Complications of HIV Disease and Antiretroviral Therapy

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Metabolic Complications

The numerous sessions and more than 60 abstracts presented at this year's conference provide evidence of the growing interest and concern about body shape changes and metabolic complications of HIV infection. The focus has begun to shift away from considering these changes as a single syndrome commonly referred to as "lipodystrophy" to distinct complications that may have different etiologies. Fat atrophy, fat accumulation, lipid abnormalities, and glucose dysregulation characterize the major syndromes observed to date. Although protease inhibitors continue to be linked to several of these changes, the role of the nucleoside reverse transcriptase inhibitors (nRTIs) and the role of HIV suppression per se are receiving increased attention. In addition, the long-term consequences of these metabolic changes, such as premature cardiovascular disease, are being considered. In this unfolding story, little is understood of the underlying mechanisms and optimal monitoring and treatments for these complications.

Epidemiology and Risk Factors

Prospective studies with standardized questionnaires and physical examination continue to catalogue the changes in body shape that are occurring among HIV-infected patients. Although the prevalence of body shape changes ranges widely in these series (5% to 63%), several potential risk factors have begun to emerge (Abstracts 13, 14, 15, 23, 26, and 201). In several studies, older age, duration of HIV infection, and duration of HIV therapy appear to be important risk factors (Abstracts 14, 15, 23, and 201). Increasingly, body shape changes are being reported among patients who have not received protease inhibitors.

The original reports of lipodystrophy were derived from cohorts that included predominantly white men and have left unanswered the question about the prevalence of these disorders in more diverse populations. Wanke and colleagues used anthropomorphic measures to assess the prevalence of fat depletion and fat accumulation in a cohort of HIV-infected adults (Abstract 24). They found a lower rate of fat depletion among African American men and women and a higher rate of fat depletion in women overall compared with men, a finding that is in contrast to other reports. Data from the Self-Ascertained Lipodystrophy Syndrome Assessment (SALSA) study (Abstract 26) confirm results of earlier reports suggesting that women are more prone to fat accumulation and men are more likely to experience fat loss. In this cohort, 37% of the women who were noted to have body shape changes were naive to protease inhibitors. In another study that included 130 patients (85% African American and 15% Latino), protease inhibitor use was associated with a higher prevalence of larger abdominal girth and increased waist-to-hip ratio in men but not in women (Abstract 27).

Finally, results from the Women's Interagency HIV Study (WIHS) (which includes a group of HIV-uninfected controls) remind us of the importance of objective measures of body shape changes (Abstract 25). In an analysis of 1471 nonpregnant women enrolled in WIHS, HIV-infected women reported both increased and decreased abdominal size more often than uninfected women. These changes were reported more commonly among those on therapy than among those not receiving treatment for HIV infection. In addition, the presence of a dorsocervical fat pad was noted in a greater number of HIV-infected women (14%) than in the HIV-seronegative controls (8%). Of note, only 20% of the dorsocervical fat pads noted by an examiner were reported by the study subject.

There appears to be a strong association between duration of HIV infection and the development of metabolic complications. However, studies in early HIV infection had previously been lacking. One new finding at this year's meeting was a report of metabolic changes and fat maldistribution among patients with primary HIV infection treated with a regimen of indinavir/stavudine/lamivudine (Abstract 12). In an observational study of 14 people with primary HIV infection, body shape changes were noted in 6%, 14%, 40%, and 57% of the patients after 6, 12, 18, and 24 months, respectively. In addition, triglyceride elevations were noted in 53% and cholesterol elevation above 240 mg/dL in 33%.

The role of nRTIs in the development of metabolic complications continues to be explored. Stavudine was the focus of several studies presented at this year's meeting, and the results remain inconclusive partially due to the fact that stavudine became available several years after zidovudine. Hence, it is often difficult to untangle stavudine use from a longer duration of HIV therapy (Abstracts 19, 20, and 23). In a cross-sectional study of patients receiving therapies that did not include a protease inhibitor, 36% were noted to have lipodystrophy. Of these, 28% had fat wasting, 39% had fat accumulation, and 32% had a mixed picture. The prevalence of body shape changes was higher in those exposed to the combination of nRTIs and nonnucleoside reverse transcriptase inhibitors (NNRTIs)(56%) than in those who received nRTI-only combinations (37%). In this series, the prevalence was higher among stavudine recipients (55%) than zidovudine recipients (38%). However, the duration of antiretroviral therapy was on average 10 months longer in those who were receiving stavudine.

