Complications of HIV Infection and Its Therapies

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The term lipodystrophy has often been broadly applied to describe both body shape changes and other metabolic abnormalities that occur during the course of HIV infection. To date, a standard definition for this term has been elusive but several groups are actively working toward this goal. Many (but not all) of the studies presented at the Conference reflect the growing trend to investigate the components of this syndrome as distinct but possibly related clinical phenomena. Increasingly, objective measures are replacing self-reports and a few randomized studies are beginning to appear. Following this trend, this section of the Conference review is divided into specific metabolic complications (body shape changes, lipid abnormalities, bone disease, lactic acidosis, and cardiovascular disease). New research on antiretroviral switch strategies and hepatitis coinfection are also reviewed.

Body Shape Changes

Data from several cohort studies have identified an association between the duration of HIV infection and the development of body shape changes. At last year's meeting we learned that lipid changes were common in a small group of patients treated during primary infection. Further evidence that patients treated during primary HIV infection are at risk for developing body shape changes was described by Goujard and colleagues (Abstract 403) in their prospective study of 121 patients diagnosed and treated with antiretroviral therapy during primary HIV infection. The presence of "lipodystrophy" was assessed by physical examination. The cumulative incidence of lipodystrophy increased over time, and was reported to be 6% at 12, 18% at 24, and 30% at 36 months. Of note, patients with lipodystrophy tended to have higher CD4+ and CD8+ T cell counts and lower HIV RNA levels at the last visit. These findings suggest a possible role for immune reconstitution in the pathogenesis of these changes.

The prevalence of body shape changes has varied widely in earlier studies, and has rarely been considered in the context of age- and race-matched HIV-uninfected controls. An important report at this year's meeting, by Kingsley and colleagues (Abstract 538), compared the prevalence of body shape changes and lipid abnormalities among HIV-seropositive men grouped by treatment history and among HIV-uninfected men in the Multicenter AIDS Cohort Study (MACS). Body shape changes were characterized as either peripheral fat wasting or central fat accumulation and were stratified into mild, moderate, and severe. The preliminary report focused on physical examination findings and laboratory parameters only and not on patient self-reports. A third of the HIV-seronegative men and 2 thirds of the HIV-seropositive men were noted to have body shape changes.

The finding that best distinguished the groups by their HIV status and treatment history was the combination of moderate or severe peripheral fat wasting and central fat accumulation. The presence of both of these changes was noted among 20% of the men who were treated with highly active antiretroviral therapy (HAART) but in few of those who were not being treated with antiretroviral drugs or who were being treated with monotherapy or combination therapy and in few of the HIV-seronegative controls. The finding of central fat accumulation alone was not more common among HIV-seropositive men than the age-matched control group. In addition, the prevalence of body shape changes appeared to increase with time on HAART (20% at 2 years) but no further increase was noted out to 4 years of follow-up. Metabolic abnormalities that were more common among the men treated with HAART than among the controls were low levels of high-density lipoprotein (HDL) and high triglyceride, glucose, and fasting insulin levels. The prevalence of lipodystrophy among the HAART-treated MACS participants was similar to that reported from a series of patients treated with HAART for the first time (18%) (Rubio et al, Abstract 646). These results highlight the need to include HIV-uninfected control groups in studies of the metabolic complications of HIV infection. The apparent plateau in the prevalence of lipodystrophy over time warrants further investigation.

