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**Liz
Highleyman**

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

The Conference on Retroviruses and Opportunistic Infections, which this year took place February 5–8, 2007, in Los Angeles, is one of the two major annual scientific meetings covering HIV/AIDS and its management. Highlights from the meeting are described below, along with recent news from medical journals and other sources.

O N T H E W E B

RETROVIRUS ABSTRACTS ON THE WEB

www.retroconference.org/abstractsearch

NELFINAVIR RECALLED OUTSIDE THE U.S.

On June 6, Roche announced an immediate recall of its entire stock of nelfinavir (Viracept) tablets and powder in countries outside the United States, Canada, and Japan due to a chemical impurity discovered in some of these formulations. The recall affects all nelfinavir manufactured at Roche's factory in Switzerland. Pfizer, which manufactures a slightly different formulation of nelfinavir for sale in the United States, announced that its product was not contaminated and is not affected by the recall; nelfinavir marketed by Japan Tobacco is also unaffected.

The problem was discovered after patients reported that their nelfinavir emitted a foul odor. Some batches of the drug were found to be contaminated with methane sulfonic acid ethylester (ethyl mesylate), a byproduct of the manufacturing process that is usually present in minute quantities (less than three parts per million); in the worst contamination cases, the level reached 2300 parts per million. Roche attributed the problem to "human error" rather than deliberate tampering. The contamination is a concern because the chemical is a genotoxic agent that has been shown to cause cancer in rats that ingested large amounts. Roche recommended that patients in the affected regions contact their health care providers as soon as possible to discuss switching to a nelfinavir alternative.

FDA ANNOUNCES CHANGES TO ENFUVIRTIDE AND EFAVIRENZ PRODUCT LABELS

On January 31, the FDA announced changes to the product label for efavirenz (Sustiva), reflecting new information

from studies of drug interactions with the anti-tuberculosis medication rifampin; the antifungal drugs itraconazole (Sporanox), ketoconazole (Nizoral), and voriconazole (Vfend); the lipid-lowering agents atorvastatin (Lipitor), pravastatin (Pravachol), and simvastatin (Zocor); calcium channel blockers, including bepridil (Vasacor) and diltiazem (Cardizem, Tiazac); and the antipsychotic drug pimozide (Orap). The contraindications section was revised to state that efavirenz should not be used concurrently with bepridil or pimozide. If administered together, efavirenz doses should be lowered and maintenance doses of voriconazole should be increased. For details, see the complete efavirenz package insert on the Bristol-Myers Squibb Web site at www.bms.com.

TWO NEW ANTIRETROVIRAL CLASSES NEARING APPROVAL

A major highlight of this year's Retrovirus conference was the presentation of promising data on two experimental agents, Pfizer's CCR5 antagonist maraviroc (Celsentri) and Merck's integrase inhibitor raltegravir (Isentress; formerly MK-0518). For the first time in years, two new classes of antiretroviral agents—both of which target novel steps in the HIV lifecycle—are nearing the end of the development pipeline. This offers new hope for treatment-experienced individuals who have HIV that is resistant to existing drug classes, and the best outcomes may be obtained by using the new drugs together. John Mellors, MD, of the University of Pittsburgh characterized the findings as the most exciting development since the advent of protease inhibitors in the mid-1990s.

MARAVIROC

On June 20, Pfizer announced that the U.S. Food and Drug Administration (FDA) has issued a letter granting approvable status to maraviroc. This status change does not mean that maraviroc is approved for sale; further details must be resolved before the agency can approve the drug for marketing. The FDA's Antiviral Drug Advisory Committee unanimously voted to recommend accelerated approval in April, but the panel requested additional data on use of the drug in women and people of color.

The recommendation was based on data from the MOTIVATE-1 and MOTIVATE-2 studies, as presented at the Retrovirus conference (*abstracts 104aLB, 104bLB*). These two identical Phase IIb/III trials included heavily treatment-experienced subjects with triple-class antiretroviral resistance. MOTIVATE-1 included 601 participants in North America, while MOTIVATE-2 included 475 subjects in Europe, Australia, and the U.S. Participants in all study arms were generally similar; about 90% were men, the median CD4 cell count was 150–180 cells/mm³, and the mean HIV viral load was about 65,000 copies/mL.

Subjects with CCR5-tropic HIV were randomly assigned to receive oral maraviroc at doses of 150 mg once or twice daily or else placebo, in combination with an optimized background regimen. About 40% also took enfuvirtide (Fuzeon; T-20); 62%–76% had two or fewer other active drugs in their regimens.

After 24 weeks, virological response rates were about twice as high in the maraviroc arms compared with the placebo arms; 45.6%–48.5% of patients in the maraviroc twice-daily arms and 40.8%–42.2% in the maraviroc once-daily arms achieved viral loads below 50 copies/mL, compared with 20.9%–24.6% in the placebo arms. Among individuals with no active background drugs, 29%, 18%, and 3%, respectively, achieved virological suppression; participants who also received enfuvirtide had a better response. CD4 cell counts increased from baseline by 102–112 cells/mm³ in the maraviroc arms, compared with 52–64 cells/mm³ in the placebo arms.

Adverse events were similar in the maraviroc and placebo arms, with about 5% of participants discontinuing treatment prematurely. However, there were no signs of significant liver toxicity, which had led to the abandonment of another CCR5 inhibitor candidate, aplaviroc. More subjects in the maraviroc arm experienced a shift in HIV coreceptor usage from CCR5-tropic to CXCR4-tropic or dual/mixed-tropic virus (for an explanation of HIV coreceptor tropism, see Drug Watch in the Winter 2007 issue of *BETA*).

Pfizer is conducting another Phase III trial of maraviroc in treatment-naïve patients. The drug is currently available

to eligible patients through an international expanded access program (see www.maraviroceap.com for more information).

RALTEGRAVIR

On June 27, Merck announced that the FDA has accepted a New Drug Application (NDA) for the company's investigational HIV integrase inhibitor raltegravir and granted the drug priority review status. This status is designed to speed approval of experimental agents that address unmet medical needs. The FDA is expected to review and act on the NDA within six months.

Raltegravir, which prevents HIV from inserting its genetic material into host cells, is the first drug in its class to be considered for approval. Data included in the NDA submission support the use of raltegravir in combination with other antiretroviral drugs for treatment-experienced patients with evidence of continued HIV replication despite ongoing antiretroviral therapy.

In two presentations at the conference, researchers described results from BENCHMRK-1 and BENCHMRK-2 (*abstracts 104aLB, 104bLB*), also identical Phase IIb/III trials involving heavily treatment-experienced and drug-resistant patients; BENCHMRK-1 included 350 participants in Europe, Asia, and Peru, while BENCHMRK-2 included 349 subjects in North and South America. Here, too, participants in the study arms were similar, with about 90% men, a mean CD4 cell count of about 150 cells/mm³, and mean HIV viral loads of 30,000–50,000 copies/mL.

Participants were randomly assigned to receive either 400 mg oral raltegravir twice daily or placebo, in addition to an optimized background regimen. Results at 16 weeks were presented for all subjects, and 60% had 240-week data available. Further raltegravir study data were published in the April 14, 2007, issue of *The Lancet*.

In the two studies combined, 61%–62% of patients in the raltegravir arms achieved virological suppression below 50 copies/mL, compared with 33%–36% in the placebo arms. Among subjects with no other active drugs in their regimens, 61% achieved viral loads below 400 copies/mL with raltegravir, compared with only 5% taking placebo. Among subjects who started enfuvirtide and darunavir (Prezista) at the same time, 98% achieved virological suppression with raltegravir. CD4 cell gains were about 85 cells/mm³ in the raltegravir arms and 30–40 cells/mm³ in the placebo arms.

While the FDA considers Merck's NDA, raltegravir is available to qualified patients through an expanded access program (see www.benchmark.com/secure/earmrk/earmrk.html or call 1-877-EARMRK1).

OTHER INVESTIGATIONAL DRUGS

Researchers also recently presented data on other experimental agents further back in the development pipeline.

ELVITEGRAVIR

Andrew Zolopa, MD, of Stanford University (*abstract 134LB*) presented 24-week results from a trial of Gilead Science's experimental oral integrase inhibitor elvitegravir (formerly known as GS-9137 and JTK-303). In this Phase II study, treatment-experienced patients receiving the highest dose of elvitegravir (125 mg once daily) boosted with 100 mg ritonavir (Norvir) experienced greater virological suppression than those receiving a boosted protease inhibitor (PI), all in combination with an optimized background regimen. After 24 weeks, 36% of patients in the 125-mg elvitegravir arm achieved HIV RNA levels below 50 copies/mL, versus 27% in the comparator boosted-PI arm. CD4 cell increases were similar across all arms. Elvitegravir was well tolerated, with few participants discontinuing the study due to adverse events.

TMC278

TMC278 is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) developed by Tibotec that appears to have a higher genetic barrier to resistance than currently approved drugs in its class. Anton Pozniak, MD, of Chelsea and Westminster Hospital (*abstract 144LB*) presented preliminary results from an ongoing study of 368 treatment-naïve patients randomly assigned to receive one of three once-daily doses of TMC278 (25, 75, or 150 mg) or else 600 mg efavirenz; both drugs were combined with either AZT/3TC (Combivir) or tenofovir/emtricitabine (Truvada). In a 48-week analysis of time to loss of virological response (TLOVR), there were no statistically significant differences in efficacy among the treatment arms. Patients taking TMC278 were slightly more likely to experience nausea, but less likely to develop neuropsychiatric side effects or skin rash.

VICRIVIROC

Phase II data on another experimental oral CCR5 antagonist, Shering-Plough's vicriviroc, were published in the June 2007 issue of *AIDS* and in the July 15, 2007, *Journal of Infectious Diseases*. In the first study, 48 HIV positive participants were randomly assigned to receive 10, 25, or 50 mg twice-daily vicriviroc monotherapy or placebo for 14 days. HIV viral load decreased significantly in all vicriviroc arms, and virological suppression persisted for two to three days after drug discontinuation. In the three ascending dose groups, 45%, 77%, and 82% of subjects, respectively, achieved at least a 1-log reduction in HIV

RNA. Although adverse events were common, they occurred with similar frequency in the vicriviroc and placebo arms (72% and 62%, respectively). The researchers concluded that the 50- and 100-mg total daily doses were most effective, and that the drug's long half-life suggests it may be used once daily.

The second study (ACTG 5211) included 118 treatment-experienced subjects with CCR5-tropic HIV who experienced virological failure while receiving ritonavir-containing regimens; the median CD4 cell count was 146 cells/mm³ and the median viral load was 36,380 copies/mL. Participants were randomly assigned to add vicriviroc at doses of 5, 10, or 15 mg, or else placebo, to their failing regimens for 14 days. At week 24, mean decreases in HIV RNA were significantly greater in the three vicriviroc dose groups (1.51, 1.86, and 1.68 logs, respectively), compared with the placebo arm (0.29 log). The incidence of severe (grade 3/4) adverse events was similar across all arms. However, malignancies occurred in six subjects receiving vicriviroc, compared with two receiving placebo. The researchers concluded that "vicriviroc demonstrated potent virologic suppression through 24 weeks" in treatment-experienced patients, but the higher rate of cancer remains a concern.

MORE EVIDENCE OF DARUNAVIR EFFICACY

Tibotec's second-generation PI darunavir (marketed as Prezista), approved in June 2006, continues to demonstrate efficacy at 48 weeks in treatment-experienced patients with drug resistance, according to a study published in the April 7, 2007, issue of *The Lancet*. Bonaventura Clotet, MD, and colleagues reported combined data from the ongoing international POWER 1 and POWER 2 trials, which together included more than 230 subjects who had experienced treatment failure using nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), NNRTIs, and other PIs. Participants received 600 mg darunavir boosted with 100 mg ritonavir twice daily or else a boosted comparator PI, all combined with an optimized background regimen.

After 48 weeks, in an intent-to-treat analysis, 45% of subjects taking darunavir achieved undetectable viral loads (below 50 copies/mL), compared with 10% of those taking other boosted PIs. As expected, those with more active drugs in their background regimens responded better, as did those who started enfuvirtide and darunavir at the same time. The darunavir arm also experienced a larger mean CD4 cell count increase (102 vs 19 cells/mm³). Overall, side effects—mostly mild or moderate—occurred with similar frequency in the two arms, but fewer subjects in the darunavir group discontinued for this reason.

A naturally occurring human peptide has been shown to inhibit some 60 strains of HIV-1, including those resistant to current antiretroviral drugs.

Darunavir was not associated with any particular severe adverse events, although subjects in this arm were more likely to experience elevated triglycerides and to develop herpes simplex infection (possibly a manifestation of immune response syndrome in patients with pre-existing latent herpes infection). Darunavir did not cause severe liver toxicity, even in individuals coinfecting with hepatitis B or C.

Clotet characterized the results as “very unexpected and very impressive,” given the extent of the study participants’ drug resistance. The POWER trials are continuing, and Tibotec is also conducting studies of darunavir in treatment-naive individuals.

BOOSTED ATAZANAVIR MONOTHERAPY

Maintenance monotherapy using a single boosted PI has been studied as a way to reduce side effects and improve adherence to antiretroviral therapy. However, according to a study in the April 1, 2007, *Journal of Acquired Immune Deficiency Syndromes*, boosted atazanavir (Reyataz) monotherapy may be a risky strategy. Swedish researchers conducted a pilot trial to assess the feasibility of 300 mg/100 mg atazanavir/ritonavir monotherapy in patients on stable combination antiretroviral regimens who had maintained HIV viral loads below 20 copies/mL for at least 12 months. Although the study was intended to recruit 30 patients, it was terminated early after five cases of virological failure were observed among the 15 patients enrolled to date. The investigators concluded that “Ritonavir-boosted atazanavir as maintenance monotherapy in HIV-1 infection might not be as potent as conventional antiretroviral therapy.”

NATURAL HIV ENTRY INHIBITOR DISCOVERED

In the April 20, 2007, issue of *Cell*, German researchers reported on the discovery of a naturally occurring human peptide that blocks HIV entry into cells. After screening a comprehensive “library” of more than one million small peptides generated from human blood filtrate (the residue left after kidney dialysis), they found a 20-residue amino acid sequence that reduced HIV infection by 99%. The sequence—dubbed “virus inhibitory peptide,” or VIRIP—blocks HIV entry by interacting with the gp41 fusion peptide on the viral envelope. VIRIP was shown to inhibit some 60 strains of HIV-1, including those resistant to current antiretroviral drugs, and the researchers were able to increase its potency 100-fold by changing a few amino acids. VIRIP appeared non-toxic even at high doses and did not encourage the emergence of drug-resistant virus in cell cultures. The authors suggested that their discovery might lead to the development of a new type of antiretro-

viral drug (which would probably have to be injected, like enfuvirtide) and possibly a microbicide to prevent infection. German biotechnology company Viro Pharmaceuticals is currently conducting animal studies to determine whether VIRIP is safe enough to test in humans.

BENEFITS OF EARLY TREATMENT

Since the advent of potent combination antiretroviral therapy in the mid-1990s, researchers have debated the value of early treatment. Proponents of the “hit early, hit hard” philosophy suggested that starting therapy at the earliest stages of infection might lower the viral load “set-point” (level of stabilization), but as the long-term toxicities of therapy became more apparent, experts began to favor delaying therapy until there was evidence of disease progression. Two studies presented at the Retrovirus conference provided further data on early therapy.

In the first study, Dutch researchers looked at individuals with primary HIV infection in the Amsterdam Cohort Study and the ATHENA cohort (*abstract 124LB*). Out of 332 subjects with primary HIV infection, 64 started HAART within six months of infection, of whom 32 then stopped treatment. After interrupting therapy, the viral load set-point was 0.6 log copies/mL lower in patients who started treatment early compared with those who did not do so. However, there was no difference in the rate of CD4 cell decline between the two groups.

In the second study, researchers analyzed participants in two German cohorts (*abstract 125LB*). Out of 200 subjects with primary HIV infection, 144 started treatment immediately after infection and 56 remained untreated. Untreated subjects had a lower median first viral load measurement than those who started and then interrupted early therapy. But one year after seroconversion, the untreated subjects had a median viral load of 52,880 copies/mL, compared with 38,056 copies/mL for treated patients 12 months after they stopped therapy. In addition, while treated patients experienced a CD4 count increase of 60 cells/mm³ from baseline after stopping therapy, untreated subjects had a median decrease of 87 cells/mm³.

Taken together, these studies indicate that early therapy is associated with lower HIV viral loads and possibly a slight benefit in terms of immune function. But a related study of the Johns Hopkins HIV Clinical Cohort, reported in the February 1, 2007, issue of *Clinical Infectious Diseases*, showed that CD4 count at the time of treatment initiation influenced long-term immune recovery. In this study of 655 participants followed on treatment for up to six years, subjects across all baseline CD4 cell levels experienced significant increases during the first four years on HAART, but then reached a plateau. After six years,

median CD4 cell counts were 493 cells/mm³ among patients with baseline counts of 200 or less, 508 cells/mm³ among those with baseline counts of 201–350, and 829 cells/mm³ among those with baseline counts above 350. Only 12% of patients who started treatment with 200 cells/mm³ or less eventually attained 750 cells/mm³ or greater, compared with 21% of those with baseline counts of 201–350 and 46% of those with baseline counts above 350. The researchers concluded that only individuals with baseline CD4 cell counts above 350 cells/mm³ returned to nearly normal levels after six years of follow-up.

In a similar analysis reported in the June 1, 2007, *Journal of Acquired Immune Deficiency Syndromes*, researchers found that people who started treatment early in the ATHENA cohort were more likely to eventually attain CD4 cell counts of 800 cells/mm³ or more. In this study, 20% of subjects who started treatment with CD4 counts below 50 attained at least 800 cells/mm³ after seven years on HAART, compared with 26% of those with 50–200 cells/mm³, 46% of those with 200–350 cells/mm³, 73% of those with 350–500 cells/mm³, and 87% of those with counts above 500 cells/mm³. While even patients who started treatment with very low CD4 cell counts experienced robust immunological responses, their recovery was slower and did not reach the same levels as those who started therapy earlier. The benefits of early treatment were most apparent in individuals aged 50 years or older. The authors concluded that it may be beneficial to start therapy earlier than current guidelines recommend, particularly in older patients.

In an accompanying editorial, Evan Wood, PhD, and Julio Montaner, MD, of the British Columbia Centre for Excellence in HIV/AIDS wrote that with the availability of simpler and safer antiretroviral regimens, it may be time to re-evaluate the ideal time to start therapy.

TREATMENT INTERRUPTION

Even as some researchers are encouraging earlier therapy, others are continuing to explore treatment interruption in an effort to reduce drug toxicities, inconvenience, and cost. As reported in the Winter 2007 issue of *BETA*, data from the large SMART study suggested that interruption of antiretroviral therapy in individuals with CD4 cell counts between 250 and 350 cells/mm³ was associated with a greater risk of disease progression and death (data were published in the November 30, 2006, *New England Journal of Medicine*).

Current U.S. government treatment guidelines do not recommend starting therapy until the CD4 cell count falls below 350 cells/mm³. In two recent studies, investigators looked at whether people who started therapy “too

soon”—with CD4 counts above this level—could safely stop treatment.

In ACTG study 5170 (reported in the May 15, 2007, *Journal of Infectious Diseases*), 167 HIV positive subjects with CD4 cell counts above 350 cells/mm³ underwent treatment interruption. After stopping therapy, the initial mean CD4 cell decrease was 20 cells per week during the first eight weeks, decreasing to two cells per week for the remainder of the follow-up period. By week 96, 17 patients had CD4 counts that had fallen to 250 cells/mm³ or less, and 46 had resumed antiretroviral therapy. Four were diagnosed with AIDS-defining events, all of whom still had CD4 counts above 350 cells/mm³. “Disease progression after treatment interruption was low in this cohort,” the authors concluded.

Similarly, as reported in the April 1, 2007, *Journal of Acquired Immune Deficiency Syndromes*, Dutch researchers evaluated the safety and efficacy of HAART discontinuation in the ATHENA cohort. Out of 71 enrolled participants with CD4 counts above 350 cells/mm³, 46 elected to interrupt therapy and 25 continued on HAART. After 48 weeks, the median viral load in the discontinuation group stabilized at about the pretreatment level (4.55 logs) and the median CD4 count remained above the pretreatment level (563 cells/mm³); no AIDS-defining conditions or deaths occurred after treatment interruption. Although the authors said that “HAART can safely be interrupted in patients with a high CD4 T-cell nadir,” they added that discontinuation led to no improvement in quality of life and presented a potential risk of HIV transmission to sexual partners. “We would not actively advise stopping treatment in patients who started treatment too early according to current guidelines,” the authors concluded.

CARDIOVASCULAR AND METABOLIC COMPLICATIONS

Numerous studies looking at cardiovascular and metabolic complications related to HIV infection and its treatment were presented at the Retrovirus conference or published in recent journal articles.

HEART DISEASE AND MI INCIDENCE

At the conference, two research teams presented further data on such complications in the SMART study. Of the 5472 total participants, 79 (1.4%) developed major cardiovascular events, including death, non-fatal heart attacks, silent myocardial infarctions (MIs), strokes, coronary heart disease (CHD), and related medical problems. Andrew Phillips, MD, and colleagues (*abstract 41*) showed that subjects in the intermittent therapy arm who took NRTI-only regimens had a somewhat higher risk of cardiovascular

events compared with those taking PI-based regimens, while those taking NNRTI-based regimens—especially ones containing nevirapine (Viramune)—had approximately twice the risk. However, in the continuous therapy arm, there was a small increase in the risk of cardiovascular events per additional year of exposure to PI-based, but not NNRTI-based, regimens. The researchers concluded that there was a “borderline significant excess risk of cardiovascular disease” among patients receiving intermittent therapy. Looking at body shape changes in a substudy of 275 subjects, Fehmida Visnegarwala and colleagues (*abstract 803*) found that limb fat increased after 12 months in the intermittent therapy arm, but decreased in the continuous therapy group; in addition, there were significant reductions in blood lipids in the intermittent compared with the continuous therapy arm.

Researchers from Kaiser Permanente health plan (*abstract 807*) analyzed data from a cohort of about 5000 HIV positive men and about 43,000 HIV negative men followed from 1996 through 2006; they also reported data from a surveillance cohort of all HIV positive plan members aged 35–64 years and age- and sex-matched HIV negative members. In the first comparison, age-adjusted rates of CHD and MI were 6.1 and 3.7 per 1000 person-years (PY), respectively, among HIV positive participants, compared with 2.9 and 2.2 per 1000 PY among HIV negative individuals. Both CHD and MIs were more common in patients who used PIs, and the risk increased with each additional year of PI exposure. In the surveillance cohort, MI risk increased with the introduction of HAART in 1996, but then leveled off after 1999. In this comparison, the increased risk of MI associated with HIV was especially pronounced among women.

LARGER RISK INCREASE IN WOMEN

As reported in the April 24, 2007, online edition of the *Journal of Clinical Endocrinology and Metabolism*, Steven Grinspoon, MD, and colleagues found that the link between HIV and cardiovascular disease was especially strong in women. This analysis included 3851 mostly HAART-treated HIV positive participants (about 30% women) and 1,044,589 HIV negative individuals (about 60% women) receiving care at Massachusetts General Hospital (MGH) and Brigham and Women’s Hospital in Boston between 1996 and 2004. Overall, rates of acute MI were significantly higher in HIV positive compared with HIV negative individuals (11.13 vs 6.98 cases per 1000 PY). HIV positive subjects were significantly more likely to have hypertension, diabetes, and dyslipidemia. After adjusting for these factors, as well as age, sex, and race, HIV positive individuals were nearly twice as likely to experience acute

MIs. However, separate analyses by sex showed that the difference in MI rates between HIV positive and HIV negative men was no longer statistically significant, but HIV positive women had nearly three times the MI rate of women without HIV.

ISCHEMIC HEART DISEASE

MIs are often preceded by ischemic heart disease, which involves reduced blood flow in the coronary arteries that supply the heart muscle. As reported in the June 15, 2007, issue of *Clinical Infectious Diseases*, researchers analyzed data collected between January 1995 and December 2004 from 3953 HIV positive participants in the nationwide Danish HIV Cohort Study, as well as a population-based control group of nearly 374,000 HIV negative individuals. HIV positive patients who had not started HAART were slightly more likely than control subjects to be hospitalized for ischemic heart disease, but the difference did not reach statistical significance. Soon after starting HAART, the risk became “substantially higher,” and the authors estimated that the increase was equivalent to that associated with smoking one to four cigarettes per day; after this initial jump, however, the risk did not increase further during the first eight years on therapy. Since the risk did not rise with additional time on HAART, the researchers suggested that mechanisms besides antiretroviral-associated lipid elevation might be responsible.

