Complications of HIV Disease and Antiretroviral Therapy

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Metabolic, opportunistic, and other infectious complications of HIV infection and antiretroviral therapy continue to be major areas of active investigation. This year's Conference on Retroviruses and Opportunistic Infections included many important presentations on the clinical aspects of HIV complications. In each successive year, the studies reported in the area of complications have matured and now include more randomized trials evaluating interventions for the management of HIV complications and more well-designed observational studies with long-term follow-up. This article will review new data presented on metabolic complications, including cardiovascular risk, lipid disorders and lipoatrophy, renal complications, hepatic complications (hepatitis B and C virus infections), tuberculosis, and other bacterial infections.

Cardiovascular Risk

There continues to be great interest in examining the relationship between treatment with combination antiretroviral therapy and the risk of atherosclerosis. Several important analyses from the D:A:D study, the largest prospective study of cardiovascular risk in HIV-infected patients, were presented at this year's conference. The mean exposure time to combination antiretroviral therapy in this cohort is now 4.46 years. With more than 76,577 person-years of follow-up, 277 patients have experienced a myocardial infarction (MI). The risk of MI continues to increase with longer exposure to therapy. The MI incidence increased from 1.39/1000 person-years of observation in those not exposed to therapy, to 6.07/1000 person-years in those exposed for 6 years or more (relative risk [RR] compared with no exposure, 4.38 [95% confidence interval (CI), 2.39-8.04], $P = .0001$). The overall adjusted risk of MI per additional year of combination antiretroviral therapy exposure is estimated to be 17% (1.17-fold [95% CI, 1.11-1.24]). The MI risk associated with treatment was similar in men and women, and the relationship was similar in younger and older patients (men > 45 years and women > 55 years). Adjustment for lipid levels (total cholesterol, high-density lipoprotein [HDL], and triglycerides) reduced the association of an additional year of combined antiretroviral therapy with myocardial infarction to 1.10 (95% CI, 1.01-1.19). This finding suggests that some, but not all of the relationship between combination antiretroviral therapy and MI risk is explained by dyslipidemia. Of note, these researchers found no association between CD4+ cell count nadir or lipodystrophy and future risk of MI (Abstract 42). In another analysis, D:A:D investigators noted that the prevalence of cardiovascular risk factors does not appear to be declining in the cohort, but the incidence of MI appears to be on the decline when examined by calendar year; this suggests that higher-risk patients may be adopting interventions to reduce the rate of MI (Abstract 866).

A number of studies examined risk factors for subclinical atherosclerosis using noninvasive imaging such as carotid intima-media thickness (IMT) or coronary calcium as measured by computed tomography (CT) scan. Mangili and investigators from the Nutrition for Healthy Living (NFHL) study investigated the relationship between metabolic syndrome (MXS) and IMT and coronary calcium scores in 327 HIV-infected subjects in a cross-sectional analysis. MXS was defined as having at least 3 of the following: abdominal obesity (waist circumference > 102 cm for men, > 88 cm for women); hypertriglyceridemia (> 150 mg/dL); low HDL cholesterol (< 40 mg/dL for men, < 50 mg/dL for women); high blood pressure (≥130/85 mm Hg); or high fasting glucose (≥110 mg/dL). The prevalence of MXS in this cohort was 23%, similar to the prevalence in other cohorts of HIV-infected patients (26%; Abstract 867). A higher proportion of the group with metabolic syndrome (17%) had carotid IMT values greater than 0.8 mm, than did those without it (7%). In addition, the presence of any coronary calcium was also greater in the MXS group, leading these authors to suggest that interventions to reduce cardiovascular risk should be targeted with patients with evidence of MXS.

Longitudinal studies that include measures of subclinical atherosclerosis may help to determine which factors are associated with progression (or regression) of disease over time. Thiebaut and colleagues from the Agence Nationale de Recherches sur le SIDA (ANRS) in France reported on a 3-year study of carotid IMT in 233 HIV-infected subjects. At baseline, 59% of the cohort smoked and the majority were on a potent antiretroviral regimen. After 12 months of follow-up, the median carotid IMT increased from 0.55 mm to 0.57 mm ($P < .001$). After 2 more years of follow-up, the median carotid IMT had significantly decreased to 0.53 mm. During the 3 years of the study, a total of 94 subjects discontinued protease inhibitor (PI) therapy, 46 added lipid-lowering treatments, and 24 quit smoking. In the last 2 years of the study, smoking cessation was associated with improvement in carotid IMT in the univariate analysis only. These results suggest that interventions to reduce the prevalence of dyslipidemia may reduce the risk of cardiovascular disease in the HIV population and also highlight the importance of smoking cessation as effective intervention. This study also underscores the importance of controlling for smoking and other traditional risk factors when assessing the relationship between HIV treatments and atherosclerosis (Abstract 871).

Maggi and colleagues previously reported a higher prevalence of carotid plaque, as measured by ultrasound, in PI-treated patients than in nonnucleoside reverse transcriptase inhibitor (NNRTI)-treated patients. This group now reports follow-up in these same subjects 1 year later (Abstract 863).

