Complications of HIV Disease and Therapy

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Metabolic Complications

As in past years, there was a great deal of new information on metabolic complications at the 9th Conference on Retroviruses and Opportunistic Infections. In contrast to prior years, there were no plenary lectures or symposia; instead, the data this year were concentrated in the posters, late breakers, and a slide session. In this review, the new information is summarized by topic, with an emphasis on data that may have direct clinical application.

Diabetes

What is the risk of diabetes in HIV infection? Several presentations addressed the incidence of and risk factors for the development of diabetes in patients with HIV infection. Yoon and colleagues conducted a matched case-control study to examine risk factors for diabetes in a group of age-, sex-, and race-matched HIV-infected patients (Abstract 678-T). Although protease inhibitor use and hepatitis C virus (HCV) coinfection appeared to contribute to the risk of diabetes, only body mass index, family history, and alanine aminotransferase level were associated with diabetes mellitus in a multivariate model. Using the MediCal claims database, Currier and colleagues examined age- and sex-specific rates of diabetes in HIV-seropositive adults compared with HIV-uninfected adults (Abstract 677-T). They reported an overall incidence rate of 10.68 per 100 person-years of observation for those with HIV infection compared with 2.91 per 100 person-years of observation for the HIV-uninfected group, yielding a

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relative risk of 3.32. This increased risk of diabetes was seen in both men and women and in all age groups. No information about the effect of HIV therapy on diabetes rates was included in this analysis.

Mehta and colleagues (Abstract 679-T) examined the effect of highly active antiretroviral therapy (HAART) and HCV infection on the development of diabetes among patients on a first HAART regimen at the Hopkins Moore Clinic (Table 1). Although diabetes was more common among the HCV-coinfected patients, the presence of HCV did not appear to increase the risk of incident diabetes among those receiving HAART. In a multivariate analysis, the development of diabetes was associated with older age, African-American ethnicity, and failure to gain weight during HAART.

How should patients with HIV infection be screened for diabetes? Falutz and Gardiner (Abstract 676-T) examined this issue in a prospective assessment of several screening tests for diabetes in 32 HAART-treated patients. They compared the oral glucose tolerance test to measurements of fasting insulin and glucose, with calculation of the homeostasis model assessment (HOMA) score (fasting insulin × fasting glucose/22.5). Overall, 9 (28%) of 32 patients had impaired glucose tolerance as measured by the oral glucose tolerance test. Of these 9 patients, only 3 had impaired fasting glucose, 5 had elevated fasting insulin, and 5 had an elevated HOMA score. A total of 8 of the 32 patients had a HOMA score above 4.0, and 6 of those 8 had abnormal oral glucose tolerance test results. The results of this study confirm prior observations demonstrating that fasting glucose measurements alone will miss cases of diabetes. At the current time, oral glucose tolerance testing remains the best option for screening for diabetes in this population. The optimal frequency for use of this test in clinical practice remains to be determined.

Lipid Abnormalities

To date, most of the data comparing lipid profiles among patients receiving currently available antiretroviral agents have been generated in cross-sectional studies. It was encouraging to see more prospective data emerge this year. Gatell and colleagues (Abstracts LB17 and 699-T) reported the results of a Spanish switch study. Patients with viral suppression on a protease inhibitor-based regimen were randomized to substitute the protease inhibitor component with abacavir, nevirapine, or efavirenz, allowing the first head-to-head comparison of the lipid effects within the same trial. After 48 weeks of follow-up, the proportion of patients with triglyceride levels above 400 mg/dL was lowest in the abacavir arm compared with the efavirenz or nevirapine arms. In addition, while mean total cholesterol levels were lowest in the abacavir arm, high-density lipoprotein (HDL) cholesterol values rose only in the nevirapine and efavirenz arms. The results of this study suggest that abacavir has less of an impact on triglyceride and total cholesterol levels than nevirapine or efavirenz, but that the elevations in total cholesterol levels seen in the nonnucleoside reverse transcriptase inhibitor arms are offset by an increase in HDL cholesterol level not observed for abacavir.

