SELECTED COMPLICATIONS OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN HIV DISEASE: AN OVERVIEW FOR THE PRIMARY CARE PROVIDER

By

MARY VAN HOLDE TODD

A project submitted in partial fulfillment of the requirements for the degree of

MASTER OF NURSING

WASHINGTON STATE UNIVERSITY
Vancouver, Washington

August 2003
To the faculty of Washington State University:

The members of the Committee appointed to examine the project of

MARY VAN HOLDE TODD find it satisfactory and recommend that it be accepted.

Chair: Renee Hoeksel, Ph.D., RN, CCRN

Carol Brown, Ph.D., RN, FNP

Lorna Schumann, Ph.D., FAANP, ARNP
ACKNOWLEDGEMENTS

First, to my parents, who taught me integrity, perseverance, and the value of a job well done. Thank you.

Next, to my husband and children: you have been my gracious supporters through this long process, and taught me that following a dream is more important than housework. You have loved me through interminable bad moods, exams, and papers. Thank you all.

To the excellent staff at the Immunodeficiency Clinic at Kaiser Permanente, in Portland, Oregon: you have taught me most everything I know so far about HIV. My gratitude to all, and particular thanks to Drs. Diana Antoniskis and Robert Lawrence, who took from their always-short time to help me with the manuscript.

To my Committee, Drs. Carol Brown, Renee Hoeksel and Lorna Schumann: thanks for all your time, work and helpful input. Each of you has unique and special gifts I have had the privilege of experiencing in my years at WSU. It has been an honor learning from you, and getting to know you.

To Linda Smither, who aided in preparation of the manuscript. And finally, a very special thanks to Kristine Brown, secretary of the Nursing Department at WSUV, whose smiling face and kind words always made my day brighter.
SELECTED COMPLICATIONS OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN HIV DISEASE:
AN OVERVIEW FOR THE PRIMARY CARE PROVIDER

Abstract

Mary Van Holde Todd
Washington State University, Vancouver
August 2003

Chair: Renee Hoeksel

Human immunodeficiency syndrome is now treated with combinations of powerful antiretroviral medications, whose use can lead to a variety of toxic side effects. The primary care practitioner is becoming of increasing importance in the management of HIV disease, and should be familiar with the more important and frequently encountered of these complications. Metabolic disturbances, including fat maldistribution syndrome, dyslipidemia and insulin resistance; nucleoside-related toxicities, including liver disease and lactic acidemia; and medication-related skin rashes, are discussed in this review article. Clinical presentation, management, and fit of these abnormalities into the larger picture of HIV disease and cardiovascular risk are summarized.
TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIGNATURE PAGE</td>
<td>ii</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>iii</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>iv</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>SKIN DISORDERS</td>
<td>2</td>
</tr>
<tr>
<td>HEPATIC TOXICITIES</td>
<td>4</td>
</tr>
<tr>
<td>DYSLIPIDEMIA</td>
<td>8</td>
</tr>
<tr>
<td>Treatment Options</td>
<td>13</td>
</tr>
<tr>
<td>Regimen Changes</td>
<td>13</td>
</tr>
<tr>
<td>Lifestyle Changes</td>
<td>14</td>
</tr>
<tr>
<td>Diet</td>
<td>14</td>
</tr>
<tr>
<td>Exercise</td>
<td>14</td>
</tr>
<tr>
<td>Lipid-lowering Medications</td>
<td>15</td>
</tr>
<tr>
<td>FAT DISTRIBUTION ABNORMALITIES</td>
<td>17</td>
</tr>
<tr>
<td>Lifestyle changes</td>
<td>20</td>
</tr>
<tr>
<td>Insulin Sensitizers</td>
<td>20</td>
</tr>
<tr>
<td>Hormones</td>
<td>21</td>
</tr>
<tr>
<td>Regimen Changes</td>
<td>22</td>
</tr>
</tbody>
</table>
ABNORMALITIES IN GLUCOSE METABOLISM 22

Treatment options 24

Medications 24

SPECIAL POPULATIONS 25

CONCLUSION 25

BIBLIOGRAPHY 27
LIST OF TABLES

1. Summary of National Cholesterol Education Program Treatment Recommendations Based on LDL Cholesterol 33
2. Effects of Interventions Evaluated for Treatment of Body Fat Changes 34
3. Summary of Recommendations for Assessment, Monitoring, and Treatment of Metabolic Complications of HIV-1 and Antiretroviral Therapy 36
Introduction

As the human immunodeficiency virus (HIV) infection continues to evolve and mature, the primary care practitioner is seeing increasing numbers of HIV positive patients in daily practice. Several categories of major side effects associated with the highly active antiretroviral therapy (HAART) now used in HIV treatment have been described, including metabolic complications (fat redistribution syndrome, dyslipidemia, and insulin resistance), nucleoside-related toxicities (hepatic steatosis, lactic acidemia, liver failure, and myopathy), and skin rash, among others. While many of these disorders existed in the HIV positive population prior to the advent of current advanced antiretroviral therapy, their frequency and intensity have increased since the development of protease inhibitors in 1995.

Since HIV has now become a chronic disease for economically advantaged persons, issues of long-term complications are increasingly driving decision-making in patient management. Adherence problems and potential for emergence of drug resistance are both adversely impacted by patient responses to side effects of medications. The purpose of this article is to provide an overview of several of the major problems associated with the antiretroviral medications, in order to assist the primary care provider in maintaining an evidence-based vigilance when handling these potent drugs.

The advent of highly active antiretroviral therapy has dramatically reduced HIV-related death and disability. Unfortunately, each class of drug has also been associated with serious toxicities, which may adversely effect quality of life, and potentially mortality. This paper, based on current review articles, original research studies, and most importantly, the collective recommendations of two recent HIV expert panels (the
Panel on Clinical Practices for Treatment of HIV, chaired by Dybul\(^1\), and the International AIDS Society — USA panel, chaired by Schambelan\(^2\), presents an overview of these toxicities, clinical presentations of associated disease states, and evidence-based treatment strategies. Where clinical evidence is lacking, guidelines for treatment are based on the expert opinion of specialists.

