

## Rapid Communications

# Management of Metabolic Complications Associated With Antiretroviral Therapy for HIV-1 Infection: Recommendations of an International AIDS Society–USA Panel

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**Objective:** Alterations in glucose and lipid metabolism, lactic acidemia, bone disorders, and abnormal body fat distribution have been recognized recently as frequent complications associated with HIV-1 infection and potent antiretroviral therapy, but limited data are available regarding the appropriate management of these disorders. These recommendations were developed to guide physicians actively involved in HIV care in the management of metabolic complications that occur primarily within the context of potent antiretroviral therapy.

**Participants:** A 12-member panel representing international expertise in HIV-1 patient care, antiretroviral therapy, and endocrine and metabolic disorders was selected in the spring of 2000 by the International AIDS Society–USA, a not-for-profit physician education organization. Panel members met in closed meetings beginning in May 2000. All work was funded by the International AIDS Society–USA; the panel members are not compensated for their participation.

**Evidence:** The panel reviewed published results of clinical, epidemiologic, and basic science studies and data and abstracts presented at research conferences, primarily from 1997 to 2002. The panel also considered studies of the pathophysiology and treatment of similar metabolic abnormalities in noninfected persons. Emphasis was placed on results from prospective, randomized, controlled clinical trials when available.

**Process:** For each metabolic complication, 1 or more member(s) reviewed and presented all available evidence to the panel, and then wrote a summary of the evidence and preliminary recommendations. Final recommendations were determined by

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full group consensus. The summaries were combined into a single working document and all panel members edited and approved all subsequent drafts.

**Conclusions:** Carefully controlled studies to determine the incidence, etiology, risk factors, and most appropriate treatments for metabolic complications in HIV-1 infection are urgently needed. In the absence of these data, and to prevent acute illness and mitigate long-term risks, the panel recommends routine assessment and monitoring of glucose and lipid levels and assessment and monitoring of lactic acidemia and bone abnormalities if clinical signs or symptoms are detected. With the exception of body fat distribution abnormalities, specific treatments for these complications are also recommended. Successful long-term antiretroviral therapy will require diligent monitoring and preemptive treatment of metabolic complications to optimize the risk-benefit ratio of antiretroviral therapies.

**Key Words:** HIV—Antiretroviral—Insulin resistance—Hyperlipidemia—Lipodystrophy—Lactic acidemia—Osteoporosis—AIDS—Guidelines—Metabolic complications.

The availability of potent combination antiretroviral regimens has resulted in a dramatic reduction in HIV-1-associated morbidity and mortality in the developed world (1). However, the optimism generated by such treatment has been tempered by the recognition of an increasing array of adverse metabolic effects, including insulin resistance and glucose intolerance, dyslipidemia, changes in body fat distribution, lactic acidemia, and osteopenia (2–14). Although intensive investigation is in progress, the mechanisms underlying these abnormalities and their relationship to specific antiretroviral therapies remain unclear. For many patients, these adverse effects have had a substantial negative impact on quality of life, and have raised concerns about possible cardiovascular and other long-term risks that they may confer (15–17). Although there are no approved therapies for body fat abnormalities, reports of treatments that have reversed similar abnormalities in non-HIV-1-infected persons have led patients and clinicians to use unproven, and in some cases, potentially deleterious, therapies.

In light of these concerns, there is a pressing need for appropriate guidelines for the assessment and management of these metabolic complications, as there is for updated antiretroviral therapy recommendations (18). The International AIDS Society–USA selected and convened a panel of clinicians and investigators experienced in HIV-1 patient care, antiretroviral therapy, and endocrine and metabolic disorders, to comprehensively review and evaluate relevant published and unpublished clinical and basic science data (including original articles, national and international research conference abstracts and presentations, and review articles), and to develop recommendations for the clinical management of these metabolic complications based on the published evidence and the expert opinion of the panel members. The recommendations were developed by group consensus, with particular emphasis accorded to results from prospective, randomized, controlled clinical trials in

HIV-1-infected individuals, when available. The panel also considered data from trials in progress, information from laboratory-based investigations, and extrapolations from studies of the pathophysiology and treatment of metabolic abnormalities in non-HIV-1-infected individuals. Although recommendations regarding diagnostic assessment, monitoring, and treatment interventions for each disorder are provided, in many instances precise algorithms for treatment of specific conditions are not included, as available data from controlled clinical trials are not sufficient to provide a definitive approach in this patient population.

## INSULIN RESISTANCE AND ABNORMAL GLUCOSE HOMEOSTASIS

### Background

Insulin resistance, impaired glucose tolerance, and frank diabetes mellitus were uncommon in HIV-1-infected individuals prior to the availability of potent antiretroviral therapy. When identified, frank hyperglycemia and diabetes mellitus were most often associated with specific medications (eg, pentamidine or megestrol acetate) or known predisposing factors (19,20). Although fasting glucose levels remain normal in most patients receiving potent antiretroviral therapy, up to 40% of patients on a protease inhibitor-containing regimen will have impaired glucose tolerance (21) due to significant insulin resistance (4,22).

The proportion of HIV-1-infected patients with insulin resistance that will develop fasting hyperglycemia and diabetes mellitus is unknown. Patients with traditional risk factors for type 2 diabetes mellitus and who are taking protease inhibitors may be at particularly high risk (23). Insulin resistance in non-HIV-1-infected individuals is associated with increased risk of cardiovascular complications due to effects on thrombosis, lipid metabolism, blood pressure regulation, and direct vascular

effects (24–26). Whether similar risk is associated with drug-induced insulin resistance in HIV-1–infected individuals remains to be established.

Insulin resistance is characterized by the reduced ability of insulin to inhibit hepatic gluconeogenesis and to increase muscle uptake of glucose. The pathophysiologic basis of insulin resistance in patients on potent antiretroviral therapy is unknown. Potential mechanisms include direct effects of antiretroviral drugs that impair cellular glucose uptake (27), or indirect mechanisms related to body fat changes, including central obesity and/or peripheral lipoatrophy (21,22,28). Protease inhibitors may have an early direct effect, inducing insulin resistance independent of changes in body composition (5,23). Inhibition of glucose transport mediated by GLUT-4, the predominant transporter involved in insulin-stimulated cellular uptake of glucose in humans, appears to contribute to protease inhibitor-associated insulin resistance (27). Indinavir may also induce insulin resistance by inhibiting peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) expression via decreasing sterol regulatory element binding protein-1 (SREBP-1) (29,30). Whether all protease inhibitors induce such changes remains uncertain. One study demonstrated that 4 weeks of indinavir monotherapy in healthy volunteers was associated with the development of insulin resistance without changes in visceral fat (23). Similarly, 8 weeks of indinavir-based therapy in HIV-1–infected subjects was associated with insulin resistance (31), but 8 weeks of amprenavir-based therapy was not (32). Indinavir has also been shown to induce insulin resistance after a single dose (33), consistent with the GLUT-4 hypothesis. However, comparative clinical studies regarding association of the different protease inhibitors with insulin resistance are lacking. As in HIV-1–uninfected patients, increased visceral fat and loss of extremity fat in patients with HIV-1 infection may be associated with insulin resistance (34). In addition, nRTI use is associated with increased lipolysis, which may further contribute to insulin resistance (35,36).