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They found that a higher percentage of the subjects who had abnormal measures at baseline in the PI group (24%) showed new lesions, than did those with previously normal measures in the NNRTI group. No difference in the prevalence of new lesions was seen among subjects who had normal measures at baseline in the 2 treatment groups. The role of PI therapy was also examined by Knobel in a cross-sectional study that measured carotid IMT (Abstract 862). In this study, equal numbers of HIV-infected subjects who were deemed to be at low risk (<5%), moderate risk (5%-10%), and high risk (>10%) of coronary events within 10 years using the Framingham scoring system, were evaluated with ultrasound of the carotid artery. Subclinical atherosclerosis was defined as the presence of plaques in 1 or more sites. The prevalence of subclinical atherosclerosis in relation to the Framingham risk score group was 34.4% in the low-risk group, 70.6% in the moderate-risk group, and 94.1% in the high-risk group ($P = .0001$). In a multivariate analysis, PI use was identified as an independent risk factor for the presence of plaques after controlling for Framingham score.

Interventions for Hyperlipidemia

PI Switching

Prospective studies have suggested a lack of lipid elevations with the use of atazanavir; however, there are limited data on the safety and efficacy of switching therapy in patients whose virus is suppressed on a PI regimen (including those containing ritonavir) to atazanavir. Sension and colleagues reported the preliminary results of a trial in which subjects on a PI regimen with HIV RNA levels below 50 copies/mL and low-density lipoprotein (LDL) levels above 130 mg/dL were randomized to receive unboosted atazanavir (400 mg/d) or to continue their initial therapy (Abstract 858). The primary endpoint was evaluated at week 12. The decrease in lipid levels was greater for the atazanavir group than for the control group for LDL cholesterol, total cholesterol, and triglycerides, as well as apolipoprotein B and lipoprotein a. Virologic suppression was maintained, with exceptions in 2 atazanavir recipients and 1 control recipient. Further follow-up of this trial is continuing to 48 weeks.

In a complementary nonrandomized trial, Martinez and colleagues described their experience in substituting boosted atazanavir for other PIs among 162 subjects with 1 or more lipid abnormalities (fasting triglycerides >500 mg/dL, total cholesterol >200 mg/dL, or LDL >130 mg/dL; Abstract 850). The majority of subjects were receiving another boosted PI at entry. The proportion of patients with triglyceride levels above 500 mg/dL decreased from 33% to 10% ($P < .0001$), the proportion with total cholesterol levels above 200 mg/dL decreased from 90% to 51% ($P < .0001$), and the proportion with LDL levels above 130 mg/dL decreased from 65% to 36% ($P < .0001$). Patients were not required to have an undetectable viral load at entry, and after 6 months the proportion with HIV RNA levels below 500 copies/mL increased from 45% to 58%. Together these trials confirm that substitution with atazanavir (boosted or not) is a viable strategy for improving elevated lipid levels; however, a significant proportion of subjects remain above current National Cholesterol Education Program (NCEP) thresholds after this change, suggesting that other interventions may be needed.

Nucleoside Reverse Transcriptase Inhibitor Substitutions

Nucleoside reverse transcriptase inhibitor (nRTI) substitutions have been examined in an effort to reverse lipoatrophy. Moyle reported the results of a study of 105 subjects with lipoatrophy while on zidovudine- or stavudine-containing regimens (Abstract 44LB). The primary endpoint of the study was change in limb fat as assessed by dual-energy x-ray absorptiometry (DEXA) scan. Lipid changes were examined as a secondary endpoint. Virologic suppression was maintained in both treatment arms. After 48 weeks of follow-up, limb fat increased in both study arms and there was no difference between arms. Mean changes in total cholesterol, LDL, and triglyceride levels were significantly more favorable in the tenofovir arm than in the abacavir arm.

Spanish investigators reported the results of a small study of 56 patients that compared the impact of dose reduction of stavudine (from 40 mg BID to 30 mg BID) with tenofovir substitution or maintenance of full-dose stavudine on lipid parameters and subcutaneous fat (Abstract 857). Significant mean changes in lipids were only detected in triglycerides (+19 mg/dL for stavudine 40 mg, –40 mg/dL for stavudine 30 mg, –133 mg/dL for tenofovir; $P = .02$) and total cholesterol (+4 mg/dL for stavudine 40 mg, –4 mg/dL for stavudine 30 mg, –28 mg/dL for tenofovir; $P = .04$). Mean changes in total and limb fat were also seen in the low-dose stavudine and tenofovir arms, but the magnitude of the improvement in limb fat was greater for those randomized to tenofovir. Mean changes in total fat (–597 g for stavudine 40 mg, +332 g for stavudine 30 mg, +1005 g for tenofovir; $P = .04$) and limb fat (–247 g for stavudine 40 mg, +77 g for stavudine 30 mg, +440 g for tenofovir; $P = .008$) significantly differed among groups. Viral load remained suppressed in all subjects except for 1 on the full-dose stavudine arm. Previous studies have suggested a modest benefit of adding the statin pravastatin or a fibric acid drug to PI therapy for the treatment of hypercholesterolemia (Aberg, CROI 2004). Calza conducted the first randomized trial in which the addition of lipid-lowering therapy was directly compared with antiretroviral substitution (Abstract 859). Subjects with viral suppression (<50 HIV RNA copies/mL) on a PI-containing regimen (N = 142) with mixed hyperlipidemia were randomized to 1 of 4 arms: add pravastatin, add bezafibrate, switch to nevirapine, or switch to efavirenz. In an as-treated analysis, after 12 months of follow-up, a greater reduction in total cholesterol and triglyceride levels was observed in the pravastatin and bezafibrate arms than in the 2 NNRTI arms. Triglycerides decreased by 41% and 47% for the pravastatin and bezafibrate arms, respectively, compared with 25% for nevirapine and 9% for efavirenz. Total cholesterol decreased by 46% and 37% for pravastatin and bezafibrate, respectively, compared with 27% and 10% for nevirapine and efavirenz, respectively. When grouped together, the lipid-lowering agents had a significantly greater impact on both triglyceride and cholesterol levels than did the NNRTI-substitutions. Additionally, nevirapine substitution led to a greater decrease in both cholesterol and triglyceride levels

than efavirenz did. This is the first clinical trial that has directly compared the approach of adding lipid-lowering therapy with a change in antiretrovirals, and it appears that the lipid-lowering therapy was more effective. The magnitude of the decrease in cholesterol and triglyceride levels (~40%) observed with lipid-lowering therapy in this trial appears greater than previously described in other trials.