Kumar and colleagues (Abstract 33) presented the results of a prospective study comparing the lipid effects of 3 regimens in treatment-naive patients. The study arms were lamivudine/zidovudine (fixed dosage) and abacavir, lamivudine/zidovudine (fixed dosage) and nelfinavir, and stavudine/lamivudine/nelfinavir. The primary endpoint of this trial was change in lipid parameters at 48 weeks. Importantly, this 258-patient study included a diverse patient population (50% women, 36% African Americans, and 40% Hispanics). After 48 weeks of follow-up, the increases in total cholesterol, LDL cholesterol, and

Table **1.** Overlapping Incidence Rates for Diabetes Among Patients on Their First Antiretroviral Therapy Regimen

Group	Incidence of Diabetes per 100 Person-Years of Observation (95% CI)
Overall	4.0 (2.8-5.6)
Protease inhibitor users	4.7 (3.2-6.8)
NNRTI users	2.6 (0.9-8.2)
HCV-seronegative	4.1 (2.4-6.1)
HCV-seropositive	4.6 (2.8-7.5)

CI indicates confidence interval; HCV, hepatitis C virus; NNRTI, nonnucleoside reverse transcriptase inhibitor. Adapted from Mehta et al (Abstract 679-T).

triglyceride levels were greater in the nelfinavir-containing arms than in the triple nucleoside reverse transcriptase inhibitor (nRTI) arm. In addition, within the nelfinavir-containing arms, those who received stavudine were more likely to experience increases in triglyceride and total cholesterol levels than those who received zidovudine. Interestingly, this increase in triglyceride and cholesterol levels was driven by increases seen in the men and not the women in this study.

Additional prospective data on the lipid profiles of patients receiving the investigational protease inhibitor atazanavir or nelfinavir were reported from 2 ongoing prospective trials (Abstract 706-T). The median percent increase from baseline for triglycerides was 2% to 7% among atazanavir recipients compared with increases of 42% to 50% for nelfinavir recipients. Increases in total cholesterol levels ranged from 5% to 7% for atazanavir, which were also lower than the 25% to 28% increases seen with nelfinavir.

The limited data that exist on the efficacy of statins and fibrates for managing hyperlipidemia in the setting of HIV therapy have been disappointing. Niacin has not been extensively studied because of concerns that this drug may worsen insulin resistance. Fessel and Follansbee examined the impact of niacin (median dose, 3000 mg/d) in a group of protease inhibitor-treated patients with hyperlipidemia and central fat accumulation (Abstract 703-T). After an average of 1 year of niacin therapy,

intra-abdominal fat as measured by single-slice computed tomography (CT) was reduced in 13 patients (81%), with an average loss of 26% intra-abdominal fat. The percentage decrease in intra-abdominal fat was associated with an increase in HDL level and a decrease in the total cholesterol/HDL ratio. No data on insulin resistance was reported. These preliminary results suggest a possible role for niacin for the management of hyperlipidemia in HIV infection. Confirmation of the impact on intra-abdominal fat and more information about insulin resistance is needed from larger studies.

Cardiovascular Disease

Several presentations this year addressed the ongoing concern regarding risk of cardiovascular disease in patients with HIV infection. Dubé and colleagues (Abstract LB10) demonstrated changes in endothelial function (reduced flow mediated dilatation in the femoral artery) among HIV-uninfected patients receiving short-term indinavir therapy. The long-term consequences of these changes are unknown.

Klein and Hurley updated previously reported data on rates of hospitalization for men enrolled in the Kaiser Permanente insurance program (Abstract 696-T). As in the past, overall myocardial infarction (MI) rates were higher in the HIV-seropositive group than in the HIV-seronegative group, but no differences between protease inhibitor recipients and non-protease

inhibitor recipients could be demonstrated. The distribution of cardiovascular risk factors was compared by HIV serostatus and the most notable finding was the higher rate of smoking in the HIV-infected group than in the non-HIV-infected group.