Data from a clinical trial in which patients were randomized to either zidovudine/lamivudine, stavudine/didanosine, or sequential therapy with zidovudine/lamivudine followed by stavudine/didanosine (the ALBI study) identified body shape changes in 35% of

the subjects after 30 months on study. Data were available for only 83 of the 151 original study patients (Abstract 19). The rate of "lipodystrophy" was twice as high among subjects in the stavudine/didanosine arm than in the other arms. However, the high number of subjects with missing data limits the conclusions that can be drawn.

Finally, the issue of specific drug exposures and metabolic complications was addressed in the HIV Outpatient Study (HOPS), an ongoing cohort set in practice settings across the United States (Abstract 23). In this analysis that included more than 1000 patients, several factors were associated with an increased risk for developing fat maldistribution: older age, history of an AIDS diagnosis, months since nadir CD4+ cell count, and years since HIV diagnosis. In addition, use of indinavir and use of stavudine were associated with a higher risk. These exposures had the strongest association with body shape changes in subjects who had one or more of the other risk factors identified. Ultimately, prospective randomized trials that include objective measures of body shape and metabolic changes will be required to sort out the unique contributions of specific drugs in the pathogenesis of these changes.

Interventions

Exercise. One of potential interventions proposed for the management of fat redistribution and metabolic complications is exercise. Yarasheski and colleagues reported the results of a 16-week study of supervised progressive resistance exercise training in 17 HIV-infected men (Abstract 54). After 1.5 hours per day, 3 days per week sessions, lean mass in the whole body, appendicular, and trunk regions increased and there was no change in adipose tissue mass. Triglyceride levels were reduced in 11 of 17 subjects studied. This is the second study reported in HIV-infected men to demonstrate the benefits of exercise.

Switching Therapy. Interim results from at least 10 studies evaluating antiretroviral therapy switches were reported at this year's conference. These ranged from substituting an NNRTI for a protease inhibitor (either nevirapine or efavirenz) (Abstracts 45, 46, 48, 49, 50, and 206), substituting abacavir for the protease inhibitor component of therapy (Abstracts 47, 51, and 457), discontinuing stavudine (Abstract 52), and changing the entire regimen (Abstract 205).

These switch studies may help to shed some light on the etiologic role of specific drugs in the metabolic changes being observed. However, some of the results are potentially difficult to reconcile. In a nonrandomized trial, Saint-Marc and colleagues described the changes that occurred among 36 subjects with documented fat atrophy who discontinued stavudine (Abstract 52). After a median of 9 months of follow-up, triglyceride levels fell by 29% and lactate by 37%; cholesterol and glucose measurements were unchanged. Most notably, increases in abdominal and mid-thigh subcutaneous fat of 32% and 36%, respectively, were seen. This is one of the first studies to date to demonstrate improvement in subcutaneous fat loss. Yet in one of the few randomized switch studies, subjects who developed lipodystrophy on a regimen that included stavudine/lamivudine and a protease inhibitor were assigned to either continue or to switch to stavudine/didanosine/nevirapine. A comparable decline in triglyceride levels was noted (31%). In contrast to the previous study, there were no objective changes in fat redistribution identified. Hence, in 2 different studies, one in which stavudine was stopped and another in which the drug was continued, improvements in triglycerides were observed. These results may reflect differences in syndromes that are characterized by fat loss and those in which fat accumulation predominates, or they may reflect the multifactorial etiologies of the metabolic abnormalities.

