# Complications of HIV Disease and Antiretroviral Therapy

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*This year's conference provided newer insights on the complications of antiretroviral therapy, as well as into the complications that arise from HIV infection itself. Many presentations at the conference centered around metabolic complications of therapy, including lipid abnormalities, diabetes, body composition changes, bone disorders, and cardiovascular disease. New data on complications of HIV infection itself were presented, including those on coinfections with hepatitis B, C, and herpes simplex viruses, malaria, and tuberculosis, as well as complications that are important during pregnancy. This article summarizes these presentations.*

## Metabolic Complications

Metabolic complications continue to play a major role in the management of HIV infection. This year's conference featured more than 50 abstracts describing research directed toward understanding the pathogenesis, treatment, and long-term consequences of metabolic abnormalities associated with HIV infection and the use of antiretroviral therapy. This section is divided into sections about the pathogenesis of metabolic complications, lipid abnormalities, diabetes, lipoatrophy and lipohypertrophy, bone disorders, and cardiovascular disease.

## Pathogenesis of Metabolic Complications

In vitro studies have suggested that protease inhibitors (PIs) may influence lipid metabolism by interfering with the degradation by proteasomes in hepatocytes and adipocytes, thus influencing the expression of genes involved in lipid metabolism. Specific PIs differ in their lipid effects in vitro. Most earlier studies have shown conflicting results with respect to lipid effects in vitro and in vivo. Parker and colleagues compared the effects of lopinavir, ritonavir, nelfinavir, and atazanavir on gene expression in vitro in hepatocyte and adipocyte cell lines (Abstract 706). Using drug concentrations designed to mimic those observed in vivo, they measured induction and inhibition of gene expression each qualitatively and quantitatively. Lopinavir, ritonavir, and nelfinavir each had a greater impact on induction of genes involved in lipid metabolism than did atazanavir in both cell lines. In addition, it appeared that genes involved in lipid synthesis were also upregulated in hepatocytes by lopinavir, ritonavir, and nelfinavir, but repressed in adipocytes, consistent with the observations in vivo of increased hepatic lipid synthesis but reduced storage in fat cells. These investigators proposed that inhibition of proteasomes in vivo with the resultant impact on lipid biosynthesis may be the etiology of PI-associated dyslipidemia, and the absence of an effect of atazanavir on these pathways may explain the absence of dyslipidemia seen with this drug in vitro. Further clinical studies are needed to determine whether the absence of lipid effects of atazanavir translates into a reduced impact on body composition over time.

Previous studies have suggested that insulin resistance may be associated with drugs in the PI class. In vitro and clinical studies suggest PIs may vary in their propensity to cause insulin resistance. For example, atazanavir—unlike indinavir, lopinavir, and ritonavir—does not appear to block the glucose transporter GLUT 4 in vivo. Noor and colleagues at Bristol-Myers Squibb, with collaborators at University of California San Francisco, conducted a randomized, double-blind, placebo-controlled trial with a 2 period crossover design to examine the impact of atazanavir and lopinavir/ritonavir (lopinavir/r) on insulin-stimulated glucose uptake in HIV-uninfected adults. This labor-intensive, hyperinsulinemic, euglycemic clamp study is considered the gold standard for determining the presence of insulin resistance. Subjects were randomized to receive standard doses of atazanavir (400 mg/d), lopinavir/r (400 mg/100 mg twice daily), or placebo. Following 5 days of treatment, the clamp procedure was performed to determine the rate of glucose disposal at steady state following a continuous infusion of insulin. Mean values of insulin-stimulated glucose disposal (M/I) did not vary between atazanavir and placebo; however, the difference between lopinavir/r plus atazanavir and lopinavir/r plus placebo was statistically significant, suggesting that lopinavir/r, but not atazanavir, had an unfavorable impact on glucose metabolism.

Atazanavir also had no impact on measures of insulin sensitivity; however, a statistically significant decrease in insulin sensitivity was observed with lopinavir/r. The results of this well-designed and carefully conducted study suggest that lopinavir/r has acute effects detected by a sensitive measure of glucose metabolism in non-HIV-infected adults. Previous studies in a smaller number of non-HIV-infected volunteers using this same euglycemic, hyperinsulinemic clamp method demonstrated that 4 weeks of treatment with indinavir was associated with the development of insulin resistance, whereas lopinavir/r treatment had no effect on insulin sensitivity (Abstract

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705). It is not clear whether the difference in results between these studies is perhaps due to the shorter treatment period (5 days) or the larger sample size of the most recent study. The impact of these findings on long-term outcomes of HIV-infected patients taking these drugs merits close attention.

Lipid and glucose metabolism kinetics were also examined in HIV-infected subjects who had evidence of metabolic complications (ie, body fat maldistribution assessed by dual-energy x-ray absorptiometry scanning [DEXA], triglyceride level > 200 mg/dL, or impaired glucose tolerance) and were compared with a control group of HIV-infected subjects who did not have such evidence of metabolic complications (Abstract 703). Glucose and lipid disposal were examined using a euglycemic, hyperinsulinemic clamp technique and stable isotope tracers. The subjects with HIV-related metabolic complications had marked impairment of insulin-mediated suppression of lipolysis and glucose production, and a reduction in the ability of insulin to promote glucose disposal. These findings led the investigators to conclude that increased mobilization of lipid stores may contribute to the dyslipidemia and changes in body composition observed in HIV infection.

