Metabolic and Morphologic Complications in HIV Disease: What's New?

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It has been more than five years since the first case reports describing bizarre metabolic and morphologic alterations among HIV-positive patients receiving highly active antiretroviral therapy (HAART) first began to trickle out of hospitals, clinics, and doctors' offices around the world. A handful of years later, everything—but seemingly little—has changed. Scattered case reports rapidly evolved into cohorts and huge patient populations experiencing metabolic complications and body-habitus changes; medical journals now struggle to keep up with the volume of submitted research and review articles attempting to define the epidemiology and etiologies of these complications; and numerous standing-room-only workshops, conferences, and educational forums focusing specifically on HIV-related metabolic abnormalities have sprung up all over the world. At the same time, the progress made can be measured in inches. The incidence and prevalence of hypercholesterolemia, hypertriglyceridemia, insulin resistance and impaired glucose tolerance, and lipodystrophy remain high; the risk of comorbidities, such as heart disease and frank diabetes, continues to be of major concern; and treatment options remain limited.

But progress is at hand. Slowly but surely, more conclusive data regarding the epidemiology, pathogenesis, and potential management of the various HAART-related metabolic complications are emerging. To put these advances into perspective, Drs. Kathleen Mulligan and Donald Kotler—two seasoned metabolic experts who cut their teeth on HIV-related wasting syndrome research and have since expanded their scope to include lipodystrophy and its related complications—gave a joint presentation at a jam-packed meeting of PRN in November 2002. Their comments embodied much of their own research, along with other pertinent reports that have either been published or presented over the past few years. Drs. Mulligan and Kotler also drew upon clinical management recommendations that were published recently by the International AIDS Society-USA: the first set of guidelines to be drafted by a blue-ribbon panel that included Dr. Mulligan, Dr. Kotler, and several other well-versed experts (Schambelan, 2002).

The International AIDS Society-USA Recommendations for the Management of Metabolic Complications can be viewed, in their entirety, at:
http://www.iasusa.org/pub/metcomp.html

I. Insulin Resistance and Impaired Glucose Tolerance

Insulin resistance, impaired glucose tolerance, and frank diabetes were uncommon among HIV-positive patients prior to the availability of HAART. The tide began to turn in 1997, when the U.S. Food and Drug Administration (FDA) issued a health advisory on an association between protease inhibitor use and hyperglycemia and diabetes cases. Then, in 1998, two prospective investigational studies concluded that insulin resistance and, to a lesser extent, diabetes were occurring in a significant number of patients receiving HAART (Carr, 1998; Viraben, 1998). In 1999, a paper published in *AIDS* found that long-term use of protease inhibitors, but not nucleoside reverse transcriptase inhibitors (NRTIs), were associated with insulin and glucose abnormalities (Saint-Marc, 1999). Conversely, a second paper published the same year concluded that significant hyperinsulinemia occurs independent of protease inhibitor use, particularly in women (Hadigan, 1999). More recently, in 2001, published data emerged suggesting that protease inhibitors may directly impair glucose transport, hence the rise in insulin resistance and diabetes in HIV-positive patients receiving protease inhibitor-based HAART regimens (Nolte, 2001).

With respect to incidence rates, diabetes mellitus has arisen in 0.5% to 4.4% of patients receiving HAART (Martinez, 2000; Quirino, 2002). The incidence rate has been highest among patients receiving protease inhibitor-based regimens and higher still among HIV/HCV-coinfected patients receiving at least one protease inhibitor. As for subclinical impaired glucose tolerance, the incidence rate was in the ballpark of 16% in at least two cohorts (Aproco Study Group, 1999; Carr, 1999). And insulin resistance has been seen in as many as 55% of patients receiving protease inhibitor-based antiretroviral regimens (Goebel, 1999).

Of particular concern to Dr. Kotler is the fact that insulin resistance, like most of the other metabolic and morphologic complications associated with lipodystrophy, is associated with an increased risk of cardiovascular complications. Studies in HIV-negative patients have consistently demonstrated that insulin resistance has effects on thrombosis, lipid metabolism, blood pressure regulation, and vascular function. There have also been data concluding that the risk of cardiovascular disease is similar in patients with type 2 diabetes mellitus and no prior myocardial infarction (MI) as it is in nondiabetic patients with a prior MI. Although it has not yet been determined whether similar risk is associated with insulin resistance in HIV-positive patients receiving HAART, Dr. Kotler cautioned that, "the presence of type 2 diabetes is considered a coronary heart disease equivalent. In turn, interventions aimed at preventing type 2 diabetes mellitus should favorably modify coronary risk factors."

Pathogenic Mechanisms

THE MECHANISM BY WHICH INSULIN RESISTANCE OCCURS IN HIV-POSITIVE patients receiving HAART has not been established. In fact, a number of hypotheses are still under investigation. As for possible direct effects of antiretroviral therapy, a team of researchers at the Washington University School of Medicine has reported that three protease inhibitors —indinavir (Crixivan), ritonavir (Norvir), and amprenavir (Agenerase)—impair glucose uptake by adipocytes (Murata, 2000). The link between impaired glucose homeostasis and the protease inhibitors was GLUT-4, an intracellular glucose transporter that facilitates glucose entry into adipocytes. Upon transfecting *Xenopus laevis* oocytes—African frog eggs—to express GLUT-4, the researchers found that the ability to transport glucose was significantly impaired within minutes of exposing the oocytes to varying concentrations of the protease inhibitors.

More recent data from studies conducted at the Washington University School of Medicine were reported at the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, held this past September in San Diego (Koster, 2002). In the study presented, indinavir was also found to inhibit GLUT 2 on pancreatic beta cells—the cells that secrete insulin—at concentrations equivalent to those used in the treatment of HIV. In turn, the pancreatic beta cells were unable to sense levels of extracellular glucose, resulting in subnormal insulin secretion. While other protease inhibitors also impaired glucose detection by pancreatic beta cells, concentrations above and beyond those used to treat HIV were necessary to achieve this effect.

There are also clinical data to draw upon. In one prospective study published in the *Journal of Acquired Immune Deficiency Syndromes*, Dr. Mulligan and her colleagues analyzed paired data in HIV-infected patients before and after beginning an antiretroviral regimen (Mulligan, 2001). Twenty patients initiated a regimen that included a protease inhibitor, and nine patients initiated therapy with a combination that contained lamivudine (Epivir) but no protease inhibitor. These 29 patients were compared to a control group of 12 patients on stable regimens that included neither a protease inhibitor nor lamivudine.

Neither weight nor total or regional fat content changed significantly in any group during the follow-up period. However, patients who initiated therapy with a protease inhibitor showed significant increases in several metabolic parameters, including glucose (+9 mg/dL) and insulin (+12.2 U/mL). None of these increases were seen in control patients or patients initiating therapy with lamivudine but no protease inhibitor.

In another study presented by Dr. Mustafa Noor of the University of California, San Francisco, insulin resistance was documented in HIV-negative subjects receiving indinavir (Noor, 2001). Ten subjects were enrolled, and all received standard-dose indinavir monotherapy for four weeks. A baseline and a single follow-up evaluation were conducted to assess glucose levels, glucose tolerance (using the hyperinsulinemic clamp technique), insulin levels, lipid levels, and body-habitus changes.

