Complications of HIV Infection and Antiretroviral Therapy

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Metabolic Complications

Atherosclerosis and HIV Infection

More attention has increasingly been focused recently on determining whether patients with HIV infection who are treated with highly active antiretroviral therapy (HAART) regimens are at an increased risk of cardiovascular or cerebrovascular (CVD) events. Several presentations at this year's conference addressed this issue. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study group presented the preliminary results of the first prospective study to examine the incidence of myocardial infarction (MI) among more than 23,000 patients being followed up in 11 cohorts in Europe, Australia, and North America (Abstract 130). Monitoring for rates of MI began in 1999. As of September 2002, the D:A:D investigators noted a 26% increase in the MI rate per year of exposure to combination antiretroviral therapy (nonnucleoside reverse transcriptase inhibitor [NNRTI] and protease inhibitor [PI] regimens were considered together). The overall incidence of MI remains low at 3.5 events per 1000 person-years. Importantly, risk factors for MI in addition to time on combination therapy included age, male sex, smoking (60% were never smokers), and previous cardiovascular disease. In addition, elevated cholesterol level, diabetes, and hypertension were also predictors of increased risk. Surprisingly, a clinical diagnosis of lipodystrophy conferred a decreased risk of MI. Data from the Johns Hopkins cohort were also examined for trends in the rates of both coronary heart disease (CHD) and cerebrovascular events (Abstract 132). In that retrospective review, the rates of CHD and CVD were 5.9 and 5.0 per 1000, respectively. A case-control analysis identified PI use and stavudine use as independent predictors of CHD, and investigators noted that the overall rates of both CHD and CVD were higher than those reported for an age-, sex-, and race-matched group in the general population. Continued follow-up from the Northern California Kaiser Permanente cohort continues to show an increased risk of hospitalization for MI among HIV-seropositive enrollees compared with HIV-seronegative controls; however, no association with PI use has been noted (Abstract 747). A retrospective assessment of 8 US cohorts suggested an increased risk of MI among PI-exposed patients; however, PI use was no longer a statistically significant predictor of MI after the analysis was adjusted for other cardiovascular risk factors (Abstract 746).

Data from 2 studies of carotid intima medial thickness (IMT) (measured by ultrasound) as a marker of subclinical atherosclerosis were reported (Abstracts 131 and 139Ib). The AIDS Clinical Trials Group (ACTG) 5078 study investigators reported baseline results on the first prospectively matched cohort of HIV-seropositive PI-treated patients with both HIV-seropositive (but non-PI-treated) and HIV-seronegative controls (Abstract 131). The groups in this study were matched for race, age, sex, smoking status, and blood pressure measurement. With a mean of almost 4 years of PI use at baseline, and despite increased values for cholesterol and triglycerides in the PI group, no difference in baseline carotid IMT was seen between the PI and non-PI groups or between the HIV-seropositive and HIV-seronegative groups.

An uncontrolled study of 104 HIV-seropositive patients suggested that age, low-density lipoprotein cholesterol (LDL-C), hypertension, and nadir CD4+ cell count of 200/µL or below were associated with greater carotid IMT (Abstract 139lb). In a preliminary analysis of the first 21 patients with 1 year of follow-up, age and duration of PI therapy were predictive of the rate of progression of carotid IMT. Compared with age-matched historical controls, the HIV-seropositive patients had increased carotid IMT and greater rates of carotid IMT progression within this small group. More data on the relationship among duration of HIV infection, antiretroviral treatment, and rates of carotid IMT progression from both of those studies are eagerly awaited.

Collectively, these cohort studies and clinical trials indicate an association between long-term use of combination antiretroviral therapy and an increase in the relative risk for CHD. The absolute risk of CHD, however, remains low and needs to be balanced against the known benefits of treatment for HIV infection. In addition, other modifiable risk factors, such as smoking, that may be more common in some HIV cohorts than in the general population must be accounted for when determining the strength of the association among HIV infection, HIV therapy, and CHD. Appropriate control for known risk factors for CHD, such as smoking, family history, and diabetes (pre-HIV infection), needs to be considered when attributing an increased risk of cardiovascular disease to HIV infection or its treatment.