There is also great interest in the role of adiponectin, a hormone secreted by adipocytes, in the pathogenesis of body composition changes observed during treatment of HIV infection. Cross-sectional studies have demonstrated reduced circulating levels of adiponectin in patients with both lipoatrophy and lipohypertrophy. In addition, reduced levels of adiponectin have been correlated with the presence of insulin resistance. Lee and colleagues assayed samples collected during their previously reported clamp studies of indinavir and lopinavir/r and found that adiponectin levels were increased following exposure to both of these drugs, and this increase in adiponectin appeared to be independent of insulin resistance (Abstract 705). Jones and colleagues examined adiponectin and tumor necrosis factor (TNF) expression from adipocytes obtained from HIV-infected subjects undergoing surgical procedures (Abstract 707). Adipocytes were obtained from subcutaneous and omental fat depots, and the cells were later exposed to a variety of antiretroviral drugs in vitro. Adiponectin expression was higher in subcutaneous than in omental fat cells in these drug-naive subjects, and adiponectin messenger RNA (mRNA) expression appeared to be inversely related to TNF mRNA expression. PIs (with the exception of atazanavir) and nucleoside reverse transcriptase inhibitors ([nRTIs]; zidovudine and stavudine) significantly decreased adiponectin expression in adipocytes obtained from the subcutaneous depots, suggesting a mechanism by which these drugs might lead to the development of insulin resistance and lipoatrophy. Prospective studies of antiretroviral-naive patients taking on different antiretroviral regimens are needed to determine the relationship between early effects drug exposure on insulin resistance and adiponectin levels, both in adipose tissue and in the circulation, and the subsequent development of lipoatrophy or lipohypertrophy.

The nRTIs have been implicated in the pathogenesis of lipoatrophy. Most of the previous work in this area focused on the impact of nRTIs on mitochondrial DNA content in peripheral blood mononuclear cells (PBMCs), and more recently in fat biopsies. At this year's conference, several groups extended our understanding of this important area of research. Casula and colleagues reported longitudinal data on levels of mitochondrial DNA (mtDNA) and RNA content from PBMCs collected in a randomized clinical trial comparing a regimen containing indinavir with a regimen containing efavirenz, each with or without stavudine (Abstract 709). Following 48 weeks of antiretroviral treatment, levels of mtDNA and mtRNA increased above baseline in both groups, and there was no statistically significant difference between the treatment arms. These results suggest that PBMCs may not be the cells to assess mitochondrial toxicity. A cross-sectional study (Abstract 710) in which lipoatrophic HIV-infected patients had reduced levels of mtDNA in adipose tissue but not in PBMCs reached this same conclusion and also suggested that fat tissue may be the best tissue to examine the impact of nRTI treatment. McComsey examined markers of mitochondrial function from skeletal muscle samples from subjects who had participated in a trial replacing stavudine with abacavir or zidovudine. This trial had previously demonstrated improvements in lipoatrophy following the nRTI switch. Despite this clinical improvement, only a partial improvement in mitochondrial function was seen at 48 weeks, suggesting that the mtDNA depletion may not be the sole mechanism involved in mitochondrial dysfunction. Finally, Mallon and collaborators reported the results of an elegant study of the impact of short-term nRTI therapy in HIV-uninfected volunteers (Abstract 76). In this randomized trial, 20 subjects received either stavudine/lamivudine or zidovudine/lamivudine for 6 weeks, followed by a washout period. Adipose tissue biopsies were obtained from the flank region at baseline and at week 2 and studies were conducted to examine the impact of the nRTIs on mitochondrial and nuclear genes. Mitochondrial and peroxisome proliferator-activated receptor-γ (PPAR–γ) gene expression decreased significantly at week 2 in both groups, but sterol regulatory binding protein 1 (SREBP1) was not affected. These early changes in mitochondrial and nuclear gene expression predated any changes in fat mass in the study subjects. These results suggest that combination nRTI therapy may have a direct effect on expression of metabolism genes (both mitochondrial and nuclear genes) in adipocytes in the absence of HIV infection, and these changes could contribute alone or in combination with PIs to the pathogenesis of lipoatrophy over time.

### Lipids

Several groups reported on the prevalence and risk factors for dyslipidemia within ongoing cohorts and controlled clinical trials (Abstracts 74, 712–717). Investigators in the Community Programs for Clinical Research on AIDS (CPCRA) examined risk factors for low levels of high-density lipoprotein cholesterol (HDL-c) in a cross-sectional analysis of 1028 subjects enrolled in

the ongoing Strategies for Anti-Retroviral Therapy (SMART) study (Abstract 712). Nearly half (44.5%) of the cohort had a baseline HDL-c level of less than 40 mg/dL. As expected, low HDL-c was more common among those not on antiretroviral therapy, and it appeared to be associated with higher values of HIV RNA. Among those on antiretroviral therapy, use of an nonnucleoside reverse transcriptase inhibitor (NNRTI) was associated with higher HDL-c, and traditional risk factors were associated with low HDL-c. In a multivariate model of risk factors for low HDL-c among those on treatment, younger, age, female sex, black race, and NNRTI-containing antiretroviral therapy regimens were protective against low HDL-c, and diabetes and triglyceride levels above 200 mg/dL increased the risk of low HDL-c. Among those on NNRTI plus nRTI-based antiretroviral therapy, the presence of 3 or more traditional risk factors increased the prevalence of low HDL-c from 15.7% for those with no risk factors to 45% for those with 3 or more risk factors. These results suggest that traditional risk factors and type of antiretroviral therapy are both important determinants of low HDL-c in HIV infection.

