COMPLICATIONS OF HIV DISEASE AND ANTIRETROVIRAL THERAPY

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METABOLIC COMPLICATIONS

Metabolic complications of HIV infection were the topic of more than 30 abstracts and a state-of-the-art symposium at the Conference. Research in this area has focused on describing the different components of what may or may not be a single syndrome. Active areas of investigation include glucose metabolism (including the role of insulin resistance), lipoprotein changes (cholesterol and triglyceride elevations), and body fat redistribution (fat accumulation and peripheral fat wasting). There were some data presented on the incidence and prevalence of the abnormalities, analysis of risk factors for developing specific changes, and some early data on possible interventions and outcomes in patients taking antiretroviral drugs. Many of the studies were retrospective, uncontrolled, and lacked objective measures and hence are difficult to interpret or compare. However, there were several well-designed studies that serve to move this area of investigation forward.

In the state-of-the-art symposium on metabolic complications, Grunfeld reviewed data on lipid changes from before the protease inhibitor era **(Abstract S3)**. He reminded the audience that many of the changes we are seeing today are occurring on a background of metabolic disturbances that may be attributable to HIV infection itself. He cautioned that this must be kept in mind as we work to understand the mechanisms of metabolic perturbations and as new treatment strategies are evaluated.

Incidence and Prevalence

The incidence and prevalence of specific metabolic abnormalities in patients taking antiretroviral therapy (1994 to 1998) were described in a retrospective clinic-based study of 964 patients by Lee and Mathews from San Diego **(Abstract 644)**. No significant increases in random glucose levels were identified. Modest increases in total cholesterol values between 20 to 50 mg/dL and average increases in random triglyceride levels of 100 mg/dL were noted. Patients taking protease inhibitors did appear to be at increased risk for abnormalities compared with patients taking no therapy or compared with those taking nucleoside reverse transcriptase inhibitors (nRTIs) alone. Of additional interest in this study was the characterization of other known cardiovascular risk factors among the HIV-infected patients receiving care. More than 60% of patients in their clinic had a least 1 risk factor for cardiovascular disease, and 23% had 2 or more risk factors. These results highlight the importance of interventions to control known risk factors for cardiovascular disease, ie, smoking cessation, therapy for hypertension and diabetes, and interventions to reduce lipid levels.

Metabolic complications in children taking protease inhibitors have recently been recognized and were highlighted in a poster by Watson and Farley from Baltimore **(Abstract 435)**. Increases in cholesterol (34 mg/dL mean) and triglycerides were reported among 82 perinatally infected children (aged 6 months to 13 years) on protease inhibitor therapy. They were associated with use of each of the available protease inhibitors, were highest in children receiving a ritonavir and saquinavir combination, and appeared to be of the same order and magnitude as has been reported in adults.

Risk Factors for Metabolic Changes

Several groups attempted to identify risk factors for developing body shape changes and lipid abnormalities among patients taking antiretroviral therapy. Dieterich **(Abstract 674)** evaluated more than 700 patients receiving care and examined the association between the use of androgen and anabolic therapies and the risk of developing body shape changes. In this cross-sectional study, a high proportion of patients (56%) reported using anabolic or androgen therapy. "Lipodystrophy", defined visually, was noted in 7% of patients on these therapies, 5% of patients on testosterone, 16% on nandrolone, and 25% (1 of 4 patients) on growth hormone. More than half of the patients with clinical lipodystrophy had elevated cholesterol and triglyceride levels. The retrospective nature and visual definition of lipodystrophy used limit the conclusions that can be drawn. However, the low rates of lipodystrophy in patients taking androgens or anabolic therapy suggest prospective controlled trials are justified.

Carr and colleagues **(Abstract 641)** assessed the prevalence and severity of peripheral fat wasting and central obesity in a single practice setting using patient self-reports. Previous work by this group has demonstrated that self-report of body shape changes appears to correlate with some objective measures. In their study, only 17% of the patients denied any changes in body shape. The severity of body shape changes

noted by the participants appeared to correlate with total body fat. Retrospectively, they identified prior elevation in triglyceride levels and in C-peptide values as risk factors for body shape changes. These investigators postulate that early changes in triglycerides and C-peptide levels may be important in the pathogenesis of this syndrome.