**Skin Disorders**

Skin rash occurs among patients using all classes of HIV drugs, but is seen most frequently among those on the nonnucleoside reverse transcriptase inhibitors (the NNRTIs). Most cases of HAART-induced rash occur in the first few weeks of treatment, and are mild to moderate in severity. In these situations, many clinicians recommend attempting to control the dermatitis with oral and topical antihistamines for symptom relief and "wait it out", although it is unclear whether continuing the drug treatment through the rash is beneficial.\(^1,6\) Systemic reactions, including Stevens-Johnson syndrome and toxic epidermal necrosis, do occasionally occur. These severe reactions should precipitate immediate and permanent discontinuation of the offending medications.

Among the NNRTI class, skin rash occurs most frequently and seriously with nevirapine (Viramune). Many clinicians use a two-week lead-in dose escalation protocol with this medication to help reduce cutaneous reactions. Severe dermatitis, including Stevens-Johnson syndrome or toxic epidermal necrolysis, has been reported in 7% of patients on a nevirapine-containing regimen.\(^3\) Systemic reactions may include severe cutaneous involvement, eosinophilia, and symptoms including fever, hematological abnormalities, and multiple organ involvement. Prophylactic use of antihistamines or
systemic corticosteroids has not been shown to be effective in preventing or reducing rash. Since skin rash appears to be a classwide reaction in the NNRTIs, care must be taken in trying other nonnucleosides. Most HIV clinicians avoid challenging the patient with another medication in the same class, when the initial reaction was severe or life-threatening, but may be willing to cautiously attempt another in moderate cases. Efavirenz (Sustiva), another NNRTI, also causes rash, but less frequently than nevirapine, and in a limited number of studies, has been shown to be tolerated by patients with previous history of nevirapine-associated rash.

Among the nucleoside reverse transcriptase inhibitors (NRTIs), abacavir (ABC, Ziagen) is the drug most frequently associated with skin rash. An erythematous, maculopapular rash, appearing on the face, trunk, and extremities, has been reported to occur in 70% of ABC-hypersensitivity reactions, and typically occurs within the first six weeks of treatment. If there is reason to suspect that a skin rash appearing with abacavir use might constitute a component of an ABC-hypersensitivity reaction, the medication should be discontinued permanently, and the patient should be advised to inform all subsequent health care providers of a history of adverse reaction to the drug, since rechallenging an ABC-hypersensitivity reaction can be life-threatening. If the dermatitis is due to such a hypersensitivity reaction, it will usually resolve within several days after discontinuation of the offending agent.

In the protease inhibitor class (PI), amprenavir (Agenerase) has been most frequently associated with dermatitis, occurring in less than a quarter of clinical trials. Amprenavir, a sulfonamide, should be used cautiously in patients with histories of sulfa
allergies. Unfortunately, cross reactivity of amprenavir with other sulfa drugs is unknown.¹

**Hepatic toxicities**

Liver disorders, including hepatotoxicity, hepatic steatosis, lactic acidemia and lactic acidosis, occur with varying frequency among patients on advanced antiretroviral therapy. Hepatotoxicity, defined as a 3 to 5 times normal increase in serum transaminases (including alanine- (ALT), and aspartate- (AST) aminotransferase, and gamma-glutamyltransferase, (GGT), with or without clinical hepatitis, is frequently seen in-patients on HAART. Other risk factors for hepatotoxicity include hepatitis B and C co-infections, especially in patients taking PIs, alcohol abuse, and baseline elevation of liver enzymes.¹⁰⁻¹² All NNRTIs and PIs have been associated with elevations in transaminases.¹ The majority of patients with transaminase elevations are asymptomatic, and many liver enzyme abnormalities resolve spontaneously without therapeutic intervention or treatment interruption.

Each class of antiretroviral medication has been implicated in liver toxicity. Among the NNRTIs, nevirapine is most frequently cited, with a reported hepatic toxicity incidence of around 12%, and clinical hepatitis of approximately 1%.¹³ Hepatitis may present as a component of the nevirapine hypersensitivity syndrome, with its attendant skin rash, fever, and possibly eosinophilia. Hepatitis is more likely to appear in the female gender, and early on in treatment, usually within the first three months.¹,¹⁴ Liver enzyme abnormalities are variably present, and gastrointestinal symptoms nonspecific and flu-like. Progression to hepatomegaly and hepatic failure can occur very rapidly, within days to weeks.¹
As in the rash, many clinicians use a two-week lead-in dosing regimen with nevirapine, starting at 200 mg once daily, and then increasing to twice daily after 14 days, in order to defuse hepatic toxicity.\(^1-^3\) Close monitoring of liver enzymes and clinical symptoms at the start of therapy, and subsequently every two weeks for the first month, then bimonthly to monthly for 3 months, and thereafter every one to three months, is advised.\(^1\) Patients who experience severe liver problems with nevirapine should not be rechallenged.\(^1\)

Protease-inhibitor associated hepatotoxicity can occur at any time during a PI treatment regimen. Ritonovir-containing, and ritonovir-saquinavir-based regimens have been implicated in severe liver enzyme elevations (>5 times increase over baseline ALT or AST) more frequently than other tested PIs (indinavir, nelfinavir, or saquinavir).\(^1^1\) Coinfection with hepatitis C is of particular concern with PI regimens due to increased risk of hepatic morbidity.\(^1^5\)