Studies in which the protease inhibitor component of a virologically successful regimen is substituted with an NNRTI also showed variable results that depended on which NNRTI was used. In 3 of the studies in which nevirapine was substituted for a protease inhibitor (Abstracts 45, 205, and 206), improvements in triglyceride levels with or without significant changes in cholesterol values were noted. On the other hand, studies in which efavirenz was used in place of the protease inhibitor demonstrated variable effects on lipids, with both decreases (Abstract 50) and increases (Abstract 48), or no changes noted (Abstract 46). Differences in sample size, prevalence of baseline abnormalities, and duration of follow-up may have accounted for some of these disparities. The one area of agreement between these different NNRTI switch studies was the lack of change in fat redistribution even in the studies with the longest follow-up (Abstracts 205 and 206). In the randomized study conducted by Carr and colleagues (PILLR) in which a regimen of nevirapine/abacavir/adefovir/hydroxyurea was substituted for a protease inhibitor regimen, improvements were noted in lipid parameters, although peripheral fat wasting appeared to worsen by objective criteria. Interestingly, improvement in body changes was noted by self report. Rates of maintenance of viral suppression were generally high in all of these studies and did not differ between arms in those studies that were randomized and that included a control arm.

The other type of switch study reported involved the substitution of abacavir for the protease inhibitor component of the regimen (with or without switching the other nRTIs) (Abstracts 45, 47, and 51). Opravil randomized 164 subjects to continue their current regimen or to switch to a combination of abacavir/zidovudine/lamivudine (Abstract 457). Although not designed to focus on patients with fat redistribution or metabolic abnormalities, this study reported decreases in total cholesterol and increases in high-density lipoprotein (HDL) during follow-up. Comparable rates of viral suppression were seen in both arms of the study. A second randomized study reported improvements in triglycerides and cholesterol and a reduction in insulin resistance among the group randomized to the substitution of abacavir for the protease inhibitor component of a triple-drug regimen (Abstract 51).

HMG-CoA Reductase Inhibitors ("Statins"). There has been ongoing concern about the potential drug interactions between the statin drugs and protease inhibitors. Fichtenbaum and colleagues presented the preliminary results of a formal pharmacokinetic study to evaluate the interaction between 3 statin drugs, ator-

vastatin (40 mg), simvastatin (40 mg), and pravastatin (40 mg), and the combination of ritonavir/saquinavir in normal volunteers (Abstract LB6). Significant increases in the levels of active atorvastatin (74%) and simvastatin (2676%) were noted, and levels of pravastatin fell by 47%. These results suggest that simvastatin should be avoided in patients receiving protease inhibitors, and that further study is needed to determine the optimal dosing of atorvastatin and pravastatin with protease inhibitors.

Lactic Acidosis

Lactic acidosis is a rare but often fatal complication of nRTI therapy that was recognized early in the development of nRTIs. Inhibition of DNA polymerase-γ by nRTIs produces mitochondrial DNA depletion, leading to a cascade of events culminating in lactic acidosis and liver failure. This complication has been observed in children and in adults. Church and colleagues described a 2-year-old boy undergoing treatment with zidovudine/didanosine/nelfinavir who presented with fulminant lactic acidosis (Abstract 58). In addition to the classic clinical presentation, this child had hyperdense areas in the white and grey matter of the brain on magnetic resonance imaging (MRI). Muscle biopsy revealed 79% depletion of mitochondrial DNA. The child survived with supportive treatment and was successfully rechallenged with an antiretroviral regimen without nRTIs. In a small study of 11 infants and 36 children treated with a variety of nRTI therapies, lactic acid levels were transiently elevated in infants but not associated with symptoms acutely (Abstract 67).

The clinical course of 4 adults with fatal outcomes from lactic acidosis was described by Brinkman and colleagues (Abstract 59). Subjects had received nRTIs for 6 to 20 months, had all experienced an nRTI-associated toxicity prior to presentation, and were all receiving stavudine. Authors emphasized that screening methods are needed to identify patients at risk because of the often precipitous and fulminant course. At the opposite end of the spectrum of this syndrome, Lonergan and colleagues (Abstract 56) described the clinical profile of 20 patients with hyperlactemia and either abdominal symptoms or abnormal alanine aminotransferase (ALT). The authors suggested that these cases represented an earlier and milder form of the classic lactic acidosis syndrome. All patients were receiving stavudine plus either a protease inhibitor or an NNRTI with a mean duration of treatment of 1 year. Pancreatitis was present in 3 cases, 5 patients had underlying hepatitis B virus or hepatitis C virus, and liver biopsies performed on 6 of 7 patients showed hepatic steatosis. An elevated anion gap was present in only 4 patients. All patients survived and only 3 patients required hospitalization. In this clinic, there were 1.4 cases per person-months-of-observation in patients receiving nRTI regimens and no cases among patients not receiving stavudine. Supporting the association of stavudine with this syndrome, Moore and colleagues reported a higher anion gap distribution in patients receiving stavudine/lamivudine than those receiving other dual nRTI combinations (Abstract 55).

