REVIEW ARTICLE

MEDICAL PROGRESS

Cardiovascular Risk and Body-Fat Abnormalities in HIV-Infected Adults

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METABOLIC COMPLICATIONS, INCLUDING DYSLIPIDEMIA, INSULIN RE- sistance, and altered fat distribution (loss of subcutaneous fat and a relative increase in central fat), are common in adults infected with the human immunodeficiency virus (HIV) who are receiving highly active antiretroviral therapy (HAART). These complications may increase these patients' risk of cardiovascular disease. In this review, we discuss progress in the understanding of pathogenetic mechanisms of cardiovascular risk in this population and the development of treatment strategies.

BODY-FAT ABNORMALITIES

Abnormalities in body composition have been reported in 40 to 50 percent of ambulatory HIV-infected patients[1-3]; the proportion is greater in those receiving combination antiretroviral therapy. Prevalence rates vary widely, from 11 to 83 percent, in cross-sectional studies.[4,5] Lipoatrophy rates may be even higher,[6] depending on the characteristics of the cohort (sex, age, and possibly race), the type and duration of antiretroviral therapies, the criteria for changes in body composition, and the comparison population. Definitions of clinically significant loss of subcutaneous fat and gain in truncal fat have not yet been established. A preliminary case definition based on data obtained by dual-energy x-ray absorptiometry and computed tomography (CT) was validated in a prospective study but is not yet recommended for use in clinical practice.[7]

Subcutaneous lipoatrophy and relative or absolute accumulation of central fat may occur in HIV-infected patients. Subcutaneous lipoatrophy is most noticeable in the face, limbs, and buttocks but can also occur in the trunk.[8] Central fat accumulation, when present, most often represents the accumulation of visceral fat. Total abdominal fat accumulation may vary and may occur independently of peripheral fat loss.[6] Fat accumulation may also be found within the breasts and over the dorsocervical spine (resulting in a "buffalo hump"), in lipomata (Fig. 1), and within the muscle and liver.

Prospective studies investigating body composition in patients starting antiretroviral treatment for the first time[9,10] have demonstrated initial increases in limb fat during the first few months of therapy, followed by a progressive decline during the ensuing three years; in one study, the decline was estimated to be 14 percent per year among white men receiving regimens containing stavudine or zidovudine with lamivudine and either a protease inhibitor or nonnucleoside reverse-transcriptase inhibitor (Fig. 1F).[9] In contrast, truncal fat increases initially and then remains stable during the ensuing two to three years, resulting in relative central adiposity. Changes in limb and central fat masses are clinically evident in 20 to 35 percent of patients after approximately 12 to 24 months of combination antiretroviral therapy.[11,12]

