, and that it typically occurs in people with other risk factors, such as pre-existing kidney dysfunction or concurrent use of other nephrotoxic drugs. Gilead recommends that people with severe kidney impairment should not take tenofovir, and that those with mild-to-moderate impairment may require dose-interval adjustment because they clear the drug from their kidneys more slowly; additional caution is warranted with

the fixed-dose combination pills because the tenofovir dose cannot be independently adjusted.

HIGHLIGHTS FROM THE CLINICAL PHARMACOLOGY WORKSHOP

One of the key refinements in antiretroviral therapy in recent years has been a growing recognition of the need for individualized therapy. The 7th International Workshop on Clinical Pharmacology of HIV Therapy featured numerous presentations looking at the influence of individual variability—including genetic polymorphisms—on drug metabolism and toxicity. For example, a genetic polymorphism in the deoxythymidylate kinase (dTMPK) enzyme, which converts AZT to its active form in the body, may increase the risk for anemia and neutropenia (*abstract 32*). Variations in another enzyme, uridine diphosphate glucuronosyltransferase (UGT), were associated with high bilirubin levels in individuals taking atazanavir (*abstract 30*).

Four studies offered conflicting data about interactions between PIs and tenofovir. Certain ritonavir-boosted PIs can slow tenofovir clearance and thereby increase concentrations in the kidneys—potentially raising the risk of toxicity—by interfering with the activity of the transporter proteins MPR2 and/or MPR4 (*abstracts 34, 38, 39, 49*). Another drug interaction study showed that efavirenz reduces blood levels of the PI darunavir, while darunavir increases efavirenz concentrations (*abstract 55*). Several other studies looked at the pharmacokinetics and pharmacodynamics of various antiretroviral agents, as well as new methods of therapeutic drug monitoring. One study that generated considerable interest (*abstract 82*) found that in 45 healthy volunteers, the recently approved fixed-dose tenofovir/emtricitabine/efavirenz combination pill, Atripla, is bioequivalent to the three separate drugs taken together (see news item on page 5).

ABACAVIR HYPERSENSITIVITY TEST

One of the most practical current applications of “pharmacogenomics” is genetic testing to determine which patients will develop hypersensitivity reactions to abacavir (Ziagen, also present in the combination pills Trizivir and Epzicom). The reaction, characterized by nausea, abdominal pain, fever, skin rash, shortness of breath, cough, and/or sore throat, has been observed in 3%–9% of patients in various studies. If abacavir is stopped due to hypersensitivity and restarted in the future, a life-threatening reaction may occur. Past research has linked abacavir hypersensitivity with a genetic variation known as HLA-B*5701, which occurs most frequently among whites. A study presented at the Retrovirus conference (*abstract 667a*) found that 13% of whites and 7% of blacks tested

Shering-Plough previously announced that it would halt development of vicriviroc due to virological breakthrough, but decided, based on the latest safety data, to continue a Phase II trial using higher doses.

in the United Kingdom carried this variant—both higher than expected rates.

At the Clinical Pharmacology Workshop, Elizabeth Phillips, MD, and colleagues (*abstract 33*) presented data showing that a genetic patch test can be used to detect the HLA-B*5701 variant. Among 46 patients at four international sites, all 23 participants with positive patch test results carried HLA-B*5701, compared with only two of 23 individuals with negative patch test results. Six people with previous suspected hypersensitivity reactions who had negative patch tests and lacked HLA-B*5701 did not experience hypersensitivity after abacavir was carefully reintroduced, suggesting that their former symptoms were not truly indicative of a reaction.

Similar results were reported by Australian researchers in the July 1, 2006 issue of *Clinical Infectious Diseases*. Andri Rauch, MD, and colleagues conducted a prospective study in which 260 abacavir-naive individuals were given a genetic test for hypersensitivity; 7.7% tested positive for the HLA-B*5701 gene. Among 148 subjects who tested negative for HLA-B*5701, none experienced hypersensitivity reactions after they started abacavir; however, among patients who tested positive, three developed hypersensitivity symptoms.