INFLUENCE OF DRUG CLASS

A study by Judith Shlay, MD, and colleagues, reported in the April 15, 2007, *Journal of Acquired Immune Deficiency Syndromes*, looked at metabolic parameters and body composition in 422 previously treatment-naïve participants in the CPCRA Flexible Initial Retrovirus Suppressive Therapies (FIRST) study; one-third started PI-based regimens, one-third started NNRTI-based regimens, and the remainder started regimens that included both drug classes. After a median follow-up period of five years, triglyceride and low-density lipoprotein (LDL or “bad”) cholesterol levels increased by similar amounts in patients taking PI-based or NNRTI-based regimens, but were higher in those whose regimens included both classes; high-density lipoprotein (HDL or “good”) cholesterol increased significantly more in patients taking NNRTI-based regimens. Glucose levels, insulin levels, and insulin resistance increased to a similar extent in all three groups, and changes in body composition did not differ based on treatment strategy.

TRADITIONAL RISK FACTORS

Experts continue to debate the extent to which cardiovascular complications in people with HIV are related to antiretroviral therapy as opposed to traditional risk factors. As

reported in the March 1, 2007, issue of *Clinical Infectious Diseases*, Kristin Mondy, MD, and colleagues retrospectively analyzed data from 471 HIV positive patients and matched HIV negative individuals. The overall prevalence of metabolic syndrome was similar in both groups (25.5% vs 26.5%), but the HIV positive subjects had a significantly smaller waist circumference, lower body mass index, lower HDL cholesterol levels, higher triglyceride levels, and lower glucose levels. Framingham 10-year cardiovascular risk scores were similar in the two groups, and the type or duration of antiretroviral therapy was not an independent risk factor for metabolic syndrome. “The prevalence of metabolic syndrome is high among HIV-infected persons, but not higher than the prevalence among HIV-uninfected persons,” the authors concluded, adding that “Traditional risk factors play a more significant role in the development of metabolic syndrome than do HIV treatment-associated factors.”

The latest data from the large international D:A:D study were reported in the April 26, 2007, *New England Journal of Medicine*. This ongoing study includes 23,437 HIV positive participants, mostly in Europe. Through February 2005, 345 patients had MIs during 94,469 PY of observation. The incidence of MI increased from 1.53 per 1000 PY in patients not exposed to PIs to 6.01 per 1000 PY in those who received PIs for more than six years, mainly due to dyslipidemia. In contrast, NNRTI use was not associated with an increased MI risk. In an accompanying editorial, James Stein, MD, stressed that the magnitude of the increased heart attack risk associated with PI use was low compared with other known cardiovascular risk factors, suggesting that “perhaps more effort should be spent assisting our patients with smoking cessation and the prevention of diabetes, rather than our focusing so intently on the dyslipidemic effects of antiretroviral therapy.”

EFFECT OF DIET

In another study reported at the Retrovirus conference, researchers from MGH (*abstract 813*) evaluated the relationship between diet and metabolic parameters in 356 HIV positive individuals without wasting syndrome (197 men and 159 women) and 162 HIV negative control subjects; about 90% of the HIV positive subjects were on HAART, including about two-thirds taking PIs. One-third of the HIV positive individuals met the criteria for metabolic syndrome, compared with about one-quarter of the control subjects. HIV positive participants consumed more daily calories overall, although the difference did not reach statistical significance. However, the HIV positive group consumed significantly more total dietary fat, saturated fat, and cholesterol. Saturated fat consumption was significantly associated with elevated triglyceride levels after con-

trolling for PI use and other factors. These results suggest that patient education and diet modification could play an important role in managing metabolic complications in this population.

MANAGEMENT OF ELEVATED LIPIDS

With regard to management of metabolic complications, another Kaiser Permanente study reported at the Retrovirus conference (*abstract 814*) found that lipid-lowering therapy may not work as well in people with HIV. While LDL declined to a similar extent in HIV positive and HIV negative individuals treated with lipid-lowering agents (primarily statins), those with HIV experienced smaller decreases in total cholesterol and triglyceride levels; HIV positive patients also were less likely to attain recommended blood lipid levels.

In more promising news, a French study reported in the March 1, 2007, *Journal of Acquired Immune Deficiency Syndromes* found that fish oil (which contains N-3 polyunsaturated, or omega-3, fatty acids) reduced triglyceride levels in HIV positive people on HAART. This study included 122 HIV positive participants on antiretroviral therapy who still had elevated triglyceride levels after a four-week diet. Subjects were randomly assigned to receive Maxepa fish oil capsules or placebo capsules for eight weeks, followed by an open-label phase during which all participants received fish oil. Median triglyceride levels decreased by 25.5% in the fish oil group, but rose by 1% in the placebo group. At week 8, triglyceride levels normalized in 22.4% of subjects in the fish oil arm compared with 6.5% in the placebo arm. Subjects in the fish oil arm also experienced a slight decline in total cholesterol, compared with a small increase in the placebo arm.

LIPOTROPHY TREATMENT

In late December, the FDA approved Radiesse, a new injectable therapy for facial fat loss (lipoatrophy) in people with HIV. Manufactured by BioForm Medical, Radiesse contains a synthetic material that stimulates collagen production. Approval was based on a prospective study of 100 subjects with HIV-associated facial lipoatrophy who had been receiving HAART for at least three years; 94% were men and 56% were Caucasian. Three months after injection, mean cheek thickness increased by more than 2 mm. The most common adverse events were temporary swelling, bruising, redness, and pain at the injection site. Radiesse is not a permanent treatment, but is expected to last at least several months, and possibly as long as a few years.

In other lipoatrophy news, a study in the June 15, 2007, *Journal of Infectious Diseases* showed that the thiazolidinedione drug rosiglitazone (Avandia), usually used to

Over five days, medical marijuana reduced daily peripheral neuropathy pain by 34%, compared with 17% for placebo.

treat type 2 diabetes, provided no benefit in improving fat loss in HIV positive people on HAART. The trial included 96 mostly male subjects randomly assigned to receive either 4 mg per day rosiglitazone or placebo for 24 weeks. At week 24, median changes in arm, leg, trunk, and total body fat did not differ significantly between the two groups. Individuals who switched off AZT (zidovudine; Retrovir) or d4T (Zerit), however, experienced more pronounced fat gains in the rosiglitazone arm. In related news, a meta-analysis of more than 40 prior studies, published in the June 14, 2007, *New England Journal of Medicine*, suggested that rosiglitazone may increase the risk of heart attacks. The FDA issued an advisory to health care providers, but did not ask manufacturer GlaxoSmithKline (GSK) to take any specific action; GSK contested the findings and issued a statement that included data from studies attesting to the drug's safety.

MEDICAL MARIJUANA FOR PERIPHERAL NEUROPATHY PAIN

A study reported in the February 13, 2007, issue of *Neurology* provided the first evidence from a randomized controlled trial demonstrating the therapeutic benefits of medical marijuana. Donald Abrams, MD, and colleagues from the University of California at San Francisco assessed the effect of smoked cannabis on pain related to peripheral neuropathy, a potential side effect of certain antiretroviral drugs. Between May 2003 and May 2005, 50 adults with painful HIV-associated sensory neuropathy were randomly assigned to smoke either cannabis cigarettes containing 3.56% tetrahydrocannabinol or similar placebo cigarettes with the cannabinoids removed three times daily for five days. Participants then rated their pain and underwent controlled pain testing using heat and other stimuli.

Smoking the first cannabis cigarette reduced chronic pain by a median of 72%, compared with 15% for placebo cigarettes. Over five days, smoked cannabis reduced daily pain by a median of 34%, compared with 17% for placebo cigarettes. Half the individuals who smoked marijuana experienced at least a 30% reduction in pain, compared with 24% of subjects in the placebo group. Cannabis also reduced experimentally induced pain, but had little effect on sensitivity to heat stimuli. The authors concluded that "Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings are comparable to oral drugs used for chronic neuropathic pain."

NEW HIV/HCV COINFECTION GUIDELINES

In the May 31, 2007, issue of *AIDS*, an international panel of experts led by Vincent Soriano, MD, published updated

guidelines for the management of hepatitis C virus (HCV) coinfection in HIV positive individuals, reflecting an improved understanding of concurrent infection and its treatment since the previous guidelines were issued in 2004. HIV/HCV-coinfected individuals tend to experience more rapid liver disease progression and typically do not respond as well as HCV-monoinfected individuals to treatment with pegylated interferon (Pegasys or PegIntron) plus ribavirin.

The panel issued recommendations in 11 areas. With regard to who should receive treatment for hepatitis C, the authors recommended that coinfecting individuals should be considered for therapy regardless of alanine aminotransferase (ALT) level, since the coinfecting population is more likely to develop significant fibrosis despite normal ALT. They also wrote that "liver biopsy is not mandatory for considering the treatment of chronic HCV infection," given that new noninvasive methods "accurately predict fibrosis in most cases."

In terms of treatment optimization, studies have shown that weight-based ribavirin (1000 mg/day for patients weighing under 75 kg and 1200 mg/day for those over 75 kg) is superior to a fixed dose of 800 mg/day. While some studies have tested higher doses of pegylated interferon in coinfecting subjects, the benefits have not been established and the panel recommended that such patients should receive the standard doses used for HCV-monoinfected individuals. The panel further advised that all coinfecting patients should receive 48 weeks of combination therapy regardless of genotype, although they acknowledged that 24 weeks may be adequate for those with genotypes 2 or 3, while slow-responding individuals with genotypes 1 or 4 might benefit from extended therapy (60–72 weeks). As is the case for HCV-monoinfected individuals, coinfecting patients who do not achieve early virological response by week 12 or who still have detectable HCV RNA at week 24 should be advised to stop treatment. For HIV positive individuals with acute HCV infection, the panel recommended 24-week treatment with pegylated interferon plus weight-based ribavirin, after waiting 12 weeks to allow for possible spontaneous clearance.

The panel noted that investigational drugs—including new types of interferon and directly targeted agents such as HCV protease and polymerase inhibitors—offer the prospect of improved outcomes, and recommended that "Trials exploring the efficacy and safety of these drugs in coinfecting patients should be prioritized, without waiting for the final results of Phase III trials conducted in HCV-monoinfected individuals."

Looking at antiretroviral therapy in coinfecting individuals, the panel noted that the major drug interaction con-

cerns are concurrent use of ribavirin with ddi (Videx) or AZT. They recommended that ddi and ribavirin “should never be used” together, since both can cause mitochondrial damage, while the combination of AZT and ribavirin “should also be avoided when possible,” since both can cause anemia. Finally, the panel discussed the various mechanisms by which antiretroviral drugs can cause liver toxicity. Despite the complexities of antiretroviral therapy in coinfecting patients, the panel concluded that the benefits of HAART outweigh the risks. “Since severe immunosuppression accelerates HCV-related liver fibrosis progression, it may be advisable to start HAART without unnecessary delays in coinfecting patients and even consider earlier initiation of treatment,” they wrote.

LIVER DISEASE IN HIV/HCV-COINFECTED PEOPLE

Several past studies have shown that HIV/HCV-coinfecting people experience more rapid liver fibrosis progression compared with HCV-monoinfecting individuals. However, other research suggests that this may not be the case for coinfecting patients with well-preserved immune function and high CD4 cell counts. A French study presented at the annual European Association for the Study of the Liver meeting in Barcelona in April, for example, found that HIV positive subjects with normal CD4 counts did not have worse fibrosis progression compared with HCV-monoinfecting individuals, and their HCV-specific immune responses were not impaired.

There are also conflicting data regarding the influence of antiretroviral therapy on liver disease progression. At the Retrovirus conference, Spanish researchers (*abstract 935*) reported on an analysis of liver biopsy results from 213 coinfecting patients (58% with genotype 1 HCV) who had not received HCV treatment. At the time of biopsy, the subjects had well-controlled HIV (73% with HIV RNA below 50 copies/mL) and the median CD4 count was 460 cells/mm³. Based on an estimated median time of 21 years since HCV infection, the subjects as a group had been off HAART for about 17 years and on HAART for about four years since they acquired HCV. Most subjects had mild-to-moderate (METAVIR stage F1–F2) fibrosis. Only 0.5% had absent or minimal (stage F0) fibrosis, 19% had stage F3 fibrosis, and 12% had severe bridging fibrosis or cirrhosis (stage F4). The rate of fibrosis progression decreased with additional time on HAART, while the odds of having lower (F0–F2) versus higher (F3–F4) fibrosis stages increased. The investigators concluded that “HAART reduces the fibrosis progression rate and the development of bridging fibrosis and cirrhosis in HIV/HCV-coinfecting patients.”

As discussed in a review by Stephen Shafran, MD, in the April 15, 2007, *Journal of Acquired Immune Deficiency Syndromes*, these findings confirm data from 11 previous cohort studies showing that HAART is associated with a reduced rate of HCV-related liver disease progression, four of which also demonstrated a reduction in liver-related mortality. However, treatment of chronic HCV remains more difficult in coinfecting compared with HCV-monoinfecting patients. According to Shafran’s analysis, anti-HCV therapy with pegylated interferon plus ribavirin produces sustained response in up to 40% of coinfecting patients, but only about 10% of this population are considered suitable candidates for therapy. Thus, he concluded, “Although offering HCV therapy to the few eligible HIV/HCV-coinfecting patients is important, early initiation of HAART in coinfecting patients has a greater public health impact in reducing liver-related mortality.”

The importance of HCV treatment was underlined by another recent study showing that coinfecting individuals may still experience fibrosis progression despite use of effective antiretroviral therapy. As reported in the April 1, 2007, issue of the same journal, researchers used the non-invasive AST-to-platelet ratio index (APRI) to assess fibrosis progression in 673 HIV positive individuals without liver complications at baseline; 540 had HIV alone and 133 had also had HCV. At baseline, the coinfecting patients had a higher median APRI score than HIV monoinfecting subjects (0.59 vs 0.33). Over a median follow-up period of 4.6 years, coinfecting patients were four times more likely to develop liver complications (4.5% vs. 1.1%), and did so in a shorter amount of time (2.85 vs. 3.96 years) compared with HIV monoinfecting subjects. Unexpectedly, however, HAART use was associated with greater progression of APRI scores in both HIV-monoinfecting and coinfecting subjects. A possible explanation is that drug-related liver toxicity can cause elevation of one factor in the index, the liver enzyme AST (aspartate aminotransferase). “There was clearly a complex relationship between HAART and fibrosis,” the researchers wrote. “While a higher CD4 cell count and better HIV control were indeed associated with lower rates of fibrosis progression as expected, HAART was additionally associated with increased progression in the APRI scores.” Despite the association between antiretroviral therapy and higher APRI scores, the authors noted that this did not translate into an increased rate of adverse liver-related outcomes over time, leading them to suggest that while HAART may accelerate progression to moderate-to-severe fibrosis, it may have less of an impact on further progression to end-stage liver disease. “Our findings highlight the need to treat HCV infection specifically,” they concluded, “because immune restoration from HAART alone cannot be relied on to improve outcomes in HCV coinfection.”

ENTECAVIR ACTIVE AGAINST HIV

Researchers at the Retrovirus conference (*abstract 136LB*) reported that entecavir (Baraclude), which is approved for the treatment of chronic hepatitis B virus (HBV) infection, is also active against HIV and can select for a mutation that confers resistance to certain antiretroviral drugs. Since most approved and investigational anti-HBV drugs (including adefovir [Hepsera], 3TC [Epivir], emtricitabine [Emtriva], and tenofovir [Viread]) have anti-HIV activity, entecavir—which was previously believed to have no such effect—was recommended for treating hepatitis B in HIV/HBV-coinfected patients who do not yet require antiretroviral therapy.

But this recommendation has now changed, since investigators described three HIV positive individuals not on antiretroviral therapy who experienced a 1-log drop in HIV RNA after starting hepatitis B treatment with entecavir, indicating that the drug was active against HIV, as well. Entecavir also suppressed HIV replication in laboratory tests, and *in vitro* resistance assays demonstrated the emergence of the M184V mutation, which confers resistance to 3TC and emtricitabine. Bristol Myers-Squibb, the manufacturer of entecavir, did not detect evidence of anti-HIV activity in its own studies of the drug. Nevertheless, based on the recent findings, the company issued a letter to health care providers in February, stating that the risk of developing HIV resistance “cannot be excluded” when entecavir is used in HIV/HBV-coinfected patients not receiving HAART. In April, the Department of Health and Human Services released a supplement to its HIV treatment guidelines, recommending that “For HBV/HIV-coinfected patients, entecavir should not be used for the treatment of HBV infection without concomitant treatment for HIV.”

LONGER TUBERCULOSIS TREATMENT FOR PEOPLE WITH HIV

Tuberculosis (TB) is the leading cause of death in people with HIV worldwide. An extremely drug-resistant form of the disease (XDR-TB) was described in South Africa last year and has now been reported in several countries—including a recent case in an American man who was quarantined after taking an international airline flight. Standard treatment for TB is a combination of antibiotics taken for six months. While current guidelines indicate that this regimen is adequate for both HIV negative and HIV positive individuals, a study in the June 1, 2007, *American Journal of Respiratory and Critical Care Medicine* indicated that HIV positive patients are more prone to relapse and may benefit from longer treatment.

Investigators retrospectively reviewed data from 700 TB patients (264 HIV positive, 315 HIV negative, and 121

untested) reported to the San Francisco Tuberculosis Control Program between 1990 and 2001. The overall relapse rate among HIV positive subjects was 9.3 per 100 PY, compared with 1.0 among HIV negative and unknown-serostatus individuals. Among patients with HIV, those who received the standard six-month course of therapy were significantly more likely to relapse than those treated for longer durations, as were those who received intermittent rather than daily therapy. While some experts recommend that antiretroviral therapy should be deferred until TB treatment is completed in order to avoid drug interactions and immune reconstitution syndrome, the study found that concurrent use of HAART was associated with a lower TB relapse rate, more rapid conversion to negative TB sputum smears and cultures, and improved survival.

CANCER RATES IN PEOPLE WITH HIV

Studies have produced conflicting evidence regarding the occurrence of malignancies among HIV positive people in the HAART era. While combination antiretroviral therapy can improve immune function and may thereby reduce the risk of AIDS-defining cancers such as non-Hodgkin’s lymphoma (NHL) and Kaposi’s sarcoma (KS), patients have more opportunity to develop non-AIDS-related malignancies as they live longer thanks to effective treatment.

Researchers at the Retroviruses conference (*abstract 84*) presented the latest data on rates of fatal cancer in the D:A:D study, which includes more than 23,000 HIV positive patients followed since 1999. Overall, rates of both AIDS-defining and non-AIDS-defining cancers were significantly lower in 2004–2005 compared with 1999–2001. Out of 1246 total deaths reported up to the time of the analysis, 305 were due to any type of cancer. About two-thirds of these (63%) were due to non-AIDS-defining malignancies (for a rate of 1.79 per 1000 PY) and 37% were due to AIDS-defining cancers (1.05 per 1000 PY). Among the fatal AIDS-defining malignancies, there were 82 cases of NHL, 28 cases of KS, and two cases of cervical cancer. The most common fatal non-AIDS-defining cancers were lung cancer (62 cases), gastrointestinal cancer (41 cases), hematological malignancies (20 cases), and anal cancer (20 cases).

The risk of death due to either AIDS-defining or non-AIDS-defining cancers increased with lower CD4 cell counts, but patients with fatal non-AIDS-defining cancers had a higher median CD4 count at the time of death (211 vs 75 cells/mm³) and a higher median nadir CD4 count (87 vs 30 cells/mm³) than those who died from AIDS-defining malignancies. The investigators concluded that among HIV positive individuals with access to potent antiretroviral therapy, deaths due to non-AIDS-defining cancers are now more common than those due to AIDS-defining

Gonorrhea is the second most common sexually transmitted infection in the U.S.; like many other sexually transmitted disease, it can increase the risk of contracting and transmitting HIV.

malignancies. Since lower CD4 counts are associated with a significantly increased risk of fatal cancer, they suggested that prevention of advanced immunodeficiency should be a key strategy for preventing cancer-related deaths in this population, along with attention to known risk factors such as tobacco smoking and chronic hepatitis B (a risk factor for liver cancer).

In a related study reported in the July 2007 issue of *Clinical Infectious Diseases*, researchers found that people with HIV appear to be at significantly higher risk for lung cancer, independent of smoking. This study looked at a cohort of 2086 injection drug users in Baltimore followed since 1988; about 75% were HIV positive at study entry and a further 16% seroconverted during follow-up. Most subjects (84%) reported that they smoked, and the proportion of smokers was similar in the HIV positive and HIV negative groups; 45% reported smoking 20 cigarettes (one pack) or more per day, and 10% said they smoked two packs or more. Overall, lung cancer mortality increased during the HAART era. Over 19,835 PY of observation, the investigators identified 27 lung cancer deaths, 14 of them among HIV positive individuals. All but one of the patients with lung cancer (96%) smoked, consuming a mean 1.2 packs per day. While smoking remained the major risk factor for lung cancer, HIV infection itself was associated with about a 3.5-fold increased risk after adjusting for age, sex, smoking status, and calendar period. Pre-existing lung disease (particularly noninfectious diseases and asthma) demonstrated a trend toward increased lung cancer risk, but use of illicit drugs was not associated with an increased risk. In contrast with the D:A:D findings, CD4 cell count and HIV viral load were not strongly associated with an increased risk of lung cancer.

REVISED GONORRHEA TREATMENT GUIDELINES

In April, the Centers for Disease Control and Prevention (CDC) issued updated guidelines for the treatment of gonorrhea due to an increase in drug-resistant cases nationwide. Gonorrhea is the second most common sexually transmitted infection in the U.S., with an estimated 700,000 new cases per year; like other sexually transmitted diseases that cause genital inflammation and ulceration, it can increase the risk of contracting and transmitting HIV. As reported in the April 13, 2007, issue of *Morbidity and Mortality Weekly Report*, a survey of men seen at sexual health clinics in 26 areas found that fluoroquinolone-resistant gonorrhea was reported at all but one of the surveillance sites, covering all regions of the U.S. Among heterosexual men, fluoroquinolone-resistant strains accounted for 6.7% of all gonorrhea cases reported during the first half

of 2006, up from 0.6% in 2006. The increase among men who have sex with men during the same period was even more dramatic: from 1.6% to 38.3%. Resistant gonorrhea accounted for at least 20% of all reported cases in Philadelphia, Honolulu, Long Beach, San Diego, and San Francisco.

According to the revised guidelines, gonorrhea should no longer be treated with fluoroquinolone antibiotics, including ciprofloxacin (Cipro), levofloxacin (Levaquin), or ofloxacin (Floxin). Instead, it should be treated with cephalosporins, such as injected ceftriaxone (Rocephin); oral formulations, including cefpodoxime (Vantin) or cefuroxime (Ceftin), may be appropriate alternatives. Spectinomycin (Trobicin) may be used for patients who are allergic to cephalosporins, but this drug is not yet available in the U.S. In 2000, the CDC advised against using fluoroquinolones to treat gonorrhea acquired in Asia or the Pacific Islands. The recommendation was extended to California in 2002, and then to all men who have sex with men in 2004. It now applies to all cases of gonorrhea in any population anywhere in the U.S. "We are running out of options," said John Douglas of the CDC. "There are currently no new drugs for gonorrhea in the drug development pipeline."

SAFETY OF ANTIRETROVIRAL DRUG EXPOSURE DURING PREGNANCY

While the prophylactic use of antiretroviral agents such as AZT and nevirapine has reduced the risk of mother-to-child HIV transmission to less than 2% in developed countries, there have been persistent concerns about the effects of drug exposure on babies. In an analysis of data from the Women and Infants Transmission Study reported in the March 1, 2007, *Journal of Acquired Immune Deficiency Syndromes*, researchers examined the medical records of 2527 infants born to 2353 HIV positive U.S. women between 1990 and 2004. Birth defects were identified in 90 infants, for an overall rate of 3.56 per 100 live births, which was not significantly different from the rate for babies born to HIV negative mothers. Birth defect rates were 4.05 among infants with no antiretroviral exposure, 3.19 for those with first-trimester exposure, and 3.54 for those with second- or third-trimester exposure. The only type of birth defect observed more often among babies born to women with first-trimester exposure was hypospadias, a male genital abnormality. The authors concluded that the "data were reassuring," although they acknowledged that information regarding newer antiretroviral agents was limited.