RISK FACTORS AND PATHOGENESIS

The type, duration, and current use or nonuse of antiretroviral therapy are strongly associated with the severity of lipoatrophy. Combination therapy based on the use of two
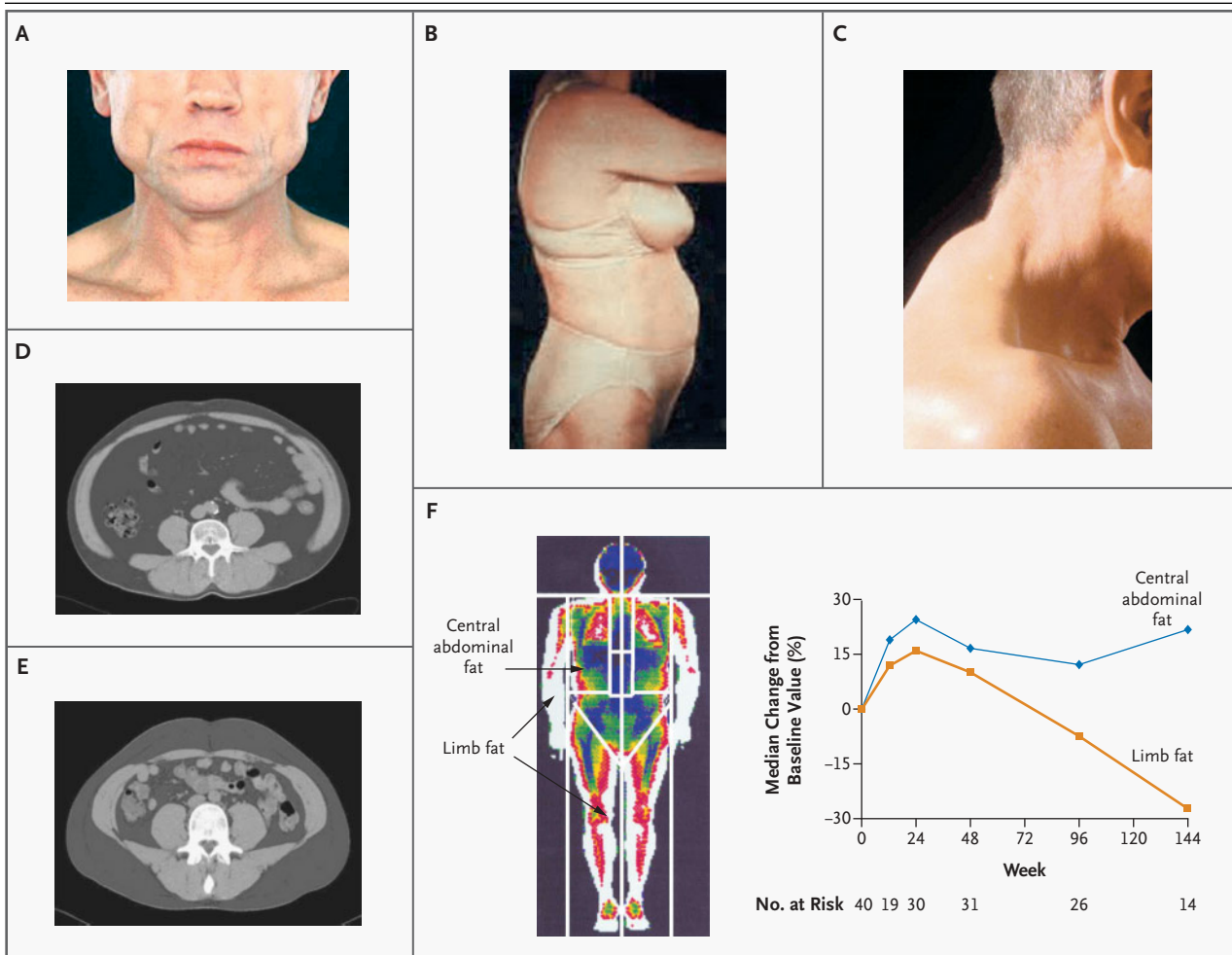
Figure 1. Lipoatrophy and Fat Accumulation in HIV-Infected Adults.

Panel A shows a patient with facial lipoatrophy; Panel B, a patient with abdominal fat accumulation and breast hypertrophy; and Panel C, a patient with a dorsocervical fat pad (or "buffalo hump"). Panel D shows a single-cut abdominal CT scan at the mid-L4 vertebral level; the scan reveals a reduced amount of subcutaneous adipose tissue (scan area, 9 cm²) and an increased amount of visceral adipose tissue (106 cm²) in a patient with lipodystrophy. By contrast, a scan from a patient without lipodystrophy reveals 53 cm² of visceral adipose tissue and 144 cm² of subcutaneous adipose tissue (Panel E). Panel F (left) shows a whole-body dual-energy x-ray absorptiometry study, with standardized regions of interest for analysis of body composition. Panel F (right) shows prospective data reflecting changes in limb and truncal fat over time among adults commencing their first antiretroviral regimen. (The images in Panels A and C are from Carr and Cooper[8]; the graph in Panel F [right] is adapted from Mallon et al.,[9] with the permission of the publisher.)