Fish oils containing omega-3 polyunsaturated fatty acids have been proposed as a possible treatment for isolated hypertrigylceridemia in patients on antiretroviral therapy. De Truchis and colleagues reported the results of a randomized double-blind trial in 122 antiretroviral therapy–treated patients who had triglyceride levels greater than 200 mg/dL (Abstract 39). Patients received 2 gm of a fish oil preparation 3 times per day or a placebo. Fish oil preparations vary in the content of omega-3 polyunsaturated fatty acids; each 1-gm capsule of this particular preparation contains 18% eicosapentaenoic acid (EPA) and 12% docosahexaenoic acid (DHA), which are standard amounts. The study design compared the fish oil preparation with placebo, and was followed by an 8-week open-label treatment period. In an intent-to-treat analysis, treatment with fish oil was associated with a 25% median decrease in triglyceride level, compared with a 1% increase with placebo ($P = .0033$). Additionally, triglyceride levels normalized (<200 mg) in 22.4% in the fish oil arm, compared with 6.5% in the placebo group. The initial decrease in triglyceride levels was maintained during the open-label period and no significant safety concerns were identified.

Lipodystrophy

Patterns of Fat Changes

Ideally, studies designed to examine the timing and patterns of peripheral and central fat changes related to antiretroviral therapy should be longitudinal evaluations conducted in the context of randomized antiretroviral treatment, and they should also include a population-based control group. Two important longitudinal studies were presented, each of which fulfills one of these criteria (Abstracts 38, 849). Mulligan described patterns of peripheral and central fat changes in the 64-week metabolic substudy of the large AIDS Clinical Trials Group (ACTG) treatment-naive study 384 (ACTG 384). Measurements included waist and hip circumference in all subjects and DEXA scans in a subset. The proportion of subjects with an elevated waist-hip ratio increased from 35% at baseline to 47% at week 64, with significantly more subjects experiencing a gain over time. The patterns of change were mixed: one quarter of subjects had an increase in waist measurement and a decrease in hip measurement; one half of subjects had an increase in waist circumference and no change in hip circumference; and one quarter had a decrease in hip circumference only. This mixed pattern of changes in regional fat was also seen with the DEXA results. Equal proportions (35%) of subjects *gained* in both regions or *lost* fat in both regions, but only 26% had the previously defined lipodystrophy phenotype of central-fat gain with limb-fat loss. These results suggest that there are several distinct patterns of fat change associated with antiretroviral therapy. The changes reported in this study were averaged over a 64-week period, and it is possible that certain types of changes occur at different points in time. Further work is needed to identify the factors that determine the pattern of change in fat over time in individual patients.

The second study reported on 4-year follow-up data from men who have sex with men (MSM) in the Multicenter AIDS Cohort Study (MACS) who received antiretroviral treatment compared with a control group of HIV-uninfected MSM also followed prospectively. Measurements in this study included body mass index (BMI) and circumference measurements of waist, hip, and limbs (arm and thigh). During the follow-up, BMI increased in the control group but did not change in the HIV group. Waist circumference increased similarly in both groups; however, hip circumference increased more slowly in the HIV group, yielding a greater increase in waist-to-hip ratio in the HIV group. Thigh circumference increased in the control group but decreased in the HIV group. In a multivariate analysis, cumulative exposure to nRTIs was associated with decreases in circumference in waist, hip, thigh, and arm, independent of PI use. These results confirm some earlier observations suggesting that some of the increase in waist circumference observed in patients treated with antiretroviral therapy is due to normal aging, and lipoatrophy is associated with nRTI treatment.

Interventions for Lipoatrophy

Previous studies have demonstrated improvement in lipoatrophy when stavudine (and to a lesser extent zidovudine) is replaced with abacavir (Carr et al, *JAMA*, 2002; McComsey et al, *AIDS,* 2005). As noted previously, Moyle (Abstract 44LB) reported the results of a randomized open-label 48-week study evaluating changes in limb fat following substitution of zidovudine (n = 34) or stavudine (n = 71) with abacavir or tenofovir in 105 virologically suppressed patients on antiretroviral therapy. Objective assessments of limb fat were obtained using DEXA scans. After 48 weeks of follow-up, there was a statistically significant increase in limb fat in both the abacavir- and tenofovir-treated groups but no difference between the study arms. Bone density was also evaluated and no differences were seen between the treatment groups. A smaller, uncontrolled trial also suggested an improvement in facial fat after stavudine was changed to tenofovir (Abstract 860). The results of this trial suggest that these nonthymidine nRTIs are effective in improving established lipoatrophy, albeit slowly.