In another study, published in the March 12, 2007, issue of *AIDS*, researchers conducted a meta-analysis of

past trials of antiretroviral exposure during pregnancy; 13 prospective cohort studies and one retrospective study met the inclusion criteria. The analysis showed that use of antiretroviral therapy during pregnancy did not increase the risk of premature delivery overall. However, use of PI-based regimens and starting combination therapy before pregnancy or during the first trimester were associated with a slight increase in premature births, which may have been related to more advanced HIV disease in such women.

As reported in the May 11, 2007, issue of *AIDS*, another study analyzed data from 1037 HIV-uninfected children (born between 1991 and 1992) in PACTG study 219/219C. Overall, 20 children had evidence of possible mitochondrial toxicity (damage to energy-producing structures within cells). While there was no overall association between *in utero* NRTI exposure and mitochondrial dysfunction, children with mitochondrial problems were about 10 times more likely to have been exposed to AZT or 3TC during the third trimester.

CIRCUMCISION REDUCES HIV INFECTION RISK

In December 2006, the National Institutes of Health halted two adult male circumcision trials in Kenya and Uganda after an interim analysis showed that the intervention reduced the risk of HIV infection by about half. Results of the Uganda trial were presented at the Retrovirus conference (*abstracts 155aLB, 155BLB*), and data from both studies were published in the February 24, 2007, issue of *The Lancet*.

In both trials, young HIV negative heterosexual men (2784 in Kenya and 4996 in Uganda) were randomly assigned to undergo the procedure either immediately or after a waiting period; all participants received condoms and HIV prevention counseling. In the Kenya study, after a median 24 months of follow-up, there were 47 new HIV infections among uncircumcised men, compared with 22 among circumcised men. The two-year HIV incidence rate was 2.1% in the circumcised group and 4.2% in the control group, representing a risk reduction of 53% in an intent-to-treat analysis; in an as-treated analysis, the risk reduction was 60%. In the Uganda study, there were 43 new HIV infections among uncircumcised men and 22 among circumcised men, for an overall risk reduction of 53%, or 60% in an as-treated analysis. In both studies, circumcision did not appear to increase high-risk sexual behavior.

“Circumcision is the most potent intervention in HIV prevention that has been described,” said Kevin DeCock, MD, director of the World Health Organization (WHO) HIV/AIDS Programme, though he emphasized that it

should not be considered a replacement for other HIV prevention methods, such as condoms.

WHO and UNAIDS officials met in March to discuss the implications of these studies. Adding a further note of caution, data presented at that meeting showed that circumcision may actually increase the risk of HIV transmission to women if men resume sexual activity before their surgical wound has completely healed. Following the meeting, WHO and UNAIDS recommended that adult male circumcision be made available as part of a comprehensive prevention program in developing countries heavily affected by HIV/AIDS. They also stressed the importance of performing circumcision in a safe and sanitary manner, in light of the shortage of medical personnel and lack of health care infrastructure in many developing countries.

The benefits of adult male circumcision in developed countries with lower HIV prevalence remains open to debate. In a statement responding to the Kenya and Uganda studies, the San Francisco AIDS Foundation emphasized that circumcision does not provide absolute protection, since it “may reduce, but does not eliminate, risk of HIV infection.” The statement noted that the recent studies do not provide answers regarding men who have sex with men, anal intercourse, or circumcision of newborns or children. In conclusion, the agency wrote, “Circumcision is a personal decision that should be made in consultation with providers, pediatricians, and others.” For the full statement, see www.sfaf.org/policy/statements/circumcision.html.

USHERCELL MICROBICIDE STUDY HALTED

In January, researchers announced the discontinuation of a study of an experimental vaginal microbicide, Ushercell, due to worrisome early trial data. Ushercell, or cellulose sulfate gel, produced by Polydex Pharmaceuticals, was being developed by the nonprofit health agency CONRAD. The product had advanced through 11 Phase I and II clinical trials involving more than 500 women and about 50 men, with no evidence of safety problems. But preliminary results from a Phase III study of more than 1300 women in Benin, South Africa, Uganda, and India showed that women using Ushercell had a higher rate of HIV infection compared with women using a placebo gel. These data led the trial’s Independent Data Monitoring Committee to stop the study. As a precaution, Family Health International halted a similar trial of Ushercell in Nigeria, although a higher rate of HIV infection was not observed in that study. “While the findings are unexpected and disappointing, we will learn scientifically important information from this trial that will inform future HIV prevention research,” said principal investigator Lut Van Damme, who spoke about the CONRAD trial discontinuation at the Retrovirus

conference, but did not disclose actual data about the number of infections in the Usher cell and placebo arms.

Three other microbicides are currently in advanced clinical development. As reported in the February 19, 2007, issue of *AIDS*, researchers found that PRO2000 appeared to reduce vaginal inflammation in a study of 24 HIV negative women randomly assigned to receive either the microbicide or a placebo gel for 14 days. These are promising data, given that an earlier microbicide candidate, nonoxynol-9, was suspended after studies showed that it damaged the vaginal and rectal mucosal linings.

COULD SEROSORTING INCREASE HIV TRANSMISSION RISK?

Some harm reduction proponents, including officials with the San Francisco Department of Public Health, have proposed that serosorting—whereby people have unprotected intercourse only with others of the same HIV status—may help reduce the risk of transmission. But as reported in the May 31, 2007, issue of *AIDS*, a mathematical model by researchers from the University of California at San Diego suggests that serosorting may increase the risk of HIV transmission under some circumstances.

Newly infected individuals often have very high viral loads, and one recent study found that about half of all new infections may be transmitted during acute or primary infection. Such individuals may have become infected since their last test, or may have been tested during the “window period” before the body has had a chance to produce enough antibodies to be detected. Thus, they may inadvertently misinform prospective sex partners that they are HIV negative. According to the model, the benefits of serosorting decrease as the proportion of recently infected individuals in a population of potential sex partners increases. “The effectiveness of a serosorting strategy for HIV prevention depends on the accuracy of individuals’ serostatus disclosures,” the researchers wrote. “The effectiveness of serosorting on the basis of mutual disclosure of perceived HIV status is a flawed strategy for reducing sexual transmissions of HIV when it does not consider the prevalence of recent HIV infections in specific populations.” For more on serosorting, see the feature article in the Winter 2007 issue of *BETA*.

HIV PREVENTION AND TESTING IN PRISONS

This past January, Congresswoman Barbara Lee (D-California) reintroduced HR 178, also known as the Justice Act of 2007, a bill that would require federal, state, and county correctional facilities to provide comprehensive HIV education and counseling to inmates. The legislation also would allow community-based organizations to distribute condoms to inmates, who would be permitted to possess

them without punishment; while a few jurisdictions—including San Francisco—allow prisoners to possess condoms, most states regard them as contraband. “Ninety-five percent of inmates come back into our community,” Lee said at a press conference. “People need to understand that when a prisoner is infected, we all are affected.”

In a related measure, Representative Maxine Waters (D-California) in April introduced HR 1943, the Stop AIDS in Prison Act of 2007, which would require federal correctional facilities to offer all inmates HIV testing at the beginning of their sentences and prior to release (individuals would be allowed to decline the test). Although some state prisons now require routine HIV testing of all inmates, federal facilities currently do not. The bill would also require HIV education for all inmates and treatment for those who test positive.

At the state level, Assemblyman Mervyn Dymally (D-Los Angeles) introduced AB 66, a bill that would require that all inmates be offered HIV testing 30–60 days after entry into a state prison and again 30–60 days prior to release; treatment plans would be developed for those who test positive. Finally, in March, the California Assembly Committee on Public Safety approved the Inmate and Community Public Health and Safety Act (AB 1334), a measure introduced by Assemblyman Sandre Swanson (D-Oakland) that allows nonprofit and health care agencies to distribute condoms in state correctional facilities and specifies that condom possession may not be used as evidence of illegal activity.

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TH9507: An Experimental Treatment for Lipodystrophy

Anne
Monroe, MD

As the use of highly active antiretroviral therapy (HAART) became widespread, HIV positive individuals and their physicians began to notice changes in body fat distribution, with excess fat or fat loss noted in different areas. These body shape changes are sometimes accompanied by metabolic abnormalities, such as insulin resistance and elevated blood fats. Collectively, these changes are known as lipodystrophy syndrome.

Treatment options for lipodystrophy are somewhat limited. Growth hormone has been used with success in clinical trials to reduce visceral adipose tissue, fat that collects around the abdominal organs. A new product, TH9507, a synthetic growth hormone releasing hormone analog made by the Canadian pharmaceutical company Theratechnologies, is currently showing promise in clinical trials and may represent a new treatment option for people with some types of lipodystrophy.

Lipodystrophy

Lipodystrophy is a broad term that refers to a variety of body shape changes and metabolic abnormalities associated with the treatment of HIV infection. Lipoatrophy, one form of lipodystrophy, is fat loss from the face, upper and lower extremities, and buttocks, and loss of subcutaneous fat of the abdomen. Lipoatrophy differs from AIDS wasting in that it is associated with HAART and immune reconstitution, not progression of disease. In addition, lipoatrophy does not include loss of lean tissue mass.

Fat accumulation, the other half of lipodystrophy syndrome, can occur in the upper back and neck (sometimes called “buffalo hump”), around the abdominal organs as visceral adipose tissue (VAT), and in the breasts. Fat accumulation around the abdominal organs can occur with normal or decreased amounts of subcutaneous abdominal fat.

The causes of lipodystrophy syndrome are still unclear. Lipoatrophy is associated with use of non-nucleoside reverse transcriptase inhibitors (NRTIs), especially d4T (stavudine; Zerit) and AZT (zidovudine; Retrovir),

but not with abacavir (Ziagen) or tenofovir (Viread). Body shape changes develop after several years of use of the drugs and are attributed to mitochondrial toxicity (damage to the energy-producing organs in the body’s cells). Risk factors associated with lipoatrophy include higher viral load and lower nadir CD4 cell count.

Many risk factors for fat accumulation have been identified, including patient factors like older age and baseline body composition, disease factors like progression to AIDS and more robust immune reconstitution, and medication factors like increased length of treatment. The prevalence of fat accumulation among HIV positive people is estimated at 40%.

Lipoatrophy and fat accumulation can be difficult to diagnose based solely on patient perception and clinical exam. In research studies, whole-body dual-energy X-ray absorptiometry (DEXA) scanning is used to confirm abnormal distribution of fat, and computed tomography (CT) and/or magnetic resonance imaging (MRI) scans are used to document visceral fat accumulation.

Treating Lipodystrophy with Growth Hormone Products

There are important reasons to develop and study treatments for lipodystrophy. First, the metabolic abnormalities associated with lipodystrophy (hyperlipidemia and impaired metabolism of glucose, or blood sugar) can contribute to diabetes and heart disease. Second, fear of developing lipodystrophy may keep some people from starting an antiretroviral drug regimen or taking their medications consistently; relieving distress related to body shape changes may remove an obstacle to treatment and dramatically improve adherence to antiretroviral therapy.

Tactics to treat fat accumulation have included exercise and various medical and surgical therapies. Also successful in clinical trials are growth hormone products and related agents.

Growth hormone, produced by the pituitary gland, breaks down fat tissue and stimulates gluconeogenesis (production of glucose by the liver). Growth hormone also stimulates the secretion of insulin-like growth factor-1 (IGF-1) from the liver. The production of IGF-1 leads to the muscle-building and bone-growth properties of growth hormone.

When compared with HIV negative men and HIV positive men without lipodystrophy, HIV positive men with VAT tend to have lower growth hormone concentration. When exogenous (not produced by the body) growth hormone is provided, visceral fat decreases.

Recombinant human growth hormone (rhGH) has been marketed under various brand names. Serostim, one growth hormone product, has been used to treat AIDS wasting, and it was observed that patients treated with Serostim gained lean body mass while losing fat.

For example, in the STARS (Serostim in the Treatment of Adipose Redistribution Syndrome) trial, daily growth hormone therapy was associated with an 8.6% reduction in VAT from baseline—a significant decrease over placebo at week 12. (Serostim administered every other day was associated with a VAT decrease of 4.2% from baseline, which was not a statistically significant change.) Reductions in trunk-to-limb-fat ratio were significant in both Serostim dosing groups. The effect on VAT was maintained to the trial's end at week 24, even in a study group that was re-randomized from daily therapy to placebo at week 12.

In addition to changes in VAT, decreased levels of low-density lipoprotein (LDL, or “bad”) cholesterol and increased levels of high-density lipoprotein (HDL, or “good”) cholesterol were seen in the daily-treatment group at week 12. No significant change in triglycerides was observed.

One potentially negative side effect seen in the Serostim groups was an increase in fasting blood glucose levels. However, the higher levels remained within normal limits in all study participants. Other bothersome side effects of Serostim included fluid retention and muscle and joint aches.

A smaller study by Polyxeni Koutkia, MD, of the Massachusetts General Hospital Program in Nutritional Metabolism and colleagues tested growth hormone releasing hormone (GHRH, marketed as Geref) for the treatment of fat accumulation. Thirty-one patients with increased waist-to-hip ratio were randomized to receive GHRH or placebo for 12 weeks. Lab tests and DEXA/CT scanning were employed to track the change in levels of IGF-1 (used to detect overall changes in levels of growth hormone in

Lipodystrophy and Cardiovascular Risk

Lipodystrophy is often associated with metabolic abnormalities, including hypertriglyceridemia (elevated levels of certain blood fats), decreased HDL cholesterol levels, and high serum glucose levels and accompanying insulin resistance. These abnormalities, along with increased visceral fat, are associated with increased cardiovascular risk.

HIV infection was associated with hypertriglyceridemia and low levels of HDL and LDL cholesterol prior to the introduction of HAART. With HAART, increases in triglycerides and LDL cholesterol with persistently low HDL levels have been observed. This change is worrisome because of the increased risk of cardiovascular disease associated with hyperlipidemia.

Lipid abnormalities should be treated following guidelines for HIV negative individuals and by watching for interactions between antiretrovirals and cholesterol-lowering agents. For treating high cholesterol, pravastatin (Pravachol) is the preferred statin drug in terms of interactions with HAART drugs.

In a large, global case-control study of cardiovascular risk factors, Dr. Salim Yusuf and colleagues from the Population Health Research Institute assessed the effect of various risk factors on cardiovascular disease in HIV negative participants. Abnormal lipids was one of the two most important risk factors for cardiovascular disease worldwide (the other was smoking). Abdominal obesity was associated with increased risk of cardiovascular disease even when adjusted for other risk factors.

response to GHRH), as well as the secondary study endpoints of change in body composition and other lab values.

Concentrations of IGF-1 increased significantly in the GHRH group. Lean body mass also increased significantly, and total fat mass did not change significantly. DEXA scans indicated significant decreases in trunk fat, and CT scans showed that abdominal VAT decreased 9% on average in the GHRH group and increased by 1% in the placebo group.

TH9507: A New Treatment Option?

TH9507 is a synthetic analog of GHRH and triggers the release of growth hormone in a similar way. Growth hormone is usually released from the pituitary in “pulses” based on stimulation by GHRH. Administration of TH9507 results in similar pulsatile secretion of growth hormone.

A Phase II study of TH9507, described in the August 12, 2005, issue of the journal *AIDS*, enrolled 61 patients in three groups (placebo or 1 mg or 2 mg TH9507 daily). The primary outcome measure was change in abdominal fat. Trunk fat (assessed by DEXA scanning) decreased by 9% in the 2-mg treatment group at 12 weeks—a significant decline. Visceral fat decreased by 15% in the 2-mg treatment group, and lean body mass increased in the treatment groups compared with the placebo arm. There was no change in limb fat. Decreased cholesterol and triglyceride levels were observed in the treatment group. TH9507 was generally well tolerated, with no effect on blood glucose levels.

Building on these results, a study presented at the 2007 Conference on Retroviruses and Opportunistic Infections examined the effect of TH9507 on HIV-associated abdominal fat accumulation. This randomized, double-blind, placebo-controlled trial enrolled over 400 participants at sites throughout the United States. In a press conference, investigator Steven Grinspoon, MD, of Harvard Medical School’s Division of Nutrition emphasized the importance of developing agents to reverse fat accumulation as a means of improving the cardiovascular disease risk profiles of individuals living with HIV.

In the Phase III study, 412 participants were randomized in a 2:1 ratio to receive 2 mg TH9507 or placebo. Eligibility requirements included CD4 cell count greater than 100 cells/mm³, abdominal fat accumulation in the setting of HIV therapy, large waist circumference and high waist-to-hip ratio, and a fasting glucose level below 150 mg/dL (normal is up to 100 mg/dL). Patients could be on stable treatment with a lipid-lowering agent. Most participants (84%) were male.

Other Treatment Options

Exercise

A small study by Dr. Gilles Thoni and colleagues of the Sports, Performance, Health Laboratory at the University of Montpellier, France, showed loss of visceral fat with individualized, supervised exercise. In a small study with 19 participants, VAT was assessed by CT scan at baseline and after four months of regular aerobic exercise. There was a 12.8% reduction of total adipose tissue, with a 12% reduction in VAT and improvement in lipid parameters.

Metformin

Metformin, a drug used to treat diabetes, reduces hepatic gluconeogenesis, decreases absorption of glucose from the gastrointestinal tract, and increases insulin sensitivity, resulting in increased peripheral glucose uptake.

Metformin was tested in a randomized, placebo-controlled study by Dr. Colleen Hadigan of Massachusetts General Hospital and colleagues involving 26 HIV positive participants with abnormal glucose tolerance, high waist-to-hip ratios, and fat redistribution. Participants in the treatment group experienced decreased insulin resistance with reduction in insulin levels. There was significant reduction in weight and a 6% decrease in VAT in the treatment group, with an 8% increase in the placebo group. However, metformin is not currently recommended for patients who are not diabetic because the evidence to date is insufficient to support its use for treating fat accumulation.

The primary study endpoint was decreased VAT as measured by CT scan. Secondary endpoints included improved lipid profile (triglycerides and total cholesterol:HDL ratio), improved production of IGF-1, patient perception of body shape, and safety data (blood glucose level, hyperinsulinemia). The study was powered to detect an 8% difference between the two groups.

At 26 weeks, a 15% reduction in VAT was seen in the treatment group, compared with a 5% *increase* in VAT in the placebo group, for a net effect of 20%. The treatment did not increase subcutaneous adipose tissue. Waist circumference decreased three centimeters on average in the treatment group—roughly a pants size, Dr. Grinspoon observed.

Lipid profiles improved in the treatment vs placebo group, and no increase in fasting glucose was noted in the

treatment group. Additionally, there was no effect on immune parameters—TH9507 did not appear to either raise or lower CD4 cell counts in either group. Side effects included headaches and arthralgias in more than 10% of participants in both groups. There were slightly more events of extremity swelling, muscle aches, and urticarial (allergic) rash in the treatment group.

A theoretical safety concern with both Serostim and TH9507 is that increased levels of IGF-1 caused by increased growth hormone may contribute to tumorigenesis. Individuals with active malignancies are advised to avoid either agent, although no increase in cancer incidence or risk has been observed to date.

In conclusion, the investigators stated that TH9507 appears to decrease VAT and improve cardiovascular disease risk, but noted that more safety data and data on the durability of the treatment effect are needed. The study is ongoing to one year, with the participants who were originally randomized to receive TH9507 re-randomized to receive either continued treatment or placebo to assess the durability of the drug's effect. Another Phase III trial is also now underway in North America and Europe (see "Open Clinical Trials," page 49).

Interestingly, in addition to undergoing studies of its application in HIV-associated lipodystrophy, TH9507 is also in a Phase II trial to assess the cognitive effects of GHRH in patients ages 55–80 with mild cognitive impairment. This study is based on preliminary indications that GHRH improves cognitive function in healthy older people.

Conclusion

Lipodystrophy diagnosis and management remains a major challenge in HIV clinical care. Growth hormone has been used successfully to treat fat accumulation, and TH9507 appears to hold promise for the management of HIV- and HAART-associated fat accumulation and metabolic abnormalities with fewer side effects than previous treatments. "If you look at [our] data compared to data on growth hormone," Grinspoon stated at the Retrovirus Conference, TH9507 is "much more palatable, yet you get the same thing for the buck. You get the same about 15 to 20 percent reduction in visceral fat, with an improvement across lipids, but without toxicity in terms of glucose."

A new, affordable, and more tolerable lipodystrophy treatment option is needed to decrease cardiovascular risk factors in HIV positive individuals—and to improve self-perception and quality of life. Unfortunately, a major issue with TH9507, if approved, will be cost of therapy. Currently, the growth hormone product Serostim is only approved for treatment of HIV wasting and is prohibitively expensive for most patients. A sustained benefit must be

demonstrated by TH9507 in order to justify the cost to insurers, and this evidence will take time to accumulate. TH9507 is one to watch as it progresses in the clinical development pipeline.

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Skin and Soft Tissue Infections Caused by Community-Acquired Methicillin-Resistant *Staphylococcus aureus*

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Skin and soft tissue infections (SSTI) are a source of significant illness and accounted for over 2 million visits to emergency room departments in the United States in 2004.

While most infections are minor and do not require hospitalization, some can be life-threatening—particularly for people living with HIV.

The majority of outpatient SSTI are caused by gram-positive bacteria, typically *Streptococcus* and *Staphylococcus* species. In the past, SSTI caused by these organisms were reliably treated with beta-lactam antibiotics (penicillins and cephalosporins). Resistance to these antibiotics was uncommon and was typically only seen in infections caused by *Staphylococcus aureus* that had acquired a gene conferring resistance to all beta-lactams, including the drug methicillin. These resistant infections typically only occurred in hospitalized or recently-hospitalized individuals.

Since the late 1990s, however, there has been a startling rise in the incidence of SSTI caused by methicillin-resistant *Staphylococcus aureus*

(MRSA) in individuals with no prior exposure in hospitals. These infections were termed “community-acquired MRSA” (CA-MRSA) infections. The vast majority of CA-MRSA infections in the United States are caused by one particular bacterial clone that is remarkable for its transmissibility, persistence, and virulence.

SSTI caused by CA-MRSA have disproportionately affected the HIV positive population, and the reason for this phenomenon remains unclear. This article provides an overview of CA-MRSA SSTI in HIV positive people, providing a brief history of the microbiology of skin and soft tissue infections and outlining the epidemiology of CA-MRSA SSTI in the HIV positive patient, the

types of SSTI that can be caused by CA-MRSA, and available treatment and prevention options.

The Microbiology and Treatment of Skin and Soft Tissue Infections

With the advent of penicillin in the early 1940s, streptococci and staphylococci were initially universally sensitive to penicillin and its related synthetic versions. While most streptococci have remained sensitive to penicillins since that time, staphylococci—particularly *Staphylococcus aureus*, the most virulent of all staphylococci species—have become increasingly resistant to penicillin and its derivatives. This phenomenon began in the mid-1940s, when certain strains of

S. aureus found in hospital settings (where penicillin was widely used) developed an enzyme called penicillinase that broke down penicillin, rendering it ineffective against the bacterial strains. This property had spread to most *S. aureus* strains in the community by the 1970s.

Penicillin-resistant *S. aureus* was checked with the advent of the penicillinase-resistant penicillin drugs methicillin, nafcillin, and oxacillin, as well as the cephalosporin compounds cefazolin (Ancef) and cephalexin (Keflex). However, in a manner similar to their development of penicillinase, *S. aureus* strains exposed to selection pressure from antibiotics used in hospital settings evolved resistance to all penicillins and cephalosporins. By the mid-1990's, these MRSA strains accounted for greater than 25% of all in-hospital *S. aureus* infections.

In contrast to the slow, gradual movement of penicillinase-producing *S. aureus* strains from the hospital to the community over the course of multiple decades, MRSA has exploded into the community setting since the late 1990s. While initial cases of CA-MRSA appeared to result from the introduction of the in-hospital strain into the community by people with frequent contact with the health care system and inpatient care, subsequent reports emerged of severe and fatal MRSA infections in children in Chicago and in rural Minnesota and North Dakota with no prior hospital exposures, indicating the presence of new virulent strains distinctly different from previously observed MRSA.

Epidemiologic studies in several communities throughout the United States have since identified increasing incidence of disease caused by a particular CA-MRSA clone termed "USA300." USA300 was initially described in reports of cases from fairly discrete populations, such as prisoners, military recruits, athletic teams (including high school wrestling teams and a professional football team), and HIV-positive men who

have sex with men (MSM). However, it has been increasingly recognized over the past three years that USA300 is now responsible for infections among all populations in the United States and has become an important cause of hospital-acquired infection, as well. In particular, a recent study published in the *New England Journal of Medicine* determined that, in August 2004, among eight different emergency departments scattered around the United States, MRSA was responsible for 59% of all SSTI in which a bacterial culture was available. Of the cases caused by MRSA, 97% were caused by the USA300 clone. While USA300 has classically been described as a cause of SSTI, it can also cause several other infections, such as pneumonia, endocarditis (infection of the heart valves, often seen in injection drug users), urinary tract infections, osteomyelitis (infection of the bone), and orthopedic hardware infections.