nucleoside analogue reverse-transcriptase inhibitors and a protease inhibitor is especially strongly associated with severe lipoatrophy.[9,10]

Protease inhibitors may induce lipoatrophy by inhibiting sterol regulatory enhancer–binding protein 1 (SREBP1)–mediated activation of the heterodimer consisting of adipocyte retinoid X receptor and peroxisome proliferator–activated receptor γ (PPARγ) or related transcription factors such as PPARγ coactivator 1.[13,14] In vitro studies have demonstrated that protease inhibitors can inhibit lipo-

genesis and adipocyte differentiation,[15] stimulate lipolysis,[16] and impair SREBP1 nuclear localization.[17]

The nucleoside analogue linked most strongly to lipoatrophy is stavudine, particularly when used in combination with didanosine.[9,10] Lipoatrophy associated with nucleoside analogues may be due in part to mitochondrial injury resulting from inhibition of mitochondrial DNA polymerase γ within adipocytes[18] and depletion of mitochondrial DNA,[19] although the extent and specificity of this effect remain unknown. Nucleoside analogues can in-

hibit adipogenesis and adipocyte differentiation,[20] promote lipolysis,[21] and exert synergistic toxic effects with those of protease inhibitors in vitro and in vivo.[22]

Older age, lower body weight before therapy, prior diagnosis of the acquired immunodeficiency syndrome (AIDS), and a lower nadir CD4+ cell count are associated with lipoatrophy. Central fat accumulation may be more common among women than among men.[23] Storage of increased circulating fatty acids, impaired fatty acid oxidation, or both may contribute to increased intramyocellular lipid content, hepatic steatosis, and insulin resistance.[24-26] Changes in body composition have been reported in a limited number of patients who have never received antiretroviral therapy,[1] but most changes occur in response to highly active antiretroviral therapy, when the viral load is markedly diminished.

ASSESSMENT

Given the loss of limb fat observed in several prospective studies,[9,10] annual assessment of body fat is recommended for adults who begin combination antiretroviral therapy that includes two nucleoside analogues or a protease inhibitor, as well as for any patients who switch antiretroviral agents. Dual-energy x-ray absorptiometry is useful for assessing fat in the limbs over time.[9,10,27] Anthropometric measurements of truncal and limb fat, including measurement of waist, hip, and thigh circumferences, may provide additional information about cardiovascular risk.[28] CT scanning provides information about abdominal subcutaneous and visceral fat, but it is associated with radiation exposure and should not be used clinically for this purpose. No technique has been validated for the assessment of facial lipoatrophy.

DYSLIPIDEMIA

PREVALENCE

Friis-Møller et al., reporting the results of a large cross-sectional study,[29] noted hypercholesterolemia (total cholesterol level, more than 240 mg per deciliter [6.2 mmol per liter]) in 27 percent of subjects receiving combination therapy that included a protease inhibitor, 23 percent receiving a nonnucleoside reverse-transcriptase inhibitor, and 10 percent receiving only nucleoside reverse-transcriptase inhibitors, as compared with 8 percent of previously untreated subjects. The corresponding percentages for hypertriglyceridemia (triglyceride level, more than 200 mg per deciliter [2.3 mmol per li-