Several cohort studies have identified an association between exposure to stavudine and an increased risk of developing peripheral fat atrophy. Unfortunately, most of these reports have been limited by their cross-sectional design and the strong correlation between use of stavudine and longer durations of HIV infection. Joly and colleagues (Abstract 539) presented results of the NOVAVIR study, in which patients with prior use of zidovudine, didanosine, or zalcitabine were randomized to receive either stavudine or zidovudine combined with lamivudine and indinavir. Body shape changes were assessed by a physician at one time point approximately 30 months into the study. Importantly, the groups were well matched at study entry in terms of prior nucleoside reverse transcriptase inhibitor (nRTI) use and duration of therapy and by CD4+ cell count and viral load. Subjects assigned to stavudine were more likely to develop fat atrophy than those in the zidovudine arm, and the differences were statistically significant. The proportion of patients with fat atrophy in 2 or more body areas was 44% in the stavudine arm compared to 18% in the zidovudine arm, (P = .003). In addition, female sex was identified as a predictor of a higher risk for fat atrophy. No difference was noted in the prevalence of fat accumulation between groups. Despite the potential bias of an open-label design, these results are strong evidence that stavudine may play a unique role in the development of lipoatrophy. Results from ongoing blinded studies in treatment-naive patients will be important to corroborate these findings.

How do age and race and ethnicity

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influence the risk of developing body shape changes? In adults, older age has been associated with an increased risk of developing body shape changes; unfortunately, this does not mean that children are spared this complication. Several reports of small series of HIV-infected children (Abstracts 649, 650, 651, 652, and 653) described changes both in lipid and insulin levels and in body composition. In one of these reports (Meneilly et al, Abstract 650) the prevalence of body shape changes among children was 18% and an association with stavudine use was identified.

Previous research has identified a higher rate of body shape changes in whites than in blacks or Hispanics. Chang and colleagues (Abstract 648) examined the prevalence of body shape changes and lipid abnormalities in a cross-sectional study of 122 Koreans. As predicted, the insulin and triglyceride levels were higher and the HDL cholesterol levels lower in the HAART-treated patients. However, no difference was noted in the ratio of trunk to appendicular fat (as measured by dual-energy x-ray absorptiometry) between the HAART-treated patients, the treatment-naive patients, and the controls. It was not clear whether the absence of fat redistribution was related to a short duration of HAART therapy; regardless, these results are further evidence that genetics may play a role in the development of abnormal fat distribution.

One of the issues that continue to hinder the study of body shape changes is the need for reliable and low-cost measures of body composition. Andrade and colleagues (Abstract 644) compared an anthropometric measure of body fat (using the Durnin-Wormersley equation) with magnetic resonance imaging (MRI). The main finding of this study was that the calculations of total adipose tissue and subcutaneous adipose tissue with the low-cost Durnin-Wormersley equation correlated best with the MRI findings and that the estimation of visceral adipose tissue using this formula was less accurate. These results have implications for use in prospective studies that are focused on changes in subcutaneous fat. Viciana and colleagues (Abstract 645) compared the measurement by calipers of skin-fold thickness in the cheek adipose area of the face (Bichat's area) with self-reports of facial fat wasting and found a very strong correlation. The correlation between caliper measures and MRI findings and the reliability of the caliper measure to capture changes over time remain to be demonstrated, but these preliminary results hold promise for use in prospective studies.

An entire section of an afternoon poster session this year was dedicated to mechanisms and pathogenesis of the lipodystrophy syndrome. While none of these studies presented in this session were conclusive, they provide evidence that many groups are diligently pursuing several avenues of research toward understanding the pathogenesis of metabolic complications in HIV infection.

A direct etiologic link between mitochondrial injury and body shape changes is yet to be established. One challenge to unraveling this potential pathogenic mechanism is the identification of a reliable measure of mitochondrial function in vivo. Several groups working in this area presented preliminary results at this year's Conference. Shikuma and colleagues (Abstract 665) reported on the use of a semiquantitative analysis of tissue-specific mitochondrial DNA (mtDNA) content from samples of subcutaneous fat in a cross-sectional study. They reported decreased amounts of mtDNA levels among subcutaneous adipose tissue of lipodystrophic individuals treated with nRTI-containing HAART therapy compared to nonlipodystrophic patients or HIV-seronegative controls. Of note, specific mutations in the mtDNA were not found. Vigano and colleagues (Abstract 651) used flow cytometry to examine mitochondrial function by measuring markers of mitochondrial membrane potential and apoptosis in peripheral blood lymphocytes. Signs of mitochondrial toxicity were not present in HAART-treated children with or without lipodystrophy. These preliminary results suggest that peripheral blood lymphocytes, while readily available, may not be the best cells in which to evaluate mitochondrial function in vivo. Further work is clearly needed to make the link between mitochondrial dysfunction and body shape changes in HIV infection.