While it is ultimately unclear exactly what is responsible for the propensity of USA300 to spread throughout the United States in such a short time period and to cause, in general, more severe SSTI than other clones, genetic analysis of USA300 has revealed the presence of two genes—the Arginine Catabolic Mobile Element (ACME), a gene heretofore unrecognized in *S. aureus*, and the gene for Panton-Valentine leukocidin (PVL)—that may play roles in colonization and virulence.

S. aureus typically preferentially colonizes the anterior nasal mucosa (the tissue lining the inside of the nose), where it will often reside without causing disease. The relationship between colonization of the anterior nasal mucosa and the development of subsequent skin disease is not well understood, but SSTI caused by *S. aureus* are typically caused by the individual's colonizing strain. It is thought that ACME, a gene that USA300 likely acquired from *Staphylococcus epidermidis* (a typically non-virulent colonizer of human

skin), may promote survival on skin surfaces, suggesting that USA300 may more readily colonize human skin than other *S. aureus* strains.

The role of PVL remains unclear. It was initially described as being toxic to human white blood cells and to promote abscess formation, but recent studies have contradicted this idea. USA300 has also been described as a cause of severe, necrotizing pneumonia, and it is also thought that PVL has a role in the ability of the organism to invade lung tissue. Again, however, the exact causal mechanism remains unclear.

The Epidemiology of MRSA SSTI in the HIV Positive Population

Studies have demonstrated that people living with HIV generally have a higher proportion of colonization and disease caused by CA-MRSA. One of the first studies to focus on risk factors for CA-MRSA SSTI among HIV positive MSM was performed at the Los Angeles County Department of Health Services outpatient clinic in 2002. Thirty-five individuals presenting with MRSA SSTI were compared with 76 control HIV positive MSM individuals matched by treating physician and week of presentation. HIV positive MSM with MRSA SSTI were more likely to have had close contact with a person with a skin infection; to have routinely used public saunas or hot tubs; to have used methamphetamine, nitrates, or sildenafil (Viagra); and to have had high-risk sexual behavior in the three months prior to presentation. Use of the antibiotic trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim, Septra) as prophylaxis for opportunistic infections appeared to be protective in this small study. No significant relationship was found between CD4 cell count or HIV viral load and MRSA SSTI.

The link between high-risk sexual activity and the acquisition of MRSA SSTI remains relatively unexplored. While MRSA has not been explicitly documented to spread sexually among MSM, heterosexual transmission of

USA300 has recently been demonstrated. The early association made between USA300 SSTI and contact sports suggested an enhanced role for skin-to-skin transmission of USA300, which may explain this relationship between CA-MRSA SSTI and risky sexual behavior among HIV positive MSM. It may, in fact, be worthwhile to conceptualize CA-MRSA as a sexually transmitted disease, at least in a broader sense of skin-to-skin transmission.

Another study examining the incidence of and risk factors for MRSA infection among HIV positive people was performed at the Owen Clinic at the University of California, San Diego. Ninety-four infections were identified in the clinic cohort of 3455 HIV positive individuals between January 2000 and December 2003. Paralleling the rise of USA300 across the United States over this time frame, the investigators noted a dramatic rise in the number of infections toward the end of the study period, with over 60 of the infections occurring in the last year of the study. In their analysis, acquisition of MRSA infection was associated with acquisition of HIV via sex or intravenous drug use, low CD4 cell count, high HIV viral load, and lack of TMP-SMX prophylaxis for opportunistic infection.

One other aspect of the epidemiology of CA-MRSA SSTI in the HIV positive population concerns multidrug resistance. The hallmark of CA-MRSA—and USA300 in particular—in comparison with the traditional MRSA acquired in the health care setting, has been its susceptibility to multiple non-beta-lactam antibiotics, such as trimethoprim-sulfamethoxazole, clindamycin (Cleocin), and doxycycline. However, multidrug resistance in USA300 has begun to emerge over the last four years, and much of it has been mediated by a cluster of genes on a plasmid carried by the organism that encodes resistance to clindamycin, macrolides (erythromycin and its

derivatives azithromycin [Zithromax] and clarithromycin [Biaxin]), and mupirocin (Bactroban), an antibiotic ointment often used for eradication of *S. aureus* colonization and for treatment of impetigo. Our laboratory at San Francisco General Hospital (SFGH) has noticed an association with USA300 carrying this drug-resistance plasmid and HIV positive MSM presenting with SSTI. More research is planned to determine why this relationship exists.

Types of SSTI that can be Caused by MRSA

MRSA can cause a wide variety of SSTI. They are summarized very well in the treatment guidelines for SSTI put forth by the Infectious Diseases Society of America and are as follows:

IMPETIGO

Impetigo is an infection of the superficial layers of the skin that is characterized by its discrete, well-defined borders. Lesions are typically seen on the exposed parts of the body, most often the face and extremities, and may be single or multiple. Often, these lesions develop into blisters (bullous impetigo). Systemic symptoms (such as fever) are rare.

Impetigo is most commonly seen in young children and is most commonly caused by streptococci. However, CA-MRSA has been recognized as an increasingly more common cause of impetigo, particularly in populations where CA-MRSA is more frequently seen, such as among people living with HIV.

CUTANEOUS ABSCESSSES

Cutaneous abscesses are collections of pus that arise within the deeper structures of the skin. They typically present as painful red nodules that are exquisitely tender to the touch. They arise when bacteria are introduced into the deeper layers of the skin, such as with skin popping or intravenous drug use. However, abscesses may also arise without any preceding event known to the patient. Abscesses

may contain more than one species of bacteria, but when *S. aureus* is present, it is often the only pathogen isolated. Abscesses caused by MRSA have been said to resemble spider bites.

FOLLICULITIS, FURUNCLES, AND CARBUNCLES

Folliculitis is an infection of the hair follicle that is confined to the superficial layers of the skin. While they are frequently caused by *S. aureus*, and CA-MRSA in particular, other organisms, including fungi, are common causes as well. It also may be difficult to distinguish folliculitis caused by CA-MRSA from eosinophilic folliculitis, a non-infectious rash commonly seen in HIV positive individuals with CD4 counts lower than 300 cells/mm³ that can frequently flare with the initiation of antiretroviral therapy.

Furuncles, also known as “boils,” are infections of hair follicles in which purulence (presence of pus) extends down the hair follicle shaft into the deeper layers of the skin, forming a small abscess. Furuncles are most commonly caused by *S. aureus*. They can occur anywhere on the skin where hair is present.

When the infection from one furuncle extends to involve several adjacent hair follicles, it is termed a carbuncle. Carbuncles are often seen on the back of the neck and are frequently seen in people with diabetes mellitus.

Folliculitis, furuncles, and carbuncles are very common presentations of CA-MRSA; several of the well-described outbreaks of CA-MRSA infection have involved these infections. CA-MRSA is also remarkable for its ability to cause repeated attacks of these infections.

CELLULITIS AND ERYSIPELAS

Cellulitis and erysipelas are terms for diffuse, spreading skin infections without underlying purulence or necrosis (tissue death). The terms are often used interchangeably but, classi-

cally, erysipelas is defined by the fact that the lesion is raised above the level of the surrounding skin and that there is a clear line of demarcation between involved and uninvolved tissue. Cellulitis, on the other hand, is not so clearly demarcated and tends to involve the deeper skin tissues and subcutaneous fat. The microbiology is typically different as well. Streptococci are by far the most common cause of erysipelas, although *S. aureus* may also be involved in the more severe, blistering form of the disease. Cellulitis, on the other hand, can be caused by a wide variety of pathogens, though streptococci are still the most common etiology if no underlying abscess is present.

Both erysipelas and cellulitis are characterized by rapidly spreading areas of warmth, redness, and edema (swelling). Both may also be associated with lymphangitis (inflammation of the lymph vessels manifest by “streaking” erythema, or redness, extending from the lesion) and swelling of regional lymph nodes. Often, the skin can take on a brawny, wooden texture. Superficial blisters may develop, as well. Systemic symptoms, such as fever, rapid heart rate, and low blood pressure, can often accompany erysipelas or cellulitis and are signs of serious illness that requires prompt evaluation and treatment with systemic antibiotics. In less than 5% of all cases, the infecting organism can be isolated from the bloodstream.

Conditions that predispose to the development of erysipelas or cellulitis typically make the skin more fragile or impair the local immune response; these include obesity, prior cutaneous damage, venous insufficiency, or lymphatic obstruction from any cause, such as from prior surgeries on the affected limb. Damaged, disrupted skin is a frequent portal of bacterial entry. Cellulitis is often confused with other skin disorders, such as allergic, eczematous, or contact dermatitis, gout, and herpes zoster (shingles).

NECROTIZING FASCIITIS

Necrotizing fasciitis is a rare infection of the deep subcutaneous tissues that can spread beneath the skin very rapidly from the initial site of infection. The initial lesion is often minor, such as an abrasion, an injection site, or a small abscess. Approximately 20% of patients have no visible skin lesion.

In its initial stages, the presentation is very similar to cellulitis. However, severe systemic symptoms (high fever, low blood pressure, disorientation and/or lethargy) typically develop rapidly, and the site of infection may show skin discoloration or gangrene. Other factors that may distinguish necrotizing fasciitis from cellulitis include severe, constant pain, severe blistering, gas in the soft tissues that can be palpated or seen on X-ray imaging, and edema that extends beyond the redness of the affected area and also extends much deeper into subcutaneous tissues. Most patients who present with necrotizing fasciitis have an underlying predisposing factor, such as diabetes or arterial or venous insufficiency. Immediate medical and surgical attention is warranted for the management of this aggressive and often fatal infection.

There are two main types of necrotizing fasciitis: one that is caused by a single bacteria (monomicrobial) and one caused by multiple bacteria at the same time (polymicrobial). In the monomicrobial form, streptococci and *S. aureus*, including CA-MRSA, are the most common causes. The polymicrobial form typically involves anaerobic organisms that arise from the normal bacteria found in the large intestine and is often seen in patients who had surgical procedures involving the bowel, sacral ulcers, or trauma to the abdomen.

PYOMYOSITIS

Pyomyositis is the presence of pus within muscle. It is characterized by pain localized within a single muscle

group, muscle spasm, and fever. *S. aureus*, including CA-MRSA, is a common cause. Often, it may not be possible to delineate a specific abscess, but the area will often have a firm, wooden feel. Surgery and intravenous antibiotics are typically required in the management of these infections.

People presenting with pyomyositis will often have a predisposing cause, such as injection drug use, but these infections can arise spontaneously, as well.

SURGICAL SITE INFECTIONS

Infections of surgical wounds are the most common adverse events in patients who are hospitalized and have undergone surgery, accounting for 38% of all hospital-acquired infections in surgical patients. They are classified according to how deep the infection is: superficial incisional infection, deep incisional infection, and organ/space infection. Superficial incisional infections do not extend below the subcutaneous space and are notable for purulent drainage from the incision, pain, tenderness, swelling, and redness. They typically occur within 30 days of the initial surgery. A deep incisional infection extends into the underlying fascia and muscle. It presents in a similar fashion as the superficial incisional infection and also typically arises within 30 days of initial surgery. However, if a prosthesis was inserted, deep incisional infections can occur up to a year after initial surgery. An organ/space infection involves any part of the body other than the incision site itself. Any deep incisional infection that does not resolve as expected raises the possibility that, in fact, the incisional infection may just be a superficial manifestation of a deeper organ/space infection.

Diagnosis and treatment of surgical site infections are highly individualized. Diagnosis of surgical site infections may be delayed in those who are morbidly obese or in those who had deep, multilayer incisions. Oftentimes, there may be redness and

other inflammatory changes around or near a surgical incision that just reflect wound healing or allergic sensitivity to tape or other dressing and do not indicate true infection. Intravenous antibiotics that are given immediately before the time of surgery reduce the incidence of surgical site infections, but prolonged courses of antibiotics following surgery do not prevent surgical site infections and only serve to promote antibiotic resistance and other side effects associated with antibiotic use.

A wide variety of bacteria can cause surgical site infections, and the type of bacteria involved typically depends on the type of surgery (particularly whether the operation involved the gastrointestinal or genital tracts), when the infection occurred relative to the time of surgery, and how long the patient has been in the hospital. When *S. aureus* (including CA-MRSA) is the cause of a surgical site infection, the preceding surgery typically did not involve the gastrointestinal or genital tract, and the infection typically does not manifest until two to five days after the operation. Data from SFGH and other institutions suggest that patients who are colonized with the USA300 *S. aureus* clone as outpatients are more likely to have infections caused by USA300 while hospitalized, blurring USA300's distinction as "community acquired."

Treatment of MRSA SSTI in the HIV Positive Patient

The treatment of SSTI in the HIV-positive person depends on a number of factors: the type of SSTI (as described above), the extent and severity of the infection, the immune status of the individual, the likelihood that the lesion is caused by MRSA, and the person's prior antibiotic exposure.

ANTIBIOTICS ACTIVE AGAINST MRSA

One of the most reliably active oral antibiotics against CA-MRSA, and USA300 in particular (>98% susceptible), is TMP-SMX, even though it is

not approved by the Federal Drug Administration for the treatment of SSTI. Its advantages in treatment of HIV positive people include familiarity with its use (as it is also used for prophylaxis and treatment of *Pneumocystis* pneumonia) and affordability. Disadvantages include intolerance due to gastrointestinal upset (particularly with higher doses) and an inability of individuals to take the medicine if they have a sulfa allergy or G6PD deficiency. Another disadvantage is that it has poor activity against streptococci, so if the etiology of the SSTI is more likely to be streptococcal (such as impetigo, erysipelas, or cellulitis without underlying abscess), another antibiotic may be more appropriate. TMP-SMX also does not penetrate well into the anterior nares (nostrils) for eradication of nasal colonization. For serious infections in which MRSA is suspected, the dose given should approximate 8 to 12 mg of TMP-SMX per kilogram per day, divided two to three times daily—a larger dose than for what is used for *Pneumocystis* prophylaxis or for the treatment of urinary tract infection. For the average 70-kg (154-pound) person, two double-strength tablets twice a day is appropriate.

An antibiotic with excellent activity against both streptococci and MRSA is clindamycin, though the susceptibility of MRSA to clindamycin is lower than that to TMP-SMX (85%–90% susceptibility in CA-MRSA; much lower in traditional hospital-acquired MRSA). Clindamycin is recommended if the etiology of the SSTI (i.e., streptococcal vs staphylococcal) is in question. Clindamycin also penetrates well into the anterior nares and has been effective in eradicating nasal colonization of *S. aureus* in low doses.

Clindamycin is inexpensive and generally well tolerated, though occasionally its eradication of a significant proportion of the normal bacteria in the large intestine can cause diarrhea. It may also in rare cases promote a particular infection of the large intes-

tine called *Clostridium difficile* ("C-diff") colitis. Another disadvantage of clindamycin in the HIV positive population is the issue of increasing resistance, as mentioned above. Resistance is most likely to be encountered in individuals who have recurrent MRSA SSTI and have received multiple courses of clindamycin.

Doxycycline (and its relatives tetracycline and minocycline) are typically active against MRSA (80%–95% susceptibility in CA-MRSA). Doxycycline, tetracycline, and minocycline are inexpensive and well tolerated, though skin phototoxicity (accelerated sunburning with exposure to sunlight) is common. However, there is limited clinical experience in the treatment of MRSA infections with this class of drugs; they should not be relied upon alone for serious infections. These medications are contraindicated in pregnant women due to defects in bone and enamel development.

Linezolid (Zyvox) is highly active against MRSA (near-100% susceptibility in CA-MRSA) and has performed well in studies of complicated SSTI. It is generally well tolerated, though bone marrow toxicity, manifest by anemia and/or thrombocytopenia (low platelet count), is a common side effect and often limits extended or repeated use. It is also extremely expensive, as a 10-day course costs over \$1300.

Rifampin is highly active against MRSA (90%–100% susceptibility in CA-MRSA) but must be used in combination with other drugs in order to avoid potential resistance. It is particularly useful in the treatment of infections involving orthopedic hardware and also in eradication of nasal colonization. A major disadvantage of its use in HIV positive individuals is its metabolism by the cytochrome p450 system in the liver, the same route of metabolism as efavirenz (Sustiva) and most protease inhibitors (PIs). Rifampin induces the metabolism of efavirenz and PIs, resulting in decreased levels of these drugs in the

body. Rifabutin, a relative of rifampin, also has anti-MRSA activity and has less of an effect on the metabolism of efavirenz and PIs, so it can be substituted for rifampin in individuals on these antiretrovirals. Consultation with a pharmacist or health care provider knowledgeable about antiretroviral drug interactions is recommended to determine the proper dosing of rifampin/rifabutin along with antiretroviral therapy.

Oral antibiotics that are *ineffective* against MRSA include beta-lactams and cephalosporins, such as amoxicillin (with or without clavulanate), dicloxacillin, and cephalexin (Keflex). Macrolides (erythromycin, azithromycin, clarithromycin) are also largely ineffective against MRSA. Fluoroquinolones (ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin) have unreliable activity against MRSA (30% to 60% of CA-MRSA is quinolone-susceptible), and resistance can develop rapidly.

If intravenous therapy is required or deemed necessary, vancomycin is typically the first-line intravenous drug used against MRSA. It is typically given twice a day, but blood levels should be drawn to determine if more or less frequent dosing is required. Resistance to vancomycin in MRSA is extremely rare, though there is concern that, during long courses of treatment in a particular individual, sub-strains of MRSA that have reduced susceptibility to vancomycin may persist and lead to recurrent disease when the antibiotic treatment is discontinued. Very recently, a research team at SFGH reported the first strain of USA300 to display reduced susceptibility to vancomycin in an individual who had recurrent, deep-seated MRSA infections. Other new intravenous drugs that are active against MRSA include daptomycin and tigecycline, both of which have been approved by the Federal Drug Administration for the treatment of complicated SSTI.

TREATMENT ACCORDING TO TYPE OF SSTI

For impetigo with a limited number of lesions, topical mupirocin (Bactroban) is the treatment of choice, though resistance to mupirocin in MRSA is on the rise in the HIV positive population. Impetigo with multiple lesions may require a short course of an oral antibiotic, such as clindamycin or doxycycline. Folliculitis and small furuncles will typically respond to the application of warm compresses, which appears to promote drainage. Antibiotics may not be necessary for these SSTI, particularly if the lesions are limited in number and extent and the infected person is not particularly immunocompromised. If, however, there is extensive surrounding redness or systemic signs such as fever, antibiotics should be considered. If cellulitis without underlying abscess is present, adequate coverage of streptococci is necessary, so clindamycin is favored over TMP-SMX. If cellulitis is extensive and associated with severe systemic symptoms, prompt medical evaluation is required to rule out necrotizing fasciitis. Surgical wound infections are best evaluated by the surgeon who performed the preceding surgery, and treatment is highly individualized.

The most effective treatment of abscesses, large furuncles, and carbuncles is surgical excision and drainage, which, depending on the extent of the lesion, are typically performed on an outpatient basis. It is important that drainage be done in a controlled, sterile setting—it should not be performed at home. Manual squeezing of an abscess may only push bacteria into deeper layers of skin and soft tissue, causing worsening of the infection. Surgical probing of the abscess cavity at the time of drainage to break up collections of pus may speed healing. After drainage, simply covering the wound with a dry dressing, with or without gauze packing, is typically sufficient. Antibiotics are not necessary if complete drainage is achieved, but they

can be considered for those who present with multiple lesions, extensive surrounding erythema, or systemic symptoms such as fever, or in patients who are more severely immunocompromised.

The treatment of individuals who have recurrent abscesses or furunculosis due to CA-MRSA is not well established. Classically, efforts to reduce recurrent disease have focused on eradication of nasal colonization. One strategy has been to apply mupirocin to the anterior nares for the first five days of each month. Another is a single small (150-mg) dose of clindamycin given daily for three months. However, there may be several problems with eradication of nasal colonization as a strategy to reduce disease recurrence. First of all, while eradication of nasal colonization may lead to an immediate reduction in subsequent staphylococcal disease, individuals often just become re-colonized when treatment is stopped. Secondly, the emergence of resistance to mupirocin and clindamycin that we have seen in HIV positive individuals in San Francisco may severely limit options for nasal decolonization in this population. Lastly, the identification of the *ACME* gene in the USA300 clone suggests that colonization of the skin and other areas instead of the anterior nares may be one of the driving forces in the emergence of CA-MRSA. Combining nasal decolonization with body cleansing with chlorhexidine has been suggested and may be of benefit.

While not yet formally evaluated in a clinical trial, prophylaxis with TMP-SMX may be of benefit to those with recurrent staphylococcal abscesses or furunculosis. Another approach to treat recurrent disease, which has not been formally evaluated, is to combine TMP-SMX with rifampin or rifabutin for a two-week course, as rifampin and rifabutin penetrate well into the anterior nares. Again, consultation with a pharmacist or health care provider knowledgeable

about antiretroviral drug interactions is advised if this approach is to be considered.

Prevention of MRSA Infection

As with many aspects of staphylococcal disease, strategies for prevention have not been well evaluated. Inadequate personal hygiene has been demonstrated to promote CA-MRSA SSTI, so measures such as regular bathing, frequent hand-washing, and keeping fingernails trimmed may be beneficial. Alcohol-based hand sanitizers are active against MRSA, and their use is highly encouraged in all health care environments. Routine examination of the skin is important to identify small cuts and abrasions that could serve as points of bacterial entry. Any person who has an active SSTI should keep draining wounds covered and thoroughly wash or dispose of all material that comes into contact with the wound.

Studies of the emergence of CA-MRSA among athletic teams have demonstrated that fomites (inanimate objects such as towels, bars of soap, and whirlpools) may harbor MRSA and facilitate transmission of the organism. Avoiding public hot tubs and saunas may reduce the risk of SSTI and may be recommended for people with recurrent SSTI. Avoidance of close contact (including sexual contact) with those with active SSTI is also likely to be beneficial. Pets, including dogs and cats, have also been demonstrated to have MRSA infections and to facilitate MRSA transmission, so examination of them for the development of skin disease and veterinary treatment when indicated may also reduce transmission.

In the setting of an outbreak, several strategies can be employed: daily bathing with chlorhexidine soap; thorough laundering of clothing, towels, and bedding materials; separate use of towels and washcloths; and eradication of nasal colonization. An excellent source of suggestions for control of the spread of CA-MRSA is available

from the Los Angeles County Department of Health Services (www.lapublichealth.org/acd/MRSA.htm).

Conclusion

Within a very short period, CA-MRSA (and USA300 in particular) has become epidemic throughout the United States as a cause of many diseases, of which SSTI have been the most common. The rapid spread of CA-MRSA and USA300 may be related to genetic factors within the organism that promote its transmissibility, persistence, and virulence. While CA-MRSA has now been recognized to cause disease among a wide variety of individuals across socioeconomic and health-related strata, the HIV positive population has been particularly afflicted. The reasons for the disproportionate effect of CA-MRSA on the HIV-infected individual remain unclear but may be related to immunosuppression and the bacteria's propensity to spread via skin-to-skin contact. CA-MRSA causes a wide variety of SSTI, but folliculitis, abscesses, and furunculosis have proved to be particularly vexing to HIV positive individuals, particularly when these conditions are recurrent.

Fortunately, most CA-MRSA infections are not life-threatening, and several treatment options remain available. Treatment may involve surgical drainage, antibiotic therapy, or a combination of the two. There remain several antibiotics that are highly active against MRSA, such as TMP-SMX, clindamycin, doxycycline, linezolid, rifampin, mupirocin, and vancomycin. However, increasing antibiotic resistance in CA-MRSA, particularly increasing resistance to clindamycin and mupirocin among people with HIV, is concerning. Efforts to prevent the spread of CA-MRSA should revolve around close attention to personal hygiene and avoidance of skin-to-skin contact with people who have active SSTI.

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RENAL COMPLICATIONS OF HIV/AIDS

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Renal complications are common among people living with HIV; in fact, up to 30% of HIV positive individuals may have protein in their urine—a sign of kidney dysfunction. It is difficult to estimate precisely how many people develop kidney disease—and, therefore, to implement effective disease prevention or early intervention—because kidney dysfunction may be asymptomatic or may result in only vague symptoms, such as fatigue or general malaise. Without specific symptoms, many individuals are diagnosed later in their disease course, reducing the efficacy of available treatments.

Given the risks associated with kidney disease, developing awareness of kidney function and getting the necessary tests are essential to maintaining good health with HIV. This article explains how kidney function is assessed, describes the renal complications that are most commonly seen in HIV positive people, and outlines treatment options.