All study volunteers had normal metabolic parameters prior to starting indinavir. After four weeks, no changes in lipid levels were reported. However, there were notable increases in two-hour postprandial glucose levels and increased insulin levels. One subject had decreased glucose tolerance. Because these subjects were neither HIV-positive nor receiving nucleoside analogues, Dr. Noor's team suggested that indinavir—and possibly other protease inhibitors—may be involved in the development of insulin resistance.

Similar data have been documented in prospective studies involving HIV-positive patients. In one study conducted by Dr. Michael Dubé and his colleagues, HIV-positive patients who received an indinavir-based regimen for eight weeks exhibited signs of insulin resistance (Dubé, 2001). And in another study reported by Dr. Dubé's team, there was a trend toward insulin resistance—in association with weight gain—developing by 48 weeks in a prospective study of HIV-positive patients selected to receive an amprenavir-based regimen (Dubé, 2002).

Beyond the possible direct links between protease inhibitors and impaired glucose tolerance, Dr. Kotler pointed out that a number of studies have indicated that fat distribution changes—including increases in visceral adipose tissue (VAT) and decreased subcutaneous adipose tissue (SAT)—are indirect causes of insulin resistance. Increased VAT, for example, is associated with an elevation in fatty acids, which may contribute to an abnormal metabolic cycle that can result in altered insulin signaling. As for SAT, a significant decrease in the number of adipocytes may ultimately affect the physiologic action of insulin as well.

In one study reviewed by Dr. Kotler, insulin sensitivity was assessed in 12 HIV-negative subjects and two groups of HIV-positive patients: 14 patients without signs of lipodstrophy and 15 patients with lipodystrophy (Mynarcik, 2000). Peripheral insulin sensitivity was determined with the hyperinsulinemic-euglycemic clamp. The patients with lipodystrophy had significantly reduced (twofold) peripheral insulin sensitivity, but normal levels of free fatty acids and reduced levels of circulating insulin-like growth factor (IGF) binding protein-1, relative to the nonlipodystrophy groups, indicating that the loss of insulin sensitivity was more pronounced in skeletal muscle than in the liver or in fat. The significant loss of peripheral fat—lipoatrophy in the extremities—among HIV-positive patients with lipodystrophy closely correlated with the reduced peripheral insulin sensitivity.

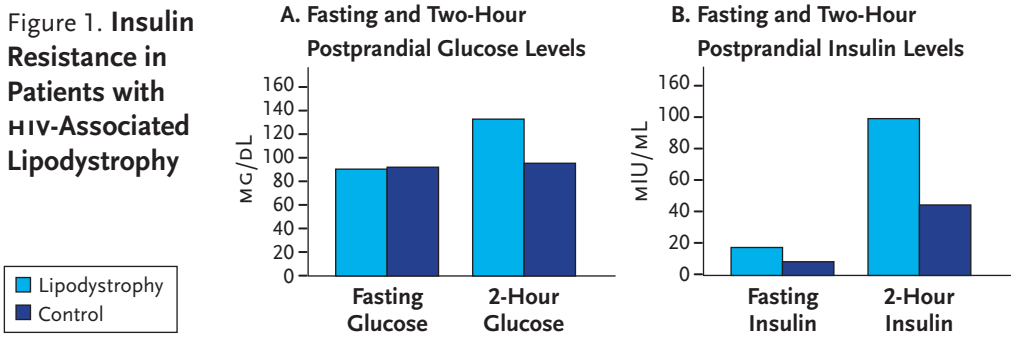
This study also measured serum levels of soluble type-2 tumor necrosis factor-alpha (TNF-α) receptor (STNFR2), an indicator of immune activation. Interestingly, both insulin resistance and lipoatrophy were associated with increased levels of STNFR2. "My personal opinion is that TNF drives body fat changes and insulin resistance and that this may be a primary phenomenon," Dr. Kotler surmised. In turn, Dr. Kotler strongly supports additional studies to ferret out possible hormonal and/or cytokine abnormalities that may promote insulin resistance, including TNF-α and other proinflammatory cytokines, such as interleukin-6. There may also be genetic factors at play, including polymorphisms of the regulatory portion of the TNF-α gene (discussed in greater detail in section III).

HIV/HCV-Coinfection: A Greater Risk of Insulin Resistance?

IT IS WIDELY KNOWN THAT PATIENTS WITH CHRONIC HCV INFECTION ARE at increased risk for insulin resistance and type-2 diabetes mellitus. In turn, there has been much concern regarding the possibility that HIV/HCV-coinfected patients receiving HAART are more likely to be in harm's way. To examine this possibility, a cross-sectional study was performed to investigate whether chronic HCV infection constitutes a risk factor for insulin resistance in HIV/HCV-coinfected patients undergoing antiretroviral therapy (Duong, 2001). A total of 29 HIV/HCV-coinfected patients, 76 HIV-infected patients, and 121 HCV-monoinfected controls were evaluated for various metabolic parameters. According to the study team's paper published in the *Journal of Acquired Immune Deficiency Syndromes*, HIV/HCV-coinfected patients and HCV-positive controls had a significant increase in insulin resistance when compared with HIV-positive patients. Lipoatrophy was more frequently seen in HIV/HCV-coinfected patients in comparison with those infected only with HIV (41% versus 14%, respectively). Interestingly, the HIV/HCV-coinfected pa-

tients had total cholesterol and triglyceride levels that were significantly lower than those seen in the patients who were infected only with HIV. "However," Dr. Kotler commented, "this could be related to the liver disease in these patients."

Figure 1. **Insulin Resistance in Patients with HIV-Associated Lipodystrophy**



In a study to assess the potential link between lipodystrophy and insulin resistance, Dr. Colleen Hadigan and her colleagues evaluated a number of metabolic and clinical features seen in 71 HIV-infected patients with lipodystrophy and compared them with 213 healthy control subjects, matched for age and body mass index, enrolled in the Framingham Offspring Study. With respect to glucose and insulin parameters, patients with lipodystrophy had fasting glucose levels similar to control subjects. However, there were significant differences in the two-hour post prandial glucose levels and both the fasting and two-hour postprandial insulin levels—three telltale signs of compensated normoglycemia and insulin resistance.

Source: Hadigan, 2001. *Clin Infect Dis* 32(1):130-9, 2001. Reprinted with permission of the University of Chicago Press and the Infectious Diseases Society of America.

Assessment and Monitoring

AS PROTEASE INHIBITOR THERAPY MAY induce new or accelerate preexisting abnormalities in glucose tolerance, the IAS-USA recommends that fasting glucose be assessed before and during treatment (three to six months after starting and annually thereafter), if therapy with a protease inhibitor-based regimen is prescribed. Oral administration of glucose (75 g) in a standard two-hour oral glucose tolerance test can also be done to identify patients with impaired glucose tolerance, particular those with risk factors for type-2 diabetes mellitus and/or severe body-fat changes.