### Recommendations for Assessment and Monitoring

Institution of protease inhibitor therapy may induce new or accelerate preexisting abnormalities in glucose tolerance. Fasting glucose should be assessed before and during treatment (3–6 months after starting and annually thereafter) with potent antiretroviral therapy that includes a protease inhibitor. Oral administration of 75 g of glucose may help to identify patients with impaired glucose tolerance, particularly those with risk factors for type 2 diabetes mellitus and/or severe body fat changes.

Diabetes mellitus (fasting blood glucose  $\geq 126$  mg/dL [7.0 mmol/L] or a glucose level  $\geq 200$  mg/dL [11.1 mmol/L] 2 hours after oral administration of glucose) and impaired glucose tolerance (glucose level  $\geq 140$  mg/dL [7.8 mmol/L] 2 hours after oral glucose) are defined as for HIV-1–uninfected individuals.

### Treatment

Studies identifying optimal treatment of fasting hyperglycemia associated with insulin resistance or glucose intolerance in HIV-1–infected patients have not been completed. Treatment recommendations of the panel are based on expert opinion and extrapolation from data in patients without HIV-1 infection.

Consideration should be given to avoiding use of a protease inhibitor-based regimen as initial therapy, or to substituting alternatives to protease inhibitors if possible in patients with preexisting abnormalities of glucose metabolism or with first-degree relatives with diabetes mellitus. Substitution of the protease inhibitor component of a regimen with nevirapine (37), efavirenz (38), or abacavir (39) has been associated with short-term improvements in insulin resistance and may be considered in this setting.

For patients with persistent fasting hyperglycemia, established guidelines for treating diabetes mellitus in the general population should be followed (40). A healthy, balanced diet and regular exercise are recommended for all patients, and are particularly important for those with impaired glucose tolerance to prevent development of diabetes mellitus. Similarly, weight loss is recommended for overweight subjects with impaired glucose tolerance or insulin resistance, or who are at higher risk for the development of diabetes mellitus. When drug therapy is required, consideration should be given to using insulin-sensitizing agents, such as metformin or a thiazolidinedione. Studies in small numbers of HIV-1–infected patients using metformin suggest potential benefits in reducing insulin levels, waist circumference, blood pressure, and cardiovascular risk (41,42). The thiazolidinediones increase insulin sensitivity in both non-HIV-1–infected and HIV-1–infected patients with insulin resistance and evidence of lipodystrophy (43,44). Oral hypoglycemic agents and insulin may also be appropriate for patients with more severe degrees of fasting hyperglycemia, although oral sulfonylureas, meglitinides, and related hypoglycemic agents may be of less benefit in HIV-1–infected patients with insulin resistance and may induce hypoglycemia. Insufficient evidence exists to recommend drug treatment of HIV-1–infected patients with evidence of insulin resistance who have normal fasting glucose levels.

Careful monitoring for potential adverse effects, such as hepatic dysfunction (thiazolidinediones) and lactic acidemia (metformin), is recommended after initiation of these drugs. Clinicians should inform patients about the typical symptoms of hepatic dysfunction and lactic acidemia. Liver enzymes should be monitored every 2 months for the first 12 months of thiazolidinedione treatment. Plasma lactate levels should be measured if new symptoms suggesting lactic acidemia develop during metformin treatment. Patients with significant preexisting liver disease (aspartate aminotransferase or alanine aminotransferase >2.5 times the upper limit of normal [ULN]) should not take thiazolidinediones. Patients with serum creatinine above the ULN for their age or lactic acidemia (venous lactate levels >2.0 times the ULN) should not take metformin. Other considerations with respect to possible drug-drug interactions with antiretroviral agents are reviewed in Table 1.

## LIPID AND LIPOPROTEIN METABOLISM ABNORMALITIES

### Background

Multiple abnormalities in lipid metabolism were reported in HIV-1-infected patients prior to the current treatment era. These included decreased levels of high-density lipoprotein (HDL) cholesterol (45–49), low-density lipoprotein (LDL) cholesterol, and apolipoprotein B (45–47,50,51), and increased triglyceride levels due to increased levels of very low-density lipoprotein

(45–47). In general, reported reductions in LDL cholesterol levels were of lesser magnitude than those in HDL cholesterol, resulting in a proatherogenic profile. Patients with high triglyceride and low HDL cholesterol levels have an increased prevalence of LDL-B cholesterol or small dense LDL cholesterol (52), the most atherogenic form of LDL cholesterol. Lipoproteins in HIV-1 infection also have increased platelet-activating factor (PAF) acetyl hydrolase, which is proatherogenic (53).

In the current treatment era, the use of protease inhibitors has been associated with marked elevations in triglyceride levels and increases in LDL cholesterol to levels similar to or above those observed in HIV-1-uninfected individuals, depending on the protease inhibitor used (2,3,5,7,8,54–63). Newer protease inhibitors may have less of an effect on levels of triglycerides or LDL cholesterol (64), but may also be less efficacious. Specific protease inhibitors differ in their effects on plasma triglyceride and cholesterol levels. Ritonavir has the most robust effect (8,57,62,63,65–67) and can induce hypertriglyceridemia after only 2 weeks of administration in HIV-1-seronegative subjects (7). In contrast, indinavir has minimal effects on lipid levels after 4 weeks of administration to HIV-1-seronegative subjects (23). Lopinavir/ritonavir increased triglyceride and cholesterol levels to a greater degree than nelfinavir in one randomized clinical trial (68). Use of amprenavir with abacavir and lamivudine led to a 30% increase in total cholesterol and directly measured LDL cholesterol (32). Most studies, with one exception (55), have found no change in HDL cholesterol levels associated with prote-

**TABLE 1.** Studied and potential drug interactions between oral hypoglycemic and lipid-lowering drugs when used concomitantly with antiretroviral drugs

Drug/drug class	Metabolism pathway(s)	Potential drug interaction(s)
Rosiglitazone*	CYP 2C8	Ritonavir, nelfinavir induce CYP 2C9; may have a 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 adversely affect repaglinidine concentrations and effect.
Fibric acid derivatives*	Hepatic glucuronidation	Ritonavir, nelfinavir induce glucuronidation; may reduce fibrate concentrations.
Simvastatin	CYP 3A4	Ritonavir/saquinavir increased plasma exposure of simvastatin 30-fold (205). Concomitant use of PIs and simvastatin or lovastatin is contraindicated.
Lovastatin		
Pravastatin	Intestinal, hepatic glucuronidation	Ritonavir/saquinavir decreased pravastatin exposure by 50%, (205); low dose ritonavir (100 mg bid), and indinavir, amprenavir, saquinavir are unlikely to substantively affect pravastatin exposure (206).
Atorvastatin	CYP 3A4 (active metabolites)	Ritonavir/saquinavir increased atorvastatin plasma exposure by 343% (205); decreased active metabolite exposure, resulting in overall 74% increase in total active atorvastatin exposure (205) (similar interaction demonstrated with nelfinavir (207)).