Assessing kidney function

Kidney function is assessed using both blood and urine tests to measure two key indicators: serum creatinine and protein in the urine. The presence of an abnormality in either of these measures indicates a functional or structural problem in the kidneys. These two parameters complement each other and should be performed simultaneously.

Creatinine is a product of creatine, a molecule used by muscle cells to break down fatty acids. Creatine is

excreted as creatinine by muscle cells in an amount that correlates with the muscle mass of the individual. When the kidneys function well, creatinine is filtered effectively out of the blood serum, and the level is low. As kidney function declines, it is less effectively cleared from the blood, and the level rises. Serum creatinine is assessed using a blood sample.

Urine analysis is the second primary test of renal health and can provide a tremendous amount of information on the presence and activity of disease in the kidneys. A significant majority of kidney diseases

(i.e., those related to the glomeruli, tiny structures that help filter the blood) result in abnormal levels of proteinuria, or protein in the urine. Proteinuria can be assessed using a dipstick on a random specimen. The urine dipstick is an inexpensive, efficient way to screen for proteinuria, and if positive, the test is followed up with a measurement of the actual amount of protein excreted per 24 hours.

The amount of protein in the urine can be assessed either from a urine sample taken at a random time (as is often used for a dipstick test) or

from a 24-hour collection. Proteinuria levels can provide not only prognostic information about the level of activity of the kidney disease but also a target with which to guide treatment.

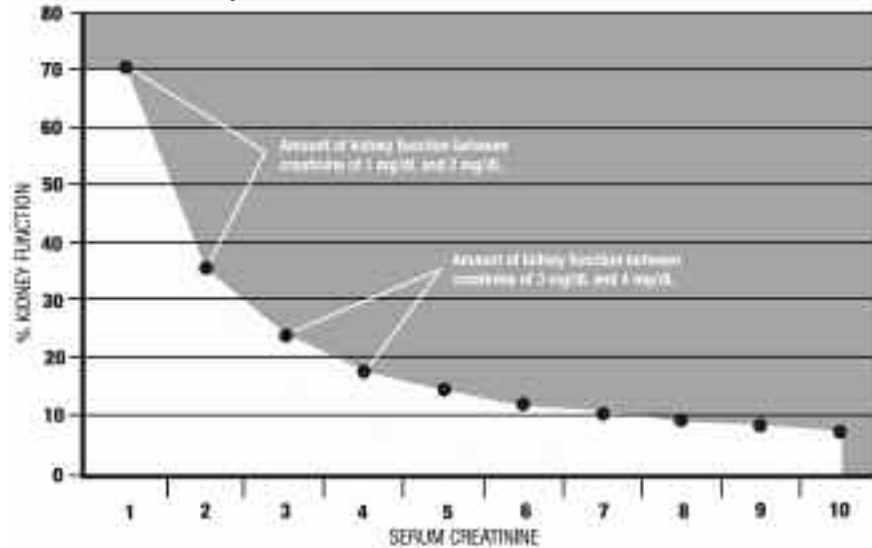
An individual with healthy kidneys puts less than approximately 300 mg of protein into their urine in a 24-hour period. The higher the 24-hour urine protein excretion of a person with kidney disease, the greater the activity of the disease within the kidney and the more likely that the disease will become aggressive, resulting in loss of kidney function over time. Further, once a disease has been diagnosed and a treatment plan initiated, tracking the level of urine protein excretion can help direct the course of drug therapy, with the goal of lowering urine protein excretion.

The level of serum creatinine is slightly more complex to interpret. In all individuals, creatinine levels quantify the ability of the kidneys to clear the blood of waste products. But because the absolute amount of creatinine produced per day is proportional to the muscle mass of the individual, the amount of kidney function that is implied by a given level of creatinine must be normalized for the individual's size. A specific absolute value (such as 1 mg/dL) reflects a different amount of kidney function depending on the muscle mass of the individual measured.

It must be recognized that the concept of "normal range" for creatinine is an oversimplification of how creatinine reflects kidney function. For example, many laboratory reports list

Association between Increase in Creatinine and Loss of Kidney Function

The amount of kidney function as calculated by the Cockcroft-Gault formula for a 55-year-old white male.



the normal range for creatinine as less than 1.4 mg/dL. However, a 55-year-old white male with a creatinine of 1.3 mg/dL will have his kidney function estimated at approximately *half* of normal (54.5 cc/min using the Cockcroft-Gault formula, shown below). This discrepancy highlights the importance of transforming the value of serum creatinine into an estimate of kidney function, such as creatinine clearance or estimated glomerular filtration rate. Each approximates the amount of blood cleaned per minute by the kidneys. Given that "normal" is around 100 cc/min, one could consider the value calculated by these formulae to be a "percentage of normal." In the example above, the individual with a creatinine clearance

of 54.5 cc/min would then have approximately 50% of normal kidney function.

A seemingly small and technical (but equally if not more important) point is that kidney function and creatinine are not linearly related. The amount of kidney function that "lives" between a creatinine of 1 and 2 mg/dL is far, far greater than the amount of kidney function between a creatinine of 3 and 4 mg/dL. An increase in serum creatinine from 1 to 2 mg/dL likely represents a loss of roughly 50% or more of an individual's kidney function, while an increase of 3 to 4 mg/dL in someone with established kidney disease actually represents a relatively small progression (see graph above).

Cockcroft-Gault formula

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight in kg (multiply by 0.85 if calculating for a woman)}}{(\text{blood creatinine level} \times 72)}$$

Lastly, the usual symptoms of kidney disease can be safely summarized as “particularly nonspecific.” Fatigue, malaise, and loss of appetite may be attributed to many other possible causes, and elevated blood pressure may be treated immediately without identification of its cause. The combination of a nonstandard reference range of normal creatinine, the potential to cut kidney function in half without producing a noticeable rise in serum creatinine, and the exceptionally nonspecific symptoms makes kidney disease easy to miss and insidiously progressive.

Types of Kidney Disease

The kidneys receive approximately 25% of the blood that is pumped out of the heart at any given time. It is therefore not surprising that in addition to diseases that are primary to the kidney, most diseases that affect the system of blood vessels (the vasculature) also affect the kidneys. Diseases of the kidney itself—ailments that do not stem from a disease of the rest of the body—are termed primary kidney diseases. Those diseases which are systemic, such as diabetes mellitus, in which the kidneys are affected as a secondary complication, are termed secondary kidney diseases.

Primary Kidney Diseases

While the focus among persons with kidney disease and HIV infection is frequently on those diseases that are related to the HIV, it must be clearly understood that people with HIV infection experience the same kidney diseases for which HIV negative individuals are at risk. That said, the likelihood that a primary kidney disease in an HIV positive person is related to the virus is quite reasonable.

HIVAN

HIV-associated nephropathy (HIVAN) has been demonstrated by renal biopsy in approximately 60% of African Americans with HIV; in con-

Common Symptoms of Kidney Disease
<p>Specific symptoms that may result from the presence of kidney disease or worsening of kidney function include:</p> <ul style="list-style-type: none"> • elevations in blood pressure • edema of the lower extremities or face • discoloration in the urine or changes in urinary habits
<p>Constitutional symptoms are quite nonspecific and can include:</p> <ul style="list-style-type: none"> • fatigue • loss of appetite • weight loss • change in taste of foods or a bad taste in the mouth
<p>If kidney disease is a possibility, a serum creatinine test and urine analysis should be performed.</p>

trast, it is almost nonexistent among whites. First described almost 20 years ago, HIVAN presents with substantial proteinuria and progressive loss of renal function. While early reports described an almost universal requirement for dialysis within one year of diagnosis, the progression rate for HIVAN in the post-HAART era has dramatically decreased. Case reports demonstrate the possibility of recovery of renal function following the initiation of HAART in patients who were previously dependent on dialysis. This decrease in progression rate strongly supports the potential therapeutic role of antiretroviral medications in treating kidney disease.

The clinical course of HIVAN also appears to be associated with CD4 cell count and HIV RNA level. A 2002 study involving patients enrolled in the Women’s Interagency HIV Study found that, among women with proteinuria, CD4 counts below 200 cells/mm³ were associated with a faster time to doubling of creatinine excretion—an indicator of renal failure.

HIVAN is likely caused by direct viral uptake into certain cells of the kidney, with incorporation of the viral genome into cellular DNA. This infec-

tion results in a loss of regulation of normal cell functions, proliferation of cells, and progressive renal failure. With respect to treatment, observational data suggest that antiretroviral therapy is likely the most effective option, with angiotensin-converting enzyme inhibitors and perhaps the corticosteroid drug prednisone also representing potential treatment options. Several studies suggest a benefit from nucleoside reverse transcriptase inhibitor (NRTI) monotherapy, regimens based on protease inhibitors (PIs), and HAART in general in slowing the progression of HIVAN. Current clinical practice guidelines suggest that patients with HIVAN should be treated with HAART at the time of renal disease diagnosis.

Observational data also suggest that persons with HIVAN derive a therapeutic benefit from the use of blood pressure medications in the ACE inhibitor category (ACE-I). Although studies are small and limited by their non-randomized design, the results are compelling. For example, the serum creatinine of 12 patients receiving an ACE-I drug remained stable during a three-to-six-month follow-up period, whereas the creatinine of

KIDNEY DISEASES COMMONLY DESCRIBED WITH HIV INFECTION

DIAGNOSIS	PATHOLOGY
HIV-associated nephropathy (HIVAN)	Likely a result of the direct infection of kidney cells by HIV.
IgA nephropathy	Antibodies (primarily IgA) are trapped in the areas of the kidney where filtering occurs. It is unclear whether this is related to a defect in the production of or a defect in the clearance of antibodies.
Immune-complex glomerulonephritis	All types of antibodies produced within the body are trapped in the areas of the kidney where filtering occurs. The deposition of antibodies triggers severe inflammation. Given that the filtering of blood with antigen-antibody complexes is a normal occurrence, it is not clear why certain individuals experience deposition in the kidney and the resultant inflammation.
Minimal change disease	Biopsy reveals little gross change in appearance of the kidney. Small changes apparent at very high magnifications indicate impaired ability of the kidney to maintain a barrier to keep protein from spilling into the blood. Potentially the result of a T-cell mediated abnormality.
Membranous nephropathy and membranoproliferative glomerulonephritis	Two kidney diseases in which certain types of antibodies are trapped in areas where filtering occurs. These areas are not directly adjacent to blood flow; therefore, there is little inflammation. Both are associated with the loss of potentially large amounts of protein in the urine.
Amyloidosis	Abnormal proteins in the blood (thought to be related to the inflammation caused by a chronic infection, such as HIV) are trapped in the kidney, affecting renal function. Deposition of these proteins may occur in other areas of the body—including the blood vessels, heart, and intestine—and affect their function, as well.
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome	Diseases in which the interior of the blood vessels is severely damaged. These syndromes can result in not only kidney failure, but also central nervous system changes, such as seizures, decreased platelet count, anemia, and fevers.

patients not taking an ACE-I increased from 1.5 to 7.0 mg/dL. These results have been confirmed in similar small observational cohorts. Among patients with kidney diseases other than HIVAN, the results of one study suggest a longer time from renal biopsy to kidney disease progression in patients using an ACE-I. Although these studies have significant limitations, empirically, ACE-I can be safely initiated in the majority of clinical scenarios and have a proven benefit in patients with diabetes mellitus and proteinuria.

Finally, observational studies also demonstrate an association between

improved renal function and survival and use of prednisone in cases of HIVAN. Although treatment with prednisone did uniformly improve renal function in these studies, relapses requiring repeated therapy occurred, and the risk of opportunistic infections increased. The role of corticosteroids in the prevention or delayed progression of renal dysfunction has decreased significantly with the discovery that viral suppression effectively slows loss of kidney function.

Noteworthy in this discussion is that all data available to guide therapy among individuals with HIVAN are observational. No clinical trials

have been performed to date; therefore, these studies must be interpreted carefully.

Other HIV-related primary kidney diseases

Considerably less is known about the other primary kidney diseases that affect persons with HIV infection, both with respect to their exact relationship to HIV and, more importantly, with respect to their treatment. The sidebar above lists primary diseases other than HIVAN that have been reported in persons with HIV, along with a brief description of their pathology. These diseases are united by a common theme of deposition of

antigen and antibody with a subsequent inflammatory reaction within the kidney. Given the kidneys' role in filtering 25% of the cardiac output and the fact that similar kidney diseases are seen in the presence of other chronic infections, such as hepatitis B and C, it is reasonable to suppose that the kidneys may act as a passive trap for the byproducts of chronic infection due to HIV, although this has not been proven.

In general, clinical data describing the course of diseases other than HIVAN are limited and conflicting. Two HIV-infected patients (one with membranous nephropathy and the other with an immune-complex glomerulopathy) were reported to experience a dramatic reduction in proteinuria following initiation of HAART. Additional small studies also suggest a benefit. However, the largest study (including 42 patients with similar non-HIVAN renal diseases), published in the September 2004 issue of *Kidney International*, suggested that the beneficial association between antiretroviral therapy and the suppression of viral replication and improved kidney survival demonstrated among patients with HIVAN may not be present among patients with these other kidney diseases. These differences in prognosis, clinical course, and potential response to therapy underscore the clinical utility of kidney biopsy among persons with clinical signs of kidney disease.

Secondary Kidney Disease

Diseases in which changes in the structure or function of the kidneys can occur as a complication (i.e., kidney disease secondary to another disease process in the body) are the most common cause of kidney failure. In the U.S., diabetes mellitus and hypertension are the two most common causes of end-stage renal disease (ESRD). It is therefore not surprising that these illnesses play an important role in the kidney disease of HIV positive people.

It is not always possible to determine without a biopsy whether diabetes or hypertension (if present) is the sole or major contributor to loss of kidney function. Biopsy may not be necessary, however, as the treatment for the kidney complications of these two diseases is the same, regardless of their cause. Discussion of whether or not a particular individual needs a biopsy should be held with a health care provider specializing in the care of kidney disease, such as a nephrologist. If a kidney biopsy is not initially pursued, that option should be reexamined periodically based on the course of the kidney disease and the individual's response to treatment.

Kidney disease related to diabetes or hypertension may be identified based on classic presenting features. Diabetic kidney disease usually develops approximately ten years after the diagnosis of type I diabetes and three to five years after the diagnosis of type II diabetes. Other complications, such as changes in the eyes, are also frequently noted. The "average" person with kidney disease due to hypertension is a little more difficult to describe, as the duration and degree of hypertension in the setting of other health factors play a role in susceptibility to kidney disease. However, hypertensive kidney disease is frequently associated with a low amount of protein in the urine.

The most influential factor to consider when trying to determine an individual's risk for and type of kidney disease is clearly race. HIV negative African Americans are predisposed to a greater risk of kidney disease compared with whites, and African Americans with HIV infection also have a greater risk of kidney disease. The types of kidney disease seen in HIV positive people also differ by race; for example, HIVAN is significantly more common among African Americans, whereas whites are more likely to experience kidney diseases related to concurrent illnesses, such as hypertension and diabetes mellitus.

Therapeutic options for secondary kidney diseases

Regardless of the type of secondary kidney disease, interventions focused on maximizing control of blood pressure, lipids, and diabetes, as well as management of the complications of the kidney disease, should all be considered or implemented to stop, slow, or reverse damage to the kidneys.

With respect to blood pressure control, the goal of less than 130/80 mm/Hg in individuals with abnormal amounts of protein in the urine or the presence of kidney disease is recommended by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and echoed by the National Kidney Foundation. Multiple studies of patients with diabetes mellitus, HIV-related kidney disease, and other types of kidney disease demonstrate that the use of blood pressure medications in the ACE-I or angiotensin receptor blocker (ARB) categories provide additional protection by lowering pressure within the blood vessels of the kidneys. While the data surrounding the use of HMG Co-A reductase inhibitor drugs in slowing the progression of kidney disease are not as solid, given their beneficial effects on survival, they are also frequently utilized.

Finally, among persons with diabetes mellitus, good control of blood sugar has been demonstrated to reduce complications within the kidneys. The use of a low-protein diet was also tested but was not found to affect loss of kidney function among non-diabetics. While the utility of a low-protein diet continues to be the subject of debate, most nephrologists warn against a high-protein diet.

Complications of Decreased Kidney Function

In addition to understanding the cause of kidney disease and implementing treatment, another focus in clinical

care is treating the complications of decreased kidney function. These complications include anemia and disorders of calcium and phosphorus metabolism.

Anemia is frequently seen among persons with HIV infection due to a number of etiologies, including medications and the primary infection itself. Kidney disease adds to the likelihood of anemia with a decreased ability by the kidney to produce the hormone erythropoietin. While the importance of treatment focused on improving quality of life cannot be emphasized enough, the effects of anemia management should be considered when choosing a treatment program. Recent clinical trials demonstrating an increased risk of tumor progression among oncology patients treated with erythrocytosis-stimulating agents (ESAs), which are drugs to reduce an excess of red blood cells, and an increased risk of cardiovascular events among persons with kidney disease treated to higher hemoglobin goals with ESAs have resulted in a change in the labels of these compounds, suggesting that they be utilized as the smallest dose required to

obviate the need for blood transfusions. How these data and warnings should be translated to HIV positive patients has not been defined, but patients and health care providers should be aware of them in developing a treatment plan.

Disorders of calcium and phosphorus metabolism are relevant to the segment of the population with severe kidney disease. When kidney function declines below a certain level, the kidneys lose their ability to excrete the daily intake of phosphorus. A rise in the level of phosphorus sets off a decline in serum calcium and an increase in parathyroid hormone to normalize calcium levels—potentially at the expense of bone stores.

A unique complication specific to persons with HIV may be decreased virologic response. A single study suggests that individuals with protein in their urine may be less likely to achieve and maintain undetectable viral load. Clearly, a greater understanding of whether this observation is related to the cause of the proteinuria or to underdosing of medications among individuals with lesser kidney function needs to be pursued. If con-

firmed, this link between proteinuria and viral load could lead to recommendations for earlier initiation of antiretroviral therapy among individuals with kidney disease.

The Impacts of Kidney Disease on Medications and of Medications on Kidney Disease

While awareness of kidney health and disease is important, knowledge of an individual’s kidney function is key in choosing and dosing prescription and over-the-counter medications. With respect to dosing, antiretroviral medications in the NRTI class generally require reductions from their full recommended dose when kidney function falls to below 50 cc/min. While other antiretroviral medications may not need to be reduced, care must be taken to monitor doses of medications frequently used by people living with HIV (see sidebar below).

Further, medications (antiretrovirals and others) can affect kidney function and have been associated with adverse events involving the kidneys. These medications and their mechanism of potential injury are outlined in the sidebar on page 33. Use of these medications by persons with established kidney disease should be tailored based on severity of risk, likelihood of benefit, and availability of equivalent therapeutic options.

Clinical Events that May Result from Medication Use

Fanconi’s syndrome

Fanconi’s syndrome is defined as a change in the function of the part of the kidney known as the tubule, which results in an abnormal loss of potassium, phosphorus, glucose, and/or amino acids. This change may or may not be accompanied by a loss of kidney function. Regardless of whether creatinine does or does not rise, there are deleterious effects of the loss of compounds such as phos-

People with kidney disease may be unable to tolerate the full recommended doses of the following drugs:

acyclovir (Zovirax)	isoniazid (Niaqid)
amphotericin (Ambisome)	levofloxacin (Levaquin)
cidofovir (Vistide)	pentamidine (Nebupent)
ciprofloxacin (Cipro)	pyrazinamide (Pyrazinamide, PZA)
clarithromycin (Biaxin)	ribavirin (Copegus, Rebetol, Ribasphere)
ethambutol (Myambutol)	rifampin (Rifadin)
famciclovir (Famvir)	trimethoprim-sulfamethoxazole (Bactrim, Septra)
fluconazole (Diflucan)	valacyclovir (Valtrex)
foscarnet (Foscavir)	valganciclovir (Valcyte)
ganciclovir (Cytovene)	

MEDICATIONS ASSOCIATED WITH KIDNEY-RELATED ADVERSE EVENTS

MEDICATION	ADVERSE EVENT	INTERVENTION
Aminoglycoside antibiotics	Acute kidney failure	Adjust dose according to level of kidney function
Amphotericin	Acute kidney failure	Adjust dose according to level of kidney function
Atazanavir (Reyataz)	Interstitial nephritis	None
Contrast dye for computed tomography (CT) scans and arteriograms	Acute kidney failure	Avoid use in volume deplete/dehydrated individuals; use minimal volume of contrast
Gadolinium contrast agent for magnetic resonance imaging (MRI)	Nephrogenic systemic fibrosis	Avoid use in individuals with severely decreased kidney function
Nonsteroidal anti-inflammatory drugs	Diminished blood pressure control; acute kidney failure	Avoid use in individuals with reduced kidney function
Pentamidine	Acute kidney failure	None
Tenofovir (Viread)	Acute kidney failure; Fanconi's syndrome	Adjust dose according to level of kidney function

phorous, including increased bone turnover related to increased parathyroid activity. The majority of cases occur in persons taking nephrotoxic agents, particularly tenofovir (Viread). Clinical practice guidelines suggest at least biannual monitoring of these parameters among persons receiving tenofovir.

Acute kidney failure

The kidneys are the most oxygen-sensitive organs in the body. Because they process, filter, and “reclaim” so much blood per minute, it is not surprising that they are exquisitely sensitive to the toxicities caused by a number of medications. It must be noted that many medications (particularly those excreted by the kidneys) are highly concentrated within the cells of the kidneys.

All of the medications listed in the sidebar above that promote acute kidney failure appear to do so in a

similar manner. Treatment is usually focused on identification and withdrawal of the medication causing the kidney failure, and supportive care is needed until the damaged kidney cells repopulate and begin to function normally. The decision to reintroduce a medication after recovery of kidney function should be made on a case-by-case basis, with consideration of the clinical factors not related to the medication that may have contributed, such as volume depletion (loss of water and salts from cells) or dehydration related to a diarrheal illness, and the potential for other available and equivalent therapeutic options.

Interstitial nephritis

A reasonable analogy to describe interstitial nephritis is an allergic reaction within the kidneys. While the exact mechanism of irritation is not known, medications that cause interstitial nephritis cause an influx of

white blood cells into the kidney, disrupting function. The rise in serum creatinine (indicating loss of kidney function) can be accompanied by fever and rash. Upon withdrawal of the drug, kidney function usually returns to its baseline value without specific therapy, although in severe circumstances corticosteroids may be used to accelerate recovery.

Conclusion

Our knowledge that HIV affects the kidneys is solid, but our understanding of certain areas of renal health is still rudimentary. Significant work remains to truly elucidate who is susceptible to kidney disease and why, and how to treat certain kidney diseases that occur in HIV positive people.

Early screening for kidney disease provides a greater likelihood of effective prevention and treatment. Screening is as simple as a urine analysis for protein and a blood test

for serum creatinine and should be performed in every person living with HIV. The Infectious Disease Society of America currently recommends that all HIV positive people be screened for kidney disease at least once; individuals at increased risk for kidney disease should be reassessed at least yearly, and those with abnormal screening tests should receive further evaluation by their health care provider and see a nephrologist.

Key to this recommendation is awareness of kidney disease. Without awareness in both the HIV positive community and among health care providers, potentially preventable and treatable ailments can progress unchecked in the unsuspecting and asymptomatic individual. Awareness can lead to a very simple but potentially life-saving question: "Hey doc, are my kidneys OK?"

Lynda Anne Szczech is a nephrologist at Duke University Medical Center. She has a longstanding interest in the care of people with HIV and kidney disease and has been active in research in this area for many years.

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Human Papillomavirus

Liz
Highleyman

A majority of sexually active adults carry the human papillomavirus (HPV), but until recently, this virus received little public attention. This changed in 2006 with the approval of a new vaccine that can prevent infection with certain types of HPV, and thereby reduce the risk of cervical cancer.

What is HPV?

HPV, a virus that causes excessive cell proliferation, is believed to be the most common sexually transmitted infection in the U.S. A recent analysis of data from the 2003–2004 National Health and Nutrition Examination Survey (NHANES) found that the overall prevalence of HPV among women aged 14–59 years was 27%, with the highest rate (45%) in the 20–24-year age group.

There are more than 100 identified strains of HPV. Some types, including 6 and 11, cause warts, both common skin warts and genital warts (condyloma). Oncogenic, or “high-risk,” types—especially 16 and 18—can cause cancer of the anogenital area, including the cervix and anus, and (more rarely) the vulva, vagina, and penis; in the NHANES study, about 2% of women had HPV type 16 or 18. A person may be infected with multiple types, including both wart-causing and cancer-causing varieties.