Dyslipidemia and Hypertension

Further light was shed on the relationship among HIV infection, HAART therapy, and the development of dyslipidemia and hypertension using the Multicenter AIDS Cohort Study (MACS) data (Abstracts 744 and 750). Seaberg and colleagues reported that compared with HIV-seronegative subjects not taking antiretroviral therapy (or monotherapy or combination therapy only), MACS participants infected with HIV were less likely to have systolic hyper-

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tension than those without HIV infection. After 2 years of HAART, the risk of systolic (but not diastolic) hypertension in the HIV-infected group exceeded that in the HIV-uninfected group (Abstract 744). These data suggest an increased risk of systolic hypertension following HAART exposure.

Riddler and colleagues compared lipid profiles from men in the MACS who had nonfasting blood samples available preseroconversion, postseroconversion, and pre- and post-HAART and made several important observations (Abstract 750). After HIV seroconversion, the levels of most lipid parameters fell, with decreases in total cholesterol (31 mg/dL decrease), high-density lipoprotein cholesterol (HDL-C) (12 mg/dL decrease), and LDL-C (21mg/dL decrease) compared with preseroconversion values. Investigators observed significant increases in lipid levels after 3 years of HAART (most were PI-treated); however, HDL-C levels did not rise above preinfection values, and the magnitude of the increase in total cholesterol beyond preseroconversion values (20 mg/dL increase) was consistent with what would be expected because of aging. These results suggest that a portion of the lipid increases observed after the initiation of HIV therapy may represent a "return to health" associated with treating chronic HIV infection.

Lipid changes associated with the use of NNRTIs have generally been more favorable than those seen with first-generation PIs, although there have been no studies that directly compared the lipid changes in patients treated with efavirenz with the changes in patients treated with nevirapine. The 2NN study randomized patients to receive nevirapine, efavirenz, or both, with a backbone of stavudine/lamivudine in all arms. After 48 weeks, the mean increase in HDL-C was slightly greater in the nevirapine-treated group (14 mg/dL) than in the efavirenz-treated group (9 mg/dL), and the mean increase in triglycerides was higher in the efavirenz-treated group (33 mg/dL) than in the nevirapine-treated group (11 mg/dL). Although both of these differences reached statistical significance, the clinical significance is not likely to be great for most patients.

The lipid and glucose effects of lopinavir/ritonavir were evaluated by Lee and colleagues in a study of 10 HIV-seronegative healthy men (Abstract 748). After 4 weeks of treatment with lopinavir/ritonavir monotherapy, triglyceride and free fatty acid levels increased. The increase in triglycerides was 65 mg/dL, which is slightly less than what has been reported in treatment-naive HIV-infected subjects. The 2-hour glucose tolerance testing showed a statistically significant increase in 2-hour glucose and insulin levels after 4 weeks of lopinavir/ritonavir, but there were no significant changes in the insulin-mediated glucose disposal rate (as has been seen with indinavir) by euglycemic, hyperinsulinemic clamp studies. These results highlight the concept that individual drugs within a class may have divergent impacts on glucose and lipid metabolism. It is hoped that studies such as this will become incorporated into drug development in the future. These data also demonstrate the direct effect of lopinavir/ritonavir on triglyceride, but not cholesterol, levels in HIV-uninfected subjects.

The minimal impact of atazanavir on lipids appears to be sustained with longer-term follow-up data out to 108 weeks (Abstract 555). In a randomized trial, patients treated with the amprenavir prodrug GW433908 experienced lipid changes that were comparable to those who received nelfinavir, with a mean increase in total cholesterol of 45 mg/dL and LDL-C of 33 mg/dL after 48 weeks of treatment. In both groups, the values generally remained below the National Cholesterol Education Program (NCEP) thresholds for intervention. A greater rise in triglyceride level was noted in the nelfinavir group.

Lipodystrophy

The relationship among mitochondrial DNA levels in fat, lipoatrophy, and specific drug exposure continues to be explored. This year's conference was notable for several reports of studies attempting to quantify mitochondrial DNA (mtDNA) from fat biopsy samples as well as from blood mononuclear cells. It appears that fat biopsies, although more difficult to obtain than peripheral blood mononuclear cells (PBMCs), may be a better source of tissue for examining the pathogenesis of lipoatrophy.