The metabolic substudy (A5005s) of the large randomized controlled AIDS Clinical Trials Group (ACTG) 384 trial was designed to determine whether nelfinavir- and efavirenz-based therapies differ with respect to changes in lipid and insulin levels (Abstract 74). The study also compared the impact of the nRTI-backbone regimens in the trial (zidovudine/lamivudine vs didanosine/stavudine) on metabolic parameters. Increases in total cholesterol levels were similar in the efavirenz and nelfinavir groups, and increases in HDL-c were more common in the efavirenz-treated patients, yielding a more favorable total cholesterol-to-HDL-c ratio in the efavirenz group. Neither treatment assignment was associated with large increases in triglyceride levels: Only 6% of efavirenz and 5% of nelfinavir recipients experienced triglyceride increases above 400 mg/dL at 32 weeks. Zidovudine/lamivudine treatment was associated with more favorable lipid parameters than didanosine/stavudine. Insulin resistance appeared to worsen in the group over time, with no differences noted between treatment groups.

Powderly and colleagues compared lipid values and body shape changes among subjects randomized to receive efavirenz and didanosine-EC (enteric coated) combined with either stavudine or emtricitabine over 72 weeks (Abstract 717). More favorable effects on triglyceride and HDL-c levels were seen among the emtricitabine/didanosine group compared with those who received stavudine/didanosine. In this trial, treatment with stavudine was also associated with greater decrease in body weight, body mass index, abdominal girth, waist circumference, and waist-to-hip ratio than was treatment with emtricitabine, consistent with the suspected role of stavudine in the development of lipoatrophy.

Elevated lipid levels, and in particular, increases in triglyceride levels, have been well described during treatment with the PI lopinavir/r. Almost all early data on lipids with lopinavir/r-based regimens came from studies that included the nRTI backbone of stavudine/lamivudine. Since stavudine use has been associated with increases in triglyceride levels in other trials (ie, Gilead 903, ESS4002 Study [Abstract 713]), it is of interest to examine prospective data on lipids among patients treated with lopinavir/r when combined with non-stavudine-containing nRTIs. Gathe and colleagues presented the results of a 48-week study that compared once-daily with twice-daily lopinavir/r plus tenofovir/emtricitabine (Abstract 570). Lipid changes were comparable in the once-daily and twice-daily lopinavir/r dosing arms, with modest (but statistically significant) increases in total cholesterol (27 mg/dL), HDL-c (3 mg/dL to 6 mg/dL), and low-density lipoprotein cholesterol ([LDL-c]; 13 mg/dL to 14 mg/dL). The mean change in total cholesterol level was smaller than the mean increase of about 53 mg/dL described in earlier trials with lopinavir/r. The mean change in triglyceride level was 82 mg/dL and 76 mg/dL in the once-daily and twice-daily dose groups, respectively, and this appears to be slightly less than the mean change of about 125 mg/dL change noted in early trials with lopinavir/r combined with stavudine/lamivudine. These results suggest that the use of a tenofovir/emtricitabine nRTI backbone might decrease, but might not eliminate, the hypertrigylceridemia that is observed among some patients who receive lopinavir/r-based therapy.

In another study of treatment-experienced patients, baseline triglyceride level was the best predictor of developing further increases in triglyceride level while on lopinavir/r (Abstract 714). Finally, comparative data from the MaxCmin trial demonstrated that triglyceride increases were evident (median increase, 29%) in subjects randomized to receive lopinavir/r, compared with no statistically significant change for those who received saquinavir/ritonavir (Abstract 720).

Treatment with lipid-lowering drugs in the setting of antiretroviral therapy has only been modestly successful. Aberg and ACTG colleagues reported follow-up data from a randomized trial comparing pravastatin and fenofibrate for the treatment of dyslipidemia in antiretroviral-therapy-treated subjects (Abstract 723). Subjects who did not reach the National Cholesterol Education Program (NCEP) goal for both triglyceride and LDL-c levels by week 12 on lipid-lowering monotherapy (>95% of study subjects) were offered combination fenofibrate/pravastatin therapy and were followed up for 48 weeks. The combination of fenofibrate/pravastatin was safe and well tolerated; however, few subjects met NCEP goals for cholesterol and triglyceride levels at the end of the study. For subjects with elevated triglyceride levels, treatment with fenofibrate alone followed by the combination pravastatin/fenofibrate appeared to offer the best response.

Statin therapy may have additional benefits beyond the impact on values of total cholesterol and LDL-c. This was evaluated in a small, double-blind, placebo-controlled trial of pravastatin in which lipoprotein subfractions and endothelial function were included as endpoints. Pravastatin treatment was associated with an 18% decrease in total cholesterol and a 20% decrease

in LDL-c. In addition, pravastatin was associated with reduced atherogenic lipid fractions, like small LDL-c and small very low density lipoprotein (VLDL) levels, and improved endothelial function as measured by flow mediated dilatation of the brachial artery.

Another option for lowering hypertrigylceridemia is the use omega-3 fatty acids or fish oil. Wohl and colleagues conducted an open-label study evaluating a diet and exercise intervention with or without the addition of 3 g of fish oil per day in non-diabetic HIV-infected subjects with elevated triglyceride levels on antiretroviral therapy. Although there was a transient benefit from fish oil at week 4, by the end of 4 months of treatment only modest decreases in triglyceride levels were noted, and no differences were seen between treatment arms. Whether higher doses of fish oil will offer clinically significant decreases in hypertrigylceridemia remains to be determined.