\* No drug interaction studies have been performed with these agents and antiretroviral PI or NNRTI 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 and NNRTIs on these metabolizing enzymes.

CYP, cytochrome P450 isoenzyme; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; bid, twice daily.

ase inhibitor therapy. The increase in PAF acetyl hydrolyase is also not reversed by protease inhibitor therapy (53). Thus, the proatherogenic profile of lipoproteins is not improved, and worsens slightly, with protease inhibitor therapy.

The mechanisms that induce lipid abnormalities associated with potent antiretroviral therapies remain elusive. One recent study found no association between nucleoside reverse transcriptase inhibitors (NRTIs) and hyperlipidemia (69). Data for nonnucleoside reverse transcriptase inhibitors (NNRTIs) continue to evolve. Nevirapine increases HDL and LDL cholesterol (70); hypertriglyceridemia in some patients receiving protease inhibitors is rapidly reversed by switching to nevirapine (37,71–76). The effects of efavirenz are contradictory, as numerous studies report conflicting results following initiation of or switching to efavirenz, with increases or no change in cholesterol levels and differing data as to the degree to which increases in total cholesterol are due to LDL or HDL cholesterol fractions. Reported changes in triglyceride levels are even more variable (38,69,77,78). However, an increase in HDL cholesterol level has been observed after initiation of efavirenz, and after a switch to efavirenz where it was measured (79,80).

Genetic susceptibility may greatly influence the risk for development of drug-, HIV-1-, or fat distribution-induced changes in lipid or lipoprotein levels. HIV-1-infected patients who are heterozygous or homozygous for the apolipoprotein E-2 genotype have higher triglyceride levels (81,82), and may have more dramatic changes in cholesterol and triglyceride levels when receiving protease inhibitor therapy (59,83,84).

### Recommendations for Assessment and Monitoring

As with abnormalities of glucose homeostasis, few studies have been completed to guide the optimal monitoring and treatment of lipid abnormalities in HIV-1-infected individuals. Based on available data, a fasting lipid panel, consisting of triglyceride and total, HDL, and LDL cholesterol levels, should be obtained prior to the initiation of or a switch to a new potent antiretroviral therapy, and repeated 3 to 6 months after starting or switching therapy and at least annually for those who remain on combination antiretroviral therapy. LDL cholesterol levels (in mg/dL) can be calculated using Friedewald's equation:  $\text{calculated LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - \text{triglycerides}/5$  (85). (In Système International units, the calculation is:  $\text{total cholesterol} - \text{HDL cholesterol} - \text{triglycerides}/2.18$ .) If the triglyceride levels are greater than 400 mg/dL (4.5

mmol/L), Friedewald's equation is not reliable and a direct LDL cholesterol measurement should be obtained. If direct LDL cholesterol measurement is not possible, non-HDL cholesterol levels of 30 mg/dL (0.8 mmol/L) greater than those listed for LDL cholesterol can be used to determine if intervention is needed. More frequent monitoring is advised (see below) if lipid values are abnormal or if interventions are planned.

At present, it is unknown whether the lipid elevations associated with HIV-1 infection and antiretroviral therapy carry the same cardiovascular risk as in HIV-1-uninfected populations. Evaluations of short- and long-term outcomes associated with metabolic abnormalities in HIV-1-infected patients are in progress. Until such data are available, alterations in the lipid profile need to be considered in the context of other cardiovascular risk factors such as age, gender, smoking status, presence of diabetes, family history, hypertension, and, among women, menopausal status. The decision to intervene in a patient with HIV-1 infection and abnormal lipid levels should be based on the prognosis of their HIV disease and the overall assessment of their cardiovascular risk (86). The recently updated National Cholesterol Education Program (NCEP) III guidelines serve as a framework for identifying patients whose LDL cholesterol level and total cardiovascular risk require hypolipidemic intervention (Table 2) (87). For hypertriglyceridemic patients, non-HDL cholesterol can serve as the therapeutic target (see footnote to Table 2). (For more information on NCEP III see: <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>.) In addition, an overall assessment of cardiovascular risk using nomograms developed from Framingham data may help to individualize interventions when they are warranted (88).

Since the Framingham risk equations use total cholesterol and HDL cholesterol, they can be used in significantly hypertriglyceridemic patients in whom a calculated value of LDL cholesterol cannot be obtained. (The Framingham risk equations and the NCEP III risk calculator are available at <http://hin.nhlbi.nih.gov/atp/iii/calculator.asp>.)

### Treatment

Randomized clinical trials that establish optimal treatment of hyperlipidemia associated with antiretroviral therapy in HIV-1-infected patients have not been completed. The following recommendations are based on preliminary data from small pilot studies, observational data from cohort studies, extrapolation from data in HIV-1-uninfected patients, and expert opinion of panel members.

TABLE 2. Summary of National Cholesterol Education Program treatment recommendations based on LDL cholesterol\*

Risk Category	Initiate therapeutic lifestyle changes†	Consider drug therapy	LDL cholesterol goal	Non-HDL cholesterol goal
With CHD or CHD risk equivalent (10-year risk >20%, noncoronary atherosclerotic vascular disease, or type 2 diabetes mellitus)	≥100 mg/dL (≥2.6 mmol/L)	≥130 mg/dL (≥3.4 mmol/L) 100–129 mg/dL (2.6–3.3 mmol/L): therapy optional	<100 mg/dL (<2.6 mmol/L)	<130 mg/dL (<3.4 mmol/L)
2 or more risk factors (10-year risk ≤20%)‡	≥130 mg/dL (≥3.4 mmol/L)	10-year risk of 10–20%: ≥130 mg/dL (≥3.4 mmol/L) 10-year risk of <10%: ≥160 mg/dL (≥4.1 mmol/L)	<130 mg/dL (<3.4 mmol/L)	<160 mg/dL (<4.1 mmol/L)
0 or 1 risk factor‡	≥160 mg/dL (≥4.1 mmol/L)	≥190 mg/dL (≥4.9 mmol/L) 160–189 mg/dL (4.1–4.9 mmol/L): therapy optional	<160 mg/dL (<4.1 mmol/L)	<190 mg/dL (<4.9 mmol/L)

\* 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 (0.8 mmol/L) is added to the LDL cholesterol threshold. For those with triglyceride levels above 200 mg/dL (2.3 mmol/L), the non-HDL cholesterol level 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 (1.0 mmol/L); 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 (1.6 mmol/L), subtract 1 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.

CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

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). *JAMA* 2001;285:2486–97 (87).

### Modification of Antiretroviral Therapy

For patients with preexisting cardiovascular risk factors, hyperlipidemia, or a family history of a lipid disorder, consideration should be given to initiating or switching to protease inhibitor-sparing antiretroviral regimens, as numerous studies have documented either lower risk or reversal of increased cholesterol or triglyceride levels with the use of triple nRTI regimens or those containing nRTIs and NNRTIs, particularly nevirapine (37,39,71, 72,75,89–94). However, when options are limited, antiretroviral drugs that may lead to lipid elevations should not be withheld for fear of further exacerbating lipid disorders.

### Diet

In the absence of results from randomized, controlled clinical trials evaluating specific dietary interventions in HIV-1-infected patients with lipid disorders, the panel recommends following NCEP dietary guidelines for lowering cholesterol in adults. For patients without known coronary artery disease, therapeutic lifestyle changes are the initially recommended intervention. These include dietary restriction of total fat to 25% to 35% of total caloric intake, saturated fat to less than 7% of total calo-

ries, dietary cholesterol to less than 200 mg per day, use of plant sterols (2 gm/d), increased intake of viscous (soluble) fiber (10–25 gm/d), weight reduction when indicated, and increased physical activity or exercise (87). Recent data also support the use, in hypercholesterolemic patients, of a Mediterranean diet (low saturated fat but without a severe restriction of monounsaturated or omega-3 polyunsaturated fat, replacing some of the complex carbohydrates with monounsaturated fatty acids) (95).

Lifestyle changes recommended for treatment of isolated hypertriglyceridemia, in addition to reduced fat intake, weight loss, and exercise, include reduction in alcohol intake. Patients with persistent high-grade hypertriglyceridemia (>1000 mg/dL [11.3 mmol/L]) may benefit from a very low-fat diet, even if they are not overweight.

### Use of Lipid-Lowering Agents

Lipid-lowering agents should be considered for treatment of isolated or severe hypertriglyceridemia and/or elevated LDL and total cholesterol levels that do not respond to modification of antiretroviral therapy or therapeutic lifestyle changes, or for patients in whom such modifications are not appropriate.

Triglyceride levels greater than 1000 mg/dL (11.3 mmol/L) are generally associated with an increased risk of pancreatitis (96). The threshold suggested for intervention is 500 mg/dL (5.6 mmol/L) (87). A change in diet alone can markedly improve elevated triglyceride levels, but is unlikely to return them to normal (66,97–99). Fibric acid analogues reduce triglyceride levels in HIV-1-infected patients on protease inhibitors (66) and are the preferred initial therapy. There are presently 2 fibric acid derivatives, gemfibrozil and fenofibrate, that are approved by the US Food and Drug Administration, and at present there is no reason to favor one over another.

The HMG-CoA reductase inhibitors (statins) have been shown to reduce total and LDL cholesterol levels in HIV-1-infected patients on protease inhibitors (66,100). Based on data from drug interaction studies (Table 1), pravastatin and atorvastatin are the preferred agents for use in HIV-1-infected patients on potent antiretroviral therapies who require therapy for cholesterol elevations. A low starting dose should be employed (20 mg of pravastatin or 10 mg of atorvastatin once daily) followed by cautious dose escalation tailored to treatment response.

Although both the statins and fibric acid analogs have been shown to reduce cholesterol and triglyceride levels in HIV-1-infected patients, they frequently do not restore levels to normal (66,97–100). These 2 classes of drugs work by different mechanisms and may have synergistic activity. However, both classes of drugs can cause rhabdomyolysis. If combination therapy with a fibric acid derivative and a statin is anticipated in the setting of hypertriglyceridemia accompanied by LDL cholesterol elevation, therapy should begin with a statin, followed by the addition of the fibric acid derivative after month 4 if the response is suboptimal. The prescribing information cautions that combined therapy with statins and fibric acid analogues should be used only when the benefits outweigh the risks; hence it is logical to assess the maximal effect of one class of drugs before starting the second. The long-term effects of lipid-lowering agents and their impact on cardiovascular outcomes when used for treatment of antiretroviral therapy-associated elevations of blood lipids are unknown.

## BODY FAT DISTRIBUTION ABNORMALITIES

### Background

A number of cohort studies have documented, through patient self-report and/or clinician observation, a variety of body fat distribution abnormalities in HIV-1-infected patients receiving potent antiretroviral therapies, including buffalo hump, central and visceral fat accumulation,

facial and limb fat atrophy, and lipomatosis (101–104). Recent large surveys have yielded prevalence estimates of such body fat distribution abnormalities in the range of 40% to 50% (101–103). The variance in prevalence estimates likely stems from the use of different diagnostic criteria, as well as differences in demographic factors, HIV-1 treatment practices, and disparities between patient and physician assessments (71,104).

Although several early cross-sectional studies suggested fat distribution abnormalities were associated with protease inhibitor use (2,6), other studies provided clear evidence that these could occur in protease inhibitor-naive subjects (9,13,105–107). Specific roles for each class of drugs have not been defined, but an association between lipoatrophy and nRTIs (10,108–110), possibly accelerated in the presence of a protease inhibitor (11), has been suggested. Current data do not support a role for NNRTIs in the development of these abnormalities (11).

A number of host factors, in addition to type and duration of antiretroviral drug exposure, have been associated with fat distribution abnormalities. These include older age, baseline body mass index or change in body mass index, duration of HIV-1 infection, effectiveness of viral suppression, baseline degree of immunodeficiency and subsequent immune restoration with therapy, and white race (11,102,104,111–113). Gender-based differences in presentation have been reported, with women more likely to develop fat accumulation and men fat loss (111–114); these findings may reflect differences in baseline body composition, however. Although older age is a consistently reported risk factor, body fat changes occur naturally with aging and body fat distribution abnormalities have also been reported in HIV-1-infected children (115).

The underlying mechanisms and specific site(s) of dysregulation accounting for the morphologic abnormalities have not been identified. It has been suggested that nRTI-associated inhibition of DNA polymerase- $\gamma$ , which is required for mitochondrial DNA replication, may trigger events that result in fat distribution abnormalities (116,117). Although mitochondrial damage is a recognized complication of nRTI therapy, a causal role in the development of metabolic or fat distribution abnormalities has not been demonstrated. In contrast, *in vitro* studies of protease inhibitors suggest that they might affect preadipocyte differentiation (29).