Alterations in lipid metabolism either as a direct result of protease inhibitor therapy or caused indirectly by HIV infection are also under study. Sekhar and colleagues (Abstract 663) characterized lipid kinetics by conducting stable-isotope studies of triglyceride clearance in 6 HIV-infected subjects with fat redistribution and compared the results with those in age- and sex-matched HIV-uninfected controls. Increased rates of whole body lipolysis as well as decreased rates of triglyceride clearance were identified in the HIV-infected subjects compared to controls. The stimulus for these alterations in lipid metabolism as well as the time course between these changes and the onset of body shape changes remains undefined. Other reports described the greater down-regulation of low-density lipoprotein (LDL) receptors in HIV-infected patients compared to controls (Petit et al, Abstract 661) and in vitro upregulation of scavenger receptor class B, type I (a molecule responsible for the transfer of cholesterol from HDL to cells) by saquinavir and amprenavir in vitro (Smart et al, Abstract 662).

Lipid Abnormalities

Elevations in triglyceride and reductions in HDL cholesterol levels appear to be the predominant lipid abnormalities reported in HIV infection. There is strong evidence that some of the protease inhibitors (specifically ritonavir) directly increase triglyceride levels and that decreased HDL cholesterol levels are a feature of chronic HIV infection. Several studies described the lipoprotein profiles in prospectively collected samples from patients enrolled in antiretroviral studies. Data from the Atlantic study (Van der Valk et al, Abstract 654B) found that nevirapine-treated patients had striking improvements in HDL cholesterol from baseline (37.9 mg/dL) to week 24 (50.4 mg/dL). No improvements were noted in the indinavir- or triple-nRTI–treated patients.

Current interventions to treat lipid disorders include diet, exercise, and the use of lipid-lowering agents. Few prospective randomized trials that evaluate any of these interventions have been reported. Miller and colleagues (Abstract 540) reported the preliminary results of a randomized double-blind study in 38 patients of gemfibrozil for the treatment of protease inhibitor–associated hypertriglyceridemia. After 12 weeks there was a modest reduction in the triglyceride levels in the gemfibrozil-treated group, with no changes in the total cholesterol or HDL cholesterol levels. The small sample size makes it unlikely that the trial would identify a statistically significant effect. Importantly, the treatment was well tolerated. Gemfibrozil therapy may not be sufficient to normalize triglyceride levels in the setting of continued protease inhibitor use; however, the reduction provided may be of some clinical benefit over time.

Bone Disease

At the 7th Retrovirus Conference last year, 2 independent groups reported that antiretroviral therapy was associated with osteopenia and osteoporosis. Many additional reports at this year's Conference expanded on the epidemiology of this complication. Osteoporosis, osteopenia, and avascular necrosis are well documented in the absence of antiretroviral therapy in HIV infection, and their incidence appears to increase with the progression of HIV disease. Whether or how antiretroviral therapy accelerates this process remains controversial.

Negredo and colleagues (Abstract 626) reported that antiretroviral therapy was associated with increased risks for osteopenia and osteoporosis. Other reports emphasized that untreated HIV infection is also associated with bone disease (Abstracts 627, 628, 629, and LB8). These relatively small cross-sectional studies could not demonstrate a relationship between antiretroviral therapy and bone disease. Lawal and colleagues (Abstract 627) reported that the rates of osteopenia in antiretroviral-treated and untreated patients with HIV infection did not differ, but were significantly higher than those in matched HIV-uninfected individuals. Similar findings were reported in a cross-sectional study by Knobel and colleagues (Abstract 629) of 80 HIV-infected subjects. Baseline assessments of 151 treatment-naive patients participating in a tenofovir trial by McGowan and colleagues (Abstract 628) found that the criteria for osteopenia were met in 23% of the subjects.