HIV Outpatient Study (HOPS) investigators also looked at MI rates within their HIV-seropositive cohort (Abstract 698-T). The MI rate for protease inhibitor recipients was 1.2 per 1000 person-years of observation, which was statistically significantly higher than the rate in patients not treated with protease inhibitors (0.5 per 1000 person-years of observation). This difference persisted after control for age, sex, smoking, and diabetes. It should be noted that the overall MI rate in this study was low and that most of the 15 patients who had events had other risk factors for cardiovascular disease.

The final word on this topic at this year's conference came from Bozzette's late-breaker presentation of rates of cardiovascular and cerebrovascular disease among 36,766 HIV-infected US veterans (Abstract LB9). Use of antiretroviral therapy (defined by class of agents) and rates of admission or death attributable to cerebrovascular and cardiovascular disease were analyzed from January 1993 through June 2001. There were several striking findings. Most importantly, all-cause mortality fell from 18 per 100 person-years of observation to 5 per 100 person-years of observation during this time frame (presumably because of the use of antiretrovirals). In addition, rates of cerebrovascular and cardiovascular disease remained stable or declined along with the introduction of HAART. Although there was no available comparison with HIV-uninfected, matched patients from the Veterans Affairs medical system, these results provide some reassurance that at least over the short term, there does not appear to be an increase in the risk of cardiovascular or cerebrovascular events in the Veterans Affairs patient population.

Collectively, further follow-up of all of these cohorts will be needed to determine the longer-term cardiovascular risks of HIV infection and the metabolic changes associated with current treatments. Until these data are available, clinicians should continue to weigh the

uncertain metabolic risks against the known benefits of HIV therapy.

Lipodystrophy

Proposed Case Definition. Carr presented the preliminary results from a multisite international lipodystrophy case definition study (Abstract 31). In this study, 1081 consecutive patients at 32 sites were evaluated by a physician and were questioned regarding the presence of 1 or more signs of lipodystrophy. The patient and physician assessed each body site and rated whether fat accumulation or atrophy was absent, mild, moderate, or severe. If the physician and patient agreed that the patient had 1 or more moderate or severe features of lipodystrophy, the patient was considered to be a case. When the patient and physician could not agree, the patient was considered non-assigned. All patients were prospectively evaluated with dual-energy x-ray absorptiometry (DEXA) scans and blood samples in addition to detailed case histories.

Of the 1081 patients enrolled, 417 were characterized as cases, 371 as controls, and 288 were non-assigned. The analysis then identified factors that distinguished cases from controls and a point system was developed to help characterize patients. A model was developed to calculate a lipodystrophy score that had a sensitivity of 79% and a specificity of 80%. The variables included in this model are both demographic characteristics (eg, age, sex, duration of HIV infection) and clinical features. The authors plan to make this model available on a Web site to allow clinicians to calculate a lipodystrophy score in clinical settings (A. Carr, personal communication).

Although it is very encouraging to see progress in the development of a method to characterize patients, the inclusion of both subjective and objective measures in the proposed case definition does not answer the question of what constitutes lipodystrophy. Studies that include an age-matched, HIV-infected control group will help to further define the clinical features that are specific for a diagnosis of lipodystrophy. Objective measures of the component physical findings (lipoatrophy and fat accumulation) as measured by DEXA

and CT are required to characterize patients in prospective studies, especially those studies that are evaluating interventions for the treatment or prevention of these problems.

Role of Adipocyte Hormones in Pathogenesis. The adipocyte hormones leptin and adiponectin are thought to help regulate fat deposition. Prior studies have yielded conflicting results about the levels of these hormones and their possible role in the development of lipodystrophy. Kosmiski and colleagues (Abstract 40) examined the relationship between plasma levels of leptin and adiponectin in patients with or without lipodystrophy. In addition to assessing body composition using DEXA and CT, insulin sensitivity was measured using a dynamic test, the frequently sampled intravenous glucose tolerance test. Leptin levels were significantly higher and adiponectin levels significantly lower in subjects with lipodystrophy than in controls. Leptin levels correlated with measures of body fat, and adiponectin levels correlated with the presence of insulin resistance. The cross-sectional nature of this study makes it difficult to determine the causal relationship between adiponectin deficiency and the development of insulin resistance. Prospective studies, using the same types of methods employed in this well-designed study, are needed to further these observations and determine the role of adipocyte hormones in the pathogenesis of lipodystrophy.