A group of French investigators **(Abstract 642)** evaluated the frequency of lipodystrophy and attempted to characterize different variants of fat redistribution. They defined 3 clinical descriptions of body shape changes: lipoatrophic (71%), pseudo-obesity (62%), and mixed (46%). Among patients with each of these different types of body fat redistribution, the incidence of insulin resistance and glucose intolerance were comparable and occurred in about one third. Diabetes was rare and occurred in less than 10% of each of these groups. Elevated triglyceride levels (greater than 1.7 mg/dL) occurred in more than one third of patients. Elevations in cholesterol levels (greater than 6.7 mg/dL) occurred in more than 70% of patients in the 3 types. Among patients in their study who were taking protease inhibitors but did not develop 1 of the 3 fat redistribution patterns, the incidence of glucose intolerance and insulin resistance were significantly lower than the other groups. They concluded that diabetes, glucose intolerance, and insulin resistance appeared to be a significant feature of the syndrome, and that varied manifestations of body shape changes can occur during protease inhibitor therapy.

While most of the cohort studies that have examined the development of fat redistribution and lipid abnormalities have included men, at this year's Conference there was a poster session dedicated to the metabolic complications of antiretroviral therapy in women. Bausserman and colleagues **(Abstract 659)** evaluated 33 women taking protease inhibitors for a mean of 1 year and assessed body fat redistribution and insulin, glucose, and lipoprotein concentrations. In this study, two thirds of the women had an increase in waist-to-hip ratio above the 95th percentile for normal. Less evident were increases in cholesterol and triglyceride levels. Fasting glucose levels also appeared normal; however, 9 of the women had insulin levels above the normal range. Increase in waist-to-hip ratio appeared to correlate with elevation in triglyceride, lipoprotein B, and glucose and insulin levels. The results of this and other studies suggest that women are not spared the body shape changes. In another study by Currier and colleagues **(Abstract 663)**, rates of triglyceride and cholesterol elevations were examined among women enrolled in a prospective study of a regimen of nelfinavir/saquinavir/stavudine/lamivudine. No significant increases in triglyceride levels were noted in the women evaluated in this 48-week study; however, a small but statistically significant increase in cholesterol level (55 mg/dL) between baseline and follow-up was noted. Whether this increase represents high-density lipoprotein (HDL) or low-density lipoprotein (LDL) cholesterol remains to be defined.

Data from the Women's Inter-Agency HIV study (WIHS) **(Abstract 661)** examined the association between diabetes and protease inhibitor therapy in women. After excluding women who reported pregnancy or a history of diabetes, they compared the development of diabetes in women based on the type of antiretroviral therapy they were taking. They identified a slight increase in the risk of diabetes in women who were taking protease inhibitors compared with other therapies, but no significant increase over HIV-seronegative women.

To date, most of the attention of metabolic and fat redistribution changes have implicated and focused on HIV protease inhibitors. Two groups reported on the development of body shape changes and lipid abnormalities in patients receiving nonprotease inhibitor-containing regimens. Saint-Marc **(Abstract 653)** described 17 patients with partial or generalized lipodystrophy who were on nRTIs alone for an average of 15 months. Of note, all of the patients in this series were taking stavudine in combination with lamivudine or didanosine. Fourteen of the 17 patients had low normal insulin levels, suggesting increased insulin sensitivity. They also reported that patients exhibited slight decreases in visceral adipose tissue, which is in contrast to what has been described in protease inhibitor-associated body shape changes. In the second report, Madge **(Abstract 654)** described 5 patients taking nRTIs with or without nonnucleoside reverse transcriptase inhibitors (NNRTIs) who developed changes in body shape. However, this study relied on patient self-report and lacked objective measures. Taken together with the published literature describing buffalo humps in patients prior to the availability of protease inhibitors, these reports remind us that factors other than protease inhibitors may be contributing to the development of body shape changes. The development of a consensus case definition for body shape changes would greatly strengthen the comparisons that can be drawn from these descriptive studies.