In the metabolic complications symposium, Cooper (Abstract S21) reviewed the data from the Australian experience showing that lipoatrophy syndromes occur in the absence of protease inhibitor therapy. Interestingly, elevated lactate levels were a key distinguishing feature of lipoatrophy syndromes present in patients receiving nRTIs only compared with nRTIs plus protease inhibitors. In addition to higher lactate levels, patients in the former group had greater weight loss, fatigue, nausea, and elevations in liver function tests, characteristics of lactic acidosis syndrome.

Osteopenia and Osteoporosis

A new complication of antiretroviral therapy was reported independently by Tebas and colleagues (Abstract 207) and Hoy and colleagues (Abstract 208). In the first report, bone mineral densities (BMDs) were measured in 64 patients receiving a protease inhibitor, 36 patients not receiving a protease inhibitor, and 22 HIV-seronegative individuals. Risk for diminished BMD was 2-fold greater in the protease inhibitor recipients than in the control groups. Severe osteoporosis was present in 21% of protease inhibitor recipients. There was no association between altered fat ratios (truncal to appendicular fat) and BMD, suggesting different metabolic pathways for these toxicities. In the report by Hoy and colleagues, among 74 patients receiving antiretroviral therapy, 28% had osteopenia and 9.5% had osteoporosis. Similar to the previous report, there was no association between fat distribution changes and osteopenia. The underlying mechanism to explain this observation is unknown. Much work needs to be done on the epidemiology, prevention, and treatment.

Cardiovascular Disease

The constellation of metabolic changes (increases in cholesterol, visceral fat, and insulin resistance) noted in HIV-infected individuals receiving antiretroviral therapy has raised concerns about the longer-term risk of cardiovascular disease. Studies presented at this year's conference focused on incidence rates for cardiovascular disease using existing databases and on measures of subclinical atherosclerosis. Klein and colleagues reported follow-up data on rates of coronary heart disease hospitalizations from the Northern California Kaiser Permanente health maintenance organization system among protease inhibitor-exposed and non-protease inhibitor-exposed patients with HIV (Abstract 33). In an analysis that included 4526 patients with a mean follow-up of 2.6 years, no difference in the rate of coronary heart disease (CHD) was evident (5.6 CHD hospitalization events per 1000 patient-years overall, with 5.7 for protease inhibitor-exposed patients and 5.5 for non-protease inhibitor-exposed patients). Coplan and colleagues pooled data from several completed pharmaceutical company-sponsored clinical trials to examine rates of myocardial infarction among patients receiving 4 different protease inhibitors (Abstract 34). After an average exposure of 12 months, no evidence for increased rates of myocardial infarction was seen among protease inhibitor recipients.

Since it may take several years before the metabolic abnormalities translate into clinical events, several groups have begun to utilize well-developed techniques for studying subclinical

atherosclerosis in HIV-infected patients. Sosman and colleagues reported a higher rate of endothelial dysfunction (as measured by brachial reactivity) among protease inhibitor-exposed HIV-infected patients than non-protease inhibitor-exposed HIV-infected patients (Abstract 29). Patients in the protease inhibitor group had higher lipid levels and were more likely to be overweight–factors that can influence endothelial function. The clinical consequences of the changes observed are not known. Three other studies (Abstracts 30, 31, and 32) used B-mode ultrasound to measure carotid intima medial thickness in HIV-infected patients receiving protease inhibitors compared with either HIV-infected patients on non-protease inhibitor therapy or with HIV-seronegative controls. These studies suggest that the lipid abnormalities (and other traditional cardiovascular risk factors) observed in patients may be associated with increased carotid thickening, but failed to demonstrate a direct effect of protease inhibitors. Carotid intima medial thickness is likely to be a useful tool to incorporate into larger scale longitudinal studies that examine the risk of atherosclerosis.