The nucleoside analogues (NRTIs) present the greatest risk for serious hepatic complications, including lactic acidosis and hepatic steatosis.\(^1^3,^1^2,^1^4\) Lactic acidemia is defined as an elevated lactate level (>2mmol/L) with normal arterial pH. Lactic acidemia occurs with an estimated frequency of between 8-21\%, is frequently seen in its chronic compensated form during treatment with one or more NRTIs, and may present without overt clinical features.\(^2,^1^6\) Severe decompensated lactic acidosis, by contrast, with hepatomegaly and steatosis, is rare but serious, with an estimated incidence of 1.3 cases per 1000 person-years of NRTI exposure, and a high mortality rate (80\% in patients with lactate levels >10mmol/L).\(^2,^1^7\) Mild acidemia is usually defined as between 2 and 5 mmol/L, moderate between 5-9 mmol/L, and severe, life-threatening lactic acidosis 10
mmol/l and above. Clinically, mild acidemia does not appear to predict progression to more serious acidosis. Risk factors for lactic acidosis include feminine gender, prolonged use of NRTIs, obesity, later stages of pregnancy, and concomitant treatment of hepatitis C with ribavirin. Cases of severe lactic acidosis have been described with use of all the NRTIs, but are most often associated with didanosine (DDI, Videx), stavudine (D4T, Zerit), and zidovudine (AZT, Retrovir).

Although the exact mechanism is as yet unclear, it has been suggested that NRTIs may cause hepatic cellular injury by inhibiting deoxyribonucleic acid (DNA) polymerase gamma, the enzyme responsible for mitochondrial DNA synthesis, thereby decreasing mitochondrial function, reducing cellular energy production, and eventually leading to acidosis. Whether milder cases represent an increase in lactate production, or a decrease in degradation, or both, is as yet unknown. This mitochondrial dysfunction and attendant lactic acidemia, sometimes referred to collectively as the “mitochondrial toxicity syndrome,” may also lead to other adverse events, including myopathy, pancreatitis, peripheral neuropathy, cardiomyopathy, and possibly lipodystrophy.

Symptoms of lactic acidemia are typically nonspecific, but often include fatigue, nausea, abdominal pain and distention, dyspnea, myalgias, and hepatomegaly. Ascending neuromuscular weakness, paresthesias, and weight loss are less frequently seen. Since there appears to be no reliable method to predict who may develop lactic acidemia, all patients on NRTIs should be counseled that symptoms are non-specific and can occur unexpectedly. Routine measurement of lactic acid is not recommended in the absence of clinical signs and symptoms.
Because technical problems, including variation over time and between technicians, are inherent in lactate monitoring, repeating an initially elevated level is important; however many clinicians suggest relying on other lab values and clinical symptoms when lactic acidemia or acidosis is suspected.\textsuperscript{1,2} When lactate levels are drawn, the patient should be advised to avoid heavy exercise for 24 hours preceding the draw, and blood should be collected without use of a tourniquet or fist clenching, into a pre-chilled gray-top tube, which is then transported on ice to the lab, and processed within 4 hours.\textsuperscript{19}

In hyperlactatemia, additional lab work might reveal elevated hepatic enzymes, an increased anion gap (\(\text{Na}-(\text{Cl}+\text{CO}_2)>16\)), and elevated creatine phosphokinase, lipase, lactic dehydrogenase, and amylase levels, as well as decreased bicarbonate, chloride and albumin levels.\textsuperscript{18} Elevation of the ALT may be an early indicator of developing mitochondrial toxicity. While measurement of arterial blood gases for pH can actually confirm acidosis, not all clinicians include this lab. Imaging studies (computed tomography and echotomography) may show an enlarged and fatty liver. Differential diagnoses to consider in patients with elevated lactate levels include pancreatitis, dehydration, sepsis, and acute liver failure from other causes, such as hepatitis B or C, or other antiretroviral drugs.\textsuperscript{1,2,20} Consultation with an expert in HIV care is recommended in all cases in which symptomatic lactic acidemia is suspected, and management of the acutely ill patient should be relegated to the expert provider.

In the absence of randomized, controlled clinical trials to evaluate treatment modalities for lactic acidemia in HIV-infected patients, two panels of experts have developed a standard of care based on their clinical experience.\textsuperscript{1,2} Temporary discontinuation of antiretroviral therapy in all patients with lactate levels greater than 10
mmol/L, and also in symptomatic patients with levels greater than 5 mmol/L, is advised. This discontinuation of HAART therapy is admittedly controversial, as is the use of several agents, including riboflavin, thiamine, vitamins C, D, and K, coenzyme Q-10, and L-carnitine. These medications have been tried with limited success in various congenital mitochondrial diseases, but as yet there is only anecdotal data supporting their role in NRTI-associated lactic acidosis.1,2,21

After lactate levels normalize and associated illnesses resolve, which may take several months, combination NNRTI and PI therapy may be restarted. Alternatively, some clinicians opt to carefully re-institute other NRTIs, with vigilant monitoring of lactate levels for several months. In symptomatic patients with lactate levels below 5 mmol/L, the expert panels suggest continuation of existing NRTIs with careful, frequent monitoring of lactate levels.1,2

**Dyslipidemia**

Both HIV infection and antiretroviral therapy are associated with metabolic abnormalities, including dyslipidemias. While dyslipidemia was seen in the HIV positive population prior to the current HAART era, its incidence has increased in recent years. Pre-HAART, investigators found decreased levels of total serum cholesterol, decreased high and low density lipoproteins (HDL and LDL), and modestly increased triglycerides.23,24 Endothelial dysfunction, hypercoagulability, and abnormal coronary artery pathology were also associated with HIV infection.25

Now, since the advent of advanced combination therapies, patients are increasingly presenting with normal or decreased HDLs, elevated total cholesterol, a return of LDLs to non-HIV-infected levels, and markedly elevated triglycerides.1,2,22 Dyslipidemias are
frequently seen in conjunction with other metabolic abnormalities, including fat
maldistribution (lipodystrophy/lipoatrophy) and insulin resistance/glucose intolerance, a
collection of symptoms sometimes referred to as the “HIV-related lipodystrophy
syndrome.” The pathogenesis of these abnormalities is unknown, but is most likely
multifactorial, involving host genetic factors, medications, and the disease itself. Studies
suggest that up to 50% of patients may develop at least one feature of the syndrome,
potentially leading to further difficulties from accelerated atherosclerosis, heart disease,
pancreatitidis and other hypertriglyceridemia-related complications, as well as
psychological disorders from distortions in body-image perception.22,26,27