### Recommendations for Assessment and Monitoring

The cross-sectional imaging techniques of computed tomography (CT) and magnetic resonance imaging

(MRI) are the criterion (gold standard) methods for the assessment of body fat distribution. Their ability to differentiate tissues on the basis of density makes them ideal measures for 3-dimensional reconstruction. CT and MRI measurements have been validated against measurements in cadavers (118), and each other (119). Single-slice measurements correlate strongly with whole-body measurements for both subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) (107,119,120), and are much less labor-intensive to analyze.

There are several limitations to the use of cross-sectional techniques, however, most notably their expense and limited availability. CT scanning also entails substantial radiation exposure. Very few studies have reported the results of whole-body studies; more commonly the results of single-slice measurements are reported. Data are usually expressed as the absolute values of SAT or VAT in  $\text{cm}^2$ , though sometimes the ratios VAT/TAT (total adipose tissue) or VAT/SAT are used. There are relatively few data in normal control subjects, so it is difficult to classify individual patients as having normal or abnormal fat distribution. Body fat distribution in healthy individuals is affected by age, gender, race, and total fat content. In addition, a substantial proportion of the "normal" population may have excess VAT, with associated metabolic abnormalities. Although SAT depletion is commonly observed in patients thought to have lipodystrophy, it also is a key characteristic of malnutrition, especially in women (121,122). Finally, the subcompartments of SAT and VAT are not homogeneous, and partition based only upon 3-dimensional localization might be overly simplistic. Thus, further development of these techniques is in order.

Anthropometric estimates of both VAT and SAT have been published, though more emphasis has been placed on the prediction of VAT, and the major applications have involved epidemiologic studies. Anthropometric measurements such as the waist-to-hip ratio have been repeatedly shown to correlate with health outcomes (123). The major advantages of anthropometry are its safety, portability, and low cost. The lack of specificity of changes in the waist-to-hip ratio limits its use as a clinical tool (124–132). Waist circumference alone, as well as sagittal diameter, are more sensitive and specific measures than waist-to-hip ratio (120,128–130,133). Although the measurements are standardized, they require considerable training and retraining for the results to be reproducible. In addition, only gross cutoffs are available for assigning subjects as normal or abnormal, and no published data allow translation of waist circumference to VAT.

Bioelectrical impedance analysis (BIA) estimates whole body composition, though attempts have been made to modify the measurement for regional purposes. To date, methods to use BIA for regional body composition have not been validated against criterion methods, and thus cannot be recommended for this purpose.

DEXA is suitable for examining appendicular fat, which is comprised almost entirely of SAT. Estimation of visceral fat is more difficult since changes in VAT and SAT independently affect trunk fat. The observed lack of change in trunk fat reported in early studies using DEXA may have been due to divergent changes in VAT and truncal SAT. A major finding in HIV-1-infected men and women with fat distribution abnormalities has been a loss of appendicular fat, without equivalent loss, or with gain, of truncal fat (2,105,108).

Theoretically, ultrasound is a better technique than DEXA since it can accurately separate adipose and lean compartments and allow 3-dimensional measurements. The depth of specific adipose tissue compartments can be measured, including those on the face, an area that has not been measured with cross-sectional imaging to date. However, its application to HIV infection has been very limited (134).

Thus, although a variety of methods have been applied to the measurement of body fat distribution in HIV-1-infected persons, at this time no technique has demonstrated sufficient sensitivity, specificity, or predictive value to be recommended for routine clinical assessment and monitoring of body fat distribution changes. This recommendation may change once evidence of the accuracy of a particular technique emerges or if recommendations for therapies based upon altered fat distribution are developed. For example, measurement of waist circumference, which can be done easily and inexpensively in a clinical setting, has been included among the cardiovascular risk assessments recommended in the recent NCEP III guidelines. Many of the other measures are quite useful in clinical investigations, especially in epidemiologic and intervention studies.

### Treatment

There is no consensus as to whether it is appropriate to treat fat distribution abnormalities in the absence of other metabolic complications. Regional fat accumulation has been associated with headaches, difficulty breathing, and interference with exercise and sleep. Obvious facial and extremity wasting can represent a

form of involuntary disclosure of HIV-1 status. Many patients are troubled by these changes to an extent that adherence to otherwise effective antiretroviral regimens may be threatened and unproven or deleterious treatments attempted. There are no proven or approved therapies for fat distribution abnormalities, although a number are under investigation (see Table 3). Because there is considerable etiologic and phenotypic diversity in fat distribution abnormalities, it is extremely unlikely that a single therapeutic approach will apply in all cases. Therefore, if the decision is made to intervene, it is crucial to identify the specific objectives of treatment (eg, general or regional fat loss, or peripheral fat gain) and associated metabolic factors (such as insulin resistance, hyperlipidemia, lactic acidemia, hypogonadism, or liver disease) that may require treatment or contraindicate certain therapeutic approaches. The potential direct and ancillary benefits and contrain-

dications for each therapy under investigation are listed in Table 3.

*Modification of Antiretroviral Therapy*

Studies using objective measurements have not demonstrated consistent reversal of central fat accumulation abnormalities with discontinuation of or substitution for protease inhibitor therapy (37,38,71). Thus, for individuals with isolated fat accumulation, this approach is not recommended. For patients in whom lipodystrophy is the primary complaint, data from preliminary results of randomized studies suggest that withdrawal of stavudine and substitution with abacavir or zidovudine is associated with statistically significant but clinically modest increases in peripheral fat, measured by DEXA, and maintenance of virologic control (135–137). However, in an earlier study in which stavudine was removed and no