ter]) were 40, 32, and 23 percent, as compared with 15 percent among previously untreated subjects.[29] Low levels of high-density lipoprotein (HDL) cholesterol (less than 35 mg per deciliter [0.9 mmol per liter]) were reported in 27, 19, and 25 percent of the subjects, respectively, as compared with 26 percent of those who were previously untreated.[29] Among patients with evidence of body-fat abnormalities, 57 percent had triglyceride levels above 200 mg per deciliter, and 46 percent had HDL cholesterol levels below 35 mg per deciliter, as compared with 9 and 17 percent of healthy subjects matched for age and body-mass index from the Framingham Offspring Study cohort.[28] For cholesterol levels above 200 mg per deciliter (5.2 mmol per liter), the prevalence rate in the HIV-infected group was 57 percent, as compared with 42 percent in the Framingham control group. Prevalence rates vary according to the specific antiretroviral agents used within each class (discussed below).
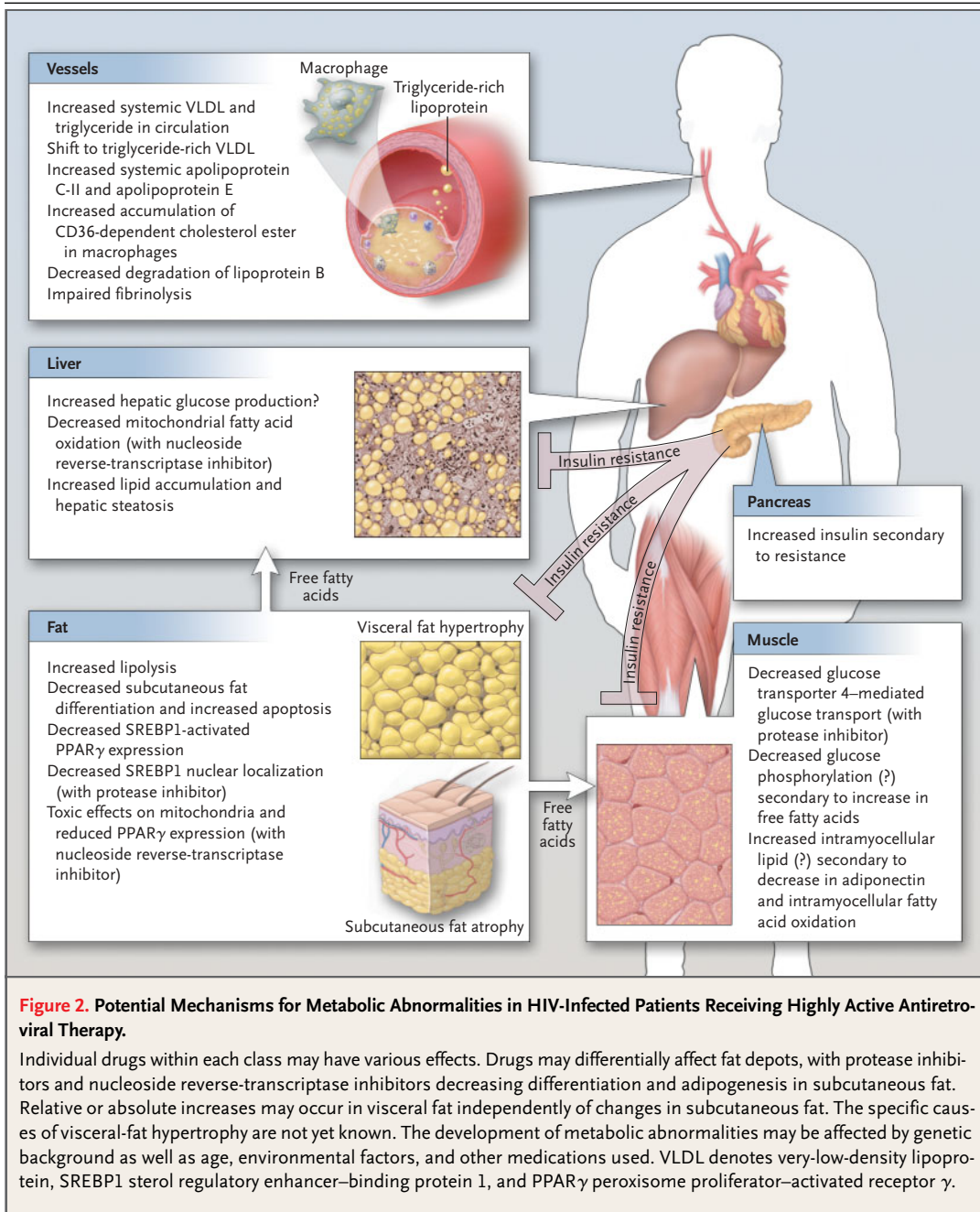
Longitudinal assessment of patients with HIV seroconversion suggests that there are decreases in total, HDL, and low-density lipoprotein (LDL) cholesterol at the time of infection, before treatment. With the initiation of HAART, total and LDL cholesterol increase to preinfection levels, but low HDL levels persist.[30]