Opportunistic Infections

Opportunistic Infection Prophylaxis

Echoing and extending reports from previous years, numerous abstracts addressed the question of the safety of discontinuation of opportunistic infection prophylaxis. Current guidelines caution against discontinuation of secondary prophylaxis for P*neumocystis carinii* pneumonia (PCP). Two presentations addressed this issue directly and concluded that data support discontinuation of secondary prophylaxis in responders to highly active antiretroviral therapy (HAART). A cooperative effort combining observations from 8 European cohort studies (17,500 patients) was presented at the late-breaker session (Abstract LB5). Among 246 patients with a prior history of PCP who were receiving HAART and who discontinued prophylaxis when their CD4+ cell count was above 200/µL, there were no cases of PCP (236 person-years of follow-up). Supporting these findings, Koletar and colleagues reported that among 125 patients discontinuing secondary prophylaxis (mean follow-up, 24 weeks), there were no cases of PCP (Abstract 243). In an interesting abstract pertaining to patients in whom PCP prophylaxis is indicated, Kazanjian and colleagues (Abstract 229) reported that the duration of prior trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis was a risk factor for the development of resistance mutations in P *carinii* dihydropteroate synthetase and that the response to TMP-SMX treatment for PCP diagnosed after a period of TMP-SMX prophylaxis was lower in patients harboring the resistance mutations.

The safety of discontinuation of prophylaxis for toxoplasmosis was addressed in 2 abstracts. Miro and colleagues (Abstract 230) reported a prospective, randomized trial of 302 patients who had a median CD4+ cell count nadir of 99/µL and a CD4+ cell count at entry of 336/µL. Twenty patients in this study had a prior history of toxoplasmosis and were receiving secondary prophylaxis. After a median of 10 months of follow-up, there were no cases of toxoplasmosis in patients continuing or discontinuing prophylaxis. Similarly, Furrer (Abstract 244) reported no cases of toxoplasmosis among 157 seropositive patients discontinuing prophylaxis (follow-up, 207 person-years) in the Swiss HIV Cohort Study.

The safety of discontinuing or withholding prophylaxis for M*ycobacterium avium* complex (MAC) was described in 3 abstracts. El-Sadr and colleagues presented results from a randomized, placebo-controlled trial of azithromycin prophylaxis (Abstract 247). Patients were eligible if their CD4+ cell count increased from less than 50/µL to more than 100/µL on HAART. Among the 520 patients, there was no difference in the risk of MAC or bacterial pneumonia (median follow-up, 1 year) between the 2 groups. Koletar and colleagues reported that infections other than MAC did not differ between patients (n=643) participating in a similarly designed trial of azithromycin prophylaxis (Abstract 242). Furrer and colleagues (Abstract 246) reported that in patients with low CD4+ cell counts demonstrating rises above 100/µL for greater than 12 weeks, no cases of MAC developed even in the absence of prophylaxis. Taken together and emphasized in an abstract presented by Burman and colleagues (Abstract 241), demonstrating low rates of opportunistic infections among patients with advanced HIV responding to HAART, the protection afforded by HAART overrides that of prophylaxis.

Finally, Aberg and colleagues (Abstract 250) reported that in 6 patients with a history of cryptococcal meningitis who were responding to HAART, maintenance antifungal therapy was safely discontinued. All patients had received at least 1 year of fluconazole, had a CD4+ cell count above 150/µL, and had received treatment with HAART for at least 16 weeks.

Viral Coinfections: Hepatitis and Cytomegalovirus

The management of HIV-infected patients coinfected with hepatitis (B, C, or both) has emerged as one of the most important and challenging aspects of HIV care. The epidemiology, virology, immunopathogenesis, and treatment of hepatitis C virus (HCV) was reviewed in a conference symposium (Abstracts S8 to S11). As summarized by Thomas, transmission of HCV is primarily via percutaneous exposure, is uncommon in the perinatal setting, and the reason for the highly variable clinical course of this disease is not completely explained by risk factors such as serum transaminase, HCV load, and genotype (Abstract S8). Cell-mediated immunity (CD4+ and CD8+) appears to play an important role in protective immune responses, but CD8+ cytotoxic T lymphocytes may also contribute to tissue damage in chronic infection. The most promising therapy for HCV currently is ribavirin and interferon (including pegylated interferon). This drug combination is currently undergoing evaluation in HIV/HCV coinfected patients. Rice reviewed the molecular virology of HCV, emphasizing that although recent advances including in vitro systems will accelerate new drug development, vaccine development will be challenged by the diversity of this virus and host immune response (Abstract S9).