**TABLE 3.** *Effects of interventions evaluated for treatment of body fat changes*

Intervention	Potential benefits for fat distribution	Ancillary benefit	Potential risks	Comment
Hypocaloric diet	↓ VAT	↓ TG, cholesterol ↓ IR?	↓ SAT	Indicated with BMI >27 Aerobic vs. PRT?
Exercise	↓ VAT	↓ TG, ↑ LDL-C, ↓ IR, ↑ HDL-C, ↑ bone density	↓ SAT	
Insulin sensitizers				
Metformin	↓ VAT?	↓ IR, ↓ TG	↓ SAT, weight, lactic acidemia, transient diarrhea; ↓ in VAT nonsignificant and modest with low dose	Start low (500 mg bid)
Thiazolidinediones	↓ VAT, ↑ SAT with troglitazone	↓ IR	Hepatic toxicity (troglitazone); ↑ TG, cholesterol in one study of rosiglitazone in HIV+ subjects	Limited data with rosiglitazone and pioglitazone in HIV+ subjects show no evidence of hepatotoxicity but inconsistent effects on fat distribution
Growth hormone	↓ VAT	↑ HDL-C	↓ SAT, ↑ IR, diabetes, joint stiffness, fluid accumulation in extremities with pharmacologic doses	Reverses with therapy discontinuation, optimal dose unknown
Testosterone (physiologic)	↓ VAT	Improved well-being; protein anabolic effect	None	Only for male hypogonadism; not recommended for women
Testosterone (supraphysiologic)	No data	Improved well-being; protein anabolic effect	↓ HDL-C, mood changes, hypogonadism	Not recommended for women
Synthetic testosterone derivatives	No data	Improved well-being; protein anabolic effect	↓ HDL-C, mood changes, hypogonadism	No data
Switch antiretroviral therapy: protease inhibitor →no protease inhibitor	Few data. ↓ VAT in one study	Metabolic improvements	Loss of virologic control	No improvement in SAT; randomized, prospective studies required
Switch nRTIs	↑ SAT with stavudine discontinuation	Metabolic improvements ?	Loss of virologic control if no agent is substituted	Improvements in SAT are modest; longer follow-up may be needed
Plastic surgery	Cosmetic; functional improvements?	Improved quality of life? functional improvement, improved adherence?	Surgical risks	Recurrence

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; IR, insulin resistance; nRTI, nucleoside reverse transcriptase inhibitor; PRT, progressive resistance training; SAT, subcutaneous adipose tissue; TG, triglyceride; VAT, visceral adipose tissue; ↑, an increase in value or measurement; ↓, a decrease in value or measurement.

antiretroviral substituted, virologic failure occurred in the majority of patients (138).

#### *Exercise*

Both aerobic (139) and resistance (140–143) exercise have considerable potential as nonpharmacologic interventions and should be encouraged for HIV-1–infected individuals with central or generalized fat accumulation. Moderate exercise is well tolerated in patients with HIV-1 infection (140,144) and does not increase viral load (145). In a small study of resistance exercise training in HIV-1–infected patients who complained of increased abdominal girth, there was a significant decline in total fat, measured by DEXA, and the majority of fat loss occurred in the truncal region (141). Another report showed that resistance exercise increased lean body mass without changing fat mass and reduced triglyceride levels without changing total LDL or HDL cholesterol in HIV-1–seropositive men on antiretroviral therapy (142).

#### *Diet*

There are no data to support a role for specialized dietary components or supplements in HIV-1–infected patients with fat distribution abnormalities in the absence of other metabolic abnormalities or a general requirement for weight reduction. Patients with HIV-1 infection should avoid diets that result in rapid weight loss, which can accelerate lean tissue loss (146–148). Overall, it would be prudent to focus dietary interventions primarily on reducing total energy content by reducing intake of saturated fat, simple carbohydrates, and alcohol, while maintaining protein and micronutrient intake.

#### *Growth Hormone*

Administration of pharmacologic doses of growth hormone (GH; 6 mg/d [approximately 10 times the physiologic replacement dose]) to patients with central fat accumulation (primarily buffalo hump and abdominal obesity) has resulted in both subjective and objective improvements in body composition (149–151). Studies using objective measurements of central fat or VAT have demonstrated consistent declines with GH treatment at lower but still pharmacologic doses (152–154). However, pharmacologic GH may at least transiently exacerbate insulin resistance and produce persistent alterations in glucose homeostasis (153–155). Because GH secretion may be reduced in patients with visceral adiposity (156), physiologic doses of GH are being studied. Importantly, the improvements noted with GH therapy have

been shown to consistently reverse following discontinuation (153). Although GH appears to be effective in reducing excess central fat, it should not be used for patients with impaired glucose tolerance or whose primary complaint is lipoatrophy. The optimal therapeutic and maintenance doses have not been identified, and potential adverse effects (glucose intolerance, insulin resistance, arthralgias, fluid accumulation in the extremities) do not warrant a recommendation for its general use at this time.

#### *Testosterone*

Decreased testosterone levels are associated with visceral obesity (157) and insulin resistance in nondiabetic (158), obese (159), and HIV-1–infected men (160). Replacement doses of testosterone in men with visceral obesity have been associated with decreases in visceral fat and improvements in insulin sensitivity (161–164). These results suggest that testosterone replacement in hypogonadal HIV-1–infected men with increased abdominal girth may be of benefit. However, to date no studies have been reported that evaluate the efficacy or safety of either physiologic or pharmacologic testosterone or synthetic testosterone derivatives in HIV-1–infected individuals with fat distribution abnormalities. Therefore, androgen therapy cannot be recommended for this purpose.

#### *Thiazolidinediones*

In vitro stimulation of PPAR- $\gamma$  by thiazolidinediones can increase adipogenesis, suggesting that these agents may be able to reverse subcutaneous fat loss. Indeed, troglitazone increased subcutaneous fat and reduced visceral fat in patients with type 2 diabetes mellitus (165,166) and in those with various syndromes of genetic and acquired lipodystrophy (43). If subcutaneous fat cells in HIV-1–infected individuals with lipoatrophy can respond similarly, then thiazolidinediones may have a unique role in treating patients with lipoatrophy. Troglitazone has been removed from the market in the United States because of hepatic toxicity, but rosiglitazone and pioglitazone are available. Preliminary studies using these agents in HIV-infected patients with abnormal fat distribution have not produced consistent evidence of improvement in central or peripheral fat (44, 167,168), and in one study triglyceride and cholesterol levels increased in patients randomized to receive rosiglitazone (167). Larger trials are under way. On the basis of currently available data, these drugs cannot be recommended to treat fat distribution abnormalities.

### Metformin

Two randomized studies of metformin in HIV-1-infected patients with evidence of insulin resistance and central fat accumulation demonstrated improvements in glucose tolerance, reductions in insulin and triglyceride levels, decreased weight and some evidence of decreased VAT (measured by CT scanning) compared with untreated controls (41,42), and decreased diastolic blood pressure, plasminogen activator inhibitor-1 and tissue-type plasminogen activator levels (41,169). These studies suggest that metformin may be effective in patients with central fat accumulation and glucose intolerance or insulin resistance, and for these reasons may be a preferred modality when treatment of the latter is necessary. The contraindications for metformin use are discussed above.

## LACTIC ACIDEMIA

### Background

Lactic acidosis is defined as an elevated venous lactate level ( $>18$  mg/dL [ $2$  mmol/L]) and low arterial pH ( $<7.30$ ) (170). Lactic acidemia is defined as an elevated venous lactate level and normal arterial pH. Since measurement of arterial pH was not performed in most of the relevant studies in HIV-1-infected individuals, the term lactic acidemia will be used in this discussion.