Data from several large-scale prospective and retrospective studies suggest a
significantly increased risk for cardiovascular events, including premature myocardial
infarction (MI), associated with HAART.4,28 Duration of therapy may be a factor, as a
three-fold increase in incidence of MI was found in a retrospective study of 19,795
patients in a French database, when PI therapy equaled or exceeded 30 months.4,29 When
4541 HIV-infected patients were compared with 41,000 HIV-negative patients in the
Kaiser Permanente database, coronary heart disease events were found to occur among
the infected population significantly more frequently than in HIV-negative patients,
matched for age and sex. Interestingly, no difference was found among those on PI-
containing regimens and those on non-PI-containing regimens.4,30

Genetic susceptibility may also influence the risk for development of changes in
lipid levels. HIV-infected patients who are heterozygous or homozygous for the
apolipoprotein E-2 genotype have higher intrinsic triglyceride levels, and may have more
significant changes in lipid levels if they receive PI therapy.2,31
PI usage is frequently associated with marked elevations in triglycerides and increases in LDL compared to levels observed in non-HIV-infected populations, with few changes noted in HDL cholesterol levels. This implies that the lipid proatherogenic profiles worsen slightly with use of protease inhibitors. Manifestations of dyslipidemia vary markedly, dependent on type of PI used and patient individuality. Ritonavir has demonstrated the most robust effect, particularly with regard to hypertriglyceridemia, and has been shown to induce hypertriglyceridemia in only two weeks of therapy in HIV-negative subjects. In contrast, indinavir’s effect on lipids was negligible, other older PIs showed mixed results, and the newer PIs, such as atazanavir, may actually demonstrate a favorable effect on lipid elevations.

The role of nucleoside reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) in hyperlipidemia is still unclear. At this point, the majority of controlled studies do not show a clear association between NRTIs and hyperlipidemia. In the NNRTI class, results are mixed. For example, while none have been definitely implicated in the development of dyslipidemia, data suggest nevirapine may both increase HDL and LDL cholesterol, and yet reverse hypertriglyceridemia in patients on PI therapy. Data on efavirenz are equally contradictory, with variable results on LDLs and triglycerides, and an increase in HDL cholesterol observed in several studies.

It is suggested that lipid panel studies be performed prior to starting or switching any HAART therapy, repeated thereafter at 3 to 6 months, and then at least annually. More frequent monitoring is generally advisable if lipid values are abnormal or interventions planned. The fasting lipid panel should include total, LDL, and HDL
serum cholesterol levels, as well as triglycerides. Patients should fast for a minimum of 8 hours, and preferably 12, for triglyceride accuracy. When triglycerides are above 400 mg/dL, direct LDL cholesterol measurements should be drawn, if possible, since calculated levels (using Friedewald’s equation, where total cholesterol minus HDL minus triglycerides divided by 5 equals calculated LDL) are not reliable. When direct LDL draws are not possible, the clinician may substitute “non-HDL levels” (total cholesterol minus HDL) for the LDL level, and then add 30 mg/dL to the LDL value, to determine need for intervention.2,37

No evidence-based guidelines for lipid management in the HIV-infected population on HAART yet exist. Furthermore, it is unknown whether lipid abnormalities in HIV positive patients carry the same cardiovascular risks as in the non-infected population. In the absence of data, HIV specialists currently base their treatment guidelines on the recently revised National Cholesterol Education Program (NCEP) III (Table I).37 According to these more aggressive guidelines, some experts estimate that at least 50% of HIV-infected patients on advanced antiretroviral therapy may require some form of pharmacologic intervention to treat their dyslipidemias.4

Elevated LDL, decreased HDL, and a high cholesterol-HDL ratio have been definitively associated with increased risk of coronary heart disease (CHD) in the non-HIV population. However, hypertriglyceridemia, the most prominent lipid abnormality in HIV infection, has not yet been independently established as a risk factor, although the recent NCEP guidelines do now accord it more consideration than in the past. Other major risk factors, including age, diabetes, family history, hypertension, gender, smoking history, and menopausal status, should also be considered in light of the patient’s HIV
disease prognosis. Cardiac risk can be estimated by using the Framingham Heart Study tables and formula (available at http://hin.nhlbi.nih.gov/atpiii/calculator.asp). Level of risk should guide therapeutic decision-making.

The primary target of therapy is lowering the LDL cholesterol level, since recent clinical trials have clearly shown that lowering LDL cholesterol reduces cardiovascular risk. Non-HDL cholesterol is seen as a secondary therapy target for patients whose triglyceride levels are >200 mg/dL, and can be calculated by subtracting the HDL cholesterol value from the total cholesterol, thereby yielding the total of all cholesterol-containing lipid components. The non-HDL goal is 30 mg/dL above the patient’s goal LDL. Importantly, for patients with triglycerides greater than 500 mg/dL, the NCEP recommends initially aiming treatment at reducing triglycerides, before addressing LDL.

Clinicians should also consider potential exacerbating factors for dyslipidemia, (including obesity, physical inactivity, excessive alcohol use, hypothyroidism, renal and liver disease, and hypogonadism), as well as the effects of drugs which can alter lipid levels (e.g. glucocorticoids, beta-blockers, thiazide diuretics, thyroid preparations and hormonal agents). Eventually, consideration may also be afforded to measurement of endothelial dysfunction and chronic inflammation accompanying viral infection, as these markers have been shown to predict future CHD events and response to lipid-lowering therapy in non-HIV-infected patients.