Interventions: Treat or Switch

Owing to the disfiguring effects of fat redistribution and the potential long-term complications of lipid abnormalities, investigators have begun to evaluate a variety of interventions targeted at patients taking

protease inhibitors who have metabolic complications and body shape changes. Several groups have focused on the role insulin resistance may play in the development of body fat redistribution and lipid abnormalities. One approach to increase insulin sensitivity is to use the drug metformin.

Saint-Marc and colleagues **(Abstract 672)** reported the preliminary results from a carefully designed and controlled study evaluating metformin in nondiabetic patients who had insulin resistance (fasting insulin concentration greater than 20 mUI/mL and central adiposity while taking protease inhibitor). After a screening period, patients underwent an 8-week observation period, followed by an 8-week double-blind, randomized period comparing metformin (800 mg orally three times a day) with no treatment. Fourteen patients were randomized to the metformin group and 13 to the no-treatment group. Objective measures of anthropometry and fat distribution were made using computed tomography (CT) scan, waist-to-hip ratio, height, weight, and bioimpedance assay. In addition, patients underwent oral glucose tolerance testing and had extensive lipid and endocrine profiles taken.

There was significant improvement in several parameters during the 8-week period of metformin treatment compared with the no-treatment group. Weight, fasting glucose level, and insulin levels fell significantly during this time. No significant difference was seen in total cholesterol or HDL or LDL cholesterol; however, triglyceride levels declined significantly over the treatment period. Visceral fat as measured by CT scan decreased by 37.5% in the metformin group and 10.4% in the no-treatment group. In addition, the ratio of visceral adipose tissue (VAT) to total adipose tissue (TAT) also declined significantly: 13.3% in the metformin group versus 5.7% in the control group. Waist-to-hip ratio also decreased significantly during the 8 weeks of metformin treatment. Metformin was well tolerated, although 2 patients were withdrawn due to gastrointestinal disorders including diarrhea and abdominal cramps. This study suggests that in a carefully selected group of patients with central adiposity, metformin is effective in restoring insulin sensitivity, reversing central adiposity, and lowering trigylceride levels over a short period of time. These results strengthen the hypothesis that insulin resistance may be one of the underlying mechanisms of the syndrome of central obesity and metabolic alterations complicating protease inhibitor-containing antiretroviral regimens.

Data using another drug that increases insulin sensitivity, troglitazone, were reported in 6 patients with diabetes mellitis and lipodystrophy who were taking protease inhibitor therapy **(Abstract 673)**. Patients were evaluated after 8 to 12 weeks of open-label therapy with troglitazone (400 mg/d). A decrease in fasting and postprandial glucose levels was observed. In addition, an initial rise in lipid values that later returned to baseline was noted. No definitive changes in body fat were demonstrated and no other laboratory abnormalities (specifically elevations in liver enzymes) were seen in this short period of follow-up. The role of troglitazone in nondiabetic, HIV-infected patients taking protease inhibitors remains undefined. The potential for hepatotoxicity and drug-drug interactions with protease inhibitors is likely to limit the use of this agent for managing metabolic abnormalities in HIV-infected patients.

Growth hormone has also been evaluated as a potential therapeutic option for body fat changes seen during protease inhibitor therapy. A noncontrolled study of 6 patients with established central obesity or buffalo hump evaluated the use of growth hormone therapy at a dose of 4 to 6 mg administered subcutaneously **(Abstract 675)**. Subjective improvement in the size and texture of the buffalo hump and central fat were noted; however, no changes in lipid profiles and no changes in fat wasting in the limbs were reported. The preliminary results of this study suggest that growth hormone may need to be combined with other agents if it is used in the therapy of fat redistribution.