The American Diabetes Association defines diabetes mellitus as a fasting plasma glucose level greater than or equal to 126 mg/dL or a glucose level greater than or equal to 200 mg/dL two hours after oral administration of glucose. Impaired glucose tolerance is characterized by a fasting blood glucose level between 110 and 125 mg/dL, or a glucose level between 140 and 199 mg/dL two hours after oral administration of glucose.

The IAS-USA guidelines do not recommend monitoring insulin levels at any point during antiretroviral therapy, despite the fact that impaired insulin sensitivity—a harbinger of impaired glucose tolerance and diabetes mellitus—has been the most frequently reported adverse event of antiretroviral therapy. The most likely reason for this is that only a percentage of HIV-negative adults who develop insulin resistance go on to develop diabetes mellitus. And because there are no treatments indicated for the management of insulin resistance, only diabetes mellitus, it's still not clear how much thought should be given to insulin levels in the clinic. Dr. Kotler, for one, does not agree with this exclusion and hopes that insulin testing will be incorporated into future guidelines, based on observations made in several studies conducted to date.

In one key study reviewed by Dr. Kotler, Dr. Colleen Hadigan and several colleagues evaluated a number of metabolic and clinical features seen in 71 HIV-infected patients with lipodystrophy and compared them with 213 healthy control subjects, matched for age and body mass index, enrolled in the Framingham Offspring Study (Hadigan, 2001). Also included in the analysis were 30 HIV-infected patients without fat distribution changes, compared with 90 matched control subjects, also from the Framingham Offspring Study [*see Figure 1*]. HIV-infected patients with lipodystrophy had fasting glucose levels similar to control subjects. However, there were significant differences in the two-hour postprandial glucose levels and both the fasting and two-hour postprandial insulin levels—three telltale signs of compensated normoglycemia and insulin resistance. "Only looking at fasting glucose levels misses the big picture," Dr. Kotler said. "Fasting glucose levels weren't a problem in this study. However, there were significant differences in both fasting and two-hour insulin levels. The elevated insulin levels point to a metabolic abnormality, but we're only supposed to be looking for signs of diabetes. I don't think clinicians are getting the whole picture if they limit themselves only to glucose testing."

Treatment

IN THE ABSENCE OF CONCLUSIVE STUDIES EVALUATING TREATMENTS FOR insulin resistance and abnormal glucose homeostasis in the setting of HIV, the IAS-USA management recommendations are based on those typically followed for patients without HIV infection. These include following a healthy, balanced diet and a regular exercise routine for all patients, particularly those with impaired glucose tolerance, to prevent the development of frank diabetes. Weight loss is recommended for all patients with either impaired glucose tolerance or insulin resistance, or who are at higher risk for the development of diabetes mellitus.

The potential therapeutic benefits of corrected diets and exercise in HIV-positive patients with metabolic irregularities—including insulin resistance—have been a major interest of Dr. Kotler's group at St. Luke's-Roosevelt Hospital. One such study—the Diet and Exercise in Women (DEW) study—involves a weight-loss program for obese HIV-infected women with varying degrees of VAT content. Preliminary results from this program were presented at the XIV International AIDS Conference, held this past summer in Barcelona (Engelson, 2002). The weight loss program involved 12 weeks of three-times-weekly supervised exercise sessions—which included both aerobic and resistance components—plus a 1,200-calorie diet.

At the time these preliminary data were reported, 15 women had completed the 12-week weight-loss program and had lost, on average, 13 pounds of their baseline body weight. Dr. Kotler explained that the women experienced reductions in both SAT and VAT but did not experience any decreases in muscle mass. Unfortunately, there were no noticeable improvements in insulin sensitivity. "In HIV-negative obese women, we see improvements in insulin sensitivity once SAT decreases," Dr. Kotler said. "In HIV, decreased SAT appears to increase insulin resistance—quantity of SAT and insulin resistance were inversely related

at baseline in our study, which has been reported by other groups as well. The factors controlling for insulin resistance are clearly different in HIV."

With respect to pharmacologic interventions, insulin-sensitizing agents—such as metformin (Glucophage) or a thiazolidinedione (e.g., Avandia)—are indicated when a diagnosis of diabetes mellitus has been made. While there have been some studies exploring insulin-sensitizing agents in lipodystrophic patients with insulin resistance (but not diabetes mellitus), they are not yet recommended for HIV-positive patients who have normal fasting glucose levels.

If insulin-sensitizing agents are used, they should be taken with caution. As specified in the IAS-USA guidelines, careful monitoring for potential adverse effects—such as hepatic dysfunction (if the thiazolidinediones are used) and lactic acidosis (if metformin is used)—is recommended after initiating therapy with these drugs.

The only HIV-specific recommendation listed by the IAS-USA pertains to the use of protease inhibitors in certain patient populations. Consideration should be given to avoiding use of a protease inhibitor-based regimen, at least as initial therapy, in patients with preexisting abnormalities of glucose metabolism or with first-degree relatives with a history of diabetes mellitus.

II. Lipid Abnormalities

LIPID ABNORMALITIES ARE NOT A NEW PHENOMENON AMONG HIV-POSITIVE patients. Prior to the widespread availability and use of HAART, some of the more common observations included decreased levels of HDL, LDL, and apolipoprotein B. Increased triglyceride levels were also frequently seen, which were likely associated with increased levels of very low-density lipoprotein. Dr. Kotler also pointed out that patients with high triglyceride levels and low HDL tended to have an increased prevalence of LDL-B cholesterol or small dense LDL cholesterol, the most atherogenic forms of LDL cholesterol.

Today, lipid abnormalities are still very much with us. Marked triglyceride increases are a frequent occurrence among HIV-positive patients receiving protease inhibitor-based regimens. And in contrast with the decreased cholesterol levels seen in HIV-positive patients in years past, clinicians are now seeing numerous HIV-positive patients with cholesterol levels that are above and beyond the "typical" elevations seen in HIV-negative patients.

The etiology of lipid abnormalities—including those seen prior to the use of HAART—remains obscure. The six protease inhibitors currently available have all been shown to increase both triglycerides and LDL cholesterol, albeit to varying degrees. According to various studies that have been conducted over the past six years, ritonavir—taken at its approved dose of 600 mg twice daily—has the most rapid and pronounced effect on cholesterol levels and triglycerides. Indinavir and amprenavir appear to be the least likely to impact lipid levels. Saquinavir and nelfinavir have been said to have a moderate effect on triglycerides and cholesterol levels, and lopinavir/ritonavir has been shown to have a more pronounced effect on these levels than nelfinavir. Based on these observations and the very real concerns many clinicians have regarding the continued use of currently approved protease inhibitors in their patients with dangerously elevated lipid levels, all eyes are now focused on atazanavir, a protease inhibitor being developed by Bristol-Myers Squibb that boasts a minimal effect on triglycerides and LDL cholesterol.

As for the non-nucleoside reverse transcriptase inhibitors, nevirapine (Viramune) has been shown to increase both LDL and HDL cholesterol. However, for patients experiencing hypertriglyceridemia while taking a protease inhibitor-based regimen, switching to nevirapine has repeatedly been shown to be a saving grace. With respect to efavirenz (Sustiva), data have been decidedly mixed. Some studies have indicated that triglyceride and cholesterol levels can increase upon initiating therapy or switching to an efavirenz-based regimen, whereas other studies have not yielded any such findings.