When triglycerides are severely elevated (>1,000 mg), immediate lipid-lowering treatment is necessary to avoid acute pancreatitis and the “chylomicronemia syndrome,” a diverse spectrum of symptoms, which can include abdominal pain accompanied by
normal pancreatic enzymes, memory loss, dyspnea, xanthomata, and lipemia retinalis (a side effect of hyperlipidemia, in which retinal vessels appear reddish white or white). In-patients with less severe hypertriglyceridemia, where cardiac risk reduction is the goal, treatment considerations should be weighed as a cost-benefit analysis, relative to degree of cardiac risk, HIV prognosis (based on current CD4 count and initial HIV viral load), and safety of therapeutic measures.

**Dyslipidemia treatment options**

Treatment options include switching antiretroviral regimens, such as substituting an NNRTI for a PI, making life-style changes, trying a lipid lowering-medication, or staying with the existing plan. When changing the antiretroviral is likely to increase viral load, questions addressing patient morbidity and mortality need to be considered. For example, which option is least likely to harm the patient now, and over time? If a change is made in the HAART regimen now, what options are left for the future? What are the relative efficacies, tolerabilities, and side effects of the available regimens? Is the current dyslipidemia reversible with medication change? Is the patient willing and able to make significant life-style changes? Patient compliance and adherence issues also need to be taken into account: what medication regimen is the simplest and least objectionable to the patient?

**Regimen changes**

For the high-risk patient, with either preexisting cardiovascular risk factors, a family history of lipid abnormalities, or severe hyperlipidemia, expert opinion suggests changing to a PI-sparing regimen, (either an NNRTI in place of a PI, or an abacavir-
containing triple NRTI regimen). Such regimens have repeatedly demonstrated a lowered risk or actual reversal of hyperlipidemia.\textsuperscript{1,2}

**Lifestyle changes**

For the patient without known CHD or CHD risk equivalent (e.g. 10-year coronary event risk >20%, non-coronary atherosclerotic vascular disease, or type 2 diabetes mellitus), initiation of therapeutic lifestyle changes is the panels' initial recommendation.\textsuperscript{1,2,37} Lifestyle changes, including smoking cessation, and alterations in diet and exercise as outlined in the NCEP guidelines, are recommended for a minimum of six months before they are deemed unsuccessful, and other options sought.\textsuperscript{2,39}

**Diet**

According to the new NCEP guidelines, saturated fat should comprise less than 7%, and total fat 25%-35%, of total daily caloric intake. Dietary cholesterol should be limited to less than 200 mg/day. Soluble fiber, between 10-25 gm/d, and plant sterols, at 2 gm/d, are also suggested.\textsuperscript{1,2,37} In individuals with isolated hypertriglyceridemia, reduction in alcohol intake is also recommended, and these patients may also benefit from a very low-fat diet, even if not overweight. Fish oil (omega-3-fatty acid supplements), which decreases triglyceride synthesis, may also be tried in moderation (1.7g/d) in patients with severe elevations in triglycerides.\textsuperscript{39} Weight loss should be encouraged in the overweight patient. When the patient is cachectic, but experiencing dyslipidemia, consultation with a dietician may be helpful.

**Exercise**

Controlled studies on the benefit of increased physical activity and regular exercise on HIV-related dyslipidemia are lacking. While it has been established that both aerobic
and resistance exercise are well tolerated by patients on antiretrovirals, and contribute positively to patient outlook and endurance, their effect on lipids appears to be mixed. One recent study of a resistance-training program in HIV-infected men showed significantly reduced triglyceride levels without change in total cholesterol, suggesting that resistance training-induced muscle hypertrophy might promote triglyceride clearance. Another study demonstrated a 21% decrease in triglycerides, and an 11% decrease in total cholesterol, with dietary changes and exercise. A relatively small study (n = 45) showed no significant reduction in lipids with NCEP dietary and exercise modifications alone. In the non-HIV-infected population, aerobic exercise has been shown to be associated with a moderate, but statistically significant decrease in LDL and total cholesterol, triglycerides, and a modest increase in HDL. A larger study of non-HIV-infected patients (n = 152), 35% of patients were able to reach their target goal through lifestyle changes alone.

**Lipid-lowering medications**

Lipid-lowering medications should be considered in patients with severe or isolated hypertriglyceridemia, in those with less severe lipid elevations who have failed therapeutic lifestyle regimens, and those in who changes in antiretroviral therapy were either unsuccessful or inappropriate. The fibric acid derivatives, gemfibrozil (Lopid) and fenofibrate (TriCor) are the preferred initial therapy for reducing elevated triglyceride levels, and are usually initiated when triglycerides are at the 500 mg/dL threshold level. These fibrates are very effective at lowering triglycerides, and have the added benefit of raising HDL cholesterol.
In the HIV-infected population, total and LDL cholesterol levels, and to a lesser degree, triglycerides, are effectively reduced with use of the hydroxymethylglutaryl CoA reductase inhibitors (HMG-CoA reductase inhibitors), also known as the "statins." Among these medications, atorvastatin (Lipitor) and pravastatin (Pravachol) are the preferred agents, as they are the least effected by the inhibitory effect of PIs on the cytochrome P450 (CYP-3A4) system. Consequently, they are less prone to dangerous drug interactions and increased statin levels, which can lead to myopathy and occasionally, rhabdomyolysis. Both drugs should be avoided in patients with active liver disease, or unexplained elevations of liver enzymes. A low starting dose (20 mg of pravastatin or 5-10 mg atorvastatin, once daily) is usually attempted, and titrated cautiously upwards. Atorvastatin tends to accumulate at higher-than-expected concentrations, and should therefore be used with care and at reduced doses. Simvastatin and lovastatin (Zocor and Mevacor) are generally contraindicated with PIs and selected NNRTIs, as they very effectively inhibit P450.