If verified in planned randomized controlled trials, genetic testing could help identify patients who have been falsely identified as hypersensitive to abacavir, potentially allowing them to try the drug again with careful monitoring.

NEW DRUGS IN AND OUT OF THE PIPELINE

The latest preclinical and clinical trial data on several experimental antiretroviral agents were presented at the Retrovirus conference. The most excitement surrounded two integrase inhibitor candidates, Merck's MK-0518 and Gilead Science's GS-9137 (also called JTK-303); these agents are covered in "Drug Watch" on page 13.

PROTEASE INHIBITORS AND NNRTIS

Researchers presented additional data on Tibotec's PI darunavir (Prezista, formerly TMC114), which was approved in June (see earlier news item). Further back in the pipeline, two PI candidates, Sequoia's SPI-256 (*abstract 501*) and the non-peptide PI GRL-02031 (*abstract 503*), were active *in vitro* against PI-resistant HIV strains. Favorable pharmacokinetic and resistance data on yet another PI candidate, Ambrilia Biopharma's PPL-100, were presented at the HIV Drug Resistance Workshop.

The recently approved PI tipranavir (Aptivus) continued to show superior efficacy over comparator PIs in heavily treatment-experienced patients who had virological failure on previous regimens (*abstract 520*). However, manufacturer Boehringer Ingelheim announced in June that it would discontinue a study comparing ritonavir-

boosted tipranavir against lopinavir/ritonavir in treatment-naive patients due to poor efficacy and concerns about liver toxicity (see earlier news item).

In the NNRTI class, Tibotec's TMC125 (etravirine) in combination with an optimized background regimen was active against HIV in patients with extensive NNRTI and PI resistance (*abstracts 154, 575b, 583*).

NRTIS

In the NRTI class, Gilead's experimental nucleotide analog prodrug GS-9148 demonstrated potent activity against NRTI-resistant HIV, good oral bioavailability, minimal mitochondrial toxicity, and low toxicity in kidney cells (*abstracts 45, 498*). A novel agent that works by a similar mechanism, the nucleotide-competing reverse transcriptase inhibitor known as NcRTI-1, blocked HIV DNA polymerase activity, but demonstrated reduced activity against viral strains with certain NRTI-resistance mutations (*abstract 47*).

In more disappointing news, Incyte Corporation announced in April that it would discontinue development of its NRTI candidate, DFC (dexelvucitabine, Reverset), after an "unacceptably high" number of participants (about 40%) in a long-term extension of the Phase IIb Study 203 developed severe lipase elevations, a sign of pancreatitis. The rate of lipase elevation was much lower among patients who also took 3TC (lamivudine, Epivir) or emtricitabine, but DFC did not work as well in these patients.

ENTRY INHIBITORS

In the entry inhibitor class, more pharmacokinetic data were presented at the Retrovirus conference for two CCR5 inhibitors, Pfizer's maraviroc (*abstracts 504, 598*) and Schering-Plough's vicriviroc (*abstracts 161LB, 582*) (both discussed in more detail in last issue's "News Briefs"). Schering-Plough previously announced that it would halt development of vicriviroc due to virological breakthrough, but decided, based on the latest safety data, to continue a Phase II trial using higher doses.

PRO 140, a monoclonal antibody targeting CCR5, was granted FDA "fast track" status in February; a poster at the Retrovirus conference (*abstract 515*) reported that PRO 140 had "favorable tolerability, pharmacokinetic, and pharmacodynamic profiles" in an initial study, and remained bound to CCR5 for more than 60 days. Researchers from Tanox reported that the monoclonal antibody TNX-355 was active against HIV that uses either CCR5 or CXCR4 coreceptors (*abstract 158LB*). Pharmacokinetic and resistance data were presented on two other monoclonal antibodies in earlier stages of development, mAb004 (*abstract 505*) and KD-247 (*abstract 506*).