Further evidence to support the notion that abacavir is less likely than stavudine to cause lipoatrophy was seen in a randomized trial in which subjects received either abacavir or stavudine in combination with lamivudine/efavirenz (Abstract 587). In a subset of subjects who had DEXA scans performed at baseline and at week 96, those randomized to abacavir had significantly more limb fat than did the stavudine recipients. In addition, triglyceride levels were lower in the abacavir-treated patients. Virologic outcomes favored abacavir in the intent-to-treat analysis, but no difference was seen between the study arms in the as-treated analysis.

Given the central role of nRTIs in the development of lipoatrophy, it follows that regimens that do not include drugs from this class might be expected to improve lipoatrophy. Tebas reported the

results of an ACTG study of antiretroviral patients who were randomized to the "nRTI-sparing" regimen of lopinavir/ritonavir and efavirenz or to efavirenz plus 2 nRTIs (Abstract 40). After a mean of 104 weeks, the median change in limb fat in the nRTI-sparing regimen was a 782 g gain, compared with a 900 g loss in the nRTI arm ($P = .0002$). Unfortunately, patients randomized to the nRTI-sparing combination of lopinavir/ritonavir/efavirenz experienced significantly greater increases in triglyceride and total cholesterol levels and had higher rates of virologic failure, as defined by a combined endpoint. No differences in bone density were noted between the arms of this study. This proof-of-concept study demonstrates that nRTI-sparing antiretroviral regimens may help to reverse lipoatrophy; however, more work is needed to identify regimens that are more lipid friendly.

Further evidence to support the efficacy of nRTI-sparing regimens in reversing lipoatrophy were presented by Murphy (Abstract 45LB). This ACTG study compared changing virologically suppressed patients with lipoatrophy on an antiretroviral regimen including either zidovudine or stavudine to an nRTI-sparing combination of lopinavir/ritonavir/nevirapine with the strategy of substituting zidovudine or stavudine with abacavir. In this trial, subcutaneous thigh fat and subcutaneous adipose tissue, as measured by CT scan, improved significantly by week 24 in both groups. Longer follow-up is ongoing to determine whether there is a difference in the impact of these 2 approaches on reversal of lipoatrophy. Collectively, these 2 studies provide the first evidence in randomized trials to support the concept of nRTI-sparing regimens for improving lipoatrophy.

Several previous randomized trials have evaluated rosiglitazone for the treatment of lipoatrophy. Although they have varied by inclusion criteria, dose, and duration of follow-up, the majority have not suggested a significant change in limb fat with this approach. A Canadian trial of rosiglitazone performed in subjects with lipoatrophy, which did not require documentation of insulin resistance, failed to demonstrate any evidence of a slower rate of limb fat loss with rosiglitazone (Abstract 854). Mallon presented data that may help to explain the lack of efficacy of rosiglitazone in the presence of continued thymidine nRTIs from his fat biopsy substudy of the Australian rosiglitazone trial for lipoatrophy (Abstract 41). In the original trial, subjects were allowed to modify nRTI therapy, an approach that is now known to lead to improvement in subcutaneous limb fat. He compared the impact of rosiglitazone on peroxisome proliferator-activated receptor γ (PPAR- γ) expression in subcutaneous adipose tissue in a group of subjects who continued thymidine nRTIs, compared with those who had stopped the drugs. At week 2, only those randomized to rosiglitazone in the no-thymidine nRTI group experienced a significant rise in PPAR-γ expression ($P = .046$). Similar significant increases in PPAR-γ coactivator 1 (PGC-1) expression were also observed in the rosiglitazone no-thymidine nRTI group. Of note at week 48, PPAR-γ expression was significantly higher only in the no-thymidine nRTI group, independent of rosiglitazone treatment. These results suggest that ongoing thymidine nRTI therapy may hinder the ability of rosiglitazone to increase PPAR-γ expression. Additionally this study suggests that nRTIs may have a direct effect on PPAR-γ as a mechanism underlying the development of lipoatrophy.

In August 2004, L-polylactic acid was approved by the US Food and Drug Administration (FDA) for treatment of facial lipoatrophy in patients with HIV infection. This absorbable material is injected into areas of facial fat loss, and short-term studies suggest that the procedure leads to improvement in the appearance of lipoatrophy. Mijch and colleagues reported on a 6-month open-label study of polylactic acid designed to quantify the impact of this treatment on facial fat using photography, quality of life measures, and spiral CT after injection of L-polylactic acid (Abstract 851). Improvements in psychological and emotional distress correlated with improvement by photography. Local pain was a common adverse event, but no subjects discontinued treatment and overall the procedures were well tolerated. Longer-term follow-up data are needed to ensure the long-term efficacy of this approach; however, the short-term results of this approach remain very promising and offer the best immediate improvement for patients suffering from the effects of facial lipoatrophy. Unfortunately, cost remains prohibitive for the majority of patients.

Hypertension and Renal Disease

Uncontrolled studies have previously suggested a relationship between antiretroviral therapy and the development of hypertension. MACS investigators examined the relationship between initiation of antiretroviral therapy and change in systolic and diastolic blood pressure in men with known normal pre-therapy blood pressure values and prospective follow-up measurements. They found that initiating antiretroviral therapy resulted in increased systolic blood pressure; each year of therapy was associated with a 0.6-mm increase in systolic blood pressure. The risk for an increase in blood pressure was greatest for men with CD4+ cell counts below 200/μL (Abstract 872). A retrospective analysis of factors related to the development of 10-mm Hg increases in systolic or diastolic blood pressure was reported by a group of University of Washington researchers. Within a cohort of 607 patients who had initiated therapy, 10% developed a 10-mm Hg increase in blood pressure or started antihypertensive therapy during follow-up. In contrast to the previous study, they found no relationship between CD4+ count nadir and risk for hypertension, but they did identify treatment with efavirenz or lopinavir/ritonavir as independent risk factors for hypertension (Abstract 873). These studies add to the growing body of evidence suggesting a relationship between certain types of antiretroviral therapy and the risk for hypertension; however, more work is needed to sort out the contributions of specific antiretroviral drugs to hypertension risk.