Oncogenic HPV can cause dysplasia, or abnormal precancerous cell changes. Over time, dysplasia can progress to cervical or anal intraepithelial neoplasia (CIN or AIN; classified as grade 1, 2, or 3), also known as squamous intraepithelial lesions (SIL; classified as low-grade or high-grade). If left untreated, intraepithelial neoplasia may progress to noninvasive carcinoma *in situ*, and eventually to invasive cervical or anal cancer. In addition, a recently published study showed that oral HPV infection—especially with type 16—is a major risk factor for cancers of the mouth and throat, and that people who have oral sex with multiple partners are at highest risk.

While it is generally considered a sexually transmitted infection, HPV may also be spread through nonsexual skin-to-skin contact. Condoms are only partially effective in preventing HPV transmission, since infection can occur through uncovered areas. Infected individuals may transmit the virus even if they have no visible external warts. Infants born to infected mothers may also contract HPV during delivery.

Anal HPV infection appears to be most common among men who have sex with men, but it also occurs in women and in men who do not practice anal sex (see “Not For Women Only,” page 37). A recent study by Susan Cu-Uvin, MD, and colleagues found that anal HPV infection was more common than cervical infection in HIV positive women, including those who did not have anal sex. On the whole, more women develop anal cancer each year than men, but they are less likely to be diagnosed during its early stages.

HPV Screening and Treatment

Fortunately, progression of dysplasia can be halted if detected at an early stage using Papanicolaou (“Pap”) smears. In this test, a sample of cells is taken from the cervix during a pelvic exam and examined under a microscope for abnormal appearance. Anal dysplasia can be detected using a similar test. The widespread adoption of routine cervical Pap screening in the 1950s led to a dramatic decrease in mortality due to cervical cancer in developed countries. Nevertheless, invasive cervical cancer still

Cervical and Anal Cancer Prevention Tips

- Smoking is a known risk factor for cervical and anal cancer.
- Having multiple sex partners increases the risk of HPV infection.
- While not completely protective, condoms can lower the risk of HPV infection and reinfection with new types.
- Women with multiple partners should consider a contraceptive method other than the pill, which may increase the risk of HPV infection.
- Women should get regular gynecological exams including Pap smears (every 6–12 months if HIV positive; at least every three years if HIV negative).
- At-risk men should get regular anal exams and ask their doctor about anal Pap smears.
- If Pap test results are abnormal, get a follow-up colposcopy or anoscopy.
- Ask your doctor about getting tested for HPV, and consider vaccination if uninfected.

strikes some 11,000 women in the U.S. each year, causing about 3700 deaths.

Experts disagree about how often HIV positive women should receive Pap tests. Some recommend every six months, while others believe women with high CD4 cell counts who have had at least two normal tests can lengthen the interval to once per year. The recommended interval for healthy HIV negative women with consistently normal tests is once every three years.

HPV DNA tests are also available that detect oncogenic types, but there remains some controversy about their usefulness, since many infections are transient and asymptomatic, and there is no treatment for HPV infection itself.

If a Pap smear shows evidence of abnormal cells, the next step is a procedure called colposcopy (for the cervix) or anoscopy (for the anus), in which the affected area is examined using a lighted microscope; in addition, a tissue biopsy sample may be taken for further analysis.

Since there is no treatment for HPV infection, therapy involves removal or destruction of affected tissue. Genital warts and areas of intraepithelial neoplasia may be removed using a variety of methods, including heat

(electrocautery), lasers, freezing (cryosurgery), or surgical excision.

Chemical therapies include imiquimod (Aldara), 5-fluorouracil (Efudex), podofilox (Condylox), and interferon alpha. Other agents are under study, including diindolylmethane, cidofovir (Vistide), and green tea extract. Once invasive cancer has developed, the usual treatment is a combination of chemotherapy, radiation, and surgery. But even after affected areas are removed, HPV may persist in surrounding tissue. Since the infection is not considered “cured,” screening should be continued to detect relapses.

HPV in Women with HIV

While HPV infection is common in the general population, it is even more prevalent among people with HIV. In Cu-Uvin’s analysis of 112 women in the SUN study, for example, 86% had cervical HPV infection and 92% had anal HPV (64% and 84%, respectively, with high-risk types).

In most healthy HIV negative individuals, the immune system is able to keep HPV under control and the infection is asymptomatic. But HIV positive people—especially those with advanced disease—have more persistent HPV, are more likely to develop HPV-related dysplasia, have a faster rate of progression to cancer, and are more likely to experience recurrence after treatment.

HIV positive people are also more likely to harbor multiple HPV types. A recent meta-analysis of data from 20 studies including nearly 5600 subjects worldwide found that 41% of HIV positive women with high-grade SIL had more than one type of HPV, compared with 7% of women in the general population. Further, HIV positive women with SIL were less likely to have oncogenic HPV type 16, but more likely to have other high-risk types such as 18, 51, 52, and 58.

Several studies have shown that HIV positive women are more likely than their HIV negative counterparts to develop CIN. In the HIV Epidemiology Research Study, women with HIV also had more vulvar, vaginal, and perianal lesions. Though invasive cervical cancer is considered an AIDS-defining condition, HIV positive women in developed countries do not appear to be at higher risk for invasive carcinoma, probably because they receive regular Pap smears. But in resource-poor countries where such care is lacking, HIV positive women have a high rate of advanced cervical neoplasia and cancer.

Research has produced conflicting data regarding the influence of CD4 cell count and antiretroviral therapy on HPV infection and development of intraepithelial neoplasia. Epidemiological studies indicate that rates of cervical

and anal neoplasia and cancer have not decreased in the HAART era; on the contrary, as effective antiretroviral therapy allows HIV positive people to live longer, they have more time to develop progressive HPV-related disease.

An analysis of 855 HIV positive and 343 HIV negative women enrolled in the Women's Interagency HIV Study (WIHS) showed that among those with normal Pap tests and undetectable HPV at baseline, 29% of HIV positive women with CD4 cell counts below 200 cells/mm³ developed CIN over three years, compared with 14% of those with 200–500 cells/mm³, 6% of those with more than 500 cells/mm³, and 5% of HIV negative women. In contrast, two recent French studies found that development of cervical or anal intraepithelial neoplasia was not associated with either current or nadir (lowest-ever) CD4 cell count.

In general, studies suggest that antiretroviral therapy has, at most, a minimal impact on HPV-related disease progression. One French study, for example, found that use of HAART did not lead to the regression of precancerous anal lesions or HPV clearance in HIV positive men. Similarly, an Italian study of 201 HIV positive women showed that over six years of follow-up, antiretroviral therapy did not prevent development of HPV-associated lesions, although women receiving HAART were more likely to experience regression of low-grade SIL. But in another French study, the incidence of SIL decreased modestly (from 10.7 to 6.5 cases per 100 person-years) in women receiving HAART. And in the WIHS trial, the chances of experiencing SIL regression increased from 0% in the pre-HAART era to 12.5% after the introduction of HAART.

HPV Vaccines

In June 2006, the U.S. Food and Drug Administration approved a new recombinant vaccine called Gardasil, developed by Merck & Company; the European Union followed suit in September. The vaccine is designed to prevent infection with HPV types 6 and 11 (which cause about 90% of genital warts) and 16 and 18 (responsible for about 70% of cervical cancer cases).

Gardasil—a series of three intramuscular injections given over six months—is approved for prevention of HPV-associated genital warts, CIN, and cervical, vulvar, and vaginal cancer in females aged 9–26 years. Approval was based on data from randomized, placebo-controlled trials involving more than 20,000 women and girls in both developed and resource-poor countries; the studies did not, however, include HIV positive women.

As reported in the May 10, 2007, *New England Journal of Medicine (NEJM)*, three-year data from the FUTURE I study, which enrolled 5455 HIV negative women aged

Not For Women Only

HIV positive men who have sex with men (MSM) are more likely than their HIV negative counterparts to have HPV infection, anal dysplasia, and anal cancer. The rate of anal cancer among gay and bisexual men is estimated to be 35 times greater than that of the general population, while HIV positive MSM have an 80-fold risk. In a study of 357 HIV positive MSM in San Francisco, for example, Joel Palefsky, MD, and colleagues found that 95% had anal HPV infection and 52% had grade 2 or 3 AIN. Yet invasive anal cancer—unlike cervical cancer—is not currently considered an AIDS-defining condition.

As with cervical dysplasia, precancerous anal cell changes can be detected through routine Pap screening. Because the test is simple, inexpensive, and effective, a growing number of experts believe anal Pap smears should become a part of routine care for at-risk individuals, including MSM.

“We haven't proven it yet, but we believe [testing is] likely to prevent anal cancer,” says Palefsky, who expects to present data from a study of anal cancer prevention later this year. He recommends that at-risk HIV positive men should get an anal Pap smear each year, while HIV negative men should be tested every 2–3 years.

Given the effectiveness of Gardasil and Cervarix in females, the vaccines are also being tested in males—both heterosexual and MSM—and data so far indicate young men will benefit, as well. Some clinicians report that gay men are already requesting off-label Gardasil (which is approved for boys aged 9–15 years in the European Union). But, as with women, the vaccine will only be effective for men who are not already infected with HPV, suggesting that it should be administered before they become sexually active.

16–24 years, showed that the vaccine was 100% effective in preventing HPV-associated anogenital lesions (warts, intraepithelial neoplasia, or cancer) in women who were not infected with HPV at baseline and received all three doses of the vaccine as scheduled. But in a “real world” analysis that included women already infected with HPV types 6, 11, 16, and/or 18 at baseline, the vaccine had only 73% efficacy in preventing external anogenital or vaginal lesions, and 55% efficacy in preventing cervical lesions caused by these HPV types. The vaccine was even less effective (20%–34%) in preventing lesions caused by other HPV types.

Similarly, the FUTURE II trial, which included more than 12,000 HIV negative women aged 15–26 years, found

that the vaccine was 98% effective in preventing grade 2 or 3 CIN or cervical carcinoma *in situ* caused by HPV types 16 or 18 in previously uninfected women who received the full vaccine series as scheduled. Among women previously infected with type 16 or 18 HPV, efficacy dropped to 44% in preventing high-grade CIN caused by these types, and 17% in preventing CIN caused by any type of HPV.

In studies to date, the vaccine was generally well tolerated, with the most frequent side effects being injection site soreness, fainting or dizziness, and flu-like symptoms. An analysis of Gardasil-related adverse events reported to the National Vaccine Information Center found that 14% were fainting episodes, and 8% involved tingling, numbness, loss of sensation, facial paralysis, or Guillain-Barré syndrome (a rare paralyzing autoimmune condition).

GlaxoSmithKline is also developing a preventive HPV vaccine called Cervarix, which targets types 16 and 18. As reported in the April 15, 2006, issue of *The Lancet* (and updated at the American Association for Cancer Research meeting this past April), a randomized, placebo-controlled trial of more than 1000 women aged 15–25 years showed that over 5.5 years of follow-up, Cervarix was 97% effective in preventing infection with HPV type 16 or 18, 100% effective against CIN associated with these types, and 68% effective against lesions due to any type of HPV. Though not designed to do so, the vaccine also provided cross-protection against HPV types 31 and 45, which are responsible for another 10% of cervical cancer cases.

Importantly, since Gardasil and Cervarix cannot prevent all anogenital cancer, and because the duration of protection is not yet known, regular Pap smears will still be needed to detect abnormal cell changes at an early, treatable stage. According to Diane Harper, MD, who worked on trials of both vaccines, “neither physicians nor women should be lulled into a false sense of security.”

While neither Gardasil nor Cervarix protect against neoplasia or cancer in individuals who are already infected with HPV, therapeutic vaccines designed to prevent progression of HPV-related disease after infection are also under study. Transgene and Roche are collaborating on a therapeutic vaccine, designated TG-4001, for the treatment of high-grade CIN. In a Phase II trial that enrolled 21 women with type 16 HPV and grade 2 or 3 CIN, half the participants experienced CIN regression and HPV clearance after six months. And in a small study by Joel Palefsky, MD, and colleagues, 13 men and two women with high-grade AIN received a therapeutic HPV type 16 vaccine known as SGN-00101. After 48 weeks, four patients experienced partial regression of AIN by 1–2 grades, while a fifth achieved more complete regression; three of the responders

also demonstrated anal HPV clearance. These promising results suggest that therapeutic HPV vaccines warrant larger studies.

Vaccine Fears and Hopes

Because Gardasil does not effectively protect women who are already infected with HPV, the vaccine is indicated for girls prior to adolescence. HPV infection typically occurs soon after a person becomes sexually active; in the NHANES study, 25% of young women aged 14–19 years already had HPV. The Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices recommended Gardasil for girls aged 11–12 years, as well as “catch-up” vaccination for those 13–26 years (though effectiveness decreases with age, as more women are already infected).

This recommendation has generated considerable controversy around proposed policies to mandate vaccination for all girls in this age group. Beyond moral concerns about sexual abstinence, some critics also worry that the vaccine has not been in use long enough to determine if there might be long-term side effects. Critics also contend that HPV is not communicable in social settings such as schools, and that cervical cancer can already be prevented through routine Pap testing. Further, vaccination against some HPV types could encourage the emergence of other strains, with unknown consequences.

According to Karen McCune, MD, of the University of San Francisco, “To be discussing mandatory vaccination when the main clinical trials are still ongoing seems extremely premature.”

At the same time, there is concern that the expensive vaccine (which costs about \$360 for the three-dose series in the U.S.) will not be available to women in poor countries, who are at greatest risk of dying from cervical cancer. Cervical cancer accounts for some 275,000 deaths per year worldwide, representing the largest cause of years of life lost to cancer in the developing world.

“Although achieving broad coverage of young adolescents, negotiating tiered pricing, and securing financing will be challenging, it is sobering to realize that with every five-year delay in bringing vaccination to developing countries, 1.5 million to 2 million more women will die,” wrote public health experts Jan Agosti, MD, and Sue Goldie, MD, MPH, in an editorial in the May 10, 2007, *NEJM*. “Let us hope that a committed global effort makes fulfillment of the promise of the new vaccine possible.”

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**IS YOUR
HEALTH
GOING UP
IN SMOKE?**

Smoking is a habit. It is often a stress-related activity. Smoking is also a risk factor for many conditions that affect people with HIV, including cardiovascular disease, bone disease, and anal cancer.

The FDA has approved bupropion (Zyban) as a nicotine-free medicinal quitting aid. Nicotine replacement therapies—in the form of lozenges (Commit), patches (Habitrol, NicoDerm CQ, Nicotrol), inhalers (Nicotrol Inhaler), and gum (Nicorette)—are another means of quitting. Complementary methods include behavior modification, counseling and support, and acupuncture.

The Stop Smoking Center (www.stopsmokingcenter.net) is a unique Web site that offers a Quit Program, online support services, and links to a wide range of smoking cessation resources, including the American Lung Association (212-315-8700) and Nicotine Anonymous (415-750-0328).

The Tobacco Education Center of UCSF/Mt. Zion (415-885-7895) is a quitting resource for San Francisco Bay Area residents.

**Learn more about the art of quitting.
There is no better time than now.**



Amelia
Glynn

Hooray for summertime! There's something about the longer days and warmer nights that helps bring out the traveler in all of us.

"Traveling has an element of spontaneity and the unknown," says Joni Lavick, MFT. "You never know what can happen." She sees this as potentially a great thing for people who are living with HIV.

Lavick has been working with HIV positive patients since 1988. She has a private practice in Santa Monica and is a clinical supervisor at the L.A. Gay & Lesbian Center. "One of the challenges of being HIV positive is having the resilience to stay on top of it," she says. "It requires a lot of mental-health energy to be able to spring back." She believes travel can play an important role in bolstering this necessary resilience.

When we arrive in a different country, we often have to deal with a different culture, language, climate—you name it. "We give ourselves credit for achieving the smallest, silliest things when we are traveling," Lavick explains, like reading a map correctly, figuring out a new transportation system to get to the next museum, or just finding our hotel.

Experiencing new things—and the resourcefulness it requires—helps us tackle other challenges, including those that are health related. "You know inside yourself that you have the ability to take on new things as they are thrown your way," says Lavick.

So, even though packing your meds, avoiding new infections, and locating medical services away from home might seem overwhelming (especially if it's your first time traveling with HIV), there are lots of good reasons for you to take that trip. Lavick considers it a great opportunity to "get out of your head" and take the focus off of yourself.

Doing your homework and being prepared—including talking with your doctor, carefully researching your destination, and getting any necessary pre-trip medications—can help take the anxiety out of traveling so you can relax and enjoy your time away.

ON THE ROAD WITH HIV: A Guide for Positive Travelers

Belize or Bust

So, you've decided it's time to take a break from your daily life. You're craving a change of scenery and perspective. Carefully considering what kind of destination, pace, and expense are best for you is essential to planning a healthy and rewarding trip.

At the most basic level, it's important to be honest with yourself about how you're feeling physically and emotionally. Are you up for that six-day white-water rafting adventure with your extended family? In some cases, opting for a more stress-free vacation (such as a cruise or some R&R at an all-inclusive beach resort) may do your mind and body more good.

Brad Hudson, founder of Travel Zone (www.travelzone-sfo.com), says all-inclusive resort vacations and cruises are good for people who don't want the hassle of moving hotels and packing and unpacking. They also afford guaranteed refrigeration for medications. "This a great option when you want to see more than one place without having to plan all the details yourself," he says. Some tour companies cater specifically to the gay and lesbian community, including RSVP Vacations, Atlantis Events, Above and Beyond Tours, Alyson Adventures, Pied Piper Travel, and Toto Tours.

One of Alyson Adventures' most popular tours is a rafting trip down the Colorado River. Even though the location is remote, owner Phillip Sheldon points out that tour guides have a built-in refrigerator: "The river can maintain everything from steak dinners to individual medications." All of the guides are equipped with satellite phones in case of an emergency, but he says there is a certain amount of self-selection involved. "We try to give people a good idea of what the trip is all about and leave it up to them to decide. The nice thing is, because we offer 50 trips a year to 35 countries, everyone can find something that works for them."

Irv, a marketing and sales consultant in Northern California, likes cruises because he can unpack once and visit several places. "The food is great and I get to pay for it all before I leave," he says. "The amenities are great. I never have to worry about having access to a refrigerator." Instead of being drawn to gay cruises, he often prefers to keep company with seniors. "They are the most compassionate people," he says. "When you sit down to dinner, everyone will look you in the eye and introduce themselves. I always have the most stimulating conversations." And if he likes a particular city, he knows he can always go back.

"There's something very therapeutic about being in a place where there is no land for miles," says Irv. "Every time I come back from a cruise, I feel like I've added a year to my life."

You needn't stray too far from home, though, to reap the benefits of travel. "I'm not a big fan of flying, and really, it doesn't take a lot of mileage to get some distance from your daily life," says Mary, a San Francisco graphic designer. "On a road trip, I don't have to worry about getting to the airport on time or getting through security with all my stuff. I can throw my meds and my flip flops in a backpack and be on vacation the minute I get in the car!"

An added benefit of local trips or less luxurious getaways is, of course, the lighter burden on your wallet. Lavick says that even many of her patients who are on disability or have fixed incomes find the means to travel—by taking really cheap flights or using frequent flyer miles and renting inexpensive apartments (equipped with money-saving kitchens) in the off-season. One such client recently spent a month in France. "Travel isn't just for my affluent patients," she says. "Everyone comes back energized and rejuvenated. I see nothing but positive mental benefits from travel."

However you decide to spend your time away—whether you're

surfing the Pacific or your best friend's couch—remember to listen to your body. You'll get more out of your trip if you stay hydrated, eat well, and take rest when you need it.

You and Your MD

The first step that any HIV-positive traveler should take is to evaluate your overall health with a physician, keeping a close eye on your CD4 cell count. If it's below 200 cells/mm³ (which indicates severe immunodeficiency), trips to areas where parasitic, bacterial, and viral diseases are highly prevalent can be risky.

Your physician or travel doctor can offer suggestions about staying healthy on the road and may be able to share names of medical providers who treat HIV in the regions you plan to visit.

Stephen E. Follansbee, M.D., Director of HIV Services and Travel Medicine for Kaiser Permanente San Francisco, encourages travel for his HIV positive patients. "I think it's a good idea and most people can travel safely," he says, with the caveat that their travel plans should be individualized and address any special health considerations and treatment regimens.

"One of the things that scared me when I first found out I was HIV positive was the idea that it might prevent me from traveling," says Ghee, a San Francisco native and avid traveler who was diagnosed in 1995. He sees his doctor regularly and checks in with him before he travels. "I always ask any questions I might have about a future trip I'm planning, but by now I'm pretty versed and secure in the choices I make," he says.

Getting Immunized

When Irv went to India, he got 22 pre-trip shots. "There are a lot of logistics involved when traveling with HIV, but it's worth it," he says.

Ask your physician or travel medicine expert and check the Centers for Disease Control and Prevention (CDC) Web site (see sidebar, page 42) for more information regarding specific

TRAVEL TIPS

Snack Savvy

If you need to take your medications with food, come prepared: whether you're traveling by train, plane, or automobile, pack a few snacks. You'll also want to bring a bottle or two of water (or purchase one once you've passed through airport security).

Jet Setting: Meds and Time Zone Changes

You may need to adjust your medication schedule when you cross into a different time zone. Stephen Follansbee, M.D., suggests waiting 24 hours and then taking your next dose at your normal time, wherever you are. If you are a few hours off it shouldn't make a huge difference, he says. The most important thing is to stick to a regimen that's been working for you.

A seasoned traveler, Irv takes his pills once in the morning and again in the evening. "I'm completely on vacation during the day and don't think about HIV again until night. One thing I've learned about HIV is that it loves attention," he says.

A Medication Vacation?

Although vacations can be a great opportunity to shift your attention beyond your HIV health, many doctors advise against taking a holiday from your meds. Treatment interruptions carry the risk of developing drug-resistance mutations, as well as other health problems (see "Structured

immunizations that are recommended for the areas you plan to visit. You'll also want to confirm that all of your routine immunizations are up-to-date; this is especially important for children with HIV. In general, all HIV positive travelers are advised to be vaccinated against polio, typhoid, and hepatitis A and B.

Anyone with a CD4 count below 200 cells/mm³ is advised to avoid "live vaccines," such as those for measles and yellow fever. In general, killed-virus vaccines are safer for people with HIV. Some countries require proof of immunization for entry. If Dr. Follansbee is not able to vaccinate one of his patients for health reasons, he provides a letter explaining why his patient has not received the required immunizations (although this precaution does not guarantee that the unvaccinated traveler will be allowed to enter the country).

Dr. Follansbee says it's also important to be aware that certain drugs may interact negatively with HIV medications; for example, malaria prevention drugs may have temporary neurological effects (for example, bizarre, vivid dreams) that compound side effects associated with some antiretrovirals, such as efavirenz (Sustiva). It is always important to talk to your primary care physician and about the

pre-trip vaccinations and medications that are right for you.

Managing Your Meds

As most people taking anti-HIV meds have learned from experience, no treatment regimen is completely free from side effects. These usually manifest within a few weeks after beginning treatment or making a switch, so it's smart to give yourself a solid month or two before wandering too far from home.

Irv takes 24 prescription pills a day and knows first-hand the importance of adjusting to a new regimen before hitting the road. "All the ads for new HIV medications say things like, 'You can ride bikes, climb mountains,' and I think, 'Are you kidding?' Maybe after you get over the explosive diarrhea and whatever other side effects they have," he says. "Once you start to jive with your medication, that's when I say it's time to get out of Dodge."

Irv has other health issues along with HIV, including a heart condition and diabetes. When he travels, he brings his doctors' contact information, a printout of the results from his most recent viral load test and CD4 cell count, and a list of all of the prescription drugs, over-the-counter medications, and alternative treatments he uses (and their dosages).

On the Web

Consult the CDC's list of recommended immunizations for destinations worldwide:

www.cdc.gov/travel/destinat.htm

Search the International Society of Travel Medicine's online directory of travelers' health clinics:

www.istm.org/WebForms/Members/IndexSecure.aspx?sUrl=%2fclinicdir%2fclinicdir.aspx

If your trip involves flying, pack as much of your medication in your carry-on bag as possible, since there is always a chance your luggage could be lost or delayed. According to the U.S. Transportation Security Administration (TSA) regulations, prescription and non-prescription medications do not need to be packaged in the usual quart-size clear plastic bag. If your medications are in liquid, gel, or aerosol form in containers greater than three ounces, you must declare them at the screening checkpoint (be sure to check the TSA Web site for updates: www.tsa.gov/travelers/air-travel/assistant/9-25_update_passenger_guidance_faq.shtm). And if the name on your prescription label does not match the name on your passport or driver's license, be prepared to explain why to a security officer.