There is also the possibility of underlying genetic predisposition. A handful of studies have suggested that HIV-positive patients who are heterozygous or homozygous for the apolipoprotein E-2 genotype have higher triglyceride levels and are more likely to experience elevated cholesterol and triglyceride levels upon initiating therapy with a protease inhibitor.

Assessment and Monitoring

AS POINTED OUT IN THE IAS-USA GUIDELINES, FEW STUDIES HAVE BEEN completed to guide the optimal monitoring and treatment of lipid abnormalities in HIV-positive patients. However, some recommendations have been deemed plausible. Prior to initiating antiretroviral therapy, blood samples should be drawn for a fasting lipid panel, consisting of triglyceride and total, HDL, and LDL cholesterol levels. This panel should be repeated within three to six months after starting the antiretroviral regimen and repeated at least once a year thereafter.

Whether or not HIV-positive patients with elevated total and/or LDL cholesterol levels face the same cardiovascular risks as HIV-negative individuals with similar lipid profiles has yet to be determined. The fact of the matter is that cohort studies have yet to find increased rates of myocardial infarction among HIV-positive patients receiving HAART, compared to age-matched HIV-negative controls.

Dr. Kotler pointed out that prospective cohort studies are still under way to evaluate this risk. In the meantime, Dr. Kotler and other IAS-USA panelists recommend using the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III interactive calculator to assess cardiovascular risk—and the need to intervene with adjunctive lipid-lowering treatment modalities—taking into account basic factors such as age, gender, smoking status, presence of diabetes, family history, and hypertension. The NCEP ATP III calculator can be accessed through the World Wide Web: http://hin.nhlbi.nih.gov/atpiii/calculator.asp.

Smoking is, by far, one of the most important cardiovascular risk factors to consider in the care of HIV-positive patients with hyperlipidemia. As illustrated by Dr. Kotler, a 45-year-old male, who smokes, with a total cholesterol level of 290 md/dL, an HDL cholesterol level of 36 mg/dL, and a systolic blood pressure of 134 mm/Hg, has a ten-year coronary heart disease outcome risk of 28%. In the same male, who does not smoke, the ten-year risk of a coronary heart disease outcome decreases to 9%. "Even if we were able to reduce total cholesterol by 40 mg/dL to 250 mg/dL in the smoking 45-year-old male, the ten-year risk only drops to 19%," Dr. Kotler explained. "Smoking cessation is probably the single most important thing that can be done to reduce the risk of myocardial infarction."

Treatment of Lipid Abnormalities

AS THERE HAVE BEEN FEW, IF ANY, WELL-DESIGNED PROSPECTIVE CLINICAL trials evaluating the impact of dietary changes on triglyceride and cholesterol increases that occur in the setting of HIV treatment, the IAS-USA recommends following NCEP dietary guidelines for individuals with hyperlipidemia (NCEP, 2001). A complete review of these dietary rec-

Table 1. **Summary of National Cholesterol Education Program Treatment Recommendations Based on LDL Cholesterol***

Risk Category	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)†	LDL Level at Which to Consider Drug Therapy	LDL Goal	Non-HDL Cholesterol Goal
CHD or CHD Risk Equivalents (10-year risk > 20%)	≥ 100 mg/dL	≥ 130 mg/dL (100-129 mg/dL: drug optional)	<100 mg/dL	<130 mg/dL
≥ 2 Risk Factors (10-year risk ≤ 20%)‡	≥ 130 mg/dL	10-year risk 10–20%: ≥ 130 mg/dL 10-year risk <10%: ≥ 160 mg/dL	<130 mg/dL	<160 mg/dL
0–1 Risk Factor‡	160 mg/dL 190 mg/dL	(160–189 mg/dL: LDL-lowering drug optional)	<160 mg/dL	<190 mg/dL

* For patients with high triglyceride levels in whom LDL cholesterol cannot be measured, non-HDL cholesterol level (total cholesterol—HDL cholesterol) may be used as an approximation if 30 mg/dL is added to the LDL cholesterol threshold. For those with triglyceride levels above 200 mg/dL, the non-HDL cholesterol is considered a secondary target of therapy and the goals of therapy are as indicated under the heading of non-HDL cholesterol goal.

‡ Risk factors include cigarette smoking; hypertension (blood pressure >140/90 mm Hg or taking antihypertension drugs); HDL cholesterol level below 40 mg/dL; family history of premature CHD (in first-degree male relatives <55 years and first-degree female relatives <65 years); age (>45 years for men and >55 years for women). Risk factor equivalent: diabetes. If HDL cholesterol is over 60 mg/dL, subtract one risk factor from the total.

† Therapeutic lifestyle changes refer to reducing saturated fat and cholesterol intake; enhancing the reduction in LDL cholesterol level by the use of plant stanols/sterols and increased soluble fiber; weight reduction; and increased physical activity.

Source: Schambelan, 2002. *J Acquir Immune Defic Syndr* 31(3):260. Reprinted with permission of Lippincott Williams & Wilkins and the International AIDS Society-USA. Adapted in part from Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP, 2001).

ommendations is included in the NCEP ATP III guidelines, which are accessible through the National Heart, Lung, and Blood Institute Web site: http://www.nhlbi.nih.gov/guidelines. Specific recommendations include reducing total fat to no more than 35% of the total daily caloric intake; reducing saturated fat intake to less than 7% of the total calories consumed daily; reducing dietary cholesterol to less than 200 mg/day; increasing intake of plant sterols/stanols and soluble fiber to enhance LDL reductions; weight reduction through reduced caloric intake; and, last but not least, exercise.

For patients who experience elevated triglyceride and/or cholesterol levels while receiving a protease inhibitor-based regimen, there has been a significant amount of research indicating that switches to regimens that do not contain protease inhibitors are beneficial. As was reviewed in an article focusing on the metabolic effects of switching antiretrovirals, published in the September 2001 issue of *The PRN Notebook*, regimens employing nevirapine, efavirenz, or abacavir as their therapeutic backbone are useful switch options to consider. A switch to a nevirapine-containing regimen has been shown to reduce both triglycerides and total cholesterol and to raise HDL cholesterol; dropping a protease inhibitor in favor of efavirenz may result in additional triglyceride increases, but with increases in HDL cholesterol seen as well; and switching to an abacavir-based regimen has been shown to reduce both triglycerides and total cholesterol.

Moving on to pharmacologic interventions, HMG CoA reductase inhibitors ("statins") are recommended by the IAS-USA for the management of hypercholesterolemia [*see Table 2*]. However, they should be prescribed with caution, given the documented likelihood of CYP 3A4 interactions with the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors. Simvastatin (Zocor) and lovastatin (Mevacor) are generally contraindicated in patients receiving protease inhibitors. Atorvastatin (Lipitor) is a possibility, though the starting dose should be reduced and then titrated, if necessary, to achieve the desired cholesterol-lowering effect. Conversely, standard doses of pravastatin (Pravachol) are generally considered safe for HIV-positive individuals being treated with a CYP3A4-inhibiting protease inhibitor or NNRTI, although a pravastatin dose increase might also be necessary if the desired effect is not achieved. No matter which "statin" is used, clinicians may find comfort in monitoring liver function tests and CPK levels to ensure the safety of these drugs.