Given the modest impact of lipid-lowering drugs on dyslipidemia among patients on antiretroviral therapy, interest remains in strategies that include substituting the component of therapy that is the likely cause of the problem. One factor that may influence the ability of single-drug substitutions to improve dyslipidemia is the presence of lipoatrophy or lipohypertrophy at the time of the switch. Fisac presented follow-up results of the lipid substudy of the larger NEFA switch study called NEFA, in which either nevirapine, efavirenz, or abacavir was substituted for the PI component of a successful antiretroviral therapy regimen (Abstract 78). Two years following the switch to PI-sparing antiretroviral therapy, the earlier improvements in total cholesterol, HDL-c, and non-HDL-c levels appeared to be maintained in all treatment groups. Of note, triglyceride levels were statistically significantly reduced at 12 months but appeared to be on the rise by 24 months. Subjects with moderate to severe clinical lipodystrophy appeared to be less sensitive to the improvements in dyslipidemia seen with changing therapy. These results highlight the possible interrelationship between changes in body composition and dyslipidemia, and may also provide insights into why conventional lipid-lowering drugs have only modest effects.

### Diabetes

There is a growing interest in the relationship between HIV infection, antiretroviral therapy, traditional risk factors for diabetes, and the prevalence and incidence of diabetes among HIV-infected subjects. Historical data on the risk of diabetes among men were reported from the Multicenter AIDS Cohort Study ([MACS]; Abstract 73). Prevalent diabetes was 4 times more common among men on antiretroviral therapy compared with an HIV-uninfected control group. The incidence of prediabetes and diabetes was increased by nearly 2 fold and 3 fold, respectively, among antiretroviral-therapy-treated men, compared with HIV-uninfected men, following adjustment for age and body mass index. Finally, among the antiretroviral-therapy-treated men, use of a PI, efavirenz, or stavudine was each significantly associated with an increased risk for prediabetes or diabetes. Howard and colleagues took the investigation of diabetes a step further by performing oral glucose tolerance testing in a group of HIV-infected and at-risk HIV-uninfected women with no histories of diabetes (Abstract 701). The prevalence of diabetes overall in this cohort of predominantly minority women (38% who had a family history of diabetes) was 6%, whereas 11% had impaired glucose tolerance. HIV infection, PI use, and antiretroviral use did not appear to increase the risk of diabetes or of abnormal glucose tolerance. In a multivariate model, only age greater than 50 years and smoking were predictive of an abnormal glucose tolerance test after controlling for HIV serostatus, antiretroviral therapy or PI use, race, and family history of diabetes. This study, which used more sensitive measures of glucose homeostasis, suggests that traditional risk factors may play a greater role than HIV infection or use of specific antiretroviral drugs in the development of impaired glucose tolerance.

Diabetes may also contribute to the neurologic sequelae of HIV infection. A cohort study (Abstract 502) examined factors associated with overall cognitive function in an aging cohort of HIV-infected adults and found that diabetes was more common among older HIV-infected people and was associated with worse overall cognitive function and psycho-motor functioning after controlling for age, antiretroviral therapy, existing hypertension, elevated cholesterol level, and smoking.

### Lipoatrophy and Lipohypertrophy

Limited data exist on the risk of lipoatrophy from controlled trials in antiretroviral-naive patients. Podzamczer and colleagues reported 48-week data from a prospective randomized trial that included objective measures of body fat assessed by DEXA scans (Abstract 715). In this study, 237 patients were randomized to receive efavirenz/lamivudine combined with either stavudine or abacavir. Although virologic and immunologic responses were similar, a greater proportion of the stavudine-treated patients (20%) than abacavir-treated patients (2.7%) noted subjective evidence of lipoatrophy in at least 1 body area at 48 weeks. These observations were confirmed among the 78 subjects who underwent DEXA scanning at baseline and 48 weeks. Among stavudine-treated, compared with abacavir-treated, patients, fat loss by DEXA was greater overall (-1152 g vs. + 1749 g, respectively) and in both the arms (-177 g vs + 136 g) and in the legs (-1234 g vs + 519 g), respectively. These data confirm those from earlier trials suggesting an increased risk of developing lipoatrophy with stavudine-containing treatment. Longer follow-up is needed to determine the risk of lipoatrophy among the abacavir-treated patients. The identification of antiretroviral therapy regimens with low-risk of lipoatrophy over long follow-up is eagerly awaited.

The only treatment option that has been previously shown to be promising for patients with lipoatrophy has been the substitution of stavudine with abacavir or zidovudine (Carr, *JAMA*, 2002; McComsey, *Clin Infec Dis*, 2004). Preliminary results from studies of rosiglitazone, an insulin-sensitizing

drug, have shown conflicting results (Sutinen, *Lancet*, 2003; Hadigan, 2nd IAS, 2003).

Carr reported the results of a randomized, placebo-controlled trial evaluating a 4 mg twice-daily dose of rosiglitazone in subjects with clinical lipoatrophy on antiretroviral therapy. Following 48 weeks of treatment, although there was evidence of improvement in insulin sensitivity in the rosiglitazone-treated subjects, there was no evidence of any effect of rosiglitazone on limb fat. In addition, rosiglitazone treatment was associated with high rates of hypertriglyceridemia. Why did these investigators see no benefit when the earlier study by Hadigan and colleagues, reported last summer in Paris, suggested an improvement in insulin sensitivity and limb fat with rosiglitazone treatment? Possible explanations include the requirement of documented insulin resistance as an entry criterion in the Hadigan study. Nonetheless, this recent study suggests that rosiglitazone therapy offers little improvement in limb fat among an unselected group of subjects with lipoatrophy.