Distinguishing Lipodystrophy From Wasting Associated With Tuberculosis. How do the body shape changes associated with lipodystrophy compare with what occurs during acute opportunistic infections? Paton and colleagues from Singapore (Abstract 687-T) examined this issue by comparing appendicular (limb) and trunk fat and lean mass as measured by whole-body DEXA in HIV-infected patients with active tuberculosis (TB; n=11) or with lipodystrophy (n=12) and in clinically stable patients with no lipodystrophy or opportunistic infections (n=24). Appendicular fat mass was lower in the patients with lipodystrophy and TB than in the stable HIV group, but trunk fat was lower among those with TB

and unchanged in the lipodystrophy group compared with controls. The ratio of appendicular fat to total body fat increased in the TB group (0.58) and decreased in the lipodystrophy group (0.39) compared with the HIV controls (0.50). The ratio of appendicular lean mass to total body lean mass was decreased in the TB arm (0.38) and unchanged in the lipodystrophy arm (0.42) and HIV controls (0.41). These results demonstrate the utility of whole body DEXA in distinguishing patients who may have peripheral lipoatrophy due to wasting from those with lipodystrophy. In addition, these findings suggest a role for DEXA scanning in determining a definition for lipodystrophy.

Stage of Disease and Risk. Lichtenstein and colleagues reported further analysis of the HOPS cohort at this year's meeting (Abstract 684a-T). They limited the analysis to examining the incidence and risk factors for the development of moderate to severe lipoatrophy. The incidence of lipoatrophy was highest among patients who had a prior CD4+ count of less than 100 cells/μL. The prevalence of moderate to severe atrophy was 30.8% among subjects with minimum and maximum CD4+ counts below 200 cells/μL, compared with 3.8% for those with minimum and maximum values all greater than 350 cells/μL. These differences persisted after controlling for time on antiretroviral therapy. These results suggest (as prior analyses from this group have suggested) that stage of HIV infection may play a role in the pathogenesis of lipoatrophy. Prospective observations of patients who have initiated therapy at higher and lower CD4+ cell counts are needed to confirm these findings. If confirmed, these results have implications for the "when to start therapy" debate.

Interventions. A current paradigm that has emerged to explain the association between HIV therapy and fat accumulation and fat atrophy includes a role for both protease inhibitors and for nRTIs. It has been shown that protease inhibitors induce insulin resistance in vitro and in vivo, which in turn might lead to fat accumulation. In addition, it has been proposed that mitochondrial toxicity induced by nRTIs leads to fat wasting

and when protease inhibitors and nRTIs are combined, this is accelerated, possibly because of fat cell apoptosis. Studies have been designed to try to test these hypotheses, and preliminary data from several studies were presented.

Three different approaches to examine the risks and benefits of switching out the nRTI component of a triple-drug regimen were reported this year. In the MITOX study led by Carr, patients with clinically apparent lipoatrophy and viral suppression on a protease inhibitor-containing regimen with either zidovudine or stavudine were randomized to substitute the nRTI with abacavir or remain in the same triple-drug arm (Abstract 32). At 24 weeks, a small (10%) but statistically significant increase in arm fat was seen in those who made the switch. This increase in limb fat was not detectable by the physicians in the study and did not impact quality of life. Among those who switched, 10% developed abacavir hypersensitivity. Further follow-up of the group is planned to see if longer time is needed to observe clinically significant improvements.

In the TARHEEL study led by McComsey (Abstract 701-T), stavudine recipients who were experiencing either lipoatrophy, symptoms of hyperlactatemia, or lactate levels above 3.2 mmol/L substituted stavudine with either abacavir (if zidovudine-experienced) or zidovudine and lamivudine (if zidovudine-naive). All 118 subjects underwent prospective evaluations of lactate and DEXA measurements for body composition. After 24 weeks of follow-up, median increases in arm (25%), leg (6%), and trunk (9%) fat were reported that were also noticeable by patient self-report. The absolute increase in arm fat in this study was similar to what was observed in the study by Carr and colleagues. No statistical analysis of these changes was reported.