The statins and fibrates work by different mechanisms, and may work synergistically, but since both can cause rhabdomyolysis, caution is advised. Generally, when hypertriglyceridemia is found in conjunction with elevated LDL, a setting in which combination therapy might be required, HIV experts recommend an initial trial of four months of a statin at maximum dosage. If therapeutic response is less than desired, a fibrate (preferably gemfibrozil) might then be added. Risk of clinically significant myopathy (defined as creatine kinase >10 times normal, with symptoms) is small in statin monotherapy, estimated at 0.5%, while combination therapy may multiply that risk by close to a factor of 10.
Niacin is also an effective lipid modulator, lowering triglycerides, raising HDL, and lowering LDL. However, it has numerous potential deleterious effects, including insulin resistance and hepatitis, both of which are already problematic with many patients on HAART, so its use here is generally avoided. Bile acid-binding resins are likewise eschewed, as they elevate triglycerides and interfere with absorption of other medications. Omega-3 fish oils, although potentially helpful, are often rejected by patients due to unpleasant aftertaste and eructation. 22

Fat distribution abnormalities

A variety of body fat distribution abnormalities have been described in HIV-infected patients. Generalized fat wasting (cachexia) is commonly seen in infected patients with advanced disease, and localized fat accumulations (lipomas) have been associated with NRTI monotherapy. However, since the advent of advanced combination therapy, new fat maldistribution syndromes, often appearing in conjunction with dyslipidemia and insulin resistance, are increasingly being seen. Common manifestations of this lipodystrophy syndrome include facial fat loss and limb wasting (lipoatrophy), and localized fat accumulations (central and visceral, the “protease paunch”), dorsocervical (the “buffalo hump”), enlarged breasts in both sexes, and lipomas (hyperadiposity). These manifestations of HIV disease can be very troubling to patients, who may perceive them as disease-identifying and stigmatizing, which can lead to problems with medication adherence. 4,50 These morphologic changes can also cause clinical symptoms, including chronic neck pain, headaches, respiratory difficulty, gastroesophageal reflux, back pain from breast enlargement, and alterations in menstrual pattern, body posture, and clothing size. 51,54
Lack of defining diagnostic criteria, differences in demographic and treatment factors, and patient-provider report variation, have lead to discrepancies in prevalence estimates for these syndromes, ranging between 25%-75% of HIV+ patients on HAART.\textsuperscript{1,26,52} Although diagnosis is easily made clinically, precise measurements have been difficult to standardize. Mechanisms and locations of lipodystrophic metabolic abnormalities have not yet been identified, although as in lactic acidosis, mitochondrial toxicity, as a function of NRTI-associated inhibition of DNA-polymerase gamma, may be involved.\textsuperscript{18}

Available evidence indicates an increased risk for fat accumulation with PIs, but correlation to specific drugs is unclear. While fat redistribution in the absence of PI therapy has been observed in several studies, and fat atrophy has also been associated with long-term NRTI exposure, PIs appear to be necessary for the full-blown presentation of lipodystrophy, with both its visceral fat accumulation and localized fat loss.\textsuperscript{4} PIs also appear to significantly accelerate fat loss in an NRTI-based regime. The preponderance of data to date do not implicate the NNRTIs in any form of lipodystrophy.\textsuperscript{53}

Pervasiveness of lipodystrophy appears to be positively correlated to duration of antiretroviral therapy.\textsuperscript{55} Other factors which have been associated with fat distribution abnormalities include Caucasian race, older age (possibly related to greater body fat mass), and body mass index. Overweight patients of both sexes (BMI>28 m$^2$), appear to have a greater tendency to develop buffalo hump and breast enlargement, and a lower tendency to facial and gluteal fat loss, than underweight individuals (BM<20 m$^2$).\textsuperscript{51} Gender may also play a role, as women are generally more likely to develop fat accumulation, and men fat loss. Duration of HIV infection, baseline immunodeficiency,
status of immune restoration, and degree of viral suppression are also correlated to
development of lipodystrophies.\(^2\)

According to the HIV expert panelists, measurement and monitoring of
lipodystrophic syndromes is problematic at present.\(^2\) They suggest that each of the
measurement methods available has its own drawbacks, and at present no one technique
is sensitive or specific enough to recommend it for routine assessment and monitoring.
For example, computed tomography (CT) and magnetic resonance imaging (MRI)
techniques are considered the gold standard assessment methods for body fat distribution,
with single-slice measurements that correlate accurately with whole-body measurements
for both kinds of tissue analyzed (subcutaneous adipose tissue, "SAT", and visceral
adipose tissue, "VAT"). However, they are expensive, difficult to interpret, and involve
radiation exposure.\(^2\) Anthropometric estimates of both VAT and SAT are widely
available in the literature, and the method is safe, portable and inexpensive;
unfortunately, both reproducibility and training can be problematic. Bioelectrical
impedance analysis (BIA), which estimates whole body composition, has not been
validated against the gold standard, ultrasound is in its infancy in the exploration of this
population, and dual energy x-ray absorptiometry (DEXA) is inadequate for analyzing
VAT.\(^2\) Simple measurement of waist circumference is more sensitive and specific than
the waist-to-hip ratio, and is probably the easiest of all methods.\(^2\) This technique has
recently gained some acceptance, as indicated by its inclusion in the new NCEP III
guidelines for cardiovascular risk assessment.\(^2\)

Multiple treatment options for HIV lipodystrophy are under investigation, but to
date, none have been approved. Since there are likely numerous and diverse etiologies
for fat distribution abnormalities, it is important to identify specific objectives for any treatment plan, and consider any concomitant factors (such as hyperlipidemia, insulin resistance, hepatic injury, etc.) which might complicate or contraindicate a given regimen. Risks and benefits of currently available treatment approaches are summarized below, and synopsized in Table 2, from Schambelan et al.2