In a cross-sectional case control study of bone mineral density (BMD) reported in the Late Breakers session (Arpadi et al, Abstract LB8), rates of bone disease were significantly higher in the perinatally infected children (aged 4 to 15 years) than in age-matched HIV-uninfected controls. The duration of HIV infection, but not of antiretroviral therapy, was the most important predictor of BMD changes. In a cross-sectional study of 40 children, Vigano and colleagues (Abstract LB9) used a combination of serum markers for bone turnover and imaging techniques to show that bone demineralization was higher in children treated with antiretroviral therapy than in those not treated. In view of other data presented at the Conference, interpretation of these findings was limited by the small size (5 subjects) in the antiretroviral-naive group.

Avascular necrosis is a less frequent, but nonetheless serious, complication of HIV disease. Increasing rates of avascular necrosis were observed in the Johns Hopkins HIV Clinic Cohort and were greater than those reported in HIV-uninfected individuals (Keruly et al, Abstract 637). Low CD4+ cell count, greater duration of HIV infection, and use of steroids (but not antiretroviral therapy) were associated with increased rates of disease. History of protease inhibitor use was present in 3 cases of Legg-Calvé-Perthes disease reported in the Pediatric AIDS Clinical Trials Group Protocol 219 observational cohort of more than 1000 children (Gaughan et al, Abstract 638). The absence of protease inhibitor use at the time of diagnosis in 2 of the 3 cases suggests that factors other than protease inhibitors are responsible for this disease.

Within cohorts of patients receiving antiretroviral therapy, several investigators have attempted to determine the risk factors for osteopenic disease, including elevations in lactic acid levels or the presence of lipodystrophy. The results of these studies have been conflicting. Carr and colleagues (Abstract 631) reported lower BMD among individuals with lower lean body mass, greater exposure to stavudine, and greater age. Reductions in spinal BMD were associated with hyperlactemia, age, and nRTI treatment duration. Huang and colleagues (Abstract 632) reported reductions in BMD among subjects with increased visceral fat due to antiretroviral therapy use. In contrast, a study by Tebas and colleagues (Abstract 633) did not find an association between intraabdominal fat accumulation and reductions in lumbar spine BMD. In a study by Claxton and colleagues (Abstract 634) monitoring subjects with osteopenia who were switched from a protease inhibitor to a nonnucleoside reverse transcriptase inhibitor (NNRTI) regimen, lactate levels at baseline were not associated with reduced BMD and switching therapy was not associated with changes in bone disease. Growth hormone had no apparent effect on BMD in one small study of 12 subjects (Lawal et al, Abstract 635).

Lactic Acidosis

The syndrome of lactic acidosis has gained increasing attention over the past several years as a complication of nRTI use, but our understanding of this complication is still very incomplete. In a state-of-the art summary of the "Metabolic Complications of HIV-1 Disease" session (Session 64), Dr Andrew Carr proposed a classification scheme for the spectrum of hyperlactemia that has been recognized to date. Individuals with lactate levels greater than 10 mmol/L have "severe" disease, are acidotic, and have highly symptomatic disease. Patients with lactate levels between 5 and 10 mmol/L have "moderate" disease, are rarely acidotic, and are only sometimes symptomatic. Those with lactate levels between 2 and 5 mmol/L have "mild" disease and are neither acidotic nor symptomatic. He estimated that only 2% to 3% of patients with any elevation in lactate levels have symptomatic acidemia. Studies to date point to stavudine use as a risk factor for hyperlactemia, although other nRTIs have also been associated with both mild and severe forms of the disease. In the Perth cohort, Dr Carr reported that elevated lactate levels have been associated with faster progression to lipodystrophy, peripheral neuropathy, and osteopenia. This observation needs to be confirmed in other cohort studies, and causality cannot be assumed.