Recombinant human growth hormone (rhuGH) at a dose of 4 mg/day for 12 weeks was previously shown to reduce trunk fat, visceral adipose tissue, total cholesterol, and non-HDL-c in subjects with fat accumulation on antiretroviral therapy; however, the improvement reverted after the drug was stopped. Kotler reported the results of a large, randomized study comparing 1 mg/day or 2 mg/day of rhuGH as maintenance therapy for up to 60 weeks among patients who had previously received higher doses of rhuGH (Abstract 80). Following 60 weeks of treatment, significant reductions in trunk fat, total cholesterol, and non-HDL-c were maintained. There was no change in limb fat or insulin resistance noted. The only difference between the two dose groups was a higher rate of arthalgia in the 2-mg dose group. Further investigation of low-dose rhuGH is currently under way.

### Bone Density

The relationships among HIV infection, antiretroviral therapy, and osteoporosis remain unclear. Data from the Womens Interagency HIV Study (WIHS) demonstrated that the prevalence of osteopenia/osteoporosis was 3-fold higher among HIV-infected women than among HIV-uninfected women. Among the women with HIV infection, older age, white race, postmenopausal status, and lower body mass index were associated with lower bone density; longer duration of nevirapine exposure appeared to be associated with higher bone density in this cohort. Whether the reduced bone mineral density reported in some studies of HIV-infected patients will translate into higher rates of pathologic fractures over time remains to be seen. McComsey reported on a series of 49 patients with fractures collected from 9 large HIV clinics serving an estimated 8600 patients, and found that most of these patients had not received an adequate work-up for osteopenia, indicating the need for better education of HIV providers on the management of these types of fractures (Abstract 743).

### Cardiovascular Complications

The long-term consequences of the metabolic complications of antiretroviral therapy on cardiovascular risk remain a topic of great interest. At this year's conference, follow-up data from previously reported studies confirmed previous observations. Investigators from the Data collection on Adverse events of Anti-HIV Drugs study group reported an increase in the relative risk of cardiovascular and cerebrovascular events with longer exposure to combination antiretroviral therapy (Abstract 737). In addition, this group reported that the Framingham risk equation came close to predicting the observed rate of events. The HIV InSight database found a link between cumulative exposure to PI therapy and cardiovascular disease (Abstract 736), but the ongoing Kaiser study continued to show a relationship between HIV infection and risk of hospitalization for coronary heart disease, and for the first time, a link between duration of PI therapy and coronary heart disease (Abstract 739).

Studies of subclinical atherosclerosis that employed measurements of carotid intimal medial thickness and coronary calcification by computed tomography scan also found that traditional risk factors, rather than PI exposure per se, appeared to be associated with these surrogate markers for atherosclerotic disease (Abstracts 738,734). However, 1 cross-sectional study found a strong relationship between exposure to PIs and the development of carotid plaques (Abstract 735). Longer-term follow-up of these cohorts is eagerly awaited.

Previous small studies have suggested that PI-based therapy might increase the risk of hypertension. However, a longitudinal analysis of the DAD study found that although there was a high prevalence of hypertension in HIV-infected patients, traditional risk factors (male sex, higher body mass index, and older age) but not duration of use of any class of antiretrovirals predicted the development of hypertension over an average follow-up time of 1.5 years (Abstract 75). In a smaller study on hypertension from WIHS, the prevalence of hypertension appeared similar between the HIV-infected and HIV-uninfected groups; however, antiretroviral therapy did appear to be associated with an increase in the incidence of hypertension among women over a longer period of observation (Abstract 741).

## Hepatitis Virus Coinfection

### Hepatitis C Virus Treatment Trials: RIBAVIC, APRICOT, and ACTG 5071

Three large randomized trials examining the activity of interferon alfa and ribavirin combinations for HIV and hepatitis C virus (HCV) coinfection provided the largest and most informative experience to date of treatment outcomes (Abstracts 117LB, 112, 110). The primary focus of these trials was the proportion of patients achieving sustained virologic response (SVR) defined as undetectable HCV RNA 24 weeks following cessation of therapy. Although the results varied slightly between these trials due to differing patient populations and specific regimens, there was consensus on the following points: The combination of pegylated interferon alfa (PEG-IFN) and

ribavirin was the most efficacious combination; patients with genotype 1 had inferior responses to those with other genotypes; virologic response at week 12 predicted sustained virologic response; and sustained virologic responses were lower than those reported for HIV-uninfected patients. Other important observations included the lack of antagonism between ribavirin and zidovudine, stavudine, or lamivudine, and the histological response rate (33%) observed in patients without an SVR in ACTG 5071. These trials are summarized in Table 1.

In the ANRS RIBAVIC study (Abstract 117LB), 412 patients (79% injection drug users) with CD4+ cell counts greater than 200/µL were randomized PEG-IFN to a 48-week treatment course of PEG-IFN (the 2b form) plus ribavirin (800 mg/day, approximately 12/mg/kg/day) or interferon alfa (IFN; 2b) plus ribavirin. Among study participants, 58% had genotypes 1 or 4, 34% had genotype 3 and 8% had other genotypes. An SVR occurred in 26% of the PEG-IFN–treated patients and in 18% of the IFN-treated patients ($P = 0.031$). Res- ponse rates were lower in genotypes 1 or 4 (15%) compared with others (43%). Virologic response at week 12 predicted SVR. Treatment discontinuation occurred in 42% of patients but did not differ between the groups.