In the pre-potent antiretroviral therapy era, there were several reports that suggested a link between chronic HIV infection and the development of pulmonary arterial hypertension (PAH), with some early case reports suggesting that antiretroviral therapy might reduce the risk of PAH. Rosenkranz and colleagues studied a consecutive sample of patients treated with antiretroviral therapy to determine the prevalence of PAH using 2D and Doppler echocardiography. PAH was defined as mean pul-

monary arterial pressure above 25 mm Hg or systolic right ventricular pressure above 30 mm Hg at rest. Surprisingly, PAH was diagnosed in 15 of the 200 patients evaluated (7.5%), 8 of whom were completely asymptomatic. These findings suggest that clinicians should have a low threshold to screen patients with echocardiography who have symptoms of unexplained dyspnea. Larger studies are needed to determine whether more widespread screening of asymptomatic subjects should be recommended and to identify risk factors for the development of PAH in the setting of HIV infection (Abstract 874).

Microalbuminuria (MA) is a well-described marker of renal disease that has been noted to be common among HIV-infected individuals. Investigators from the Fat Redistribution and Metabolic Change in HIV Infection Study (FRAM) examined the prevalence of MA in a random sample of 1027 HIV-infected individuals, compared with a population-based control group. MA was present in 8% of HIV-infected patients, but only 2% of controls ($P < .001$). In a multivariate analysis, HIV infection was found to be an independent risk factor for MA (adjusted odds ratio [OR], 4.5). Within the group of HIV-infected patients, elevated systolic blood pressure and African American race were predictors of MA. The relationship between MA and future cardiovascular risk in HIV patients remains to be determined (Abstract 821).

A number of groups continue to investigate the risk of renal dysfunction in patients receiving antiretroviral therapy, with a special focus on tenofovir-containing regimens. Gallant examined the change in creatinine clearance among 344 tenofovir recipients compared with 314 patients who received other nRTIs. In this study, creatinine clearance was calculated using the Cockcroft-Gault equation. Median serum creatinine increased by 0.15 mg/dL and 0.10 mg/dL in the tenofovir and nRTI groups, respectively ($P = .01$). There was a statistically significantly greater decline in the median creatinine clearance in the tenofovir group (13.35 mL/min decline) compared with the other nRTI group (7.5 mL/min decline; $P = .005$). Longer duration of therapy and CD4+ cell count below 50/µL were risk factors for decline in renal function. The authors of this study noted that the change in creatinine clearance, although statistically significant, was small in size and of unclear clinical significance (Abstract 820). Becker and the CHORUS investigators examined rates of renal dysfunction among tenofovir recipients by calculating glomerular filtration rate using the following formula: GFR = (196)*(serum creatinine mg/dL-1.154)*(age-0.203)*(0.742 if female)*(1.212 if African American). They reported that this may be a more sensitive way to follow renal disease in HIV-infected patients (Abstract 819). Finally, MACS investigators examined rates of chronic kidney disease (creatinine clearance < 60 mL/min) in HIV-infected patients treated with antiretroviral therapy, compared with treatment-naive HIV-infected MSM. They identified a higher rate of chronic kidney disease in patients on therapy than in untreated MSM or HIV-uninfected controls. Among those on therapy, tenofovir use appeared to be associated with a higher risk of creatinine clearance below 60 mL/min (Abstract 818).

Hepatitis C Virus Infection

Sulkowski reported that the progression of liver fibrosis was much higher than expected among a cohort of hepatitis C virus (HCV)-infected patients with little or no fibrosis on initial liver biopsy (Abstract 121). In this study, liver fibrosis was evaluated on 2 biopsies a mean of 2.8 years apart in patients without cirrhosis. Of these subjects, 84% had Ishak fibrosis stage 0 or 1 upon first biopsy. Subjects had a median age of 44 years, 21% had CD4+ counts below 200 cells/µL, 57% had HIV RNA levels below 400 copies/mL, and the estimated duration of HCV infection was 23 years. Some of the patients had received prior HCV treatment for brief periods of time. A single pathologist read all biopsy slides in a blinded fashion. At the second biopsy, 13% of subjects had 2-stage progression, and 14% had 3 or more stage progression. Higher baseline HIV RNA and elevated alanine aminotransferase (ALT) levels were associated with increased risk of progression. In a separate study, hepatic steatosis did not progress in patients over a similar time interval (Abstract 831). It is surprising that such high rates of fibrosis progression were observed among this cohort with minimal disease at baseline, and it will be important to identify the factors that identify the most rapid progressors. These findings challenge current clinical practice of delaying HCV therapy and performing liver biopsy at intervals of 3 to 5 years in patients with stage 1 or no fibrosis on initial biopsy.