Risk factors for HCV were examined in several cohorts. Kaplan and colleagues (Abstract 277) reported the interesting

observation that clearance of HCV was greater in individuals with CCR5- -32 heterozygosity than in individuals with wild-type genotype (Abstract 277). In a report by Mir and colleagues (Abstract 278), HCV levels were inversely related to CD4+ cell count, but the opposite trend was observed in patients with hemophilia (Abstract 280). Liver histology associated with HCV did not differ between HIV-infected and -uninfected individuals (Abstract 278). Another abstract suggested that hepatic fibrosis was reduced in patients receiving protease inhibitor regimens (Abstract 282). A small crossover study (21 patients) of interferon and ribavirin in HCV-infected patients demonstrated that interferon alone had no effect on HIV RNA or HCV RNA, but that the combination was associated with reduction in HCV RNA levels (Abstract 283). One-quarter of subjects discontinued therapy for toxicity. In a second small study (n=18) of interferon and ribavirin reported by Perez-Olmeda and colleagues (Abstract 284), response rates were in the range reported in HIV-seronegative patients. Once again toxicity was significant, with 38% of subjects unable to complete a 6-month course of therapy. For patients undergoing treatment of hepatitis B with lamivudine (Abstract 285) or lamivudine and famciclovir (Abstract 286), 2 small observational studies suggested that virologic relapse was common and associated with hepatitis B drug resistance mutations.

In the area of CMV retinitis, Martin and colleagues presented results of a 160-patient randomized study comparing the ganciclovir oral prodrug valganciclovir and intravenous ganciclovir for induction therapy (Abstract 231). The time to first CMV progression was not significantly different between the valganciclovir group (198 days) and in the ganciclovir arm (120 days). All other analyses supported the use of valganciclovir, providing the hope that CMV retinitis may be treated effectively with an entirely oral regimen. Other abstracts related to CMV focused on extending observations of the natural history of CMV in the HAART era. In patients withdrawing CMV maintenance therapy, risk for relapse of CMV disease is highest in patients whose CD4+ cell count then falls below 50/µL (Abstracts 266 and 267) although an interesting case report documented a case of 5 relapses in a single patient with CD4+ cell count above 300/µL (Abstract 272).

Human Herpesvirus-8 and AIDS-Related Malignancies

Pau and colleagues (Abstract 227) reported results of a study comparing the sensitivity of a modified enzyme immunoassay (EIA) using a chimeric peptide utilizing K8.1 and ORF65 human herpesvirus-8 (HHV-8) peptides to standard EIA assays and the more sensitive but costly monoclonal antibody immunofluoresence (IFA) assay. The chimeric EIA was more sensitive than standard EIAs in patients with Kaposi's sarcoma, although detection of antibody was significantly less than in the IFA in patients without Kaposi's sarcoma. In a second study (Abstract 1) looking at seroconversion with IFA and EIA, conversion was not simultaneous in many cases and antibody titers did not predict risk of Kaposi's sarcoma. A surveillance study in the United States of men with high-risk sexual behavior found an HHV-8 seroprevalence of 6% (Abstract 2) and supported current dogma that HHV-8 is sexually transmitted. Perinatal transmission of HHV-8 was reported among 3 mothers (HHV-8-seropositive, HIV-seronegative) in an ongoing evaluations of perinatal transmission in Ugandan women with HHV-8-infection and variable HIV status.

In the area of AIDS-related malignancies, Cingolani and colleagues reviewed the experience of 41 patients with AIDS-related lymphomas (Abstract 225) and reported that response to HAART was associated with a more favorable response to chemotherapy and a longer survival. One-year survival probability was 0.74 in HAART responders compared with nonresponders. Up-regulation of stromal cell-derived factor (SDF) was shown to be a risk factor in children for AIDS-related lymphomas in a report by Sei and colleagues (Abstract 226) and a genetic variant of SDF was associated with higher levels of expression of SDF.

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