Mallal reported the results from a smaller study (n=40) in which patients with viral suppression on a stavudine-containing regimen were randomized to switch to the triple nRTI regimen of zidovudine, lamivudine, and abacavir or remain on the original therapy (Abstract 700-T). At 48 weeks of follow-up, statistically significant increases in limb fat by DEXA were more apparent for the arms than the legs and were again on the same order of magnitude (ie, small) as the other switch studies. Collectively, these studies are very important in that they demonstrate that lipoatrophy may be reversible (albeit slowly) and that nRTI therapy alone may not be the sole cause of lipoatrophy (as evidenced by the Mallal study, where patients who switched off the protease inhibitor and stavudine appeared to have greater benefit). Long-term results from these studies are eagerly awaited.

Agents that improve insulin sensitivity are currently under intensive investigation to probe the pathophysiology of fat accumulation and lipoatrophy. The 2 agents that top the list of candidates are metformin and rosiglitazone. Sutinen presented the first randomized prospective data evaluating rosiglitazone for treatment of lipodystrophy (Abstract LB13). In this study, 30 stable HAART-treated patients with self-reported body shape changes (confirmed by the investigator) were randomized to receive rosiglitazone or matching placebo. Objective measures of subcutaneous fat by magnetic resonance imaging and serum samples for lipids and insulin were collected. After 24 weeks, despite improvements in insulin sensitivity, there was no change in subcutaneous fat or in the waist-to-hip ratio measurements. Interestingly, the percentage of liver fat appeared to decrease in the rosiglitazone group and increase in the placebo group.

Despite the small size of the study, the absence of any insulin resistance entry criteria, and the short follow-up time, the negative results of this study were clearly disappointing. In addition, the safety issues identified in this study with the 8 mg dose of rosiglitazone (early elevations in triglycerides and development of anemia) should be noted. Given these results, it will be critical to see if other ongoing studies evaluating the impact of rosiglitazone on visceral fat in subjects with insulin resistance show a benefit.

The collective results of studies to evaluate interventions for lipodystrophy seem to indicate that this process is multifactorial and that no one approach will be sufficient to reverse changes that have developed over years. Efforts to identify combinations of antiretroviral agents with the lowest risk of promoting these changes in treatment-naive patients are urgently needed while the work continues to identify the mechanisms by which antiretroviral drugs facilitate these changes.

Lactic Acidosis

Lactic acidosis remains a rare but serious adverse effect of nRTI therapy. A late-breaker presentation made the point that severe neuromuscular weakness may accompany lactic acidosis, but the relationship between these findings is uncertain. Marcus and colleagues reviewed US Food and Drug Administration (FDA) records and the literature after a report of a cluster of cases of profound motor weakness associated with lactic acidosis was submitted to the FDA in 2001 (Abstract LB14). They searched for reports of lactic acidosis in HIV-infected patients receiving antiretroviral therapy. There were 25 cases, 7 of which were fatal. The nRTI therapy was not interrupted promptly in 6 fatal cases and in 12 additional cases. In the same presentation, 8 cases of pancreatitis and/or lactic acidosis in pregnant women were reported. Seven women were taking didanosine plus stavudine, and 3 of these women died. This report underscores the risk of this combination in pregnant women.