The final strategy that was evaluated for the treatment of metabolic abnormalities associated with protease inhibitors was substitution of the protease inhibitor with an NNRTI. Four groups reported preliminary results from "switch" studies designed to evaluate the safety and efficacy of substituting an NNRTI for a protease inhibitor. The studies all enrolled patients who had sustained viral load levels below the limit of detection for at least 6 months on a protease inhibitor regimen. Three studies included only patients who had metabolic abnormalities or fat redistribution, and only 1 of these studies **(Abstract LB14)** had a randomized design. Carr **(Abstract 668)** reported that more than 20% of the patients (11 of 15) failed to maintain viral suppression below the limit of detection at 12 weeks after substituting nevirapine for a protease inhibitor. Moyle **(Abstract 669)** reported on the substitution of efavirenz for indinavir in patients who were clinically stable and had HIV RNA levels below 400 copies/mL of plasma. They noted a decrease in abdominal girth and an increase in weight after substituting the NNRTI; however, this was accompanied by the transient increase in

cholesterol that was reported to be caused by elevations in HDL. These changes appeared to return toward baseline between 12 and 24 weeks.

In the 1 randomized study reported, Ruiz presented preliminary data on 29 patients taking a stable protease inhibitor regimen who were randomized to receive either didanosine/stavudine/nevirapine or stavudine/lamivudine/protease inhibitor. After a follow-up period of 12 weeks, the patients randomized to the nevirapine arm had statistically significant declines in cholesterol and triglyceride levels and reported improved quality of life. In this preliminary report, no data on objective measures of fat redistribution were presented. Taken together, the data generated to date from these switch studies suggest that substituting an NNRTI for a protease inhibitor in patients with adequate viral suppression is associated with a small risk in viral rebound, and that over the short term body fat redistribution does not appear to resolve. Clearly, longer follow-up in controlled studies is needed to determine the safety and efficacy of this approach.

Long-Term Consequences and Strategies

The long-term consequences of the metabolic complications of HIV therapy have remained undefined. At this year's Conference, 3 groups attempted to quantitate the risk of myocardial infarction in patients with HIV infection who were taking protease inhibitors and nonprotease inhibitor-containing combinations and compare them with adults not infected with HIV **(Abstracts 656, 657, 658)**. Each of these series was limited by the small number of events and short follow-up time that resulted in wide confidence intervals; nevertheless, they found no statistically significant increase in risk of myocardial infarction in patients taking protease inhibitor regimens.

Specific guidelines for the management of lipid abnormalities in the setting of HIV infection have yet to be developed. In the interim, the use of the National Cholesterol Education Program (NCEP) Guidelines appears to be reasonable. Henry **(Abstract 671)** reported his clinical experience of following the NCEP guidelines for management of lipid abnormalities in patients with HIV infection. In 44 patients (48% of the patients taking protease inhibitors at their center), significant reductions in cholesterol and triglyceride levels were seen using diet and exercise as the initial intervention. Gemfibrozil was successful in lowering cholesterol by approximately 30% and triglyceride levels by 50 to 60% after 9 to 10 months of therapy. Atorvastatin was given to 21 patients, with significant improvements in both cholesterol and triglyceride levels and with no apparent toxic effect. Although further studies are still needed to quantitate the interactions between the cholesterol lowering drugs and protease inhibitors, the short-term data presented in this study should be viewed as reassuring news to clinicians.

Opportunistic Complications: Stopping Prophylaxis—How Safe Is It?

Just 3 years ago, a major focus of the annual Conference was on the optimal prophylactic regimens and strategies to prevent opportunistic infections. Guidelines were simple: When the CD4+ count drops below 200 cells/μL, start Pneumocystis carinii *pneumonia (PCP) prophylaxis; when the CD4+ drops below 50 cells/μL, start* Mycobacterium avium complex *(MAC) prophylaxis. There were no stopping rules, as continuing immune deterioration and hence a progressively increased risk for opportunistic infections were expected. Prophylaxis was for life. Potent antiretroviral regimens then became available, requiring consideration of these recommendations. Is PCP prophylaxis really necessary for patients in whom CD4+ cell counts have risen above 200 cells/μL as a result of potent antiretroviral therapy? Will cytomegalovirus (CMV) disease recur in patients treated with potent antiretroviral drugs who then discontinue CMV maintenance therapy? These questions and other related issues were addressed at this year's Conference. The discussion was not when to start prophylaxis, but rather, when to stop it.*