In 1 study, Thompson and colleagues assessed adipose tissue apoptosis, mtDNA quantification, and improvement in lipoatrophy among 14 patients who substituted stavudine with either abacavir (n = 13) or zidovudine (n = 1) (Abstract 728). Despite the small numbers of patients in this study, there appeared to be clear trends in the improvement in adipose tissue apoptosis, adipose mtDNA levels, and fat (as measured by dual-energy x-ray absorptiometry scanning [DEXA]) in the legs, arms, and trunk 48 weeks after the nucleoside reverse transcriptase inhibitor (nRTI) substitution. Cherry and colleagues presented data from 232 fat biopsies performed in independent studies with paired mtDNA PBMC samples and/or clinical data that suggested that mtDNA levels in fat were lower among patients who were current users of "d-drugs" (ie, stavudine, didanosine, or zalcitabine) compared with those taking zidovudine or abacavir (Abstract 133). Notably, levels of mtDNA also were lower in patients receiving zidovudine compared with those not receiving nRTIs. In a small subset of patients who had discontinued nRTI therapy, mtDNA levels appeared to increase rapidly (much sooner than changes in limb fat were observed in this study). Taken together with prior data from randomized trials and cohort studies, it appears that the process of subcutaneous fat loss is progressive over time and that it is associated with exposure to nRTI therapy.

Several studies at this conference (Abstracts 728, 733, and 739) and in the past suggest that the rate of fat loss may be faster with exposure to stavudine than with zidovudine, but that fat loss occurs to some degree with both drugs. The relationship between mtDNA levels in fat cells and adipose tissue apoptosis (and other markers of mitochondrial function) to changes in subcutaneous fat wasting merits further prospective investigation.

If nRTIs are a key etiologic agent in fat wasting, it would be expected that the process might reverse when that therapy is withdrawn. This notion has led to the investigation of "nucleoside-sparing" regimens. Boyd and colleagues

reported the 48-week results of a single-arm open-label study in which patients in whom nRTI therapy was failing changed to a regimen of indinavir/ritonavir and efavirenz (Abstract 738). The percentage of body fat (body fat as percent of mass) measured by DEXA increased significantly in the legs (1.7%), arms (2.8%), and trunk (1.8%). In addition, computed tomography showed an increase in square centimeters of both visceral and subcutaneous fat in the abdomen as well as mid-thigh fat. By patient assessment only, the increases in abdominal fat were apparent. Further controlled trials are needed to more fully assess the impact of "nucleoside-sparing" regimens on the process of fat wasting, both in terms of the initial development of fat wasting and as a means for reversing the problem once it has developed.

In a comprehensive and elegant conference presentation, Capeau discussed recent developments in our understanding of the pathogenesis of lipodystrophy by focusing on the role of adipose tissue in that process (Abstract 160). Capeau reviewed data demonstrating the impact of PIs and nRTIs on adipose tissue both in vitro and from patient samples. Her presentation included discussion of data suggesting that PIs may impair the nuclear localization of sterol regulatory element-binding protein-1 (SREBP-1) through an interaction with lamin A/B, and she described how disruption of this process could lead to abnormal adipose cell differentiation (with altered adipocytokine levels) and insulin resistance. She went on to show that PIs may induce the secretion of tumor necrosis factor (TNF) alpha, which could further impact fat-cell differentiation and promote insulin resistance as well as alter mitochondrial function. Coupled with the effects of nRTIs on mtDNA and consequently mitochondrial function, she built a case for the differential but synergistic effects of both classes of drugs that could conspire to produce peripheral lipoatrophy, insulin resistance, and potentially, visceral adipose hypertrophy (due to increased cortisol synthesis intracellularly).

Following Capeau's presentation was a thoughtful review by Grinspoon of clinical data that confirm a central role for insulin resistance in the pathogenesis of lipodystrophy (Abstract 161). Other clinical studies this year also focused on the relationship between adipocyte hormones and lipodystrophy (Abstracts 754 and 760). Adipocytokines may regulate fat metabolism, lipid and glucose homeostasis, and insulin sensitivity. As initially reported by Kosmiski and colleagues at last year's conference (Abstract 40), levels of adiponectin correlated inversely with insulin resistance in patients with lipodystrophy (Abstracts 754 and 760).

Clinical studies of phenotype of lipodystrophy involving women from the Women's Interagency HIV Study (WIHS) and involving men from the Fat Redistribution and Metabolic Change (FRAM) Study were reported. In a longitudinal study of 1057 HIV-seropositive and HIV-seronegative women with semiannual self-reports of body-shape changes (confirmed by anthropometric measurements) the incidence rates of peripheral and central lipoatrophy among the HIV-seropositive women were twice the rates among the HIV-seronegative women (Abstract 736). The incidences of peripheral lipohypertrophy were lower among the HIV-seropositive group, and, in contrast to what has previously been reported, the rates of central lipohypertrophy were no different between the 2 groups. The predominant syndrome that distinguished the HIV-seropositive women from controls was the presence of both central and peripheral lipoatrophy (pLA).