The primary clinical features of severe lactic acidemia are fatigue, weight loss, nausea, abdominal pain, dyspnea, and cardiac dysrhythmias (109,171–175). The onset is acute or subacute [a median of 4 months in 1 series (109)]. Features of hepatic dysfunction are common and can include tender hepatomegaly, peripheral edema, ascites, and encephalopathy, but jaundice is rare. Modest elevations in liver enzymes are common. Hepatic steatosis is frequently observed on imaging and biopsy, with necrosis noted in more fulminant cases. Features of chronic liver disease have not been described. Patients with low-level lactic acidemia ( $18$ – $45$  mg/dL [ $2$ – $5$  mmol/L]) may have milder constitutional and hepatic abnormalities, but are often asymptomatic (109).

Lactic acidemia with no or mild symptoms was detected in 8% to 21% of patients receiving at least 1 nRTI, versus 0% to 1% of patients receiving no antiretroviral therapy (109,176–178). Symptomatic lactic acidemia is less common (occurring in about 1.5%–2.5%). The incidence in 2 prospective studies was estimated to be 0.4 to 0.8 per 100-patient-years-of-observation in adults. Mild acidemia does not appear to predict more severe acidemia. There are no firm data regarding differences by

gender, race, or age. A recent report of fatal lactic acidemia in 2 pregnant women receiving stavudine and didanosine therapy throughout pregnancy suggests that pregnant women may be at higher risk (179).

Cases of severe lactic acidemia have been described in association with all nRTIs, particularly if treatment duration is longer than 6 months (109,176,180). The DNA polymerase- $\gamma$  hypothesis of nRTI toxicity suggests that intracellular drug penetration and metabolism to the triphosphate form, tissue polymorphisms in mitochondrial DNA polymerase- $\gamma$ , and tissue-specific dependence on mitochondrial function determine organ susceptibility to nRTI-associated toxicity leading to lactic acidemia. In moderate and severe lactic acidemia, the target organ is thought to be the liver (181), because of the associated biochemical, clinical, and pathologic evidence of hepatic dysfunction. It is unclear, however, whether milder lactic acidemia represents an increase in lactate production from one or more organs and/or decreased degradation. Several studies have found associations between lactic acidemia and other toxicities such as peripheral lipoatrophy, sensory neuropathy, and osteopenia (180,182–185). The risk may be increased with ribavirin when used to treat concomitant hepatitis C virus infection (186). The most important alternative diagnoses to consider in patients with lactic acidemia are sepsis, dehydration, pancreatitis, and acute liver failure from other causes (e.g., hepatitis B or C virus infections, or other antiretroviral hepatitis caused by direct protease inhibitor or NNRTI effect or as part of a hypersensitivity reaction) (187).

### Recommendations for Assessment and Monitoring

Care is required with sample collection and processing of lactate specimens to avoid falsely elevated readings. Patients should be advised not to undertake vigorous exercise for 24 hours beforehand and should be well hydrated at the time of blood collection. Blood should be collected without fist clenching or prolonged tourniquet application into a pre-chilled, gray-top (fluoride-oxalate) tube, transported immediately on ice to the laboratory, and processed within 4 hours of collection (188). An elevated lactate level should always be confirmed by repeat measurement. A confirmed lactate level above 45 mg/dL (5 mmol/L) in the presence of related new symptoms and signs, or above 90 mg/dL (10 mmol/L) regardless of the clinical presentation, should be used to establish the diagnosis of nRTI-associated lactic acidemia (170). Measurement of arterial pH confirms the presence of acidosis, but this may not be necessary in many instances.

Because there is no way to predict who will develop lactic acidemia, patients should be informed that symptoms of lactic acidemia are non-specific and can occur at any time. Routine monitoring in the absence of signs or symptoms is not recommended. Measurement is recommended in those receiving nRTIs who have clinical signs or symptoms suggestive of lactic acidemia, low bicarbonate, chloride or albumin levels, raised anion gap, unexpected increases in liver enzymes, or new onset of clinical liver failure.

### Treatment

There are no randomized, controlled clinical trials in HIV-1-infected patients to evaluate interventions for treatment of lactic acidemia. The following recommendations are based on extrapolation from observational data and clinical experience of panel members. In all patients with confirmed lactate levels greater than 90 mg/dL (10 mmol/L), and those with confirmed lactate levels greater than 45 mg/dL (5 mmol/L) who are symptomatic, antiretroviral therapy should be discontinued if no other cause is evident. Combination NNRTI and protease inhibitor therapy can be restarted after the lactate level normalizes and the associated illness resolves. Reinstitution of alternative nRTIs in patients with prior lactic acidemia may be possible in some individuals (189), but should be closely monitored with lactate measured every 4 weeks for at least 3 months. For symptomatic patients whose levels are less than 45 mg/dL (5 mmol/L), continuation of nRTIs is reasonable as long as lactate levels are measured regularly.

There is no proven intervention for lactic acidemia apart from nRTI cessation. Several agents have been used with limited success for treatment of lactic acidemia in the setting of congenital mitochondrial diseases (190). These include essential vitamin coenzymes (thiamine and riboflavin), electron acceptors (coenzyme Q<sub>10</sub> [ubiquinone]), antioxidants (vitamins C, E, and K), and L-carnitine. There are no data supporting a role for any of these agents in the treatment of nRTI-related lactic acidemia.

Prognosis of lactic acidemia depends on the level at the time of diagnosis. In the published reports of HIV-1-related lactic acidemia, overall mortality was 80% in patients with lactate levels above 90 mg/dL (10 mmol/L), but no patient with lactate levels below 90 mg/dL died. In one study, lactate levels (mean, 37.8 mg/dL [4.2 mmol/L]) returned to normal at a mean of 3 months after nRTI cessation (109). Clinical features may take longer to resolve. Whether there are any long-term sequelae of

nRTI-related lactic acidemia at any level is unknown and deserves closer scrutiny.

## BONE DISEASE

### Background

Osteonecrosis (defined as death of bone tissue usually resulting from circulatory insufficiency) has been described as a complication of HIV-1 infection since the late 1980s (191–193). The areas most often affected are the femoral and humeral heads, femoral condyles, proximal tibia, and some of the small bones in the hand and wrist. Osteonecrosis may be limited to a single site or involve several areas. In HIV-1-seronegative populations, precipitating factors include hyperlipidemia, alcohol abuse, hemoglobinopathies (sickle cell disease), systemic lupus erythematosus, chronic or acute corticosteroid use, and hypercoagulability. Osteonecrosis has been recognized with an apparent increased frequency coincident with the introduction of potent antiretroviral therapy. A recent cross-sectional study using MRI scans detected avascular necrosis of the hip in 15 (4.4%) of 339 patients surveyed (194). In addition, recent case-controlled studies in HIV-1-infected individuals have linked osteonecrosis with corticosteroid use and hyperlipidemia, but not with the use of specific antiretroviral drugs (194–196).