PATHOGENESIS

Hypertriglyceridemia in association with low HDL and LDL cholesterol levels was commonly observed in HIV-infected patients before the era of HAART.[31] Early studies suggested that contributing factors were increased apolipoprotein E levels, increased hepatic synthesis of very-low-density lipoprotein, and decreased clearance of triglycerides (Fig. 2).[31-33] Dyslipidemia may also be due in part to the effects of viral infection, acute-phase reactants, and circulating cytokines, including interferon-α.[34]

The specific effects of thymidine analogues on lipid turnover have not been determined,[35] although it is known that stavudine-based, but not tenofovir-based, antiretroviral therapy is associated with early and statistically significant increases in triglyceride and total cholesterol levels.[36] HDL cholesterol levels may improve among patients who switch from a regimen based on a protease inhibitor to a regimen based on other types of drugs.[37]

Individual protease inhibitors, most notably ritonavir, can increase hepatic triglyceride synthesis and plasma triglyceride levels.[38] A newer protease inhibitor, atazanavir, does not appear to have this effect.[39] Protease inhibitors also tend to increase

Vessels

Increased systemic VLDL and
  triglyceride in circulation
Shift to triglyceride-rich VLDL
Increased systemic apolipoprotein
  C-II and apolipoprotein E
Increased accumulation of
  CD36-dependent cholesterol ester
  in macrophages
Decreased degradation of lipoprotein B
Impaired fibrinolysis

Macrophage

Triglyceride-rich
lipoprotein

Liver

Increased hepatic glucose production?
Decreased mitochondrial fatty acid
  oxidation (with nucleoside
  reverse-transcriptase inhibitor)
Increased lipid accumulation and
  hepatic steatosis

Insulin resistance

Insulin resistance

Insulin resistance

Pancreas

Increased insulin secondary
to resistance

Free fatty
acids

Visceral fat hypertrophy

Fat

Increased lipolysis
Decreased subcutaneous fat
  differentiation and increased apoptosis
Decreased SREBP1-activated
  PPARγ expression
Decreased SREBP1 nuclear localization
  (with protease inhibitor)
Toxic effects on mitochondria and
  reduced PPARγ expression (with
  nucleoside reverse-transcriptase
  inhibitor)

Muscle

Decreased glucose
  transporter 4–mediated
  glucose transport (with
  protease inhibitor)
Decreased glucose
  phosphorylation (?)
  secondary to increase in
  free fatty acids
Increased intramyocellular
  lipid (?) secondary to
  decrease in adiponectin
  and intramyocellular fatty
  acid oxidation

Free
fatty
acids

Subcutaneous fat atrophy

Figure 2. Potential Mechanisms for Metabolic Abnormalities in HIV-Infected Patients Receiving Highly Active Antiretroviral Therapy.