Researchers from Trimeris and Roche offered preclinical data showing that two next-generation peptide fusion inhibitors, TR-290999 and TR-291144 (*abstract 48*), had potent and long-lasting *in vitro* activity against HIV, including drug-resistant strains. These agents may require injection just once per week—as opposed to twice daily for the sole approved fusion inhibitor, T-20 (enfuvirtide, Fuzeon). Researchers from Japan’s Kureha Corporation reported on two orally available CXCR4 antagonist candidates, KRH-3955 and KRH-3140, which demonstrated potent antiviral activity *in vitro* and favorable pharmacokinetic and toxicity profiles in rats (*abstract 49LB*).

NOVEL CLASSES

Based on early laboratory studies, a novel agent called CSA-54 in a class known as ceragenins appears to act on the HIV envelope, preventing the virus from attaching to CD4 cells. Another novel agent, Panacos Pharmaceuticals’ maturation inhibitor, bevirimat (PA-457), which worked well against drug-resistant HIV both *in vitro* and in a 10-day monotherapy study (*abstracts 52, 156, 509*), advanced into placebo-controlled trials in June. Finally, Pfizer’s UK201844 also appears to work as a maturation inhibitor, resulting in the production of virions with non-functional proteins (*abstract 50LB*).

TENOFOVIR TO PREVENT HIV TRANSMISSION

Antiretroviral agents have long been used for post-exposure prophylaxis (PEP) to prevent HIV from establishing itself in the body after exposure, but one agent, tenofovir, is also being studied as pre-exposure prophylaxis (PREP). Kenneth Mayer, MD, of Brown University and colleagues reported in the February 28, 2006 issue of *AIDS* that a 1% gel formulation of tenofovir may be safely used as a vaginal microbicide by HIV negative and HIV positive women; although most women reported mild side effects such as genital irritation, they also said they would use such a product if it were available.

Another recent study by Manoli Vourvahis, PharmD, and colleagues (*abstract 569*) found that oral tenofovir reaches high extracellular and intracellular concentrations—higher than plasma levels—in men’s genital tracts, and high extracellular concentrations in women’s genital tracts, after 14 days of use as monotherapy or more than 20 days after being added to an existing antiretroviral regimen. Tenofovir monotherapy significantly reduced HIV viral load in the blood and genital tract over a period of 14 days in both men and women.

However, other data presented at the Retrovirus conference suggest that a combination of tenofovir plus emtricitabine (the drugs in the Truvada pill) is more

effective than either used alone. J. Gerardo Garcia-Lerma, PhD, and colleagues from the CDC (*abstract 32LB*) administered daily subcutaneous injections of tenofovir plus emtricitabine to six rhesus macaque monkeys. After nine days, the animals were repeatedly challenged with weekly rectal exposures to a recombinant simian/human immunodeficiency virus (SHIV), in amounts similar to those present during sexual intercourse. None of the monkeys receiving combination PREP became infected after 14 exposures, compared with five out of six untreated control animals. In a third arm, two out of six monkeys became infected after receiving PREP using emtricitabine alone. In a study reported at the 2005 Retrovirus conference, all four monkeys who received PREP with tenofovir alone became infected.

Based on these results, some advocates have called for further studies of the feasibility of combination PREP in humans. “Project T” is currently looking at the safety of oral tenofovir monotherapy as PREP, but may add emtricitabine based on the latest study data (see “Open Clinical Trials” on page 52); similar studies are taking pace in Botswana and Thailand, but tenofovir PREP trials in Cambodia and Cameroon were cancelled due to ethical concerns about inadequate prevention counseling and provision of care to participants who happen to become infected.

Other concerns remain, including the fear that availability of a prophylactic medication (which may not be completely protective) might discourage people from practicing safer sex, and the possibility of the development and dissemination of tenofovir-resistant virus. Indeed, Garcia-Lerma’s team (*abstract 609*) also presented data showing that within nine weeks, all 11 monkeys who received tenofovir monotherapy as PREP showed evidence of the K65R mutation, which confers resistance to tenofovir and other NRTIs.

Lifestyle Habits That Contribute to Optimal Health

Eat a balanced diet with plenty of fruits, vegetables, and whole grains

Get some exercise every day

Sleep at least eight hours every night

Avoid smoking and second-hand smoke

Reduce alcohol intake