Asymptomatic elevations in lactate levels were the focus of a study by Vrouenraets and colleagues (Abstract 625). Similar to the findings in previous reports, mild hyperlactemia was observed in 21% of nRTI-treated individuals. The authors emphasized that fluctuations over time in patients with mild elevations are common. Observational longitudinal studies are needed to determine whether such elevations predict drug toxicity before clinicians incorporate this test in routine monitoring of patients.

Lonergan and colleagues (Abstract 624) presented data addressing a very practical management question in patients who develop the symptomatic moderate or severe form of disease: Can nRTIs be safely reintroduced in these patients? In 16 of the 17 subjects in their study stavudine was replaced with abacavir (10 subjects), zidovudine (2 subjects), or both (4 subjects) after a period of therapy interruption. Resumption of therapy has not resulted in syndrome recurrence for a period of 6 months.

Cardiovascular Disease

The concurrence of fat redistribution, lipid abnormalities, and insulin resistance has focused attention on the risk of cardiovascular disease in the setting of HIV infection. Updated reports of ongoing cohort studies tracking the rates of myocardial

infarction (MI) provide little comfort in this regard. Klein and colleagues (Abstract 655) are recording and analyzing the rates of hospital events for coronary heart disease in an open-label-treated cohort of 4541 HIV-seropositive patients and in a group of 41,000 age- and sex-matched controls. With follow-up of now just over 4 years there appears to be no difference in the rates of MI between protease inhibitor–exposed and –unexposed HIV-seropositive subjects. Of greater concern is the finding that the HIV-seropositive group appears to have twice the rate of coronary heart disease compared to the uninfected controls. Whether this could be attributed to unmeasured risk factors (eg, smoking, family history, hypertension) that are more prevalent in the HIV-infected group merits further study. In a similar type of study, researchers (Mary-Krause et al, Abstract 657) analyzed data from the French Hospital Database on HIV on the rates of MI among men observed prospectively since 1989. The incidence of MI per 10,000 person-years appeared to increase with a longer duration of protease inhibitor exposure. The relative hazard of developing an MI in those with more than 30 months of protease inhibitor exposure was 4.7 (95% confidence interval, 0.5–45.4). Once again, the contribution of other risk factors, such as smoking and hypertension, is not accounted for in this type of study. (See also Depairon et al, AIDS, 2001.)

Hypertension is an important risk factor in cardiovascular disease. Several small studies have suggested a link between antiretroviral therapy and the development of hypertension, but this association has not been fully evaluated. In a retrospective study, Hewitt and colleagues (Abstract 651) compared the incidence of hypertension in patients treated with either nelfinavir or indinavir with the incidence in protease inhibitor–naive subjects. The incidence was comparable in the nelfinavir and protease inhibitor–naive groups, and was higher in the indinavir group. Whether this association between indinavir use and hypertension will be confirmed in other studies remains to be seen. Previous reports demonstrating an impact of indinavir on insulin resistance may contribute to our understanding of this preliminary finding.

Managing Complications: Switch Strategies

Substitution of one of the components of a successful antiretroviral regimen as a strategy for managing metabolic complications (so-called switch studies) continues to be used and evaluated. In most cases the drug being replaced is a protease inhibitor and the new agent is either an NNRTI or abacavir. The quality of the switch studies presented continues to improve, with randomized trials predominating at this year's Conference. Included in the session on switch studies were 2 studies that are prospectively evaluating the metabolic effects of protease inhibitor and non–protease inhibitor regimens. One unique study, the SWATCH study (Negredo et al, Abstract 669), is comparing the effects of therapy alternated at 3-month intervals with those of continuous treatment with either stavudine, didanosine, and efavirenz or zidovudine, lamivudine, and nelfinavir. Interim results at 9 months of follow-up suggest a superior virologic and immunologic response in the alternating-therapy group and no differences in the rates of adverse events, but it is too early to draw firm conclusions. A second study (Matheron et al, Abstract 670) compared the metabolic changes among patients randomized to receive fixed-dose lamivudine/zidovudine plus either nelfinavir or abacavir. At 48 weeks of follow-up triglyceride levels were higher in the nelfinavir group, and 6% of the abacavir vs 12% of the nelfinavir group were reported to have clinical manifestations compatible with lipodystrophy.