A smaller study of body-shape changes (using DEXA scans) among women in a cohort that included 45% African American and 36% Hispanic women was reported by Howard and colleagues (Abstract 735). As a group, the HIV-seropositive women had a lower percentage of body fat and limb fat by DEXA compared with controls. However, the percentage of trunk fat was higher among the HIV-seropositive women in the study than in controls. Of note, African American women had a decreased trunk-fat percentage compared with all other women. In a multivariate analysis that included only the HIV-seropositive women, stavudine use and non-African American race were independently associated with increased truncal fat and decreased limb fat, and PI use was not. These results suggest that racial differences in changes in body fat need to continue to be examined in future prospective studies.

Cross-sectional data from the FRAM study (that had previously been reported in preliminary form in an oral presentation at the XIV International AIDS Conference in 2002 in Barcelona) demonstrated that lipoatrophy was the predominant abnormality in HIV-seropositive men compared with the control group (Abstracts 733 and 732). In this study report, both DEXA scans and total-body magnetic resonance imaging (MRI) were used to assess body composition among men who reported pLA compared with those who did not. Body mass index, median kilograms of limb fat as measured by DEXA, and median liters of both upper- and lower-trunk subcutaneous fat as measured by MRI were all *lower* among HIV-seropositive men with pLA than among those those without pLA and lower than among controls. Importantly, median liters of visceral fat assessed by MRI was also *lower* (but not statistically significantly different) among the men with pLA than among both the HIV-seropositive men without pLA and controls. In addition, men with HIV who did not report pLA (and for whom it was not noted on their exam) also had decreased subcutaneous fat compared with the control group. These findings demonstrate a predominant syndrome of subcutaneous fat loss associated with HIV infection and suggest that the degree of fat loss may not be appreciated by exam alone.

A second report from FRAM provided further details on the prevalence and character of buffalo humps among men with HIV infection compared with a control group that provided data on subcutaneous fat by MRI (Abstract 734). Although the prevalence of buffalo hump was not statistically different in the HIV-infected patients (8%) compared with controls (11%), the buffalo humps in HIV-infected men were 2.5 times larger than those in controls and tended to occur in men with a higher body mass index. In addition, patients with a buffalo hump also tended to have a greater amount of visceral fat in both the HIV-seropositive and the control

groups than those without a buffalo hump, suggesting that the presence of a buffalo hump may be a surrogate marker for visceral fat.

The prevalence and optimal management of asymptomatic hyperlactatemia remains uncertain. In general, screening of asymptomatic patients has not been recommended. Wohl and ACTG colleagues examined the prevalence of hyperlactatemia among nRTI-treated patients with 1 or more risk factors for the disorder (Abstract 761). A standardized procedure developed by the ACTG for lactate collection was followed that does not allow the use of a tourniquet or fist clenching. Hyperlactatemia was defined as a value 1.5 times the upper limit of normal, and all abnormal values prompted repeat evaluation. After the assessment of 83 patients with risk factors for hyperlactatemia, none was found to have confirmed hyperlactatemia when the careful collection procedures were followed. These results suggest that the syndrome of asymptomatic hyperlactatemia is rare and confirm that routine measurement of lactate levels is unwarranted. In addition, this study highlights the importance of following careful collection procedures when obtaining lactate levels among patients with symptoms.

Bone Effects

There continues to be interest in the relationship between HIV infection, antiretroviral therapy, and the risk of osteopenia and osteoporosis. Two studies reported at this year's conference examined bone mineral density (BMD) data among HIV-infected women. In both studies, traditional risk factors—not HIV therapy or HIV infection—were associated with decreased BMD (Abstracts 102 and 103). Jacobson and colleagues reported longitudinal data on change in BMD in 141 women enrolled in the Nutrition for Healthy Living Study, in which they found that median BMD did not change over 2 years of follow-up (Abstract 102). Factors associated with loss of BMD included recent weight loss, smoking, and being Caucasian. In a cross-sectional study of women older than age 35 years, BMD was compared in HIV-seropositive (n = 140) and HIV-seronegative (n = 144) women (Abstract 103). After the data were controlled for traditional risk factors (weight, age, smoking, and physical activity), HIV infection was not associated with reduced BMD. In contrast to previous studies, these investigators found that PI use for more than 1 year appeared to protect against the development of reduced BMD among women over age 35. Finally, Mondy and colleagues reported the results of a small randomized trial of calcium and vitamin D alone or combined with alendronate as treatment for osteopenia or osteoporosis. They found a statistically significant increase in BMD for those who received alendronate compared with those who received only vitamin D and calcium (Abstract 134). The treatment appeared to be well-tolerated in this 48-week study of 31 subjects.