It's wise to count out your pills ahead of time, and to bring extras along in case you experience any delays or decide to extend your trip. Alejandra, a counselor for the Oakland-based organization WORLD (Women Organized to Respond to Life Threatening Disease), often travels with double the amount of medication she needs. Depending on how long you plan to be away, you may also want to carry your meds in something other than their original containers (such as zip-top plastic bags) to avoid extra bulk in your luggage—just be sure to keep a copy of the prescription or the prescription label with you. If any of your medicines come with a desiccant (a drying agent), transfer it to the new container.

If you're carrying any medicines that might be controlled substances (some pain medications, for instance), it's a good idea to keep them in their original containers with your prescription information attached. Carrying a letter from your doctor that states you are taking the drugs for a chronic medical condition can also be helpful.

Regardless of where you go, bring a list of your medications, dosages, and dosing schedules, and your

doctor's name and phone number. Always be prepared to replace your medicines, just in case. You may want to ask your doctor to give you extra copies of your prescriptions.

If any of your medications are temperature-sensitive, consider storing them in a small, insulated lunch bag with an artificial-ice freezer pack until you get to your destination. And make arrangements for a refrigerator where you'll be staying. "Some medications will retain their efficacy for up to a month at room temperature," says Dr. Follansbee. "Just keep them out of direct sunlight and avoid extreme temperatures." (So, in other words, no driving through the Sahara with your meds on the dashboard.) Always read the manufacturer's guidelines and check with your doctor to confirm your options for storing medications.

HIV and International Travel

Most tourist destinations do not restrict entry to HIV positive visitors who plan to stay for three months or less. Still, there are several countries that may deport or block the entry of positive travelers. If you are planning to travel internationally, do your homework and find out what entry restrictions you may encounter at your destination.

Traveling overseas can be a great opportunity to see the resources that are available to HIV positive people in other areas. "Some of my patients make a special point to visit HIV clinics and organizations when they travel," says Lavick. "It becomes an anchoring point of their trip."

Alejandra is an enthusiastic traveler who has taken several trips to Spain (including two six-month stints). She researched the country's health care system in advance and was confident she would be able to find a clinic where she could be treated and receive her medications if necessary. She encourages other positive travelers to ask their doctors if they have any questions or con-

TRAVEL TIPS, CONTINUED

Treatment Interruptions: After SMART" in the Summer 2006 issue of *BETA*).

"I don't typically recommend taking a break from meds," says Dr. Follansbee. "And I definitely don't recommend it for travel. There are too many possible complications." Instead, he works with patients to help streamline their daily dosing schedules and manage their pill burden.

Playing it Safe

Take all of the same precautions you would at home to prevent HIV transmission. Bring a healthy supply of condoms if that's part of your safer sex practice—they may be harder to find or of inferior quality in some travel spots.

First Aid Essentials

Even though you may be able to buy many of these items during your trip, the peace of mind of having them at hand can be worth the extra bit of room they take up in your suitcase:

- local antihistamine
- hand sanitizer
- sunscreen
- pain relievers
- fever reducers
- antiarrhythmals
- antiemetics (to treat nausea or motion sickness)

Your doctor can recommend specific travelers' first-aid products that will not interact with your anti-retroviral medications.

International Travel (Restrictions May Apply)

The UK-based HIV/AIDS education organization NAM lists entry restrictions for more than 150 countries on their AIDSMap site:

www.aidsmap.com/en/docs/C92D5639-E779-44EC-B8F8-0CECCC23275A.asp

But for the most accurate and current information, call each destination's embassy or consulate and ask—**anonymously**.

cerns about emergency treatment abroad.

Irv took a month-long European cruise last October, starting in Istanbul and ending in Barcelona. “These countries were more liberal than I ever imagined,” he says. He finds that many countries (such as Turkey, which he calls “the most enlightened” place he’s visited so far) are more open and accommodating to HIV positive travelers than is the United States. He recalls that when traveling with an ex-partner who was not an American citizen, going through U.S. customs was the worst part of their trip. “England is also challenging,” he says. “It makes me think twice before I travel there.”

Ghee recently returned from ten days in Belize. “Seeing other ways of life opens your mind,” he says. “I like to get a feel for what other people think of Americans and our politics.” He recalls a particularly memorable trip to Guatemala to visit the Mayan ruins of Tecal: “Listening to the tour guides describe this ancient civilization makes you think about your own world. It reminds you that you are not invincible. Everything is temporary.”

Eat, Drink, and Be Merry

So much of traveling is about sampling the local cuisine. Having HIV shouldn't prevent you from satiating

your inner foodie. You'll just want to take a few extra precautions to keep yourself healthy.

Although the exotic smells from street vendors and outdoor markets may be tempting, it's often best to look rather than taste. Like most foreign travelers—both HIV positive and negative—you would be wise to steer clear of raw fruits and vegetables (which may retain unfamiliar microorganisms from soil or water), raw or undercooked seafood or meat (ground meats can be especially risky), and unpasteurized milk and dairy products. According to the CDC, foods that are generally safe include steaming-hot foods and fruits that you peel yourself.

Although eating food from a restaurant is usually your safest bet, be sensible about the foods you choose, especially in hotter climates where certain ingredients—such as eggs and dairy products—tend to spoil easily. Dr. Follansbee recalls a time when one of his patients who was visiting Cairo, and on his way to India to see the Taj Mahal, ate an egg-salad sandwich from his hotel restaurant. He ended up in a U.S. military hospital with severe food poisoning and shortly afterwards was on a plane back to the United States. It's better to err on the safe side than risk cutting your trip short.

If you're unsure about the local water supply, drink distilled water or bottled carbonated beverages—without ice. (A bottle labeled “purified spring water” doesn't necessarily guarantee that it will be clear of *Cryptosporidium parvum*, one of the most common infecting agents in the severe diarrhea associated with HIV disease.) This is especially important when visiting developing countries where the water supply may contain microorganisms that pose little threat to local residents (who ingest them daily) but wreak havoc on the uninitiated stomachs of foreign visitors. If bottled water is not available, boil your water for at least one full minute before drinking it.

Staying Healthy Abroad

In addition to having HIV, Alejandra also experiences lupus outbreaks. On her very first trip after her diagnosis, she packed “every medicine imaginable” in her travel kit. Now she says she's more relaxed but still plans ahead: “There are many positive things about traveling, but I always take precautions.” For example, before visiting Bolivia, she educated herself about altitude sickness so she would be prepared when she arrived. “In general, it's good to know about different sicknesses or conditions that may be associated with the place you're visiting,” she advises. “I tend to associate however I'm feeling with my HIV, but sometimes there's a simple explanation that is also very preventable.” Alejandra also recommends talking with other travelers about their experiences to learn more about your destination.

Especially before traveling to tropical or subtropical countries, consider consulting a travel medicine specialist. He or she can offer suggestions about staying healthy in places where certain illnesses, such as tuberculosis, may pose special threats to HIV positive visitors. If you're planning to be away for more than a month, it's good practice to look into facilities for treat-

ment of HIV-related problems in your destinations.

Be sure to take extra precautions against insect-borne diseases when visiting destinations where they are a problem. This includes using insect repellent that contains 30% to 40% DEET. (People with sensitive skin may prefer to wear pants and long sleeves and spray insect repellent onto their clothing rather than directly onto the skin.) Many camping-supply stores also carry insect-repelling clothing as well as mosquito nets that are pre-treated with the insect repellent permethrin. Sleeping under a mosquito net (which can often be purchased inexpensively in local markets and shops) is highly recommended in areas where malaria or dengue fever is prevalent.

To prevent possible waterborne infections, such as cryptosporidiosis and giardiasis (both caused by microscopic parasites), you may want to avoid swimming in potentially contaminated water, such as rivers, lakes, and streams, and even swimming pools if they are not properly chlorinated. If you do indulge in a dip, be extra careful not to swallow water.

The CDC and most doctors recommend avoiding areas where yellow fever is widespread. Tuberculosis is very common worldwide and can be very serious in people living with HIV; be sure to get tested when you return home.

Medical Care and Insurance

If you're traveling to a remote area or developing country, Hudson (of Travel Zone) recommends calling your medical insurance plan to ask what it covers when you are away from home. Many insurance plans have limited benefits outside the home country. For example, the Medicare/Medicaid program does not cover medical services received abroad. Very few plans cover the cost of flying you home if you become very sick.

"It could be a good idea to supplement your coverage with traveler's insurance," says Hudson. Traveler's insurance generally covers preexisting conditions, as well as MedEvac in case you need to be airlifted to a hospital. (A single uninsured trip in a MedEvac plane can cost thousands of dollars.) Hudson also advises travelers to check with their credit card issuers before buying additional coverage, as some cardholders are entitled to free emergency medical evacuation coverage. Some tour companies, such as Alyson Adventures, automatically provide traveler's insurance (which covers preexisting conditions) for their customers.

Happy Trails

"Whether or not you have the disease, it's up to you how much risk you want to take when you travel," Ghee says. He's gone on more trips in the last five years than ever before. "It's the old cliché—a blessing in disguise," he says. He still thinks about his mortality, but he has faith in the medications he's taking. "I'm a walking example that they work," he says.

And "getting away" doesn't have to mean getting into debt. "Taking short trips—road trips, day trips—can be very healing," says Mary. "I've learned that vacations don't have to be this huge thing you do, with lots of planning and lots of money. Just getting out and enjoying the environment around you can be a true vacation, even if you're only away for a weekend." She's looking forward to heading down the coast with her husband this summer.

Irv is planning his next trip, too: a cruise (of course) to Antarctica and South America. "When I travel, I get excited. I make new friends, have new experiences, and my HIV fades into the background. Every time I get out, I think, 'I'm doing this for David and Frank, and George,'" friends he lost to AIDS. For him, living well while he explores the globe is the best medicine of all.

Amelia Glynn is a freelance writer and former HIV counselor in San Francisco. An activist at heart with a keen interest in health care, she secretly dreams of wearing scrubs.

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Open Clinical Trials

Below is a list of selected currently enrolling clinical trials gathered from various sources. **TrialSearch**, operated by the **AIDS Community Research Initiative of America (ACRIA)**, is an extensive online database of clinical trials related to HIV/AIDS.

The federal government's **AIDSinfo** Web site includes a clinical trials section that features an introduction to HIV/AIDS research and study listings from the National Institutes of Health's **ClinicalTrials.gov** database. AIDSinfo also offers personalized advice about clinical trial participation via email (ContactUs@AIDSinfo.nih.gov), an interactive Web site (www.aidsinfo.nih.gov/live_help; specialists available Mon.–Fri. 9:00 am–1:00 pm PT), and a toll-free telephone service (800-874-2572, international 301-874-2572; specialists available Mon.–Fri. 9:00 am–2:00 pm PT). **CenterWatch** is a commercial Web site that includes trial listings for many diseases, including HIV/AIDS and related conditions.

Most U.S. government-sponsored HIV/AIDS trials are conducted by the adult and pediatric **AIDS Clinical Trials Group (ACTG)**. The **National Center for Complementary and Alternative Medicine (NCCAM)** conducts trials of complementary therapies for conditions related to HIV and its management. The **HIV Vaccine Trials Network (HVTN)** is an international collaboration testing preventive vaccines.

Call the telephone numbers listed for each study or see the indicated Web sites for further information about specific trials. Protocol numbers, if available, are provided in parentheses at the end of each trial description.

ACRIA TrialSearch:

www.acria.org/clinical_trials/index.html

ACTG: www.aactg.org

AIDSinfo: www.aidsinfo.nih.gov

CenterWatch: www.centerwatch.com

ClinicalTrials.gov: www.clinicaltrials.gov

HVTN: www.hvtn.org

NCCAM: www.nccam.nih.gov/clinicaltrials

SPRING Study of Tipranavir

Boehringer Ingelheim recently started enrollment in the SPRING study, an open-label Phase III trial evaluating the safety and efficacy of ritonavir-boosted tipranavir (Aptivus)

in a racially diverse population of heavily treatment-experienced individuals, half of them women. The study will also gather pharmacokinetic data and assess the utility of therapeutic drug monitoring (TDM).

“Studies have indicated that the efficacy of antiretroviral treatments may vary across races and genders,” said SPRING Coordinating Investigator Kathleen Squires, MD. “Therefore, SPRING is designed to provide insight into potential treatment differences for patient populations such as women and ethnic groups.”

All enrolled subjects will begin receiving the standard dose of 500 mg tipranavir plus 200 mg ritonavir (Norvir) twice daily; half the participants will be randomly assigned to undergo TDM, and may then have their doses adjusted as indicated.

Eligible participants must be at least 18 years of age and have used all three major classes of approved antiretroviral drugs for at least three months each. In addition, they must have documented resistance to more than one protease inhibitor (PI). However, subjects must still be able to construct a viable background regimen using approved nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), enfuvirtide (Fuzeon; T-20), and/or investigational agents. Exclusion criteria include prior tipranavir use, genotypic resistance to tipranavir, and a history of treatment interruptions of seven days or longer within the past month. Women may not be pregnant or breast-feeding and must agree to use specified methods of contraception.

The SPRING study aims to enroll 400 participants at more than 72 centers in eight countries. There are about 20 sites in the **United States**, including **Akron, Austin, Cincinnati, Decatur, Ft. Lauderdale, Houston, Jacksonville, Kansas City, Macon, New York City, Norfolk, Oklahoma City, Orlando, Philadelphia, Sacramento, Tampa, and Washington, DC**. For details and other study sites, email the Boehringer Ingelheim Study Coordinator at clintriage@rdg.boehringer-ingelheim.com. www.clinicaltrials.gov/show/NCT00440271 (1182.98).

GRACE: Gender Differences in Response to Darunavir

Tibotec's non-peptide PI darunavir (Prezista; formerly TMC114) was approved in June 2006 for use by treatment-experienced patients. The company has started an open-

label Phase IIIb trial called GRACE (Gender, Race and Clinical Experience), which will study sex- and race-related differences in the drug's efficacy and tolerability.

While HIV treatment trials have historically included mostly men, GRACE will enroll 70% women. "Women who participate in GRACE will play a very important role in advancing the understanding of HIV treatment in women," said treatment advocate Dawn Averitt-Bridge.

All subjects will receive 300 mg darunavir boosted with 100 mg ritonavir twice daily plus optimized background therapy for 48 weeks. Follow-up visits will take place at weeks 4, 8, 12, 16, 24, 36, 48, and 52.

Eligible participants must be at least 18 years of age, have a viral load of at least 1000 copies/mL, and have experienced intolerance or treatment failure on previous regimens containing PIs or non-nucleoside reverse transcriptase inhibitors (NNRTIs). Exclusion criteria include active opportunistic illnesses (OIs), abnormal laboratory test results, and use of certain other medications. Women may not be pregnant or breast-feeding.

The GRACE trial expects to enroll 420 subjects at some 50 sites in the **U.S.**, **Canada**, and **Mexico**, including **Atlanta, Baltimore, Birmingham, Boston, Chicago, Dallas, Durham, Ft. Lauderdale, Los Angeles, Miami, Nashville, Newark, New Orleans, New York City, Philadelphia, Salt Lake City, Seattle, St. Louis, and Washington, DC**. For further information, call 866-512-7943 or email GRACEstudy@wilm.ppd.com. www.clinicaltrials.gov/show/NCT00381303 (CR011869).

Switching from PIs to Raltegravir

Raltegravir (Isentress; formerly MK-0518), the first CCR5 antagonist, is expected to be approved this year. Merck is conducting two studies to assess the efficacy, safety, and tolerability of the new drug in subjects switching from PI-based regimens.

Both Phase III studies will evaluate the safety and antiviral activity of raltegravir in patients switching from regimens containing lopinavir/ritonavir (Kaletra). HIV RNA, CD4 cell counts, and tolerability will be assessed at weeks 24 and 48, and lipid changes will be measured at weeks 12, 24, and 48.

Eligible participants must be at least 18 years of age and have maintained an undetectable HIV viral load (below 50 copies/mL) for at least three months while on a stable lopinavir/ritonavir-based regimen. Exclusion criteria include acute hepatitis and use of certain other medications, including d4T (stavudine; Zerit), other investigational antiretroviral agents, or lipid-lowering medications. Women may not be pregnant or breast-feeding.

The studies will enroll 340 subjects each at about ten

sites in the **U.S.** (and others in **Australia, Canada, Europe, and Mexico**), including **Birmingham, Chicago, Houston, Newark, New Orleans, Orlando, Vero Beach, and Washington, DC**. For further information about either study, call 888-577-8839.

www.clinicaltrials.gov/show/NCT00443703 and www.clinicaltrials.gov/show/NCT00443729 (2007_507 and 2007_508).

Racivir vs 3TC in Treatment-Experienced Individuals

Racivir is an experimental NRTI undergoing Phase II testing. Since it is a cytidine analog, Pharmasset is conducting a study to determine how well the drug will work in patients who have developed resistance to another drug of this type, 3TC (lamivudine; Epivir).

Participants currently on failing antiretroviral regimens will be randomly assigned to receive racivir alone, 3TC alone, or racivir plus 3TC once daily for 14–28 days; those with a favorable response at that point may continue on open-label racivir for up to 20 weeks.

Eligible participants must be 18–65 years of age and have been on a stable HAART regimen including 3TC, but not emtricitabine (Emtriva; FTC), for at least 60 days (subjects will stop taking 3TC before they start the study drugs). In addition, they must have HIV with the M184V mutation. Exclusion criteria include current or recent OIs, acute hepatitis B or C, certain laboratory abnormalities, other drug-resistance mutations (Q151M or T69S), and use of certain medications, including other investigational agents. Women may not be pregnant or breast-feeding and must agree to use contraception.

The study will enroll 60 subjects at about ten sites in the **U.S.** and **Latin America**, including the **Bronx** (718-918-3662), **Chicago** (312-695-4997), and **Columbia, SC** (803-787-1113). www.clinicaltrials.gov/show/NCT00121979 (CI-PSI-RCV-04-201).

Treatment during Early Infection

While some experts believe antiretroviral therapy should be started soon after HIV infection, it is not yet clear whether treatment of recently infected individuals leads to long-term benefit or harm (see News Briefs, page 6). In this open-label study, sponsored by National Institute of Allergy and Infectious Diseases (NIAID), participants newly infected with HIV will be randomly assigned to receive either no treatment or a regimen of emtricitabine/tenofovir (Truvada) plus lopinavir/ritonavir for 36 weeks; after 36 weeks, subjects in both arms will have the option to continue or start treatment if they have high viral load, low CD4 count, or HIV-related symptoms. HIV viral load will

be measured at the end of treatment and at 72 and 96 weeks to determine whether early therapy appears to lower the viral “set point”; CD4 cell count, occurrence of AIDS-defining illnesses, adverse side effects, and drug resistance will also be assessed. Study visits will occur every 2–4 weeks for the duration of the 96-week trial.

Eligible participants must be at least 18 years of age. They must be recently infected with HIV and have a viral load of at least 500 copies/mL and a CD4 cell count of at least 350 cells/mm³ within 21 days prior to study entry. Exclusion criteria include various medical conditions and use of certain medications (including prior antiretroviral therapy or investigational HIV vaccines). Women may not be pregnant or breastfeeding.

This study aims to enroll 150 volunteers at more than 30 sites, including **Atlanta** (404-616-6313), **Boston** (617-724-0070), **Chapel Hill** (919-843-8761), **Denver** (303-372-5535), **Detroit** (313-916-2570), **Durham** (919-684-8216), **Indianapolis** (317-274-8456), **New York City** (212-327-7281), **Philadelphia** (215-349-8092), **Providence** (401-793-4396), **Rochester** (585-275-2740), **San Diego** (619-543-8080), **San Francisco** (415-476-9296 ext. 318), **Seattle** (206-731-8877), and **St. Louis** (314-454-0058).

www.clinicaltrials.gov/ct/show/NCT00090779
(ACTG A5217; AIEDRP AIN503).

Subjects in this trial will also be encouraged to join AIEDRP CORE01, a long-term follow-up study of HIV-positive individuals identified during early infection www.clinicaltrials.gov/ct/show/NCT00086372 (ACTG A5228; AIEDRP CORE01).

First-Line Antiretroviral Regimens

ACTG A5202 is a Phase IIIb study sponsored by NIAID that will compare four antiretroviral regimens in individuals starting therapy for the first time. Participants will be randomly assigned to one of four treatment arms:

- efavirenz (Sustiva) plus tenofovir/emtricitabine
- efavirenz plus abacavir/3TC (Epzicom combination pill)
- ritonavir-boosted atazanavir (Reyataz) plus tenofovir/emtricitabine
- ritonavir-boosted atazanavir plus abacavir/3TC

Treatment will continue for 96 weeks. Participants will undergo regular monitoring of HIV viral load, CD4 cell count, and blood lipid levels, and will complete questionnaires to assess adherence. Some participants will be asked to participate in a metabolic substudy (ACTG A5224s).

Eligible subjects must be at least 16 years of age; those with recent HIV infection will receive drug-resistance testing. Participants must not have received prior antiretroviral viral therapy for more than seven days total (exclud-

ing post-exposure prophylaxis). They must have a viral load greater than 1000 copies/mL within 90 days of study entry; there are no CD4 cell count restrictions. Exclusion criteria include major drug-resistance mutations, various medical conditions (including heart rhythm disturbances), and use of certain medications (including immunomodulators and other investigational agents). Women may not be pregnant or breast-feeding and must agree to use contraception.

This study aims to enroll 1800 participants at more than 60 sites, including **Atlanta** (404-616-6313), **Baltimore** (410-614-2766), **Birmingham** (205-975-7925), **Boston** (617-414-7082), **Chapel Hill** (919-843-8761), **Chicago** (312-572-4545), **Cincinnati** (513-584-8373), **Dallas** (214-590-0414), **Denver** (303-372-5535), **Galveston** (409-747-0219), **Honolulu** (808-737-2751), **Indianapolis** (317-274-8456), **Los Angeles** (310-557-2273), **Miami** (305-243-3838), **Minneapolis** (612-347-2690), **Nashville** (615-467-0154 ext. 108), **Omaha** (402-559-8163), **New York City** (212-746-4393), **Philadelphia** (215-349-8092), **Providence** (401-793-4396), **Rochester** (585-275-2740), **Sacramento** (916-914-6263), **San Diego** (619-543-8080), **San Francisco** (415-514-0550 ext. 354), **San Juan** (787-759-9595), **Seattle** (206-731-8877), **Stanford** (650-723-2804), **St. Louis** (314-454-0058), and **Washington, DC** (202-687-2294). www.clinicaltrials.gov/ct/show/NCT00118898 (ACTG A5202).

INCB9471: Once-Daily Oral CCR5 Inhibitor

Incyte Corporation is sponsoring a Phase II trial to assess the safety, pharmacokinetics, and antiviral efficacy of INCB009471, an orally available CCR5 antagonist. CCR5 antagonists are a new class of antiretroviral agents that block HIV entry into cells (see Drug Watch in the Winter 2007 issue of *BETA*).

Eligible participants must be 18–65 years of age and either antiretroviral-naïve or off treatment for at least three months. They must have a CD4 count above 350 cells/mm³, a viral load greater than 10,000 copies/mL, and HIV that uses only the CCR5 coreceptor (viral tropism will be assessed at study entry). Exclusion criteria include certain illnesses (including hepatitis B or C and heart conditions), laboratory abnormalities, and use of certain medications (including herbal supplements). Women may not be pregnant or breastfeeding, and participants must agree to use effective barrier contraception. Subjects will be randomly assigned to receive 200 mg INCB009471 or placebo once daily with food for 14 days. Virological and safety assessments, including electrocardiograms, will be conducted regularly throughout the study.

This trial will enroll participants in **Annandale, Boston, Los Angeles, Orlando, Vero Beach**, and

Washington, DC. For more information, call 302-498-6781 or email ksolomon@incyte.com. www.clinicaltrials.gov/ct/show/NCT00393120 (INCB 9471-201).

Protease Inhibitors and Glucose Metabolism

This randomized Phase IV study, sponsored by the Department of Veterans Affairs, will attempt to determine how PIs contribute to the development of diabetes in people with HIV—in particular, whether PIs impair insulin secretion and increase the production of glucose by the liver. In order to separate out the effects of PIs from those of HIV itself, this study will enroll HIV negative volunteers. Participants will be randomly assigned to receive either a single dose of a PI or placebo. Insulin secretion will be assessed using the hyperglycemic clamp technique. Somatostatin, growth hormone, and glucagon will be infused before and during the clamp study. Liver glucose production will be measured in the fasting and hyperinsulinemic (excess insulin) states.