Results of the other switch studies presented at the Conference are summarized in Table 1. A consistent finding is the improvements in lipid profiles when the NNRTIs are substituted for a protease inhibitor. In addition, lipoatrophy does not appear to regress and insulin resistance persists, especially in the setting of established lipoatrophy, suggesting a possible role for nRTIs (or insulin resistance) in the pathogenesis of fat atrophy.

Hepatitis C Coinfection

Dr Kenneth Sherman provided an overview of the issues surrounding hepatitis C virus (HCV) infection and HIV disease in a state-of-the-art lecture (Session 9). He reminded the audience that HCV infection was present in more than 200 million individuals worldwide and in 4 million in the United States. It is the leading indication for liver transplantation in the United States. In a recent survey of AIDS Clinical Trials Group participants, the prevalence of HCV infections was 16%, with the highest rates in injection drug users. The current generation of diagnostic tests are very sensitive and specific for HCV infection. However, in highly suspect cases with negative antibody test results, HCV RNA testing is indicated. A study by Berggren and colleagues (Abstract 562) shed further light on determinants of false-negative HCV antibody test results. A CD4+ cell count of less than 100/µL was associated with a 50-fold increased risk of a false-negative result. Interestingly, these patients did exhibit antibodies to other viral pathogens, including hepatitis A and B viruses.

The effect of HIV disease on the natural history of HCV disease was explored in several studies. Daar and colleagues (Abstract 35) evaluated HCV clearance in a cohort of patients with hemophilia identified in 1989. There was clearance of HCV in 14% of HIV-uninfected subjects compared with only 3% of HIV-infected subjects. Coinfection with HIV was associated with a 5-fold reduction in spontaneous HCV clearance. Investigators from Parkland Memorial Hospital, in Dallas, came to the opposite conclusion in their study (Jain et al, Abstract 568), in which the HCV clearance rate in patients coinfected with HCV and HIV was 15%. Prognostic factors for HCV clearance were not identified, but the authors did emphasize the importance of HCV RNA testing in HCV antibody–positive patients. The discrepancy between these 2 studies may be due to the differences in patient populations. The patients with hemophilia were probably infected with both pathogens early in life, with numerous and continuous exposures to HCV, and the patients in the Dallas cohort were probably infected later in life, through injection drug use.

Subjects coinfected with HIV-HCV appear to exhibit more rapid progression of hepatitis to fibrosis and liver failure compared to patients with HCV only. Other risk factors for progression to cirrhosis include heavy alcohol consumption and low CD4+ cell count. Several groups evaluated whether cellular and cytokine responses to HCV antigens could explain the higher rates of disease progression. The quantitative changes in immune responses to HCV antigens did not differ between HIV-infected and -uninfected patients in a study by Graham and colleagues (Abstract 563). Intrahepatic compartmentalization of □T cells was demonstrated in a report by Agrati and colleagues (Abstract 565) and was postulated to contribute to hepatic inflammation and fibrosis.

The effect of HCV infection on HIV dis-

Table **1.** Switch Studies Presented at the 8th Retrovirus Conference

Investigators (Abstract No.)	Comparison	No. of Patients	Results/Comments
Martinez et al (668)	Efavirenz vs continuous protease inhibitor	93	• Virologic suppression same in both arms • Insulin resistance improved with efavirenz • Less fat accumulation with efavirenz • Progressive fat atrophy in both arms
Estrada et al (671)	Efavirenz for protease inhibitor Lipoatrophic-lipodystrophy	41	• No improvement in insulin resistance • No improvement in lipoatrophy
Walli et al (672)	Protease inhibitor to abacavir (nonrandomized)	31	• Insulin sensitivity increased with abacavir • Triglyceride and cholesterol levels lower with abacavir
Casado et al (673)	Protease inhibitor to efavirenz or nevirapine	100	• Moderate rates of toxicity • Decreased triglyceride and cholesterol levels • Loss of virologic suppression if prior nRTI use