Although liver biopsies are considered the gold standard for evaluation of the severity of liver disease, noninvasive tests would be preferable, particularly if tests are required at frequent intervals. Sterling and colleagues evaluated the performance of noninvasive tests to predict liver histology from patients entering the AIDS PEGASYS Ribavirin International Co-infection Trial (APRICOT) data set, a randomized trial of 3 HCV treatment regimens presented at last year's conference (Abstract 120). Five hundred fifty-five of the subjects were assigned to a "training set" and 257 subjects were assigned to a "validation set." Fibrosis stage was collapsed into 3 categories: mild (0-1 Ishak), moderate (2-3 Ishak), and severe (4-6 Ishak). In the multivariate analysis, aspartate aminotransferase (AST) level, international normalized ratio (INR), and platelet count distinguished subjects in the 3 groups. The positive and negative predictive value of various cutoffs of an index called "FIB-4" was evaluated in the validation set. A cut-off higher than 3.25 had a positive predictive value of 65% and specificity of 97% for severe liver disease. The FIB-4 value did not perform as well in distinguishing patients with fibrosis scores ranging from 2 to 6. Clinicians and patients are eager for noninvasive tests to assess liver disease, but much more work is needed on these approaches before they are ready to replace liver biopsy in making important decisions for clinical management.

Accumulating data suggest that control of HIV disease with antiretroviral therapy may slow HCV progression (Abstract 947). In a prospective study of 231 injection drug users in an urban cohort, risk factors associated with liver-related morbidity and mortality were examined from 2002 to 2004. There were 22 events during the study period (5.1/100 person-years of observation). In a univariate analysis, Hispanic race and CD4+ count nadir below 100 cells/µL were associated with an increased rate of HCV disease progression; HIV RNA level below 75 copies/mL was associated

with a decreased rate of progression. In the multivariate analysis, CD4+ count nadir below 100 cells/μL was associated with a 20-fold increase in the rate of hepatic events. Starting effective antiretroviral therapy before the CD4+ nadir is below 200 cells/μL is associated not only with AIDS-related complications but with increased risk of liver-related morbidity and mortality in the HCV population. The important clinical question of the optimal timing of antiretroviral and HCV therapy in coinfected patients will require large, randomized clinical trials.

Studies of HCV-monoinfected and HIV-coinfected patients suggest that HCV causes neuropsychiatric changes. Tucker hypothesized that treatment of HIV could improve neurocognitive deficits attributed to HCV in coinfected patients (Abstract 949). Investigators performed repeated measures of neurocognitive functioning tests before and after 6 months of antiretroviral therapy in 32 subjects with HIV infection and 14 subjects with HIV/HCV coinfection. HCV/HIV-coinfected patients had higher rates of impaired visual memory and cognitive function than HIV-monoinfected subjects at baseline. Antiretroviral therapy did not cause a statistically significant improvement in neurocognitive function in this small study with relatively short follow-up. The individual and combined benefits of HIV and HCV therapy on neurocognitive function merit further study.

Standard treatment for HCV includes pegylated interferon alfa and ribavirin. Clinical trials have utilized various dosing regimens for ribavirin, and the optimal dose to maximize efficacy and minimize toxicity is not clear. Renden and colleagues measured ribavirin levels at week 4 and 12 in patients receiving weekly peginterferon alfa-2a plus 800 mg to 1200 mg of ribavirin daily (Abstract 929). Ribavirin levels showed significant interpatient variation but were stable within patients between week 4 and 12. Ribavirin dose was associated with serum levels only when adjusted for weight. Higher levels of ribavirin were associated with greater short-term virologic response, but also with greater drops in hemoglobin. Zidovudine was also an independent predictor of anemia. This study supports weight-based dosing of ribavirin and suggests that ribavirin exerts important early virologic activity.

In another presentation evaluating optimal ribavirin plasma levels in patients receiving HCV treatment, Breigh and colleagues measured plasma concentrations of ribavirin 6 and 12 hours post doses at 8 time points over a year of therapy (Abstract 928). They extrapolated the maximum concentrations (C_{max}), minimum concentrations (C_{min}), and areas under the concentration curve (AUC) from these measurements. In a multivariate analysis, higher C_{min} was associated with higher virologic response (viral suppression 24 weeks after discontinuation of HCV treatment). Based on this data set, the authors proposed that ribavirin should be dosed by weight and that plasma concentrations should be maintained above 1 ug/mL.

Higher ribavirin levels are associated with better virologic response rates during HCV treatment, but also with higher rates of toxicity, which may necessitate dose reduction. Alvarez and colleagues retrospectively evaluated the records of 217 patients receiving weekly peginterferon alfa-2a plus 800 mg to 1200 mg of ribavirin daily to determine if anemia and epoetin alfa use were higher in zidovudine recipients (Abstract 927). Hemoglobin-level declines of more than 5 g/dL were significantly more frequent in zidovudine recipients (13%) than in controls (3%; $P < .01$). Ribavirin dose reduction was also more common in zidovudine recipients (47%) than in controls (17%; $P < .0001$). By week 12, 47% of zidovudine recipients were receiving epoetin alfa, compared with 12% of controls. Hemoglobin levels were similar in both groups at week 12, as were week-12 virologic suppression rates. This study shows that hemoglobin can be maintained with a combined strategy of ribavirin dose reduction and use of epoetin alfa in zidovudine recipients. However, in view of the importance of ribavirin levels to both short- and long-term virologic response, additional studies are needed to determine the optimal clinical approach to patients who require both zidovudine and ribavirin, including those with low CD4+ cell counts.