In one clinical trial discussed by Dr. Kotler, 31 HIV-positive men receiving HAART who had cholesterol levels of, on average, 290 mg/dL, were randomized to receive either dietary counseling alone or dietary counseling in combination with pravastatin (Moyle, 2001). After 24 weeks, total cholesterol levels fell more than 17%—a drop of 46 mg/dL—in the pravastatin group, compared to a 4% drop among the patients who only received dietary counseling. This fall was accounted for entirely by a reduction in LDL cholesterol, as HDL cholesterol increased somewhat in both groups. Weight, fasting glucose, and triglycerides did not change significantly in either group.

With respect to the management of hypertriglyceridemia, the use of fibrates is indicated by the IAS-USA guidelines. "Once triglycerides are above 1,000 mg/dL, there's an increased risk of pancreatitis," warned Dr. Kotler. "Dietary improvements can help bring down triglyceride levels, but not always within normal ranges. Using a fibric acid analogue may also be useful."

One of the largest studies completed to date evaluating the potential benefits of statins and fibrates was ACTG 5087, a randomized trial comparing the safety and efficacy of fenofibrate to pravastatin in HIV-positive patients with lipid abnormalities (Aberg, 2002). A total of 159 patients were enrolled, all of whom had fasting LDL cholesterol levels greater than 130 mg/dL, triglycerides greater than 200 mg/DL, and had been receiving HAART for at least six months. The pravastatin dose used was 40 mg/day; the fenofibrate dose used was 200 mg/day.

After 12 weeks of treatment, 5% in the pravastatin group and 1% in the fenofibrate group had LDL cholesterol levels below 100 mg/dL. HDL cholesterol was above 35 mg/dL in 49% of patients who received pravas-

Table 2. **Studied and Potential Drug Interactions Between Antiretrovirals and Either Hypoglycemic or Lipid-Lowering Drugs**

Drug or Drug Class	Metabolism Pathway	Potential Drug Interaction(s)
Rosiglitazone*	CYP 2C8	Ritonavir, nelfinavir induce CYP 2C9; may have similar effect on CYP 2C8 and therefore reduce rosiglitazone exposure.
Pioglitazone*	CYP 2C8, 3A4	PIs or NNRTIs that inhibit or induce CYP 3A4 may alter pioglitazone concentrations.
Sulfonylureas*	CYP 2C9	Ritonavir, nelfinavir induce CYP 2C9; may reduce the concentrations of selected sulfonylureas.
Repaglinidine*	CYP 3A4	PIs or NNRTIs that inhibit or induce CYP 3A4 may alter repaglinidine concentrations.
Fibric acid derivatives*	Hepatic glucuronidation	Ritonavir, nelfinavir induce glucuronidation; may reduce fibrate concentrations.
Simvastatin, Lovastatin	CYP 3A4	Ritonavir/saquinavir increase plasma exposure of simvastatin 30-fold. Concomitant use of PIs and simvastatin or lovastatin is contraindicated.
Pravastatin	Intestinal, hepatic glucuronidation	Ritonavir/saquinavir decrease pravastatin exposure by 50%; low-dose ritonavir (100 mg BID), and indinavir, amprenavir, saquinavir are unlikely to substantively affect pravastatin exposure.
Atorvastatin	CYP 3A4 (active metabolites)	Ritonavir/saquinavir increase atorvastatin plasma exposure by 343%; decreased active metabolite exposure, resulting in overall 74% increase in total active atorvastatin exposure (similar interaction demonstrated with nelfinavir).

* No drug interaction studies have been performed with these agents and antiretroviral drugs. Potential interactions suggested are based on extrapolation from *in vitro* studies delineating the mode of metabolism of oral hypoglycemic and antilipid drugs and the known effect of PIs or NNRTIs on these metabolizing enzymes.

Source: Schambelan, 2002. *J Acquir Immune Defic Syndr* 31(3):260. Reprinted with permission of Lippincott Williams & Wilkins and the International AIDS Society-USA.

tatin and 66% of patients who received fenofibrate. Triglyceride levels fell below 200 mg/dL in 8% of the pravastatin patients and 48% of the fenofibrate patients. Statistically speaking, pravastatin had a significant effect on LDL cholesterol levels, whereas fenofibrate had a significant effect on both HDL cholesterol and trigylceride levels.

Looking at the big picture, 136/159 (85.5%) of patients failed to meet the NCEP "standard" for normalized lipid levels after 12 weeks of their designated study medications. While these patients were to be offered a combination of pravastatin and fenofibrate for an additional 12 weeks—as per the original protocol's instructions—enrollment was stopped because neither monotherapy arm achieved success with respect to a predetermined proportion of subjects meeting composite lipid goals.

Rhabdomyolosis, a side effect associated with statins and fibrates, has been a concern among clinicians interested in prescribing both classes together. In ACTG 5087, however, no cases of rhabdomyolosis were reported. Still, if statins and fibrates are to be combined, the IAS-USA recommends initiating therapy with a statin, followed by the addition of the fibric acid derivative after four months, if the response is suboptimal.

III. Morphologic Complications

MUCH HAS BEEN DISCUSSED AND WRITTEN ABOUT HAART-ASSOCIATED morphologic complications, including several pertinent review articles in *The PRN Notebook* (most recently in June 2000, based on a PRN lecture delivered by Dr. Kotler). Instead of providing a detailed overview of these morphologic complications—which would require an entire issue of *The PRN Notebook* in itself—Dr. Mulligan limited her discussion to some of the newest, most important data that will likely continue to guide clinical research and the medical management of lipodystrophy in the months and years to come.

Risk Factors for Morphologic Complications

ONE STUDY THAT HAS GARNERED A GREAT DEAL OF ATTENTION IN RECENT months is A5005S, a body-composition substudy of ACTG 384 (Dubé, 2002a). A5005S was designed to monitor changes in limb fat—fat in the arms and legs—and trunk fat using dual-energy x-ray absorptiometry (DEXA) scanning in association with starting various antiretroviral combinations for the first time. In essence, A5005S is the first clinical trial to prospectively study HIV-positive patients who had not taken other antiretrovirals in the past—thus avoiding the pitfalls that are usually encountered while milking data from retrospective analyses, cross-sectional cohort studies, and protocols involving patients who are antiretroviral-experienced.

ACTG 384 is a complex study. It contains six study groups with two randomizations. The first randomization involves an open-label assignment to receive stavudine plus didanosine or zidovudine plus lamivudine. The second randomization, which is blinded, assigns patients to receive nelfinavir, efavirenz, or nelfinavir and efavirenz combined. Of the 980 patients enrolled into ACTG 384, 89 patients in the zidovudine/lamivudine group underwent DEXA scanning as a component of A5005S; 87 patients in the stavudine/didanosine group underwent DEXA scanning. The preliminary data from A5005S, reported at the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, were based on 80 weeks of follow-up.