The rationale for stopping prophylaxis is supported by a series of observations first reported by Autran. She reviewed her extended observations in the Immune Reconstitution Symposium **(Abstract S44)**. While restoration of in vitro proliferative responses to HIV was limited, responses to pathogens (ie, CMV and *Mycobacterium tuberculosis* [TB]) were restored 3 to 6 months after starting highly active antiretroviral therapy (HAART), even in patients starting therapy with immune suppression. Koup and colleagues **(Abstract S42)** measured excisional DNA products of TCR-gene rearrangements and noted that potent antiretroviral therapy produced a rapid and sustained increase in thymic output. McCune **(Abstract S43)** provided further encouraging data showing that the fractional replacement rate of CD4+ cells is increased with potent antiretroviral therapy. For years, there had been a generally held belief that a decline of CD4+ cells below 50 cells/μL represented a "point of no return" in terms of immune recovery. Certainly, abundant laboratory data accumulated over the last few years and summarized in the immune reconstitution symposium argued to the contrary and supported

trials of discontinuation of prophylaxis.

The hypothesis that PCP prophylaxis could be safely discontinued in patients responding to potent antiretroviral therapy was tested in a randomized study presented by Lopez on behalf of a Spanish Collaborative Group **(Abstract LB7)**. The entry criteria for the study included a prior CD4+ cell count less than 200/μL or a history of PCP. All participants were taking PCP prophylaxis and potent antiretroviral therapy, and had a documented CD4+ cell count above 200/μL and HIV RNA level below 500 copies/mL for at least 3 months. Among the 332 patients followed up for a mean of 6 months, there were no episodes of PCP. Only 2 patients restarted prophylaxis. Of interest, 94% of patients had been taking trimethoprim/sulfamethoxazole, and no serious bacterial infections or toxoplasmosis cases were reported. Limitations of this study include the duration of follow-up to date and the small percentage (4% to 5%) with a history of prior PCP. Nevertheless, the results were supported by an observational study presented by Dworkin and colleagues from the Centers for Disease Control and Prevention (CDC) on the risk of PCP in patients who had a low CD4+ cell count and then responded to potent antiretroviral therapy **(Abstract 692)**. None of the subjects had received PCP prophylaxis after starting therapy, yet the risk of PCP was no different than that in a large group of subjects who never had CD4+ cell counts below 200/μL. These studies and 2 other observational studies presented previously by Furrer (Swiss Cohort Study **[Abstract 140]**) and by Reis (EuroSida **[Abstract 635]**) all suggest that discontinuation of PCP prophylaxis in HAART responders does not pose a significant risk.

The development of disseminated mycobacterial disease (DMD) in at-risk patients who responded to HAART was included in the analysis presented by Dworkin (692). Although this analysis included all DMD, the study addressed risk for MAC, which is the most common DMD. Data from more than 15,000 subjects in a large observational data base were incorporated, and demonstrated that risk for DMD was no different in a potent antiretroviral-treated group with a CD4+ count nadir below 50 cells/μL than in a control group without a CD4+ count value less than 100 cells/μL. With regard to MAC secondary prophylaxis or maintenance therapy in patients responding to potent antiretroviral therapy, investigators evaluated in vitro proliferative responses to MAC and gamma interferon production **(Abstract 248)**. In patients with a history of MAC who were currently taking potent therapy, cellular responses were of similar magnitude to healthy non HIV-infected controls, supporting attempts to discontinue MAC prophylaxis in this population.

Discontinuation of secondary prophylaxis for CMV has become common in patients who have responded to potent antiretroviral therapy. Support for this clinical practice was present in two observational studies, one described by Clotet on behalf of a Barcelona group **(Abstract 455)** and the other by Jouan on a cohort in Paris **(Abstract 456)**. No recurrence of CMV was noted in the 7 patients in the Spanish study who have been followed off prophylaxis for more than 2 years. In the French study, 2 cases of CMV developed among 47 subjects during the mean follow-up time of 7 months. One subject developed CMV in the ipsilateral eye (CD4+ count, 302 cells/μL) 11 weeks after stopping prophylaxis, and one subject developed presumed CMV neuropathy 6 weeks after stopping prophylaxis. In the patient with recurrent retinitis, in vitro proliferative responses to CMV present after potent antiretroviral therapy was started were absent at the time of relapse.