ease progression has been more controversial and more difficult to define. In contrast to the recently published findings from the Swiss cohort study in *Lancet*, Sulkowski and colleagues (Abstract 34) reported no influence of HCV infection on HIV disease progression (defined as progression to an AIDS-defining illness and a decrease in the CD4+ cell count to less than 200/µL). The increase in the CD4+ cell counts associated with HAART was, however, significantly lower in patients with HIV and HCV coinfection than in those with HIV infection only. This difference was also observed in a cohort of patients with HIV and HCV coinfection who were treated with HAART in a study by Torriani and colleagues (Abstract 575). Two additional studies (Rancinan et al, Abstract 570; Macias et al, Abstract 571) evaluating the influence of HCV infection on mortality in HIV-infected patients in the HAART era failed to implicate hepatitis C as an independent risk factor for death. In a cohort study in Spain by Macias and colleagues mortality attributed to HCV infection was increasing, but AIDS-related illnesses were still the most common cause of death in the HAART era. Differences in patient populations, HAART regimens, and adherence to the regimens may have contributed to the different results among these cohorts.

In studies to date, factors that influence the response of HCV to antiviral therapy in HIV-coinfected patients include CD4+ cell count, HCV genotype, HCV viral load, and the presence of cirrhosis. Dr Sherman proposed that these factors argued for earlier treatment of HCV infection in HIV disease. In a small pilot study of interferon alfa (IFN-□) plus ribavirin by Bochet and colleagues (Abstract 574), the baseline HCV RNA level was the greatest predictor of response. In this study, 18% of patients had HCV RNA suppression 6 months after the discontinuation of 6 to 12 months of therapy.

The high prevalence of HCV infection, the accelerated course of HCV infection in the presence of HIV infection, and the increasing mortality associated with chronic HCV infection underscore the urgency for developing new HCV therapies. Dr Sherman noted that interleukins 2 and 10, protease and helicase inhibitors, and antisense compounds are all under development or are already in clinical trials. Pegylated IFN-□ was recently approved by the US Food and Drug Administration.

Hepatitis B Coinfection

Treatment with lamivudine decreases the replication of hepatitis B virus (HBV), but drug resistance can be identified in 50% of patients treated for 2 years and in 90% treated for 4 years. Some of the most exciting data presented at the Conference were the results of a trial that evaluated the efficacy of adefovir in HIV-infected patients in whom lamivudine treatment for hepatitis B was failing (Benhamou et al, Abstract 36). At study entry all 35 subjects had detectable HBV DNA and the M550V or M550I mutation in the HBV DNA polymerase. Treatment with adefovir 10 mg/d produced a mean decrease in the HBV DNA level of 4 $\log_{10}$ copies/mL at 32 weeks. Three subjects who were positive for hepatitis B early antigen have become negative for it during the course of this ongoing study. No changes in renal function were observed, and no patients dropped out because of adverse effects related to adefovir. For the treatment of hepatitis B, the therapeutic index of adefovir appears favorable, and the results of additional, larger efficacy studies are eagerly awaited.

Emtricitabine is another antiviral drug that also has activity against HBV. In a randomized phase 2 study (Rousseau et al, Abstract 559) of emtricitabine 25, 100, or 200 mg/d, the 200 mg dose produced the greatest reduction in HBV DNA levels (3.2 $\log_{10}$ copies/mL). Sixty-four percent of patients taking this dose had undetectable HBV DNA levels after 36 weeks of treatment. The compound also has promising activity against HIV (Van Der Horst et al, Abstract 18) at the 200 mg dose selected for development for hepatitis B treatment.