Individual drugs within each class may have various effects. Drugs may differentially affect fat depots, with protease inhibitors and nucleoside reverse-transcriptase inhibitors decreasing differentiation and adipogenesis in subcutaneous fat. Relative or absolute increases may occur in visceral fat independently of changes in subcutaneous fat. The specific causes of visceral-fat hypertrophy are not yet known. The development of metabolic abnormalities may be affected by genetic background as well as age, environmental factors, and other medications used. VLDL denotes very-low-density lipoprotein, SREBP1 sterol regulatory enhancer–binding protein 1, and PPARγ peroxisome proliferator–activated receptor γ.

total cholesterol levels, but this effect also varies among the individual drugs in this class.[40] Alterations in apolipoprotein B occur in patients receiving combination therapy (with a nucleoside analogue and a protease inhibitor): notably, there is an increase in small, dense LDL 2; an increase in apolipoprotein B; and a shift toward triglyceride-rich very-low-density lipoprotein.[41] HIV protease inhibitors also decrease proteasomal degradation of nascent lipoprotein B in vitro.[42] In addition, the levels of lipoprotein particles containing apolipoprotein C-III and apolipoprotein E increase in protease-inhibitor-treated patients.[43]

ASSESSMENT

In all HIV-infected adults, fasting lipid levels should be measured annually before antiretroviral therapy is initiated, and within one to two months after any change in the antiretroviral regimen. It is important to determine whether there is a family history

of dyslipidemia or diabetes and to assess the patient's use of alcohol and of medications known to alter lipid levels (e.g., estrogen). Whenever possible, the antiretroviral medication least likely to worsen lipid levels should be selected for patients with dyslipidemia. The chief risk associated with markedly increased triglyceride levels is pancreatitis.

INSULIN RESISTANCE AND ABNORMAL GLUCOSE HOMEOSTASIS

EPIDEMIOLOGY

Hyperinsulinemia, a surrogate measure of insulin resistance, is commonly seen in association with excess truncal fat, loss of fat in the limbs, an increased waist-to-hip ratio, and a buffalo hump. Among HIV-infected adults with lipoatrophy or fat accumulation, diabetes mellitus was seen in 7.0 percent, as compared with 0.5 percent of otherwise healthy control subjects matched for age and body-mass index.[28] Impaired glucose tolerance was present in more than 35 percent of HIV-infected subjects as compared with 5 percent of otherwise healthy control subjects matched for age and body-mass index.[28] In a longitudinal cohort study, diabetes mellitus was 3.1 times as likely to develop in HIV-infected men receiving combination antiretroviral therapy as it was in control subjects over a three-year period of observation.[44] The rate at which impaired glucose tolerance and insulin resistance in HIV-infected adults progress to overt diabetes mellitus is not known.

PATHOGENESIS

Antiretroviral therapy may lead to altered flux of substrates, including free fatty acids,[21] as well as to accumulation of intramyocellular lipid,[25] alterations in adipokine levels (e.g., a low level of adiponectin),[45] and reduced PPARγ expression in subcutaneous adipocytes[13]; antiretroviral therapy may also contribute to altered glucose homeostasis (Fig. 2). Protease inhibitors (including indinavir, amprenavir, nelfinavir, and ritonavir[46-48]) have been shown to induce insulin resistance in vitro by reducing glucose transport mediated by glucose transporter 4,[46] without affecting postreceptor insulin signaling. The results of clinical studies have suggested that indinavir and lopinavir have short-term adverse effects on insulin sensitivity.[49,50] Delayed but long-term effects, possibly related to changes in body composition, may affect insulin sensitivity. Protease inhibitors such as atazanavir and saquinavir may

have minimal effects on insulin sensitivity.[51,52] Protease inhibitors may also reduce pancreatic beta-cell insulin secretion,[53] but insulin resistance is the primary defect. Direct effects of nucleoside analogues on glucose metabolism have not been demonstrated, but such drugs may contribute to insulin resistance indirectly through changes in fat distribution.