**Lifestyle changes**

Exercise, both aerobic and resistance, should be encouraged in patients with antiretroviral therapy-related fat accumulation. Several studies have reported decreases in abdominal and truncal fat with resistance exercise programs, and one reported an increase in lean muscle mass.43,56,57 Diet has not been shown to have an effect on HIV fat distribution abnormalities. HIV panel experts generally recommend following heart-healthy eating habits, including reducing intake of saturated fat, simple carbohydrates and alcohol, and concentrating on protein and micronutrient (vitamin/mineral) intake. Quick weight-loss diets should be avoided, as they can lead to lean tissue loss.2

**Insulin sensitizers**

Insulin sensitizers, such as metformin (Glucophage) and the thiazolidinediones pioglitazone (Actos), and rosiglitazone (Avandia), may have a role in treatment of HAART-induced morphologic changes, but results are as yet inconclusive.2 Studies on metformin in HIV-infected patients suggest it may be effective in patients with central fat accumulation and glucose intolerance or insulin resistance. These randomized studies demonstrated patient decreases in weight, visceral fat, insulin and triglyceride levels, and diastolic blood pressure, as well as improvement in glucose tolerance.58,59 Use of
metformin, however, entails significant risks, including the potential to cause lactic acidosis, and is usually contraindicated in hepatic or renal disease.

Troglitazone, a thiazolidinedione, currently off the American market due to liver toxicity, has been shown to increase SAT and reduce VAT in type 2 diabetes patients and patients with various lipodystrophic syndromes. Preliminary studies using rosiglitazone and pioglitazone in HIV-infected patients with fat distribution abnormalities have not shown a similar consistent improvement. Further research is needed to clarify this issue.

**Hormones**

Use of hormones, including growth hormone, and testosterone and other androgens, is currently not recommended for treatment of HAART-related lipodystrophy. Although administration of pharmacologic doses of human growth hormone (HGH), at 6 mg/d (10 times the estimated physiologic dose), has resulted in both subjective and objective improvements in body composition, including a reduction in central fat, its use can exacerbate insulin resistance and alterations in glucose homeostasis, and physical improvements typically reverse after its discontinuation. Additional risks of arthralgias and fluid accumulation in the extremities, as well as prohibitive cost, and lack of information on optimal dosing, preclude its recommendation by HIV experts at this time.

The role of androgenic hormones in treatment of HAART-related lipodystrophy is still unclear. Decreased testosterone levels are associated with visceral fat accumulations and insulin resistance in HIV infected men, while replacement of testosterone has been associated with improvements in both these parameters. Preliminary data suggest that testosterone replacement may benefit centrally obese hypogonadal HIV positive men.
however, no definitive studies have been conducted. In view of the current lack of information on its safety and efficacy, the Panels likewise are withholding their recommendation for androgen use in lipodystrophy.²

Regimen changes

Changes in antiretroviral therapy have not been shown to be helpful in reversing HAART-associated truncal fat accumulations in those patients suffering from these forms of lipodystrophy.⁴ ⁶³ However, for those patients suffering primarily from localized fat loss, preliminary research suggests discontinuation of stavudine, and substitution with abacavir or zidovudine, may promote a modest increase in peripheral fat. Whether virologic control can be maintained with these regimens remains questionable.² ⁶⁴

Abnormalities in glucose metabolism

In the HIV positive population, where abnormalities in glucose metabolism were previously rare, insulin resistance has now been reported in up to 40% of patients on PI-containing antiretroviral regimens.² ⁶⁵ ⁶⁶ Prior to HAART, most problems with hyperglycemia could be related to specific medications, such as pentamidine or megestrol acetate (Megace), or known predisposing factors for diabetes.² Now, protease inhibitors as a class have been independently associated with the entire spectrum of blood glucose control issues, although these morbidities have also occurred infrequently with other antiretrovirals.² ⁶⁵ Patients on PIs, with additional traditional risk factors for type II diabetes, are likely to be at especially high risk. The incidence of new onset hyperglycemia has been reported at between 3% and 17% in multiple studies, with symptoms appearing at a median of 2 months (range 2-390 days) after initiation of
protease inhibitor treatment. Frank diabetes mellitus (DM) has been reported at between 1% and 6% in the PI-ingesting population. \textsuperscript{4,66}

Insulin resistance, defined as the reduced ability of insulin to promote muscle uptake of glucose and inhibit hepatic gluconeogenesis, is known to increase risk of cardiovascular complications in non-HIV patients. Other known risk factors include hypertension, hypertriglyceridemia, elevated LDLs, and low HDLs, and central fat deposition: common issues for many patients on HAART. Whether a similar atherosclerotic effect may occur in HAART patients is unknown.

Peripheral insulin resistance is believed to be a function of pancreatic beta cell dysfunction, which along with excessive body fat contributes to hyperglycemia. \textsuperscript{4} How insulin resistance occurs in patients on potent antiretroviral therapies is still unclear. Proposed mechanisms include both direct effects, in which antiretroviral drugs may impair cellular glucose uptake by inhibiting glut-4, a principal enzyme transporter of insulin-stimulated cellular glucose, and indirect effects, related to body fat changes. \textsuperscript{8,67,68}

Since initiation of PI therapy may induce new or preexisting glucose intolerance, experts in HIV suggest that fasting glucose be checked before initiating treatment, at 3-6 months, annually thereafter, and more often if indicated. \textsuperscript{2,4,66} Patients taking PIs should be advised of the warning signs of hyperglycemia, (the classic trio of polydipsia, polyuria, and polyphagia), and the need to maintain a recommended body weight while on these medications. \textsuperscript{1} It is often helpful to request a glucose tolerance test, (oral administration of 75 g of glucose), to help identify those patients at particular risk for impaired glucose tolerance, including those with lipodystrophy syndrome, or those with risk factors for type 2 diabetes. Definitions of diabetes mellitus (fasting blood glucose
>126 mg/dL, or glucose ≥200 mg/dL 2 hours after oral glucose) and impaired glucose
tolerance (glucose ≥140 mg/dL 2 hours after oral glucose) are the same as for
HIV-uninfected patients.2