The APRICOT study enrolled patients from nearly 20 countries and 100 centers to a 48-week course of IFN (2a form) plus ribavirin (n = 285) or PEG-IFN (the 2a form) (n = 286) or PEG-IFN plus ribavirin (n = 289) (Abstract 112). The ribavirin was administered in a blinded fashion. Sixteen percent of patients had cirrhosis, and 61% had genotype 1. An SVR was achieved in 40% of subjects receiving PEG-IFN plus ribavirin, 20% receiving PEG-IFN alone, and in 12% receiving IFN plus ribavirin. All comparisons between groups were highly significant. For patients infected with genotype 1, SVR occurred in 29% of the PEG-IFN plus ribavirin group and in 62% of the patients with genotypes 2 or 3 in this group. Twenty-five percent of patients withdrew early from treatment in the PEG-IFN plus ribavirin arm, mostly due to adverse events or non-safety related reasons. The most common adverse events attributed to the study drug were fatigue, fever, headache, and myalgia. Depression was reported in 20%. CD4+ cell count levels dropped a median of 140/µL, but CD4+ percentage did not change, and there were no reports of opportunistic infections. Although not required by the protocol, 85% of patients on this study were receiving antiretroviral therapy. In a nested pharmacokinetic study evaluating for potential interac-

Table **1.** Baseline Characteristics and Sustained Virologic Response in Pegylated Interferon Alfa plus Ribavirin Treatment Arms from the RIBAVIC, APRICOT, and ACTG 5071 Studies

| | **RIBAVIC** (Abstract 117lb)* | **APRICOT** (Abstract 112) † | **ACTG 5071** (Abstract 110) ‡ |
|---|---|---|---|
| **Baseline Characteristics** | (N=207) | (N=289) | (N=66) |
| Male | 77% | 80% | 79% |
| White | n/a | 80% | 50% |
| Age (years) | 39 | 40 | 45 |
| CD4+ cells/µL | 527 | 520 | 492 |
| Antiretroviral therapy | 82% | 85% | 85% |
| Hepatitis C virus RNA | 5.9 x $10^6$ IU/mL | 5.6 x $10^6$ IU/mL | 6.2 x $10^6$ IU/mL |
| Hepatitis C virus genotype 1 | 58% § | 61% | 77% |
| Cirrhosis | 40% | 15% | 11% |
| **Sustained Virologic Response** | | | |
| All patients | 27% | 40% | 27% |
| Genotype 1 only | 15%§ | 29% | 14% |

* Pegylated interferon alfa 2b 1.5 µg/kg weekly plus ribavirin 800 mg/day.
† Pegylated interferon alfa 2a 180 µg/weekly plus ribavirin 800 mg/day.
‡ Pegylated interferon alfa 2a 180 µg/weekly plus ribavirin in dose escalation from 600 mg/day to 1000 mg/day.
§ Includes genotype 1 and genotype 4.
n/a indicates not available.

tions between ribavirin and either zidovudine, stavudine, or lamivudine (Abstract 136LB), measurements of serum and intracellular levels of these drugs revealed no evidence for antagonism.

ACTG 5071 randomized 134 patients at 21 centers to either PEG-IFN (2a) plus ribavirin or IFN (2a) plus ribavirin (Abstract 110). Of note, ribavirin was administered in a dose escalation schedule starting with 600 mg/day and increasing as tolerated to 1000 mg/day. In this study, 77% of subjects had genotype 1, and 11% had cirrhosis. Twenty-seven percent of patients randomized to PEG-IFN plus ribavirin and 12% of patients receiving IFN plus ribavirin ($P < 0.001$) had an SVR. Response rates for genotype 1 were 14% and 6%, respectively for the 2 groups. Among the patients with early virologic response (ie, a 2-log reduction of HCV RNA at 12 weeks), 51% had an SVR. None of the patients without early virologic response had an SVR.

One of the most interesting analyses from this study evaluated the histologic response in those individuals without an SVR. All samples were blinded and reviewed by the same pathologist. Approximately one-third of patients without an SVR showed evidence of histologic improvement with treatment. Although the clinical significance of this finding remains unknown, it raises many questions regarding pathogenesis and avenues for alternate treatment strategies. Of interest was a study by Rodriguez that showed histologic improvement in patients in whom treatment had initially failed by virologic response criteria who then received an additional 24-week course of treatment with PEG-IFN interferon and ribavirin (Abstract 821).

### Host Factors Associated with Natural History of HCV and Response to Treatment

Several abstracts evaluated immune correlates of outcome in patients with HCV coinfection. In the ACTG 5071 study, sequential single cell cytokine assays performed on a subset of study participants showed an overall reduction in HCV-specific responses during treatment, and a correlation between preservation of Th1 responses at week 24 and SVRs (Abstract 111). In a small study of intrahepatic lymphocyte responses from the liver biopsies obtained from patients in ACTG 5071, both CD4+ cell count and CD8+ cell count responses to HCV were detected at frequencies similar to those seen in HCV-monoinfected patients (Abstract 113). Host genetic factors were evaluated in an ACTG 5071 substudy of DNA polymorphisms thought to be involved in host inflammatory reactions and fibrosis. Predictors of liver fibrosis were found with genotype for the CCR5 promoter, tumor growth factor (TGF) beta, and interleukin-13 ([IL-13]; Abstract 116). In acute HCV infection, loss of HCV specific interferon gamma production was associated with persistent viremia in 1 study (Abstract 788). Low CD4+ nadir was associated with loss of HCV-specific responses and persistence of HCV during acute infection in another study (Abstract 790).