Osteoporosis or bone demineralization was rarely recognized prior to the current era of potent antiretroviral therapy. Previously, marginally lower spine bone mineral density was noted in HIV-1-seropositive men (197). Bone formation and markers of bone turnover are reduced in HIV-1-seropositive patients (198), with the greatest effect reported in patients with low CD4+ cell counts. The use of protease inhibitor antiretroviral therapy has been reported to be associated with increased levels of osteocalcin, indicating increased bone turnover (199). More recently, several reports suggest rates of osteopenia of 22% to 50% and osteoporosis of 3% to 21% in patients receiving mainly protease inhibitor-containing antiretroviral therapy (182,200–202). The precise mechanism is unknown, as is the association with therapy or any specific antiretroviral drugs. Although to date reports of bone fractures are rare (203), the long-term consequences of osteopenia in HIV-1-seropositive patients are unknown.

### Recommendations for Assessment, Monitoring, and Treatment

Routine screening of HIV-1-infected patients for the presence of osteoporosis or osteonecrosis is not recom-

**TABLE 4.** Summary of recommendations for assessment, monitoring, and treatment of metabolic complications of HIV-1 and antiretroviral therapy**Assessment and monitoring**

1. Glucose and lipid abnormalities
  - The following assessments are recommended before initiation of potent antiretroviral therapy, at the time of a switch of therapy, 3 to 6 months after starting or switching therapy, and at least annually during stable therapy:
    - Fasting glucose (if therapy includes a protease inhibitor)
    - Fasting lipid panel (total cholesterol, HDL and LDL cholesterol [calculated or direct], and triglyceride levels)
  - A blood glucose level after oral administration of 75 g of glucose may be used to identify impaired glucose tolerance in patients with risk factors for type 2 diabetes mellitus or those with severe body fat changes.
2. Body fat distribution abnormalities
  - No specific technique can be recommended at the present time for routine assessment and monitoring of body fat distribution changes.
3. Lactic acidemia
  - Routine measurement of lactic acid levels is not recommended.
  - Lactic acid levels should be monitored in those receiving nRTIs who have clinical signs or symptoms of lactic acidemia, and in pregnant women receiving nRTIs.
  - If alternative nRTIs are resumed in those who have interrupted antiretroviral therapy for lactic acidemia, lactate levels should be monitored every 4 weeks for at least 3 months.
4. Osteopenia, osteoporosis, and osteonecrosis
  - Routine screening for osteoporosis or osteonecrosis is not recommended.
  - Radiographic examination of involved bone is recommended for those with symptoms of bone or joint pain; the contralateral joint should also be assessed.

**Treatment**

1. Glucose intolerance and diabetes mellitus
  - Weight loss for overweight subjects is recommended.
  - Follow established guidelines for treating diabetes in the general population, with preference given to insulin sensitizing agents such as metformin (except for those with renal disease or history of lactic acidemia) or thiazolidinediones (except for those with preexisting liver disease).
  - Avoid use of a protease inhibitor as initial therapy in patients with preexisting glucose intolerance or diabetes mellitus.
2. Lipid and lipoprotein abnormalities
  - Follow NCEP III guidelines for assessment of risk factors for cardiovascular disease, and dietary and lifestyle alterations for lowering cholesterol and triglyceride levels.
  - Avoid use of protease inhibitors, if possible, in those with preexisting cardiovascular risk factors, family history of hyperlipidemia, or elevated lipid levels.
  - Follow NCEP guideline thresholds for lipid-lowering therapy.
  - Fibrates are recommended as initial therapy for those with isolated fasting hypertriglyceridemia.
  - Pravastatin or atorvastatin are preferred statin agents for those with isolated fasting hypercholesterolemia requiring treatment in the setting of protease inhibitor or other CYP 3A4 inhibitor therapy.
  - If combination therapy for hypercholesterolemia and hypertriglyceridemia is indicated, therapy should begin with a statin, followed by the addition of a fibrate if there is insufficient response after 3 to 4 months of treatment.
3. Body fat distribution abnormalities
  - No therapies for fat distribution abnormalities in the absence of other metabolic complications can be routinely recommended.
4. Lactic acidemia
  - Antiretroviral therapy should be withheld for all patients with confirmed lactate levels >90 mg/dL (10 mmol/L) or those with confirmed lactate levels >45 mg/dL (5 mmol/L) who are symptomatic.
  - No intervention apart from nRTI cessation is recommended.
  - Restart combination NNRTI and protease inhibitor therapy after lactate levels return to normal and symptoms resolve.
5. Osteopenia, osteoporosis, and osteonecrosis
  - Surgical resection of involved bone is the only effective therapy for symptomatic osteonecrosis.
  - If osteoporosis is demonstrated by radiography or regional DEXA scanning, or if a pathological fracture occurs in the setting of osteoporosis, therapy with a bisphosphonate should be considered.

DEXA, dual-energy x-ray absorptiometry; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NCEP, National Cholesterol Education Program; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor.

mended. For those with symptoms of bone or joint pain or dysfunction, the diagnosis of osteonecrosis can be made by radiographic examination of the femoral head or other involved bone. An MRI or CT scan is usually necessary to detect osteonecrosis in asymptomatic patients. The contralateral joint should also be assessed, as bilateral disease is common. Surgical resection of involved bone and joint replacement is the only effective therapy for symptomatic osteonecrosis.

Osteoporosis can be diagnosed by radiography or by regional DEXA scanning (204). If reduced bone mineral density is found, an assessment for additional factors that are associated with osteopenia should be undertaken. These include thyrotoxicosis, disruption of the parathyroid hormone axis, hypogonadism, malabsorption, prolonged bed-rest, severe weight loss, alcohol intake, and medications including corticosteroids, phenobarbital, pentamidine, and ketoconazole. All patients should have

an adequate dietary intake of calcium and vitamin D, and should be engaged in appropriate weight-bearing exercise. If osteoporosis is found (e.g., a *t* score of  $-2.5$  or lower in DEXA scans of the hip or spine), and in particular if a pathologic fracture occurs in the setting of osteoporosis, appropriate therapy (eg, with a bisphosphonate drug) should be considered.

## CONCLUSIONS

Metabolic complications of potent combination antiretroviral therapies have only been recently recognized, and prospective studies to determine the incidence, etiology, risk factors, and most appropriate treatments for these complications are only now under way or being initiated. There remains a pressing need for guidance in managing these complications while definitive data to establish firm recommendations are accrued. Extrapolation from preliminary results of ongoing studies and experience garnered from management of similar metabolic abnormalities in patients who do not have HIV-1 infection serve as the basis for many of these recommendations. Table 4 summarizes the major concluding recommendations of this report.

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