Treatment of acute HCV in HIV-uninfected patients is associated with treatment response rates greater than those seen during chronic infection. There were 2 conflicting reports on acute HCV treatment outcomes among HIV-infected subjects at the conference this year. Chaix reported outcomes in 12 patients with acute HCV. One important epidemiologic point from this study was that all patients in this series reported MSM as their only risk factor for HCV (Abstract 122). Ten of these 12 had genotype 4d virus, which clustered to single variant on phylogenetic analysis. Ten of 12 patients were asymptomatic. The patients received a variety of treatment regimens, including interferon alfa or pegylated interferon alfa, sometimes in combination with ribavirin. Treatment was started a mean of 50 days from time of diagnosis. Four patients stopped therapy for toxicity before week 12, and none of the patients had a sustained virologic response.

In a second report by Vogel, 17 patients with acute HCV were treated with pegylated interferon alfa for 6 months. Ribavirin 800 mg daily was added in patients with genotype 1 or 4 virus (Abstract 922). The mean CD4+ cell count in the study population was 426/μL. HCV RNA level was undetectable at the end of treatment in 14 of 17 patients. Ten of 14 patients had sustained virologic responses. The authors emphasized that detectable HIV RNA at week 4 or 8 predicted nonresponders. The treatment responses in this German cohort are much more favorable than in the Chaix study. The most obvious difference between the 2 studies was that the treatment regimens in the latter study were more consistent and aggressive. Based on these 2 reports, the jury is still out on the optimal composition, dosing, timing, and utility of treatment during acute HCV infection. The results from the Vogel study are encouraging, but more data are needed in this patient population.

Hepatitis B Virus Infection

Entecavir is an inhibitor of hepatitis B virus (HBV) polymerase that received a unanimous vote of approval for initial and second-line therapy of HBV by the FDA Drug Advisory Committee on March 11, 2005. Most studies have been conducted on HBV-monoinfected patients, but there are limited encouraging data for HIV-coinfected persons. Pessoa presented the results of an ongoing double-blind trial evaluating treatment of HIV-infected subjects who had lamivudine exposure and detectable HBV viremia (Abstract 123). At baseline 88% of sub-

jects had at least 1 lamivudine resistance mutation and a mean HBV DNA level of 9.1 $\log_{10}$ copies/mL. Patients were randomized to entecavir 1 mg per day (51 subjects) or placebo (17 subjects). At 24 weeks, all patients received entecavir. Lamivudine was continued during the study. The mean reduction in HBV DNA level was 3.7 $\log_{10}$ copies/mL among entecavir recipients, compared with an increase of 0.1 $\log_{10}$ copies/mL in the placebo recipients ($P < .0001$). In the entecavir group, 80% of subjects had HBV DNA levels below 400 copies/mL or a 2-log reduction in HBV DNA, compared with 0% in the placebo group. ALT normalization occurred in 49% of the entecavir group and 17% of the placebo group. Entecavir appears to be well tolerated and does not have HIV activity that could lead to HIV drug resistance. Entecavir is efficacious for patients in whom lamivudine is failing and will likely become an important treatment option for chronic HBV infection.

Following the entecavir presentation, Peters reported the results of ACTG 5127, a randomized, double-blind, placebo-controlled study comparing tenofovir (300 mg) with adefovir (10 mg) for the treatment of chronic HBV (Abstract 124). Ninety-two percent of the patients were male, they had a median CD4+ cell count of 467/µL at entry, and the median serum HBV DNA level was 8.7 $\log_{10}$ copies/mL. More than 70% of subjects were lamivudine experienced. Three quarters of the patients had HIV RNA levels below 50 copies/mL on their current antiretroviral regimen. At 48 weeks, the mean reduction in HBV DNA was 5.7 $\log_{10}$ copies/mL in the tenofovir arm and 4.0 $\log_{10}$ copies/mL in the adefovir arm. The therapy was generally well tolerated, with only 4 treatment discontinuations, and none of these discontinuations were for nephrotoxicity. The authors concluded that tenofovir and adefovir are active against HBV in HIV-infected patients, and that tenofovir is not inferior to adefovir. It is notable that HBV reductions were lower in the tenofovir group than in the adefovir group, and that the HIV activity of tenofovir makes it a logical choice for co-infected patients requiring HIV treatment. Information on drug resistance to HBV agents generated during treatment is anticipated from trials such as ACTG 5127, and will be important in designing long-term treatment strategies for both infections.

Organ Transplantation

For patients in whom therapy for HBV or HCV is failing who have liver failure, liver transplantation is an option being carefully evaluated in several specialty centers around the world. Vogel described the clinical experience of 10 patients awaiting orthoptic liver transplantation in Europe (Abstract 931). Six patients had liver disease due to HCV, 3 due to HBV, and 1 due to both. Six of these patients had hemophilia. Two patients died while waiting for liver transplant, and a third patient had improvement of liver disease with the initiation of antiretroviral therapy. Among the 7 patients who received a transplant, 1 died at day 84 due to intrathoracic hemorrhage. The other patients are all alive, and only 1 acute organ rejection episode has occurred. The median follow-up for the cohort is 620 days. The authors highlighted several points of the courses of these patients. HCV reoccurred in all patients with underlying disease but responded to aggressive therapy. Kaposi's sarcoma in conjunction with Castleman's disease was a serious complication in 1 patient. Drug interactions with cyclosporine and antiretroviral agents required careful attention and dose adjustments.