Much more common than lactic acidosis is asymptomatic or mildly symptomatic elevations in lactate levels. Cross-sectional studies presented at the conference reported an incidence of elevated lactate levels in the 5% to 10% range (Abstracts 710-T and 711-T). Predictors of elevated lactate levels included duration of nRTI use and age. Data from longitudinal studies in adults suggested that fluctuations in lactate levels are very common over time and that the predictive value of asymptomatic elevations in lactate for progression to lactic acidosis is very low. Brinkman estimated that the incidence of clinically significant hyperlactatemia was 11 per 1000 person-years on antiretroviral therapy (Abstract 709-T). Lonergan presented an analysis of the predictors of symptomatic hyperlactatemia (Abstract 35). His case definition was abdominal symptoms or elevation of liver enzymes in the presence of a confirmed elevation in lactate. A greater number of nRTIs in

the regimen was associated with a higher risk of developing the syndrome. Highest rates were observed in patients receiving stavudine, abacavir, and lamivudine and stavudine, didanosine, and lamivudine. In the pediatric population, elevated lactate levels were present in over 90% of infants exposed to antiretroviral therapy during gestation (Abstract 113). The clinical significance of this observation is not known.

Bone Disease

As reported previously, bone loss can be found in HIV-infected patients even before treatment with antiretroviral therapy (Abstract 715-T). Bone disease appears more common in patients with low CD4+ cell counts and in those with abnormalities in glucose tolerance (Abstracts 712-T and 716-T). Protease inhibitors are associated with reduced bone mineral density in cross-sectional studies, and indinavir exposure leads to bone loss in a mouse model (Abstracts 713-T and 717-T). In humans, cortical bone is more affected than trabecular bone. Data from cross-sectional studies are conflicting on the contribution of protease inhibitors to bone disease. Mondy and colleagues (Abstract 718-T) reported the results of one of the first prospective studies of bone mineral density. After 1 year of follow-up there was a slight improvement in bone mineral density among carefully monitored patients receiving protease inhibitor regimens. Clearly, longer-term data in larger population bases are needed to more fully understand this complication of HIV disease and perhaps therapy. Notably absent were any studies on approach and treatment to bone disease.

Abacavir Hypersensitivity Reactions

Hypersensitivity reactions (HSR) are an uncommon (5%) but potentially life-threatening complication of abacavir. Postulating that hypersensitivity reactions are immune-mediated reactions influenced by genetic factors, 2 groups of investigators sought to identify genetic predictors of susceptibility to abacavir hypersensitivity. Mallal examined haplotypes in 200 Australians prescribed abacavir (Abstract 91). The presence of HLA-

B*5701 and DRB1*0701 + DQ3 had a positive predictive value of 100% and a negative predictive value of 97%. In a second case control study of 200 subjects participating in clinical trials of abacavir (Abstract 92), HLA-B57 was present in 46% of cases versus 3% of controls (P<.001). These studies are very important and illustrate that in the future, clinicians may be able to use genetic testing to individualize drug regimens. Much more work needs to be done on broader patient populations before these findings are incorporated into practice; however, existing databases may facilitate this process in this rapidly moving and exciting field.

Hepatitis and Opportunistic Infections

Hepatitis Coinfection

This year, presentations on pathogenesis and treatment of HIV and hepatitis coinfection represented one of the high points of the meeting. There were randomized treatment trials and accompanying studies of viral dynamics as well as interesting studies on pathogenesis of HIV and hepatitis. Early outcomes of liver transplantation in the hepatitis-infected HIV population were presented. There was a standing-room-only symposium on HIV and hepatitis coinfection with Peters, Thomas, Ray, and Chung providing superb overviews of the field (Abstracts S13-S16).

Chung and colleagues presented 24-week data from a randomized study of pegylated interferon alfa-2a and ribavirin versus interferon alfa-2a and ribavirin for the treatment of HCV coinfection (Abstract LB15). Virologic response rates (HCV RNA <60 IU) were higher in the pegylated interferon alfa arm (44%) than in the interferon alfa group (15%). About a third of all virologic nonresponders exhibited histologic improvement on liver biopsies. CD4+ cell counts declined in both arms, but there were no changes in HIV RNA suppression. In this cohort, declines in HCV RNA could be fitted to biphasic decay curves, with faster phase I decay rates present in the pegylated interferon alfa-2a group (Abstract 122). Defining optimal treatment regimens and predictors of response will be enhanced by additional

follow-up in this cohort, incorporating relapse rates in the overall response rates.