Tuberculosis

Chaisson reviewed the global epidemiology of the HIV/tuberculosis (TB) epidemic in a symposium addressing international models and perspectives on the topic (Abstract 46). He made a compelling argument that in the developing world, the traditional definition of TB "control"—70% diagnosis and 85% cure—needs to be reevaluated. TB control will only occur when the basic reproductive rate R_o is less than 1. Because of the copathogenesis of HIV and TB, the approach to the HIV/TB epidemic needs to include more aggressive TB case identification, more directly observed therapy (DOT) for TB, evaluation of TB prophylaxis strategies, and use of HAART. HAART is already in use for coinfected patients in regions in which TB is endemic.

Patel and colleagues reported about experience with HAART in 197 patients in Ahmedabad, India (Abstract 138). Patients were treated with standard 4-drug TB therapy, generic efavirenz, and 2 nRTIs. CD4+ counts increased from a median of 104 cells/μL to 306 cells/μL at 9 months. Ten percent of patients reported paradoxical reactions, or transient clinical worsening of TB, but HAART was safely continued.

Preliminary results using this same regimen in South Africa (Abstract 783) and in Brazil (Abstract 784) were encouraging. In the South Africa program, HAART was successfully administered through a modified DOT program 5 days a week. Longer follow-up of these cohorts examining virologic suppression rates and drug resistance will be of interest.

A US study involving 431 TB patients yielded several findings of note (Abstract 137). First, despite current recommendations, 33% of patients in this otherwise model TB-control program were not tested for HIV. Second, the rate of relapse of TB was 2.3-fold higher in HIV infected-patients than in HIV-uninfected patients and was associated with lower CD4+ cell count. In a second multicenter Centers for Disease Control and Prevention (CDC)-sponsored study presented by Burman (Abstract 136), 169 patients infected with HIV and TB were examined. As in previous studies, patients responded well to TB therapy (95% success rate). Eighty patients received HAART during the period of observation. Fifteen percent of patients had paradoxical reactions. Compared with a historical control of HIV-infected TB patients in the United States in the pre-HAART era, there was a 6-fold decrease in HIV progression among the patients treated with HAART.

In 2 US studies, drug interactions between HAART and TB treatment were examined. In the first, concomitant administration of 300 mg rifabutin and 600 mg efavirenz slightly lowered rifabutin, but not efavirenz levels, supporting recommendation of a dosage of 450 mg twice weekly of rifabutin when administered with efavirenz without the need to increase the dose of efavirenz (Abstract 785). In the second study, the hepatic enzyme effects of rifampin on indinavir could not be overcome with the addition of ritonavir, eliminating indinavir as an option for patients requiring TB treatment including rifampin (Abstract 542).

GBV-C Infection

There were several conference presentations on the relationship between the GB virus-C (GBV-C) and HIV disease progression. Initial cohort studies demonstrated a survival advantage in HIV-infected patients with evidence of GBV-C infection. Among the studies present-

ed this year, there was consensus that GBV-C viremia was cleared in many HIV-infected patients (Abstracts 157, 159lb, and 848) and that early GBV-C viremia did not predict HIV disease progression (Abstract 157). The precise relationship between GBV-C and HIV remained controversial, however, and more work is needed in this area.

Williams and colleagues reported that many patients in the MACS cohort cleared GBV-C viremia and became GBV-C E2 antibody-positive (Abstract 159lb). Early GBV-C infection was not associated with HIV disease progression, but patients with sustained GBV-C viremia had a survival advantage. Patients who cleared GBV-C viremia appeared to be at the highest risk for HIV disease progression. Aboulker and colleagues reported that GBV-C viremia was associated with a greater CD4+ cell response in early trials of single- and dual-nRTI regimens (Abstract 849). Xiang et al presented data from a series of experiments designed to explore the mechanisms by which GBV-C could decrease HIV replication (Abstract 156). In an in vitro system in which GBV-C-infected cells were challenged with HIV, expression of the CCR5 chemokines RANTES, MIP-1α, MIP-1β, and SDF-1 were upregulated and were associated with decreased HIV replication compared with cells not infected with GBV-C.