### Hepatitis Virus and HIV Disease Progression

The relationship between hepatitis virus infection (treated or untreated) and HIV disease progression and response to antiretroviral therapy was examined in the EuroSIDA cohort (Abstract 799). In 5883 patients, HCV was present in 34% and hepatitis B virus (HBV) in 9%. Liver–related mortality increased in patients with hepatitis but not overall deaths. There was no detectable difference in response to antiretroviral therapy in patients with or without hepatitis. These results are in contrast to those from an evaluation of patients from Argentina participating in antiretroviral naive studies, in which hepatitis virus infection was associated with a blunted CD4+ cell response (Abstract 817). In a US-based study of more than 12,000 veterans with an HCV seroprevalence of 38%, HCV (independent of injection-drug use) was associated with increased risk for mortality (Abstract 800). Although these studies of different cohorts showed slightly differing conclusions, they all point to the increasingly important role that hepatitis virus coinfection plays in the natural history and treatment strategies for HCV and HIV coinfection.

### Hepatitic Steatosis in HCV Infection

Several studies looked at the predictors of hepatitic steatosis and their relationship to hepatitic fibrosis. Previous reports suggested that steatosis is associated with increased fibrosis progression and diminished response to therapy. In an evaluation of 113 patients presented to the Johns Hopkins University clinic who met criteria for biopsy, grade 2 steatosis was identified in only 5% of subjects. Steatosis was associated with stavudine use, cumulative PI exposure, weight greater than 190 lbs, CD4+ cell count below 200/µL, HIV suppression, and white race. In contrast, 56% of 48 patients seen at Cornell University showed evidence of steatosis that was associated with more advanced fibrosis (Abstract 812). Factors identified in the Johns Hopkins University study were not identified as predictors of steatosis in the Cornell University study. Sampling and patient characteristics may explain some of these differences, but clearly more data are needed to understand the predictors and significance of steatosis in HIV and HCV coinfection.

### Hepatitis B Virus

Several abstracts on treatment of HBV extended prior observations on the activity of adefovir, tenofovir, and emtricitabine. The TECOVIR study evaluated serum markers of HBV in a cohort of patients receiving tenofovir as part of their antiretroviral regimen (Abstract 834). HBV DNA was detectable in 88% of the 119 patients at baseline. After a median of 9 months, HBV was undetectable in 32% of patients. In the 3-year follow-up of the adefovir (10 mg/day) study for the treatment of HBV, 46% of patients had undetectable HBV DNA (Abstract 835). Increased duration of treatment was associated with an increased response, and not with rebound or viral resistance to adefovir. In a study of patients with HBV who enrolled in an emtricitabine-containing antiretroviral treatment trial, 82% of the 24 patients had a 5-log reduction in HBV DNA (Abstract 836).

## Other Coinfections: HSV, Malaria, and Tuberculosis

A session dedicated to global AIDS led off with 2 excellent mini-lectures covering herpes simplex virus (HSV) and the global epidemiology of HIV (Abstract 142) and the interaction between HIV and malaria (Abstract 143). Despite the prevalence of these infections worldwide and their copresence in HIV-infected persons, they have received relatively little attention. In her overview of HSV and HIV, Celum pointed out that numerous epidemiologic studies have found a link between the prevalence of HSV-2 and the risk of HIV acquisition. Across these studies, including the Rakai, Uganda, study of HIV-serodiscordant couples, the presence of HSV-2 in the HIV-uninfected partner was associated with a 2-fold to 4-fold increased risk of HIV seroconversion. Acyclovir prophylaxis is known to reduce HSV recurrence rates. With HSV prevalence rates in many parts of Africa in excess of 60% to70%, prophylaxis of HSV is 1 possible approach to reducing HIV transmission that will be tested in upcoming clinical trials.

Malaria may also play a role in increasing HIV transmission by causing profound anemia (which increases the requirement for blood transfusions where the blood supply is not adequately screened) and by prenatal transmission. Pregnant women and HIV-infected persons with low CD4+ cell counts appear to have more severe malaria. Response to antimalarial treatment in persons with HIV infection is an understudied area, and resistance to current widely prescribed malarial treatment regimens remains a huge challenge for malaria control. As trimethoprim-sulfamethoxazole prophylaxis and antiretroviral therapy programs are initiated in Africa, much needs to be learned about the optimal treatment of coinfection.

HIV and tuberculosis (TB) coinfection was the topic of an epidemiologic study from Rio de Janeiro, Brazil (Abstract 147). The incidence and outcome of HIV and TB were examined from 1995 and 2002 through review of surveillance databases. Temporal trends of AIDS and death paralleled the introduction of antiretroviral therapy. Although there was a slight decrease in the proportion of AIDS patients who developed TB after 1995, between 1999 and 2001 the overall proportion of AIDS patients with TB as a secondary cause of death remained stable at around 18%. TB thus remains a major contributor to mortality in the antiretroviral era in Rio de Janeiro.

The high rates of mortality associated with TB in regions without access to antiretroviral therapy were highlighted in a presentation from Chennai, India (Abstract 764). Among the 95 patients followed up, 42% had died by 24 months. Among the survivors, a second episode of TB occurred in 39%. Results from molecular fingerprinting studies revealed that these cases were all due to reinfection with a second strain of TB.

Interactions between the rifamycins and NNRTIs and PIs complicate the management of patients requiring simultaneous treatment for both HIV and TB. When efavirenz is administered with rifabutin, a dose increase of rifabutin from 300 mg twice weekly to 600 mg twice weekly is recommended to compensate for the effects of efavirenz on rifabutin levels. The effect of this dose adjustment was evaluated in a pharmacokinetic study of 15 HIV-infected patients initiating an efavirenz-based antiretroviral regimen following the start of a rifabutin-containing TB regimen (Abstract 761). With the dose increase of rifabutin to 600 mg, mean area-under-the-concentration-curve (AUC) levels of rifabutin in the presence of efavirenz were similar to levels of rifabutin in the absence of efavirenz. Cmax levels of rifabutin were higher at the 600 mg dose but were not associated with increased toxicity.