Dr. Mulligan pointed out that during the first 36 weeks of therapy, there was an increase in both trunk fat and limb fat in both groups of patients. "This doesn't really come as a surprise," Dr. Mulligan commented, "as many of the patients likely entered the study with decreased fat mass and body weight. Essentially, they all got healthier upon starting antiretroviral therapy." It was not until 12 weeks later that differences in body composition were seen between the two groups.

After 48 weeks of treatment, there was a statistically significant decrease in limb fat in the stavudine/didanosine group, compared to the

zidovudine/lamivudine group. However, it should also be pointed out that limb fat also decreased among patients receiving zidovudine and lamivudine.

As for trunk fat, Dr. Mulligan explained that increases were seen in both groups of patients. "The problem here is that, by using DEXA, it's not possible to distinguish between the two fat compartments," Dr. Mulligan said. "It could be subcutaneous fat that's increasing, or it could be visceral fat. These increases might reflect differential changes in the different compartments, but with DEXA, we have no way of knowing for sure."

Looking at the other therapeutic components employed in the study, the A5005S study team found that, after 80 weeks of therapy, patients receiving nelfinavir were statistically more likely to experience lipoatrophy than those randomized to receive efavirenz. "This suggests that the addition of a protease inhibitor may accelerate fat loss," Dr. Mulligan pointed out. Trunk-fat increases were also seen in both the nelfinavir and efavirenz groups. However, the increases in trunk fat came to a peak around the 48th week of treatment and have since shown a downward trend, toward baseline. "There appears to be more rapid trunk fat loss in the nelfinavir group compared to the efavirenz group," Dr. Mulligan pointed out. "Again, using DEXA scanning, it's not possible to determine if it's subcutaneous fat or visceral fat that's being lost. But I think these data show that we've come a long way from the days in which we were calling this 'protease paunch.' If anything, these data show that there's not a lot of clarity regarding the role of protease inhibitors in fat accumulation."

Additional, more conclusive data from A5005S is expected to be presented over the next year, which will include a total of three years of follow-up.

Dr. Mulligan also discussed data from a longitudinal study of body-habitus changes, again measured by DEXA, conducted at the Royal Perth Hospital in Perth, Australia (Nolan, 2002). Using complex nonlinear mixed-effects mathematical modeling, the investigators compared the effects of antiretroviral therapy on leg fat in a group of patients initiating treatment for the first time with regimens containing either stavudine or zidovudine. In the analysis presented at the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 26 patients had been taking a zidovudine-containing regimen and 27 had been taking a stavudine-containing regimen.

Upon entering the study, leg fat accounted for, on average, 22% of total leg weight among the patients enrolled. As in A5005S, there was an early increase in leg weight gain, followed by a decrease in leg fat. After two years of therapy, patients receiving a stavudine-containing regimen had leg fat accounting for 13% of their leg weight, compared to 19% among patients receiving a zidovudine-containing regimen. "Both the ACTG study and the Perth study underscore the importance of longitudinal data," Dr. Mulligan said. "Other analyses relying on snapshots of patients' situations don't allow us to see there may be different periods of fat gain and loss, which were definitely seen in these two studies."

As for the take-home messages from these two studies, Dr. Mulligan indicated that the role of nucleoside analogues in the development of lipoatrophy is becoming much more clear. "I don't want to demonize one drug over the other," Dr. Mulligan cautioned, "but stavudine is associated with more rapid progression of fat loss. However, zidovudine may not be totally innocent. The progression rate isn't zero in studies looking at this nucleoside analogue."

Genetic Predisposition?

JUST AS THE USE OF NUCLEOSIDE ANALOGUES AND PROTEASE INHIBITORS has been linked to the onset and progression of morphologic changes, there are also a number of non-drug factors to consider. These include age, duration of HIV infection, effectiveness of viral suppression, immune recovery, baseline body-mass index (BMI), change in BMI, gender, and race. Another possible nondrug factor may be genetic predisposition.

An increasing number of genetic association studies over the past several years have implicated various polymorphisms of cytokine genes and host genetic factors influencing susceptibility to a number of human diseases. Because not all HIV-positive patients receiving HAART experience metabolic and/or morphologic abnormalities—and because of the possibility that these abnormalities are the result of inflammation that often accompanies chronic diseases—there has been much interest in finding genetic factors that might increase susceptibility to various HAART-associated side effects.

One study discussed by Dr. Mulligan, which also comes from the Royal Perth Hospital, examined the effects of polymorphisms of the regulator portion of the TNF-α gene, namely those occurring at positions –238G/A and –308G/A, which have been suggested to increase susceptibility to other (non-HIV-related) diseases. Employing samples collected from the Western Australia HIV Cohort, the investigators found that patients who had the –238G/A polymorphism were much more likely—and more rapidly—to experience lipoatrophy than patients who had the –308G/A polymorphism or no polymorphisms at all (Nolan, 2002a). This association was found to be independent of other possible risk factors, including age and time on antiretroviral treatment.

"This was the first, and most likely not the last, demonstration of genetic factors that can modulate risk," Dr. Mulligan said. "It's interesting that we're seeing this with TNF-α, a cytokine that has frequently been implicated in HIV-related problems. Additional genetic studies may continue to provide us with clues as to the pathogenesis of these and other complications."

The Rocky Road to a Case Definition

WITH SO MUCH RESEARCH GENERATED OVER THE PAST SIX YEARS, IT'S HARD to believe that a case definition for lipodsytrophy has not yet been established. "There's been lots of talk, yet there's still no agreement on a case definition," Dr. Mulligan said. "The bottom line here is that I don't think we can expect consensus any time soon. I think the issue embodies fundamental intellectual differences about what comprises this syndrome."

A conscientious effort to come up with an objective case definition for lipodystrophy was first undertaken by the European Medicines Evaluation Agency—the European equivalent of the U.S. Food and Drug Administration—in the form of a large multinational cohort study. The results of this Herculean task were initially presented by Dr. Andrew Carr of St. Vincent's Hospital in Sydney, Australia, at the 9th Conference on Retroviruses and Opportunistic Infections (CROI) last year in Seattle and are currently being prepared for publication in *The Lancet* (Carr, 2002). The basic premise of the study was to assess various host, drug, metabolic, and morphologic variables in preselected cases and to determine the factors most likely to be associated with lipodystrophy when compared to controls.

This study collected data from 32 research centers from around the world so as to include a diverse racial and ethnic mix of patients. Each research center provided data for 12 cases and 12 controls. Cases were handpicked by investigators at each site and were defined as

patients who had at least moderate (noticeable to the patient and clinician) or severe (noticeable to a casual observer) lipoatrophy, diffuse fat accumulation, or focal fat accumulation (lipomatosis). Patients who only had abdominal obesity were excluded as cases, given the possibility that that fat gain was simply "natural" age-related adiposity. Study subjects were considered controls if there were no clinician-confirmed signs of lipoatrophy, diffuse fat accumulation, or focal fat accumulation.