Torriani (Abstract 121) presented early HCV RNA dynamics from another ongoing study of patients treated with combinations of interferon alfa-2a, pegylated interferon alfa-2a, and ribavirin. She reported a single phase of decay in HCV RNA levels and also observed declines in liver enzymes (ALT levels) that paralleled reductions in HCV RNA levels.

Sulkowski (Abstract 651-M) presented the 12-week results of a randomized treatment trial of daily versus thrice-weekly interferon alfa-2b, both given with ribavirin, in HCV/HIV coinfected persons. Early virologic response rates (undetectable serum HCV RNA) were higher in the daily dosing (25%) group than in the thrice-weekly (10%) group. Up to a quarter of patients in both arms discontinued therapy prematurely. Another randomized study was presented by Perez-Olmeda (Abstract 653-M). Subjects (n=111) were randomized to thrice-weekly interferon alfa plus daily ribavirin versus a 6-week course of interferon alfa and ribavirin followed by thrice-weekly interferon alfa and daily ribavirin. The sustained response rate was 23% and did not differ between arms. Interestingly, the reduction in HCV RNA level at 1 month was not predictive of a sustained response, as delayed reductions in HCV RNA levels were observed in some responders.

Taken together, these data suggest that continuous exposure to interferon alfa is associated with greater early response rates, but tolerance of the therapy is difficult for a significant proportion of patients. Despite good adherence, a substantial number of patients do not respond to available therapies. More data are needed to characterize the dynamics of HCV clearance and rebound and to better define predictors of response and determinants of failure.

Progress in the treatment of hepatitis B virus (HBV) infection was encouraging. In a randomized study of 3 doses of emtricitabine for the treatment of HBV in HIV-infected patients (Abstract 674-M), 61% of patients receiving the highest dose (200 mg daily) had undetectable viremia after 1 year of therapy. Half of the HBV e antigen-positive

patients in this group became HBV e antigen-negative. Among virologic non-responders, the incidence of the YMDD mutation was 6%.

Efficacy of adefovir and tenofovir disoproxil fumarate (tenofovir) against HBV was demonstrated in cohorts of patients receiving antiretroviral therapy in which one of these agents was added to the regimen. In the 907 trial (Abstract 124), HBV levels decreased by 4.6 log in groups randomized to tenofovir (n=12) and increased by 1.2 log in the 2 patients receiving placebo. An open-label study of 10 patients who added tenofovir to their regimen showed similar reductions in HBV DNA levels (Abstract 675-M). In another study of 35 patients, adefovir was added to the regimen of patients already receiving lamivudine who had the YMDD mutation in HBV DNA polymerase (Abstract 123). Serum HBV DNA levels decreased by 5 $\log_{10}$ copies/mL at week 72, and there were improvements in liver transaminase levels and liver histology. Data from an analysis of more than 13,000 patients in the US-based Adult/Adolescent Spectrum of Disease Project suggested that lamivudine may have some protective effects against HBV (Abstract 672-M). In this study, HBV vaccine and lamivudine were associated with a lower risk for development of acute HBV infection.

In HIV-infected patients who have advanced liver disease due to either HBV or HCV, liver transplantation has been performed at a small group of centers. In a summary of the experience of 23 patients, HCV was associated with a worse prognosis (Abstract 125). Overall, control of HIV replication and continued antiretroviral therapy after transplantation was associated with higher survival rates. Roland (Abstract 655-M) evaluated outcome in 23 patients who received either a liver or kidney transplant. Overall, there was a 30% rejection rate and 1 death. Better prognosis was observed in patients with higher CD4+ cell counts and control of HIV viral replication with antiretroviral therapy. These data will be very useful in developing guidelines for patients most likely to benefit from transplantation, and stress the importance of maintaining optimal control of HIV during the post-transplantation period.