Management of HIV and TB disease is also complicated by immune reconstitution syndromes (IRIS). In a retrospective study of 37 patients with HIV and TB in Paris, France, 43% had evidence of IRIS between 1996 and 2001 (Abstract 757). The strongest predictors of IRIS were the presence of disseminated TB (≥2 organs involved), low CD4+ cell count (<200/μL) and high HIV RNA (>100,000 copies/mL). The timing of initiation of antiretroviral therapy in relation to the start of TB therapy was similar between the groups of patients who did and did not experience IRIS. In another study of TB treatment regimens, IRIS was reported in 22% (Abstract 763).

## Complications of Antiretroviral Therapy During Pregnancy

The safety of antiretrovirals for both mother and infant continues to be monitored as more experience is accumulated for the highly effective combination regimens currently being utilized during pregnancy. The preponderance of data presented at the conference suggested that antiretroviral regimens were not associated with increased mortality or toxicity for infants. For pregnant women, concern still exists about the rare but serious hepatitic toxicity associated with nevirapine, particularly for women with high CD4+ cell counts.

The Pediatric ACTG (PACTG)1022 study randomized 38 pregnant women to a nelfinavir- or a nevirapine-containing regimen (Abstract 938). Zidovudine/lamivudine was the nRTI backbone for the regimen. Treatment-limiting toxicity occurred in 1 of 21 nelfinavir recipients and 4 of 17 nevirapine recipients. Hepatotoxicity was the treatment-limiting toxicity in the women receiving nelfinavir and in 3 of 4 of the women receiving nevirapine. One woman receiving nevirapine died of fulminant hepatitic failure. This woman had normal liver enzyme levels at the start of therapy and did not have HBV or HCV infections. The fourth woman who had nevirapine toxicity developed a Stevens-Johnson syndrome. All of the women with nevirapine treatment-limiting toxicity had CD4+ cell counts of greater than 250/μL at the time of therapy initiation. Although this study had small numbers and differences were not statistically significant, the trial will be modified in view of the recent warning letter about potential for increased nevirapine toxicity in women with CD4+ cell counts above 250/μL.

Another small study from the United States failed to detect increased risk of toxicity from nevirapine administered during pregnancy (Abstract

939). This was a retrospective study of 41 pregnant and 221 nonpregnant women who received nevirapine. The median CD4+ cell count was 474/µL for the pregnant women and 289/µL for the nonpregnant women. Serious adverse events occurred more frequently in the nonpregnant women (6.5%) than in the pregnant women (0%). There were no deaths reported.

Two studies examined the relationship among nRTI use, pregnancy, lactic acid elevations, and adverse outcomes among infants. The first study compared 100 children born to HIV-infected mothers with 24 children born to HIV-uninfected mothers (Abstract 941). Elevated lactate levels (2.5 mmol/L or higher) were present in approximately two-thirds of children born to HIV-infected mothers, compared with none of the children born to HIV-uninfected mothers. All elevated lactate levels returned to normal after 3 months, and no children developed neurologic symptoms during the follow-up period. In a second study from Italy, 53 infants born to HIV-infected mothers were compared with 20 infants born to HIV-uninfected mothers (Abstract 942). In contrast to the prior study, elevated lactate levels were detected among 20 infants born to HIV-uninfected mothers (40%) at a frequency similar to infants born to 53 HIV-infected mothers. Among the 53 infants born to HIV-infected mothers, 21 were exposed in utero to 2 nRTIs, and 32 to potent antiretroviral therapy. A higher proportion of infants born to HIV-infected mothers had lactate levels above 5 mmol/L compared with controls, but all elevated lactate levels in both groups resolved by 6 months. There were also no differences in mitochondrial PBMC DNA content between the groups. Similar to the first study, there were no clinical abnormalities detected.

Finally, two large studies examined the frequency of prematurity/low birth weight outcomes among women receiving antiretroviral therapy during pregnancy. The first study analyzed data from more than 23,500 pregnancies from the US-based Antiretroviral Pregnancy Registry, which formed in 1989. There was no difference in the frequency of low birth weight infants (<2500 g) or prematurity (<37 weeks' gestation) born to women receiving a PI-containing regimen versus a non-PI-containing regimen. There was a small increase (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.02-5.39) in very low birth weight (<1500 g) infants, but the overall incidence of this complication was low (3% vs. 1%). In a European Collaborative Study, pregnancy outcomes in 1415 women were evaluated in 9 countries from 1998 to 2002. The proportion of premature births increased: from 14% between 1994 and 1997 to between 27% and 31% between 1998 and 2002. Very low birth weight infants increased from 0.5% to 6% during these same intervals. Although the conclusion of this study differed from the US study, there was discussion during the session regarding potential confounding factors that may have influenced the findings from the later study.

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**Conference Abstract numbers, titles, and authors appear at the end of the issue.**

## Additional Suggested Reading

Hadigan C, Yawetz S, Thomas A, Havers F, Sax PE, Grinspoon S. A randomized, double-blind, placebo-controlled study of rosiglitazone for patients with HIV lipodystrophy. [Abstract 50.] 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment. July 13-16, 2003; Paris, France.

McComsey GA, Ward DJ, Hessenthaler SM, et al. Improvement in lipoatrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: the results of the TARHEEL study. *Clin Infect Dis.* 2004;38:263-270.

Carr A, Workman C, Smith DE, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipoatrophy: a randomized trial. *JAMA*. 2002; 288:207-215.