In another epidemiologic study from Sweden, GBV-C viremia at baseline was not associated with HIV disease progression (Abstract 157). Clearance of GBV-C viremia occurred in 11 of 44 patients without antibody seroconversion and was associated with accelerated HIV disease progression. Authors of this report concluded that GBV-C was secondary to HIV disease progression. In a report from the Viral Activation Transfusion Study (VATS), Busch and colleagues found that GBV-C was transmitted to 22% of HIV-infected patients during transfusion (Abstract 846). No cases of GBV-C viremia occurred among patients who were antibody-positive prior to transfusion.

Hepatitis and Liver Transplantation

In contrast to the 2002 CROI, no new major hepatitis therapeutic trials were presented this year. The importance of including detection for hepatitis B virus (HBV) core antibody in screening strategies was emphasized by Gandhi in a US study (Abstract 821). In patients infected with HIV and hepatitis C virus (HCV), history of HBV infection did not produce a detectable effect on liver histology (Abstract 822). Tenofovir use was associated with sustained responses to HBV in small cohort studies including patients with lamivudine-resistant HBV (Abstracts 824 and 825). In a large study of US veterans, Fultz and colleagues showed that HCV was associated with reduced survival in both the HIV-infected and the HIV-uninfected populations (Abstract 828). A second study of the Veterans Administration population suggested that HCV infection is associated with an increased risk for diabetes (Abstract 830). In a Spanish cohort, more advanced liver fibrosis (extensive portal fibrosis or cirrhosis) was more frequent in HIV- and HCV-coinfected patients compared with HCV-infected patients (Abstract 830). In a small prospective study, patients with HCV starting HAART showed no evidence of liver damage due to immune reconstitution (Abstract 831). Based on an in vitro model, Li suggested that morphine may enhance HCV replication (Abstract 158). Kim reported a higher frequency of CD8+ cell responses to HCV than previously appreciated (Abstract 837), and Graham noted Th1 responses were associated with milder inflammation and cirrhosis attributed to HCV (Abstract 839). A small, descriptive study of outcome in 23 HIV-infected liver transplant recipients suggested that outcome in patients tolerant of HAART and with CD4+ cell count greater than 200/µL posttransplant was similar to that in non-HIV-infected patients (Abstract 155).

HIV Prevention and Transmission

In the first plenary session of the conference, Valdiserri from the CDC gave an overview of the epidemiology of HIV infection in the United States (Abstract 4). Estimates of HIV cases in the United States have continued to rely on data from 25 states where HIV is a reportable disease. Despite the fact that 2 of the largest states—New York and California—are not included in these estimates, some important trends were evident. Among the 25 states, the number of cases reported increased by 8% from 1999 to 2001. Valdiserri cautioned that this increase might reflect a fluctuation of a steady rate and should not be overinterpreted. More notable, however, was the consistent and dramatic rise in rates of infection among African American men (15%) over the same time period.

Behavior and Virus Transmission

An interesting debate among modelers of the HIV epidemic has been around the effect of HAART on HIV transmission. Although it would seem intuitive that reducing HIV RNA plasma levels with HAART would reduce transmission rates, Valdiserri made the case that these benefits are lost if wider use of HAART results in an increase in high-risk behavior. He advocated a more intensive approach to risk reduction among HIV-infected patients receiving care through multidisciplinary clinic-based programs. Guidelines sponsored by the CDC and Infectious Diseases Society of America for risk-reduction counseling for HIV-infected patients in care will be released shortly.

It is estimated that at least one quarter of HIV-infected persons in the United States are unaware of their HIV serostatus. Freedberg and others have previously advocated offering HIV testing to all hospitalized patients in high-prevalence areas. "Think HIV" was a program designed by Freedberg's group to identify undiagnosed HIV-infected patients in Massachusetts presenting to urgent care centers (Abstract 39). Of patients presenting to care in a 7-month period, 1853 (31%) accepted HIV testing and 37 new HIV cases were identified. This program had a higher yield than self-referral testing in Massachusetts during the same time period and identified many patients who did not consider themselves at risk for HIV infection.