A total of 1,081 patients were initially evaluated, 265 of whom were designated as cases and 239 of whom were designated as controls. Approximately 15% of participants were female, 70% were white, and 65% were men who have sex with men. Once enrolled in the study, cases and controls were asked to answer extensive questionnaires, provide fasting blood tests, and undergo DEXA and CT scanning.

Using logistic-regression analysis, Dr. Carr's team isolated ten factors that define lipodystrophy: being of the female sex, being over the age of 40, having HIV for more than four years, reaching the CDC stage C AIDS classification, having a wider anion gap, decreased HDL cholesterol levels, increased waist:hip ratio, increased VAT:SAT ratio, higher trunk-to-limb fat ratio, and a decreased percentage of leg fat.

In reviewing these data, however, Dr. Mulligan pointed out that there are several caveats to consider. "First of all," she said, "low HDL cholesterol has been seen in HIV-positive patients for more than a decade. This isn't new to anyone and, in turn, doesn't define lipodystrophy. As for the increased waist-to-hip ratio, it's important to realize that this can be a result of either increased waist circumference or decreased hip circumference. The VAT-to-SAT ratio is also problematic, as it can mean either increased visceral fat or decreased subcutaneous fat. So this case definition forces us to consider fat accumulation and fat loss as one syndrome."

These data were validated in an additional 152 cases and 132 controls and yielded a sensitivity of 84% and a specificity of 81%. "However," Dr. Mulligan commented, "the jury is still out on how useful this case definition is going to be. The more we learn about lipodystrophy, the more we feel that it's not simply one syndrome we're dealing with. Lumping everything together into one syndrome may not be accurate."

Challenging the proposed EMEA case definition of lipodystrophy are data from the Fat Redistribution and Metabolic Change (FRAM) study, another multi-site, cross-sectional cohort. Preliminary data from FRAM, which were orally reported by Dr. Carl Grunfeld of the University of California, San Francisco, at the XIV International AIDS Conference and updated at a meeting of the Forum for Collaborative HIV Research in San Diego in September 2002 and at the 10th Conference on Retroviruses and Opportunistic Infections in February 2003, question the assumption that the various metabolic and morphologic abnormalities being seen in HIV-positive patients can actually be categorized as being of the same syndrome (Grunfeld, 2002; Gripshover, 2003; Saag, 2003).

Unlike the EMEA study, FRAM did not preselect cases and controls, but instead randomly selected 1200 HIV-positive patients through various HIV research sites in the United States and 300 HIV-negative controls (randomly selected from the Coronary Artery Disease Risk Development in Young Adults [CARDIA] study, sponsored by The National Heart, Lung, and Blood Institute). This allowed for a number of key comparisons using two distinct patient populations. What's more, FRAM was not conducted with any preconceived notions as to what the syndrome is. And for factors to be considered a part of an HIV-specific syndrome, there needed to be statistically significant differences between the HIV-positive patients and the HIV-negative controls. There also needed to be statistically significant positive associations between two factors for them to be included in the same syndrome.

The Barcelona, San Diego, and Boston presentations of the FRAM data focused on 350 HIV-positive men and will be expanded to include just as many women in the future.

With respect to lipoatrophy, HIV-positive men in the FRAM study were significantly more likely to self-report peripheral fat loss—in the cheeks, face, arms, legs, and buttocks—whereas HIV-negative controls were more likely to report gains in peripheral fat. Using MRI, the FRAM investigators found that HIV-positive men, regardless of whether or not they self-reported lipoatrophy, had significantly less SAT than HIV-negative controls. And among the HIV-positive men, MRI evidence of lipoatrophy was more pronounced in those who did self-report lipoatrophy than those who did not. Peripheral fat in the legs suffered the most profound loss, followed in decreasing order by peripheral fat in the arms, lower torso, upper torso, and back.

Perhaps the most striking and unexpected finding was the comparison of VAT content between the two groups. The HIV-positive subjects were no more likely than the HIV-negative controls to self-report increases in abdominal fat. Turning to the MRI data, the FRAM investigators determined that VAT was somewhat lower in the HIV-positive patients when compared to the HIV-negative controls—a finding that was statistically significant. "Essentially, there was no linkage between fat lipoatrophy and fat accumulation," Dr. Mulligan explained. "HIV-positive patients with lipoatrophy weren't any more likely to experience changes in VAT than HIV-positive patients without lipoatrophy." To be fair, Dr. Mulligan pointed out that body-mass indexes were higher in the HIV-negative controls, which might have some impact on the body composition data. "The FRAM team is still trying to figure out how to adjust these data in light of the differences in BMI. But these are interesting data nonetheless."

It's also important to note that buffalo humps—enlargement of dorsocervical fat pads—were statistically more likely to be reported by HIV-negative controls than the HIV-positive patients. In turn, it's not clear if this particular morphologic abnormality can be incorporated into the case definition of lipodystrophy, at least not in the FRAM study.

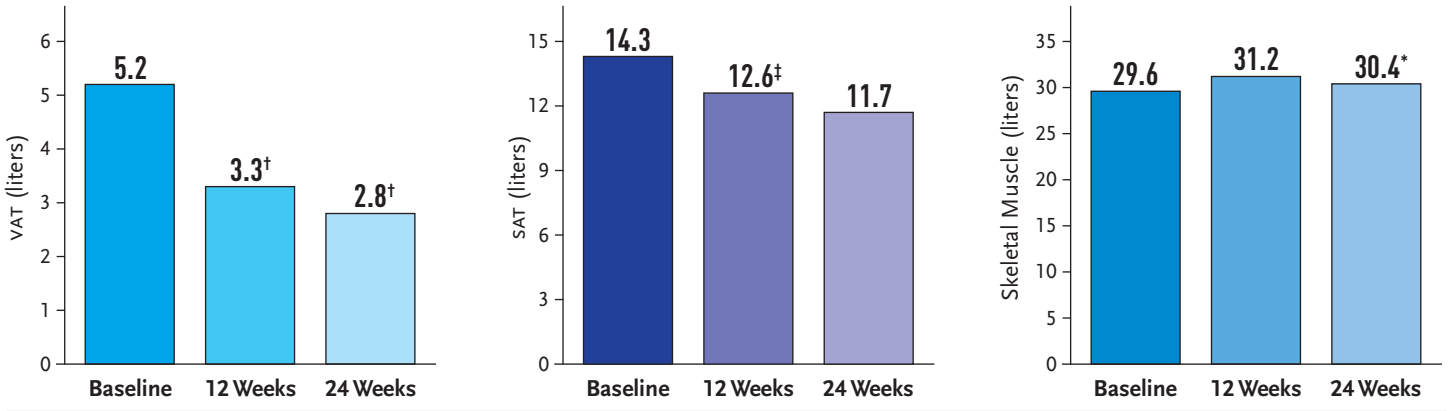
When all is said and done, Dr. Mulligan does not believe that either of these studies will necessarily lead to a consensus regarding a case definition. Despite their important differences, both studies are cross-sectional evaluations, which are capable only of providing snapshots of patients' experiences at a particular moment in time. "We need longitudinal studies with a large number of patients and long-term follow-up," Dr. Mulligan argued. "It would be nice to have a case definition. I know that the drug companies want it. I know the FDA wants it. I know the EMEA wants it. A lot of people want it. But I think we have to accept the fact that there are good reasons why we don't have a consensus case definition yet and get on with it. In the meantime, while the debate continues, so does good research."