Torriani analyzed failures of CMV prophylaxis discontinuation in a San Diego cohort of 17 patients **(Abstract 250)**. The 5 subjects with recurrent CMV after stopping prophylaxis had CD4+ cell counts that had declined to below 50/μL (4 of 5), loss of HIV RNA suppression, and loss of in vitro proliferative responses to CMV. Reactivation occurred 8 days to 10 months after CD4+ counts dropped below 50 cells/μL and a median of 15 months after discontinuation of maintenance therapy. CMV retinitis recurred in a previously active zone of the retina in 4 of 5 patients, but contralateral eye involvement and disseminated disease occurred in 2 patients. This study emphasizes the point that when potent antiretroviral therapy fails, patients are at risk for recurrence of disease. When to restart prophylaxis for patients in whom virologic or immunologic failure occurs has now become a key clinical question, but it would seem risky not to reinitiate prophylaxis at a CD4+ count below 50 cells/μL.

MAC Treatment Options, More or Less

Although clarithromycin and ethambutol are considered the cornerstone of MAC therapy, the value of adding a third drug has not been established. The results of the ACTG 223, a MAC treatment trial conducted between December 1994 and June 1998 presented by Benson shed light on this issue **(Abstract 249)**. In this study, 160 patients with AIDS and MAC bacteremia were randomized to clarithromycin/ethambutol, clarithromycin/rifabutin, or clarithromycine/

thambutol/rifabutin. The primary study endpoint was bacteriologic response, defined as 2 negative blood cultures for MAC. Response rates were 51% in the 3-drug arm, 40% in the clarithromycin/ethambutol arm, and 42% in the clarithromycin/ rifabutinarm. Evaluation of bacteriologic response at later time points suggested the superiority of the 3-drug arm. Bacteriologic relapse was noted in 6% of patients in the 3-drug arm, 7% in the clarithromycin/ethambutol arm, and 24% in the clarithromycin/ rifabutin arm. A survival advantage was observed in the 3-drug arm, but was not easily explained by the available data. While the results of this study clearly support the 3-drug approach, Benson acknowledged that the benefits of adding rifabutin need to be weighed against the potential detrimental drug-drug interactions with antiretroviral therapy this regimen could produce.

Risk of CMV Disease in Protease Inhibitor-Treated Patients

Several studies have documented the profound decline in new cases of CMV as a result of the widespread use of potent antiretroviral therapy. Nevertheless, patients with extreme CD4+ cell depletion still develop this debilitating complication. The Spanish CMV-AIDS study team attempted to identify at-risk patients by conducting an observational, prospective study of patients with detectable CMV antibody who had less than 100 CD4+ cells/μL, and who were initiating protease inhibitor therapy **(Abstract 251)**. Among the cohort of 172 patients, 11% had CMV viremia (using a PCR-based assay) at baseline. CD4+ cell count and level of plasma HIV RNA was similar between CMV PCR-positive and -negative patients. The cumulative incidence of CMV disease was 6% at 2 years. CMV viremia was highly associated with development of disease (hazard, 4.4, 95% Confidence Interval [CI], 2.1-9.0). The event rate was 38% in CMV PCR-positive and 2% in CMV PCR-negative patients. All subjects with fewer than 50 CD4+ cells/μL at the start of therapy and greater than 1000 copies CMV/mL on the quantitative CMV PCR assay developed CMV disease. Consistent with previous observations, the majority (two thirds) of the new cases developed within the first 3 months of protease inhibitor initiation, suggesting pre-existing disease. These data argue strongly that a strategy utilizing "pre-emptive" therapy for CMV in high-risk patients merits attention and study. ■

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