Clinical outcomes in both liver and renal transplantation in the United States were presented by Roland (Abstract 953). There were 11 liver transplants performed. Indications for transplantation were HCV in 45%, HBV in 36%, and both in 9%. There were 2 deaths for recurrent HCV among the liver transplants; the 1- and 3-year estimated survival rates were 91% and 82%, respectively. The cumulative rejection rate among liver transplant patients was only 10%. The 3-year estimated survival for the 18 kidney recipients was 94%. Indications for renal transplantation were HIV-associated nephropathy (44%), hypertension (54%), and diabetes (11%). Rejections were more common among kidney transplant recipients, with cumulative incidence of 67% at 2 years. However, there were only 2 graft losses, both occurring shortly after transplant occurred. Patients were aggressively managed with antiretroviral therapy, and only 3 opportunistic infections associated with HIV disease occurred. Overall patient survival from this ongoing cohort is favorable, compared with HIV-uninfected populations.

Bacterial Infections

Mathews presented an interesting analysis of the incidence trends of methicillin-resistant *Staphylococcus aureus* (MRSA) in a cohort of 3445 HIV-infected adults from a university hospital–based HIV clinic (Abstract 142). Between 2000 and 2003, there were 94 episodes; 83% were skin and soft-tissue infections and 10% were blood infections. There was an estimated 6-fold increase in the rate of MRSA infection from 2000 to 2003. In a multivariate analysis, CD4+ count below 50 cells/µL and increasing levels of HIV RNA were associated with increased risk of MRSA infections. Consistent with these observations, antiretroviral use within the past 6 months was protective against MRSA. Soft-tissue infections with MRSA appeared to be a significant problem in this university hospital–based clinic, particularly among patients with low CD4+ cell counts and poor virologic control of HIV disease. Antiretroviral therapy appears to be an intervention to reduce this complication.

The source of MRSA causing soft-tissue infections among MSM were examined in a prospective survey in a Los Angeles-based HIV clinic. Rieg tested the hypothesis that nasal colonization of MRSA was the source of the increasing incidence of community-acquired MRSA in their population (Abstract 877). Investigators found that 43 of 158 subjects had nasal colonization of *Staphylococcus aureus*, but of these 43, only 7 (16%) were MRSA. In patients with recent MRSA skin infections, there were no trends toward colonization with MRSA. These and other epidemiologic data from HIV-uninfected patients suggest that skin-to-skin contact is a likely mode of transmission of MRSA in MSM with soft-tissue infections.

Trends in invasive pneumococcal disease (IPD) spanning the eras before and after potent antiretroviral therapy were the focus of an oral presentation by Lucas and colleagues (Abstract 139). Invasive pneumococcal disease was defined as bacteremia with *Staphylococcus pneumoniae*. Investigators estimated

that the incidence of IPD in the Johns Hopkins cohort from 1990 to 2003 was 379 cases per 100 person-years of observation. This high incidence rate did not decrease during the potent antiretroviral therapy era, and was estimated at 410 cases per 100 person-years of observation between 1998 and 2004. Using a nested case-control design, authors identified female sex, injection drug use, African-American race, and HCV infection as risk factors of IPD. Variables that surprisingly had no protective effect included trimethoprim/sulfamethoxazole prophylaxis, antiretroviral therapy, and pneumococcal vaccine. There was no protective effect of vaccination, even when only those who received vaccination at CD4+ cell counts above 300/µL were included in the analysis. CD4+ cell count and HIV RNA level were borderline significant in the analysis. Even in the potent antiretroviral therapy era, rates of IPD in this population remain high. Additional information, such as serovar of the pneumococcal strain, may be helpful in explaining these findings.

With IPD remaining a significant risk for HIV-infected patients, Lesprit and colleagues evaluated whether immune responses to the standard 23-valent pneumococcus polysaccharide vaccine (PPV) could be improved with a prime vaccination with the 7-valent pneumococcal conjugate vaccine (PCV; Abstract 140). Subjects with CD4+ counts of 200 to 500 cells/µL were randomized to receive either standard PPV at week 4, or PCV at time 0 and PPV at week 4. At 8 weeks, immunologic response to the prime-boost vaccine strategy was superior to the standard vaccination strategy. The clinical significance of these findings will require much larger studies.

Tuberculosis

Swaminathan presented interim results of an ongoing randomized trial evaluating a 6-month versus a 9-month treatment course for *Mycobacterium tuberculosis* in Chennai, India (Abstract 141). The study population included patients with culture-confirmed *M tuberculosis*. At baseline, the mean CD4+ cell count was 201/µL, and 77% of subjects were smear-positive for acid-fast bacilli. None of the patients were receiving antiretroviral therapy. Of the 122 patients with end-of-treatment data available, cultures were negative in 99% of the patients receiving a 6-month course of treatment and 95% of subjects receiving a 9-month course. Eleven patients died during treatment. There was relapse of tuberculosis in 7 cases in each arm. Final conclusions from this trial await its completion; interim results support current practice of a 6-month course of tuberculosis treatment in HIV-infected persons.

In a study of 20 patients receiving antiretroviral therapy in conjunction with rifampin-based tuberculosis therapy in South Africa, Friedland and colleagues reported on trough efavirenz levels measured during the course of treatment (Abstract 891). All subjects were receiving efavirenz at a dose of 600 mg per day as part of their antiretroviral regimen. There was significant interpatient variation among patients in this study, although higher efavirenz trough levels were associated with lower weight. In this small study, efavirenz trough levels were not statistically associated with treatment outcome or toxicity. Previous data from European studies have suggested that efavirenz dosing should be increased to 800 mg in the presence of rifampin, but defining the optimal dose in the African and Asian setting will require larger studies.

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