HIV infection accelerates the course of HCV infection, and a similar trend was observed in patients with HBV infection (Abstract 656-M). Data on the influence of hepatitis on outcome of HIV disease are still conflicting. One study by Rimland reported shortened survival time from HIV and AIDS diagnosis in coinfected patients (Abstract 658-M). However, another study of 852 patients in the HOPS cohort found that survival rates in patients with and without HCV coinfection were no different when analyses were adjusted for antiretroviral therapy use (Abstract 659-M). In terms of CD4+ cell count rises in response to antiretroviral therapy, one small study found no effect of HCV coinfection after 1 year of therapy (Abstract 637-M). Two larger studies did report diminished increases in CD4+ cell counts in coinfected patients, which were most pronounced after 2 years of therapy (Abstracts 638-M and 639-M).

Data on hepatitis-specific immune responses and viral replication in various compartments were addressed in several presentations. HCV-specific immune responses appear diminished compared with HIV immune responses in the face of ongoing viral replication (Abstract 640-M). One report by Barrett proposed that induction of interleukin-10 (IL-10) by HCV proteins down-regulates HCV responses (Abstract 641-M). Laskus reported evidence supporting HCV replication in the central nervous system, acknowledging that clinical significance needs further study (Abstract 649-M). HCV can also be found in cervical-vaginal lavage specimens, and Nowicki and colleagues proposed that HCV in this compartment plays a role in sexual and mother-to-child transmission of HCV (Abstract 648-M). One study found much lower levels of HCV in the liver but higher levels in the plasma in patients with HCV and HIV coinfection, than in those with HCV infection only (Abstract 643-M).

GB Virus-C Coinfection

Several presentations focused on the mechanism to explain the epidemiologic observation that patients coinfected with HIV and GB virus-C (GBV-C) have slower rates of HIV disease progression. Nunnari proposed that more intact Th-1

cytokine profiles in patients with GBV-C infection could be contributing to slower HIV disease progression (Abstract 667-M). Differences in chemokine receptor mutations (Abstract 670-M) could not explain mortality differences between patients with and without GBV-C. George and colleagues reported differing in vitro replication capacity among GBV-C isolates (Abstract 668-M) and this same group reported reductions in GBV-C levels in patients who were treated with interferon alfa and also identified a GBV-C protein that may be involved in interferon alfa sensitivity (Abstract 669-M).

Tuberculosis

A symposium on TB provided an excellent overview of challenges of HIV and TB coinfection. Beyers presented molecular fingerprinting data demonstrating that many TB infections are recently acquired and that prolonged exposure is not necessary even in the HIV-uninfected population (Abstract S5). A presentation on TB transmission in Harare, Zimbabwe, underscored the point that many TB infections are recent (Abstract 621-W).

Whalan summarized the current model of HIV and TB copathogenesis (Abstract S6). Efforts to reduce immune activation TB, and hence HIV replication and disease progression, with immunomodulators during TB treatment have been unsuccessful to date. Flynn described the many candidate vaccines that are in the pipeline for TB (Abstract S7). The inability to define components of a protective immunologic response to TB as well as the ease with which latent infection is established and maintained represent 2 formidable obstacles. Maartens presented data on the large experience in Cape Town, South Africa, with HIV/TB coinfection (Abstract S8). He outlined the challenges of delivering HIV and TB therapy in a resource-limited setting. He showed encouraging data that the use of antiretroviral therapy in this setting was associated with dramatic reductions in TB cases. Girardi made the point that atypical presentations of TB occur both in patients with low CD4+ cell counts and in patients with immune reconstitution from antiretroviral therapy (Abstract 623-W).

Discontinuation of Opportunistic Infection Prophylaxis

The major themes of the presentations on discontinuation of opportunistic infection prophylaxis were that HIV-related complications do occur, but rarely in severely immune-compromised patients who have responded to antiretroviral therapy and have discontinued primary prophylaxis (Abstracts 630-W and 631-W). Regarding secondary prophylaxis, 1 in 17 patients with toxoplasmosis (Abstract 633-W), 1 in 48 patients with disseminated *Mycobacterium avium* complex (Abstract 634-W), and 3 of 58 patients with cryptococcal disease (Abstract 635-W) developed recurrent infections after treatment with antiretroviral therapy and discontinuation of secondary prophylaxis.