Treatments for Morphologic Complications

WHILE THERE IS LITTLE CONSENSUS REGARDING THE BEST POSSIBLE TREATments for body-habitus changes, there is no shortage of demand for them. For HIV-positive people, morphologic changes can be both disabling and stigmatizing and have profound effects on adherence and patients' perspectives of treatment. Fortunately, encouraging data have emerged over the past few years.

While there have been a number of "switch" studies—protocols analyzing the effects of switching from a protease inhibitor-based regimen to a non-protease inhibitor-including regimen—demonstrating that protease inhibitor substitution can improve insulin sensitivity and

Figure 2. **Growth Hormone for Lipodystrophy: MRI Results in Subjects Receiving 6 mg/Day rhGH for 24 Weeks**



*P< 0.05, compared to baseline ‡P< 0.01, compared to baseline †P< 0.001, compared to baseline

Source: Engelson, 2002a

lipid profiles, there isn't much in the way of conclusive evidence supporting switches to reverse body-habitus changes.

In one clinical trial conducted in Sydney, 81 HIV-positive patients receiving protease inhibitors who were experiencing lipoatrophy were randomized to continue their nucleoside analogues and substitute their protease inhibitor(s) for a heady brew consisting of abacavir, nevirapine, adefovir and hydroxyurea (switch group), or to continue on their protease inhibitor-based regimen with an option to switch after 24 weeks (control group) (Carr, 2001). There was a greater decline in total body fat in the switch group than in the control group (-1.6 and -0.4 kg, respectively) after 24 weeks. The bad news is that patients in the switch group experienced further declines in limb fat. The good news is that patients who entered the study with moderate or severe VAT accumulation and were in the switch group experienced decreases in intra-abdominal fat. Viral suppression was similar in both groups, although it's important to mention that 18 (37%) patients in the switch group ceased at least one drug before the 24th week of follow-up because of adverse events. Total cholesterol and triglycerides declined more in the switch group, and HDL cholesterol increased significantly in both groups; insulin sensitivity remained unchanged.

Recombinant human growth hormone (rhGH; Serostim), a compound Dr. Mulligan has worked closely with over the years, continues to show encouraging potential for patients with fat redistribution. In one study published last year in the *Journal of Acquired Immune Deficiency Syndromes*, 30 HIV-positive patients with VAT accumulation were enrolled in a 24-week evaluation of rhGH, administered subcutaneously once-daily at a dose of 6 mg (Engelson, 2002a). Because significant adverse events were seen during the initial 24-week study, a second evaluation using a lower dose of rhGH—4 mg every other day—was conducted for an additional 24 weeks in the same group of patients, following a 12-week washout period.

While body weight was maintained throughout the study, VAT decreased in evaluable patients by 42% with the use of rhGH 6 mg/daily and 15% with 4 mg every other day after 12 weeks, with trends toward further decrease after an additional 12 weeks at each dose [*see Figure 2*]. SAT also decreased, but proportionately less so than VAT using the 6 mg/daily dose of rhGH; using the 4 mg every other day dose, SAT decreases were not statistically significant from baseline. However, during the washout period, most patients saw their body composition rebound to or near their baseline characteristics.

Total cholesterol fell in the higher dose group and HDL cholesterol increased only in the lower dose group. There was no significant effect on triglyceride levels. Insulin sensitivity worsened in a number of patients, with 4/30 (13%) reaching a diagnosis of diabetes mellitus during the study. Another noteworthy adverse event: three patients were diagnosed with different cancers (anal carcinoma, adenocarcinoma, and basal cell carcinoma) while receiving rhGH.

There are also preliminary data from the STARS—Serostim in the Treatment of Adipose Redistribution Syndrome—trial, which were presented by Dr. Kotler at the XIV International AIDS Conference, this past summer in Barcelona (Kotler, 2002). In this study, 239 patients with signs and symptoms of lipodystrophy (including increased waist circumference and waist:hip ratio) were randomized to receive placebo or rhGH at 4 mg/day, administered subcutaneously, either daily or every other day, for 12 weeks.

Flashing some of Dr. Kotler's slides presented in Barcelona, Dr. Mulligan pointed out that, after 12 weeks of follow-up, there was a significant decrease in VAT among the patients who received daily rhGH, a non-significant trend toward decreased VAT among the patients who received rhGH on alternating days, and minimal changes among those who received placebo. DEXA scanning revealed significant reductions in the trunk:limb fat ratio in both groups of actively treated patients. In terms of the total amount of fat lost in the study among the treated groups, approximately 84% was composed of truncal VAT. There were no significant decreases in limb SAT in either of the treatment groups.

With respect to metabolic parameters, there were significant decreases in both total and non-HDL cholesterol in both treated groups, compared to the placebo group. Triglyceride levels remained, for the most part, unchanged, and there were significant elevations in fasting and postprandial glucose levels, requiring some dose reductions.

Recombinant human growth hormone is not recommended, at least not at the present time, by the IAS-USA for the control of body fat redistribution. The IAS-USA panelists correctly point out that the optimal therapeutic and maintenance doses have not yet been determined and

that the potential for adverse effects currently outweighs whatever positive effects this drug has.

Ending her talk with a brief discussion of insulin-sensitizing agents for the possible management of body-habitus changes, Dr. Mulligan first reviewed metformin data published in 2000 in the *Journal of the American Medical Association* (Hadigan, 2000). The trial enrolled 26 HIV-infected, nondiabetic patients with fat redistribution and impaired glucose tolerance and/or elevated insulin levels. They were randomly assigned to receive metformin 500 mg BID or placebo for three months. Patients treated with metformin experienced significant improvements in glucose tolerance, along with significant decreases in body weight and reduced waist circumference. No decreases in serum lipid levels were reported in patients treated with metformin. Visceral abdominal fat, measured by cross-sectional abdominal CT scans, did decrease in the metformin group, but these observations were not statistically significant. These data are similar to an earlier study, conducted in France, and published as a letter in *AIDS* (Saint-Marc, 1999a).

The thiazolidinediones have also been suggested to play a potential role in the management of morphologic abnormalities, most notably the reverse of lipoatrophy given the *in vitro* ability of these drugs to stimulate PPAR-γ and, consequently, adipogenesis. Three clinical trials employing these agents have yielded conflicting results, with no consistent data demonstrating a positive impact on either VAT or SAT (Gelato, 2002; Sutinen, 2001; Calmy, 2001). Eagerly awaited are the results of ACTG 5082, a randomized clinical trial comparing metformin, rosiglitazone (Avandia), and a combination of both drugs in HIV-positive patients with increased VAT and elevated insulin levels.

Until additional data are available from studies examining all of the possible therapies for morphologic complications, the official word from the IAS-USA is rather lackluster: "No therapies for fat distribution abnormalities in the absence of other metabolic complications can be routinely recommended."

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