Henson and colleagues reported an update of HIV prevalence among patients presenting to the emergency department at Johns Hopkins University (Abstract 38). During a 2-month period

in 2001, HIV testing was performed on 1613 individuals or patients. The seroprevalence in 2001 was 11.3% (183 patients). Twenty-four percent of seropositive patients did not know they were infected. Eight of the 183 patients were recently infected, and 7 of those 8 were unaware of their serostatus. Among patients aware of their HIV diagnosis, 24% admitted to having engaged in unsafe sex and 6% to needle sharing.

High-risk behavior among persons known to be infected also was documented in patients being released from prison. Among a group of 80 HIV-infected persons released from prison, 24% had unprotected sex within 6 months of release from jail, and 31% thought it was likely that they would infect their partners (Abstract 36). In a different study, McConnell and Grant proposed that the effects of high-risk behavior on the HIV epidemic in the United States might be less than predicted because of serosorting, a disproportionate amount of high-risk behavior among HIV-seroconcordant contacts (Abstract 41).

Important insights into HIV transmission were made from a study of the Rakai cohort in Uganda presented by Wawer (Abstract 40). In this retrospective study of 240 serodiscordant couples followed up between 1995 and 1999, the risk of HIV transmission was highest during the first 5 months after HIV-infected index case seroconversion and during the period of 5 to 15 months before death. The strongest predictor of HIV transmission was the HIV RNA level in the index case. Although it has been postulated that recent HIV seroconverters are more likely to transmit HIV to uninfected sexual partners, this is the first study to provide systematically collected data on a cohort of this size. From a public health standpoint, identification of recent seroconverters needs to be a priority in HIV-prevention programs.

The findings of HIV case identification in Malawi reported by Pilcher and colleagues take on additional importance in view of the Rakai data (Abstract 154). In this cross-sectional study of 1361 men seen at a sexually transmitted disease (STD) or dermatology clinic, 24 participants had early, antibody-negative HIV infection. Presenting to the STD (vs dermatology) clinic was associated with a higher risk of primary HIV infection. Thus, antibody tests alone are insufficient to identify HIV-infected persons presenting to care, and additional testing in targeted populations appears to be warranted.

A third study regarding HIV transmission in South Africa was reported by Sanne (Abstract 42). Because of the high prevalence of HIV infection among adults and the frequency of sexual assault, a private health care facility in Johannesburg began providing zidovudine and lamivudine for postexposure prophylaxis in 1999. Of 858 patients, HIV infection was already present in greater than 14%. Among the 644 for whom postexposure prophylaxis was prescribed within 72 hours, over three fourths returned for testing, and only 1 HIV seroconversion was documented.

Mother-to-Child Transmission

Other important studies on mother-to-child HIV prevention programs shed light on the timing of HIV transmission and drug resistance among mothers treated with short-course therapy. In an analysis of 9 randomized, placebo-controlled trials with more than 5000 mother-infant pairs, it was estimated that over 40% of all HIV transmission occurred during breast-feeding at least 4 weeks after delivery (late postnatal transmission) (Abstract 97). There was a steady accumulation of HIV infection cases during the period of breast-feeding for more than a year. Having a CD4+ cell count less than 200/μL at the time of delivery was associated with an 8-fold increase in risk for late postnatal transmission. Female infants also had a diminished risk for acquiring HIV infection during breast-feeding compared with male infants.

Lee reported results of a study examining drug resistance among 33 pregnant women in Zimbabwe receiving single-dose nevirapine for prevention of perinatal transmission (Abstract 96). Although HIV-1 RNA levels in the plasma exceeded those in breast milk, there were more women with viral mutations associated with resistance to NNRTIs in the breast milk (65%) compared with in the plasma (40%) 8 weeks after nevirapine administration. The predominant NNRTI mutations differed between breast milk and plasma within individuals.

Eshleman presented additional studies on samples from mothers receiving single-dose nevirapine for perinatal transmission in the HIVNET 012 trial in Uganda. In the first study, Eshleman showed that the NNRTI Y181C mutation emerged within 1 week of a single dose of nevirapine and then was followed by the emergence of the K103N mutation as the predominant circulating drug-resistant variant within 8 weeks (Abstract 856). In the second study, women with HIV subtype D appeared to be at higher risk for selection for nevirapine resistance mutations than were women with subtype A (Abstract 857).

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