Treatment options

Treatment recommendations for glucose intolerance and hyperglycemia are derived
from data on uninfected patients, as studies identifying optimal treatment for HIV+
patients on HAART have not been completed.2 First, in patients at high risk for diabetes
(e.g. those with preexisting glucose abnormalities, or having first degree relatives with
DM), consideration should be given to avoiding PI-based regimens entirely, or switching
to regimens containing nevirapine, efavirenz, or abacavir.2 Second, in patients with
established hyperglycemia, the standards of care for diabetes mellitus, as established for
the general population, should be followed: these include a healthy balanced diet, regular
exercise, and weight loss as needed.69

Medications

If drug therapy is required, either metformin, which has been shown to decrease
insulin resistance, diastolic blood pressure, weight, waist circumference and
cardiovascular risk, or a thiazolidinedione, which increases insulin sensitivity and
adipocyte development, can be tried.4 Dosing for both of these medications is modest, at
500 mg twice daily for metformin, and 200-600mg/dL for troglitazone.4 Careful
monitoring for side effects, including hepatic dysfunction (with the thiazolidinediones),
and lactic acidemia (with metformin) is recommended when using these medications.
Patients should be informed initially and repeatedly of symptoms, (e.g. nausea, vomiting,
abdominal pain, malaise, fever, fatigue, jaundice, shortness of breath, change in color of
urine or stool, etc.) requiring provider attention. It is suggested that liver enzymes be monitored every two months for the first year of thiazolidinedione treatment, and lactate levels checked if symptoms of lactic acidemia develop. Certain patients (those with aminotransferases >2.5 times the upper limit of normal (ULN)) should not take thiazolidinediones, and those with serum creatinines above the ULN for age, or venous lactate levels >2.0 the ULN, should avoid metformin.

Other potential drug interactions exist, and the provider may wish to consult further with a pharmacist knowledgeable in HIV drugs, or check one of the published drug interaction tables, before initiating drug therapy for glucose abnormalities or insulin resistance concurrently with HAART. Finally, while no data are yet available to help in deciding whether to continue PI therapy in patients with new or worsening diabetes, the consensus of experienced clinicians is to generally recommend continuation of PI-based HAART unless the diabetes is severe in presentation. It is unknown if insulin resistance may be reversed by switching from a PI-containing regimen to one based on NNRTIs.

**Special populations**

Certain populations required special consideration. Since pregnancy is an independent risk factor for impaired glucose tolerance, pregnant patients on PI-containing regimens will need to have their blood glucose levels followed carefully, and may need insulin for blood glucose control. Additionally, non-pregnant patients with severe degrees of fasting hyperglycemia, who have been otherwise unsuccessful with lifestyle adjustments or medications already suggested, may wish to try either oral hypoglycemic agents or insulin. Here again, scrupulous care must be used to avoid hypoglycemia.
Conclusion

In conclusion, while much has been learned about the treatment of HIV disease with our sophisticated battery of antiretroviral medications, much remains to be clarified. The complications of therapy discussed in this article have only recently been recognized, and further studies are urgently needed. HIV is rapidly becoming a chronic disease, and we know little about its course over time, and even less about the effects of these medications on this newly aging population. Every primary care provider needs to stay abreast of the current base of knowledge. Table 3, from Schambelan et al, summarizes the essential information presented in this paper, and is recommended as a reference.
Bibliography


64. McComsey G, Lonergan T, Fisher R, et al.: Improvements in lipoatrophy (LA) are observed after 24 weeks when stavudine (D4T) is replaced by either abacavir (ABC) or zidovudine (ZDV) (abstract 701-T). 9th Conference on Retroviruses and Opportunistic Infections, Seattle, WA, February 24-28, 2002.


<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Initiate therapeutic lifestyle changes $t$</th>
<th>Consider drug therapy</th>
<th>LDL cholesterol goal</th>
<th>Non-HDL cholesterol goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>With CHD or CHD risk equivalent (10-year risk &gt;20%, noncoronary atherosclerotic vascular disease, or type 2 diabetes mellitus)</td>
<td>≥100 mg/dL (≥2.6 mmol/L)</td>
<td>≥130 mg/dL (V3.4 mmol/L)</td>
<td>&lt;100 mg/dL (&lt;2.6 mmol/L)</td>
<td>&lt;130 mg/dL (&lt;3.4 mmol/L)</td>
</tr>
<tr>
<td>2 or more risk factors (10-year risk ≤20%) $t$</td>
<td>≥130 mg/dL (≥3.4 mmol/L)</td>
<td>10-year risk of 10-20%: ≥130 mg/dL (≥3.4 mmol/L)</td>
<td>&lt;130 mg/dL (&lt;3.4 mmol/L)</td>
<td>&lt;160 mg/dL (&lt;4.1 mmol/L)</td>
</tr>
<tr>
<td>0 to 1 risk factor</td>
<td>≥160 mg/dL (≥4.1 mmol/L)</td>
<td>≥190 mg/dL (≥4.9 mmol/L)</td>
<td>&lt;160 mg/dL (&lt;4.1 mmol/L)</td>
<td>&lt;190 mg/dL (&lt;4.9 mmol/L)</td>
</tr>
</tbody>
</table>

* 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); 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.

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

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 of measurement; ↓, a decrease in value or measurement. JAIDS Journal of Acquired Immune Deficiency Syndromes, Vol. 31, No. 3, November 1, 2002. Used with permission.
TABLE 3. 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 same 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 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.

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 diseases, 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.
### TABLE 3. Summary of recommendations for assessment, monitoring, and treatment of metabolic complications of HIV-1 and antiretroviral therapy (Continued)

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.

---

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. Adapted from JAIDS Journal of Acquired Immune Deficiency Syndromes, Vol. 31, No. 3, November 1, 2002. Used with permission.