This study aims to enroll 80 healthy, HIV negative participants 18–72 years of age. Volunteers may not have medical conditions associated with insulin resistance, such as obesity or elevated blood fat levels, and may not be taking glucocorticoids, growth hormone, niacin, or antipsychotic medications. Women may not be pregnant. This study will take place at the **San Francisco Veterans Affairs Medical Center** (415-221-4810 ext. 2118 or ext. 3395). www.clinicaltrials.gov/ct/show/NCT00259727 (RCD-005-05S; H574-23263).

SUN Study: Natural History of HIV/AIDS

The SUN Study is a prospective observational cohort study sponsored by the Centers for Disease Control and Prevention (CDC) with the aim of better understanding the incidence, causes, and risk factors for metabolic and other complications related to effective HIV treatment and longer survival. The study will also evaluate a behavioral intervention designed to reduce HIV transmission through prevention counseling integrated into routine medical care.

For at least five years, participants will be followed with biannual physical examinations, noninvasive imaging (e.g., DEXA scans, carotid artery ultrasound), and regularly scheduled laboratory testing.

Eligible participants must be at least 18 years of age. Treatment-naïve subjects (those with less than 30 days of consecutive exposure to antiretrovirals) must have a CD4 cell count between 100 and 500 cells/mm³. Treatment-experienced participants must have at least 100 cells/mm³ and have had at least two visits within the past year at the clinical facility where they are eligible for enrollment.

Exclusion criteria include recent OIs and use of certain medications. Women may not be pregnant.

The study aims to enroll 1000 participants at HIV specialty care centers in **Denver** (303-393-8050 or 303-320-2830), **Minneapolis** (612-873-7516, 612-325-9520, or 952-993-3131), **Providence** (401-793-4025 or 401-793-5961), and **St. Louis** (314-289-6433 or 314-454-0058). www.clinicaltrials.gov/show/NCT00146419 (CDC-NCHSTP-3979; 200-2002-00610; 200-2002-00611; 200-2002-00612; 200-2002-00613).

TH9507 for Lipodystrophy

TH9507 is a growth hormone releasing factor (GRF) that has been shown to reduce visceral adipose tissue (VAT) and trunk fat in HIV positive individuals with excessive abdominal fat accumulation (see Drug Watch, page 16).

In this Phase III trial, participants will be randomly assigned to receive 2 mg TH9507 or placebo for 26 weeks. Investigators will assess changes in VAT, blood lipids (cholesterol, triglycerides), and patient-reported perceptions of body image.

Eligible participants must be 18–65 years of age, have a CD4 cell count above 100 cells/mm³ and an HIV viral load below 10,000 copies/mL, and must have been on stable HAART for at least eight weeks. They must have evidence of abdominal fat accumulation, defined as a waist circumference greater than 95 cm for men or 94 cm for women, and a waist-to-hip ratio greater than 0.94 for men or 0.88 for women. Exclusion criteria include body mass index below 20 kg/m², opportunistic infections or malignancies, untreated hypertension, certain laboratory abnormalities, and use of certain medications. Women may not be pregnant or breastfeeding and must have had a normal mammogram within six months.

The study is enrolling participants at some 30 **U.S.** sites (plus others in **Canada** and **Europe**), including **Atlanta** (404-876-2317 ext. 336), **Austin** (512-480-9660), **Birmingham** (205-934-2721), **Boston** (617-726-1696), **Chapel Hill** (919-843-2723), **Chicago** (773-296-2400 ext. 122), **Cleveland** (216-844-1389), **Dallas** (214-590-0414), **Denver** (303-436-8229), **Ft. Lauderdale** (954-524-2250), **Houston** (713-526-9821), **Indianapolis** (317-274-8456), **Los Angeles** (310-557-9680), **Miami** (305-944-2884), **New York City** (212-924-3934 ext. 105), **Phoenix** (602-307-5330), **San Francisco** (415-750-2005), **Seattle** (206-624-0688), and **Tampa** (813-875-4374). www.clinicaltrials.gov/show/NCT00435136 (TH9507-CTR-1011).

Omega-3 Fatty Acids for High Triglycerides

This study, sponsored by Reliant Pharmaceuticals and the National Center for Complementary and Alternative Medicine, will assess whether omega-3 (also known as N-

3) fatty acids can help lower triglycerides in people with HIV. A recently published study has already shown that fish oil capsules, which contain omega-3 fatty acids, decreased triglyceride levels by about 25% in HIV positive patients (see News Briefs, page 9).

In this Phase IV trial, participants with elevated triglycerides will be randomly assigned to receive either Omacor (an FDA-approved prescription omega-3 fatty acid supplement) or placebo. Investigators will assess changes in triglyceride levels from baseline, as well as cholesterol levels and markers of systemic inflammation, insulin resistance, and bone turnover.

Eligible participants must be at least 18 years of age, have an HIV viral load below 5000 copies/mL, and have been on stable antiretroviral therapy for more than three months. They must also have been on stable lipid-lowering therapy for two months prior to study entry, but still have had a fasting plasma triglyceride value between 250 and 1000 mg/dL on two occasions. Exclusion criteria include heart, liver, or kidney disease, uncontrolled hypertension, certain laboratory abnormalities, and use of certain medications. Women may not be pregnant or breastfeeding.

The study will enroll 48 subjects in **Baltimore** (410-955-2130) and **Los Angeles** (310-478-3711). www.clinicaltrials.gov/show/NCT00346697 (K23 AT002862-01).

Lifestyle Modification for Metabolic Syndrome

This randomized, case-control efficacy study, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, is designed to assess the effects of an intensive 12-month lifestyle modification program on metabolic syndrome, with a primary endpoint of improved body composition (waist-to-hip ratio). Improvements in cholesterol and triglyceride levels, blood pressure, and other indicators of cardiovascular health are secondary endpoints of the trial.

Following an extensive screening process, participants randomized to the “Reach for Energy, Activity, and Cardiovascular Health” (REACH) cohort will complete seven-day food records, have periodic physical exams, and undergo sub-maximal stress tests and other physical therapy testing. This cohort will also attend individualized counseling sessions with a trained dietitian. Participants randomized to the observation-only cohort will attend one such counseling session and will receive monthly phone calls from the study investigators; this group will undergo the same exams and tests as those in the REACH cohort. Eligible participants must be 18 to 65 years of age, be HIV positive, and have three of the following five indicators of metabolic syndrome: waist circumference greater than 88

cm (35 inches) in women and 102 cm (40 inches) in men; triglycerides at least 150 mg/dL (or currently be taking anti-lipolytic drugs); high-density lipoprotein (HDL, or “good”) cholesterol less than 50 mg/dL in women and 40 mg/dL in men; blood pressure at least 130/85 mm/Hg (or be on antihypertensive drug therapy); or fasting glucose at least 110 mg/dL. Exclusion criteria include starting a new antiretroviral drug within one month of joining the study; taking androgens, growth hormone, or megestrol acetate (Megace) within three months of study initiation; history of severe neuropathy, uncontrolled hypertension, arthritis, or other contraindications to exercise; current drug or alcohol abuse; and certain laboratory abnormalities. Women may not be breastfeeding, pregnant, or trying to conceive. The study is enrolling 80 participants in **Boston** (617-724-9109). www.clinicaltrials.gov/ct/show/NCT00111358 (49302-P1; R01DK-49302).

NGX-4010 for Neuropathy

This randomized, double-blind, placebo-controlled Phase III study will assess the safety and efficacy of NGX-4010, a dermal patch containing capsaicin (the chemical in chili peppers that gives them “heat”), for treating HIV-associated neuropathy. Trial participants will receive either active NGX-4010 patches or identical placebo patches, to be applied to the skin and worn for either 30 or 60 minutes. At study entry, subjects will be asked to rate their neuropathy-associated pain using numeric pain rating scale (NPRS) scores, and will record average 24-hour NPRS scores daily for 12 weeks. Follow-up visits will occur 4 and 8 weeks after study participation ends.

Eligible participants must have had documented neuropathy in both feet for at least two months prior to the study screening visit, as well as other neuropathy-related symptoms in the ankles or legs, must have intact, non-irritated skin over the areas to be treated, must not be hypersensitive to capsaicin, and may not be taking certain pain medications. Women may not be pregnant and must agree to use contraception for the duration of the study and for 30 days following exposure to the study drug.

The study is currently enrolling at sites across **Australia, the United Kingdom, Canada, and the United States**. U.S. sites are located in **Arizona, California, Florida, Georgia, Hawaii, Illinois, Maryland, Michigan, Missouri, Montana, Nevada, New Jersey, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, Tennessee, Texas, Virginia, and Washington**. For more information, call 877-HIV-4010 or visit www.hivpatchstudy.com. www.clinicaltrials.gov/ct/show/NCT00321672 (C119).

Cervical Cancer

Numerous studies are underway to test various therapies for different stages of cervical cancer. Most trials involve combinations of chemotherapy drugs, and some also include radiation therapy or whole-body hyperthermia (temperature elevation). Eligibility and exclusion criteria vary, but some trials accept women with HIV. Some of the currently enrolling studies listed on the ClinicalTrials.gov Web site include:

- ABI-007 in treating patients with persistent or recurrent cervical cancer (www.clinicaltrials.gov/show/NCT00309959)
- Cetuximab, cisplatin, and radiation therapy in patients with stage IB, stage II, stage III, or stage IVA cervical cancer (www.clinicaltrials.gov/show/NCT00104910)
- Cisplatin and radiation therapy with or without hyperthermia therapy in patients with cervical cancer (www.clinicaltrials.gov/show/NCT00085631)
- Oxaliplatin and paclitaxel in patients with locally recurrent or metastatic cervical cancer (www.clinicaltrials.gov/show/NCT00057863)
- Pazopanib plus lapatinib compared with lapatinib alone and pazopanib alone in patients with metastatic cervical cancer (www.clinicaltrials.gov/show/NCT00430781)
- Topotecan in treating women with persistent or recurrent cervical cancer (www.clinicaltrials.gov/show/NCT00087126)

Anal Cancer

This open-label Phase II study, sponsored by the AIDS-Associated Malignancies Clinical Trials Consortium and the National Cancer Institute, will evaluate a chemotherapy regimen for the treatment of stage I, II, or III anal carcinoma in people with HIV.

Participants will receive the monoclonal antibody cetuximab (Erbix) intravenously for 1–2 hours on days 1, 8, 15, 22, 29, and 35, intravenous fluorouracil continuously on days 1–4 and 29–32, and intravenous cisplatin for one hour on days 1 and 29. Beginning on day 1, patients will undergo radiation therapy five days per week for 5–7 weeks. Treatment will continue until there is evidence of disease progression or unacceptable toxicity. Investigators will assess treatment failure rates along with survival, treatment-related adverse events, changes in HIV viral load and CD4 cell count, development of OIs, and quality of life.

Eligible participants must be at least 18 years of age and have histologically confirmed stage I-IIIB invasive anal or perianal squamous cell carcinoma. Exclusion criteria

include acute OIs, certain other types of cancer, peripheral neuropathy, certain laboratory abnormalities (including low blood cell counts), and prior chemotherapy or radiation therapy. Women may not be pregnant or breastfeeding.

The study will enroll 47 participants at six sites: **Boston** (617-667-9925), the **Bronx** (718-430-2302), **La Jolla** (858-822-5354), **Los Angeles** (310-206-8359), **Philadelphia** (215-829-6088), and **St. Louis** (314-362-8836). www.clinicaltrials.gov/show/NCT00324415 (CDR0000440065; AMC-045; AMC-026).

Treatment of Oral Warts

This Phase II trial, sponsored by Amarillo Biosciences, will evaluate low-dose interferon alpha lozenges as a treatment for oral warts caused by human papillomavirus (HPV) in HIV positive people on HAART.

All potential study participants will have their warts examined and measured at a screening visit, and a biopsy will be done to confirm HPV infection. Qualifying subjects will be randomly assigned to receive interferon or placebo lozenges for 24 weeks. Participants will have their warts examined every six weeks, and investigators will assess the change in the total area covered by warts at the end of therapy. Subjects will be reimbursed for travel expenses.

Eligible participants must be at least 18 years of age, taking a standard combination antiretroviral therapy regimen, and have at least two warts inside the mouth. Exclusion criteria include active OIs and use of oral or injected steroids and other medications for the treatment of oral warts.

The study will enroll 80 participants at six sites: **Baltimore** (410-706-7628), **Boston** (617-732-5500 ext. 32806), **Chicago** (312-996-4333), **Dallas** (214-828-8454), **New York City** (212-998-9626), and **San Francisco** (415-505-2408 or 415-476-3080). www.clinicaltrials.gov/show/NCT00454181 (03HUHI19).

Interactions between Emergency Contraception and Efavirenz

This open-label Phase I pilot study, sponsored by Bristol-Myers Squibb, will assess whether blood levels of the hormonal emergency contraceptive levonorgestrel (Plan B) are altered by concurrent use of efavirenz. It will also evaluate changes in efavirenz levels, as well as levonorgestrel side effects and liver function tests with and without efavirenz.

Eligible women must be 18–45 years of age and HIV negative. Exclusion criteria include obesity, hepatitis B or C, and current use of hormonal contraceptives. Participants may not be pregnant or breastfeeding. The study will enroll 24 participants in **Denver** (720-848-0819) and

Providence (401-793-4632). www.clinicaltrials.gov/show/NCT00482963 (06-1178).

Tenofovir to Prevent Perinatal HIV Transmission

This Phase I trial, sponsored by NIAID and the National Institute of Child Health & Human Development, will look at the safety, tolerability, and pharmacokinetics of single-dose tenofovir (Viread) given to women during labor and to their newborn infants. Tenofovir has been shown to effectively reduce the risk of vertical (mother-to-child) transmission in monkeys infected with a simian virus related to HIV. In this nonrandomized, open-label study, pregnant women will be assigned to one of two groups. Subjects in Cohort 1 will receive a single 600-mg dose of tenofovir at the start of labor or before planned cesarean section. They will also receive intravenous zidovudine (AZT), which is standard therapy for preventing vertical transmission in developed countries, and/or other antiretroviral medications prescribed by their physician. Infants born to women in Cohort 1 will receive the standard six-week postpartum oral AZT prophylaxis regimen. After eight-week data from infants in Cohort 1 have been analyzed, a second cohort of pregnant women will receive a single dose of tenofovir (with the dose to be determined based on pharmacokinetic data from Cohort 1) plus standard AZT prophylaxis and/or other antiretroviral drugs. Infants born to women in Cohort 2 will receive a single dose of tenofovir within six hours after birth, along with the standard six-week AZT regimen. Blood samples will be collected from mothers and infants to assess tenofovir pharmacokinetics and resistance. The women will be followed for 12 weeks postpartum; if viral resistance to tenofovir emerges during this period, they will be followed for two years. Infants will be followed until age 2.

Eligible women must be at least 18 years of age and in their third trimester of pregnancy (at least 34 weeks gestation). There are no viral load or CD4 cell count restrictions. Exclusion criteria include previous treatment with tenofovir, various medical conditions (including active OIs), abnormal laboratory results, and current or prior use of certain medications. Ultrasound screening must show a normal pregnancy and mothers must agree not to breastfeed.

This study aims to enroll 20 women at 30 sites, including **Boston** (617-355-8198), the **Bronx** (718-960-1020), **Chicago** (773-257-5717), **Denver** (303-861-6751), **Detroit** (313-745-7857), **Durham** (919-416-3447), **Houston** (832-824-1339), **Los Angeles** (323-226-2226), **Memphis** (323-669-2390), **Miami** (305-243-4447), **Newark** (973-972-3118), **New York City** (212-263-5680), **Philadelphia** (215-427-5284), **San Diego** (619-543-8080), **San Francisco** (415-

476-6480), **San Juan** (787-765-4186), **Seattle** (206-987-5020), and **Washington, DC** (202-877-5811). www.clinicaltrials.gov/ct/show/NCT00076791 (PACTG 394).

Effect of Stress Reduction on Immune Function and Side Effects

The Staying Well study, sponsored by the National Center for Complementary and Alternative Medicine, is a controlled trial of mindfulness-based stress reduction (MBSR) for people with HIV. The study aims to determine whether stress reduction through meditation is associated with reduced HIV disease progression (as determined by CD4 cell count and viral load measurements), less depression, and improved quality of life; it will also assess the mechanisms by which stress and mood may influence immune function.

In this Phase II study, subjects will be randomly assigned to participate in either MBSR or general education on health and well-being for HIV positive individuals. Both groups will attend eight weekly sessions at the Osher Center for Integrative Medicine at the University of California at San Francisco (UCSF). Participants will have blood drawn and will complete psychological questionnaires at study entry and at months 3, 6, and 12; they will receive compensation for each completed assessment. Those initially assigned to the education group may participate in the MBSR program for free after 12 months.

Eligible subjects must be at least 18 years of age and able to speak English. They must not have taken antiretroviral therapy for the past 120 days, and must have an HIV viral load greater than 100 copies/mL and a CD4 cell count above 250 cells/mm³ at study entry. They should not plan to start HAART during the 12 months following enrollment, but may do so if medically necessary and remain in the study. Exclusion criteria include previous MBSR training or current practice and recent use of certain medications.

The study aims to enroll 330 participants in **San Francisco** (415-353-9745). www.clinicaltrials.gov/show/NCT00271856 (P01 AT002024).

A related randomized Phase I/II study, also to be conducted at UCSF, will explore the effects of a mindfulness-based stress reduction program on medication-related side effects in HIV positive individuals taking antiretroviral therapy. In this study, 100 treated patients will participate in the MBSR program for eight weeks. The control group will consist of 50 subjects on the waiting list for the program. The primary outcome measure will be the number and severity of side effects reported by patients; health-related quality of life and adherence to antiretroviral therapy will also be assessed.

Eligible subjects must be at least 18 years of age and able to speak English. They must have been on standard

combination antiretroviral therapy for at least the past 30 days and must have experienced significant bothersome side effects (to be rated using a side effect and symptom distress scale) for the previous 30 days. Exclusion criteria include current enrollment in an MBSR program or related study, severe cognitive impairment, active psychosis, and active substance abuse that would interfere with MBSR participation.

The study aims to enroll 100 participants in **San Francisco** (415-597-9374). www.clinicaltrials.gov/show/NCT00312936 (R21 AT003102-01).

Project T: Tenofovir to Prevent HIV Infection

The CDC, in conjunction with the San Francisco Department of Public Health (SFDPH), the AIDS Research Consortium of Atlanta, and the Fenway Community Health Center in Boston, is conducting a double-blind Phase II trial to assess whether tenofovir can be used as pre-exposure prophylaxis (PrEP) to prevent infection, as suggested by animal studies.

Participants will be randomly assigned to receive either daily oral tenofovir or a placebo, and will be followed every three months for two years. This phase of the study will focus on the safety of the drug and whether use of a potentially protective agent leads to an increase in high-risk sexual behavior. Because it is not yet known whether tenofovir can prevent HIV infection—and because some subjects will receive placebo—participants should continue to practice safer sex, and they will receive risk-reduction counseling and free condoms. If any participants become infected, SFDPH will facilitate referrals for HIV care and treatment.

Eligible participants must be sexually active HIV negative men aged 18–60 years who have sex with men or transgender (male-to-female) women. Exclusion criteria include certain medical conditions (including impaired kidney or liver function and bone disease) and use of certain drugs (including nephrotoxic medications). The study is enrolling participants in **San Francisco** (415-554-8888; www.helpfighthiv.org/projt.htm), **Atlanta** (404-876-2317; www.aidsresearchatlanta.org/TheT), and **Boston** (617-927-6450). www.clinicaltrials.gov/show/NCT00131677 (CDC-NCHSTP-4323).

Elite Controller Study

The Elite Controller Study is a collaborative effort to understand factors associated with long-term non-progression of HIV disease. The study defines “controllers” as individuals able to maintain low HIV viral loads (below 2000 copies/mL) without treatment, and “elite controllers”

as those able to maintain undetectable HIV RNA levels (below 50 copies/mL). The investigators will assess multiple viral and host characteristics, including genetic variations such as the *CCR5Δ32* mutation, which is associated with resistance to HIV infection and slow disease progression.

Eligible participants will be HIV positive adults 18–75 years of age. They must not be on antiretroviral therapy and must have viral loads below 2000 copies/mL and asymptomatic infection. Candidates will first undergo a one-time blood draw by their local provider. The sample will be sent to the study coordinators and analyzed to determine eligibility. The coordinators will then arrange for further participation.

This collaborative study is coordinated by Bruce Walker, MD, of Partners AIDS Research Center at Massachusetts General Hospital in **Boston**, and includes participating researchers and community advocacy groups in **Chicago, Durham, Los Angeles, Nashville, New York City, San Diego, San Francisco, Seattle**, and in **Canada, Europe, and Australia**. The researchers hope to identify 700–800 HIV controllers worldwide; individuals who believe they may qualify need not live in one of these cities. For more information or to discuss eligibility, contact Rachel Rosenberg (617-726-5536; rosenberg2@partners.org) or Florencia Pereyra (fpereyra@partners.org). www.mgh.harvard.edu/aids/hiv_elite_controllers.asp.

Bupropion to Reduce Methamphetamine Use

The BUMP study, conducted by SFDPH, is designed to evaluate whether an antidepressant medication can help gay and bisexual men stop using or reduce their use of methamphetamine. Researchers also will assess whether this helps reduce high-risk sexual behavior, such as anal sex without a condom.

Subjects will be randomly assigned to receive either the antidepressant bupropion (Wellbutrin, Zyban)—which is also prescribed to aid smoking cessation—or a placebo for 12 weeks. If this approach proves feasible, the investigators plan to conduct a larger trial. Study visits will take place weekly and will include a urine test; participants will receive \$10–\$35 per visit.

Eligible participants must be men at least 18 years of age, either HIV positive or HIV negative, who have engaged in anal sex with men while using methamphetamine in the past three months. Exclusion criteria include acute illnesses, history of seizures, liver or kidney dysfunction, and use of certain medications. The study is enrolling participants in **San Francisco** (415-554-9013 or 415-703-7273; sf.bump@sfdph.org). www.clinicaltrials.gov/show/NCT00318409 or www.sfbump.com (R21DA021090-1).

APPROVED ANTIRETROVIRAL DRUGS

GENERIC (COMMON) NAME	BRAND NAME	COMPANY	YEAR APPROVED
PROTEASE INHIBITORS (PIs)			
amprenavir	Agenerase	GlaxoSmithKline	1999; discontinued 2004
atazanavir	Reyataz	Bristol-Myers Squibb	2003
darunavir (TMC114)	Prezista	Tibotec	2006
fosamprenavir	Lexiva (U.S.); Telzir (Europe)	GlaxoSmithKline	2003
indinavir	Crixivan	Merck	1996
lopinavir/ritonavir	Kaletra	Abbott	2000; Meltrex formulation 2005
nelfinavir	Viracept	Pfizer	1997
ritonavir	Norvir	Abbott	1996
saquinavir	Invirase (hard-gel) Fortovase (soft-gel)	Roche	1995 1997; withdrawn 2005
tipranavir	Aptivus	Boehringer Ingelheim	2005
NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)			
abacavir	Ziagen	GlaxoSmithKline	1998
didanosine (ddl)	Videx	Bristol-Myers Squibb	1989; extended-release Videx EC 2000
emtricitabine (FTC)	Emtriva	Gilead	2003
lamivudine (3TC)	Epivir	GlaxoSmithKline	1995
stavudine (d4T)	Zerit	Bristol-Myers Squibb	1994
tenofovir DF	Viread	Gilead	2002
zalcitabine (ddC)	Hivid	Roche	1992; withdrawn 2005
zidovudine (AZT)	Retrovir	GlaxoSmithKline	1987
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)			
delavirdine	Rescriptor	Pfizer	1997
efavirenz	Sustiva (U.S.); Stocrin (elsewhere)	Bristol-Myers Squibb	1998
nevirapine	Viramune	Boehringer Ingelheim	1996
ENTRY/FUSION INHIBITORS			
enfuvirtide (T-20)	Fuzeon	Trimeris	2003
FIXED-DOSE COMBINATIONS			
lamivudine/abacavir (NRTI)	Epzicom (U.S.); Kivexa (Europe)	GlaxoSmithKline	2004
tenofovir/emtricitabine (NRTI)	Truvada	Gilead	2004
tenofovir/emtricitabine/efavirenz (NRTI/NNRTI)	Atripla	Gilead/Bristol-Myers Squibb	2006
zidovudine/lamivudine (NRTI)	Combivir	GlaxoSmithKline	1997
zidovudine/lamivudine/abacavir (NRTI)	Trizivir	GlaxoSmithKline	2000

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