ASSESSMENT

In HIV-infected patients, fasting glucose levels should be determined before antiretroviral therapy is initiated and should be determined annually as well as within a few weeks after any change in the antiretroviral regimen. Weight, the severity of fat-distribution abnormalities, and medication history should all be assessed, as should the family history, for the presence of diabetes mellitus. Impaired glucose tolerance and insulin resistance are likely to be present for a variable period before overt diabetes mellitus develops. Impaired glucose tolerance and hyperinsulinemia are considered cardiovascular risk factors in adults without HIV infection. Thus, an oral glucose-tolerance test or measurement of the fasting insulin level should be considered in HIV-infected patients with other cardiovascular risk factors or a family history of type 2 diabetes mellitus.

CARDIOVASCULAR DISEASE

EPIDEMIOLOGY

Retrospective analyses designed to estimate the risk of cardiovascular disease in relation to antiretroviral therapy have yielded variable results.[54-56] The findings do suggest, however, that the risk of cardiovascular disease may be greater in younger patients than in older patients.[57]

The largest prospective study of cardiovascular risk with antiretroviral therapy is the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study.[58] Of 23,468 participants, 126 (0.5 percent) had a first myocardial infarction, an incidence of 3.5 per 1000 person-years. Of these infarctions, 29 percent were fatal, representing 6 percent of all the deaths in the study. There were an additional 77 events related to ischemia, including coronary-artery angioplasty or bypass surgery, ischemic stroke, and carotid endarterectomy.[59] The incidence of myocardial infarction or of any ischemic vascular event increased directly with longer exposure to antiretroviral therapy (relative risk, 1.26 [95 percent con-

fidence interval, 1.12 to 1.41] per additional year of exposure; P<0.001) (Fig. 3). Too few ischemic events occurred to determine the relative risk associated with a specific antiretroviral drug class or with individual drugs. Hypercholesterolemia, older age, smoking, diabetes mellitus, male sex, and a prior history of cardiovascular disease were also associated with an increased risk of myocardial infarction (Fig. 3).[58] The risk of myocardial infarction in relation to the duration of antiretroviral therapy remained significant but was relatively reduced in analyses that adjusted for increased cholesterol levels, suggesting that metabolic abnormalities induced by antiretroviral therapy contributed to the increased morbidity observed.[58]

Although the DAD Study Group[58] found that the relative risk of cardiovascular disease increased as the duration of antiretroviral therapy increased, the absolute risk of cardiovascular disease will remain low for most patients, except those with multiple other cardiovascular risk factors.[60] Overall cardiovascular risk can be estimated with use of standardized equations[60] (Table 1).

MECHANISMS OF CARDIOVASCULAR DISEASE

Endothelial dysfunction and reduced flow-mediated dilation in association with increased atherogenic lipoproteins have been reported among HIV-infected adults receiving protease inhibitors.[62] Hsue et al. reported increased carotid intima–media thicknesses and increased rates of progression over a one-year period in HIV-infected adults with a mean age of 45 years as compared with age- and sex-matched uninfected controls.[63] Increased thickness of the carotid intima–media was associated with traditional risk factors, including hypertension, hypercholesterolemia, and smoking.[63] Hypertension is more common in HIV-infected patients treated with protease inhibitors, nonnucleoside reverse transcriptase inhibitors, or both than in patients who have never received antiretroviral therapy and is associated with increased body-mass index among HIV-infected patients.[29]

The mechanisms of vascular disease in HIV-infected patients are not known but may relate to dyslipidemia, insulin resistance, diabetes mellitus, inflammation, impaired fibrinolysis, factors specific to antiretroviral medications, or combinations of these factors. Increased tissue levels of plasminogen activator and plasminogen-activator inhibitor 1 suggest that fibrinolysis is impaired in HIV-infected patients. Elevations in these substances

are associated with hyperinsulinemia, lipodystrophy, and protease-inhibitor therapy[64] but have not been specifically linked to vascular disease in this population. High levels of protease inhibitors may promote the formation of atherosclerotic lesions by increasing CD36-dependent cholesterol ester accumulation in macrophages, a scavenger-receptor pathway that is thought to mediate the formation of atherosclerotic lesions.[65]
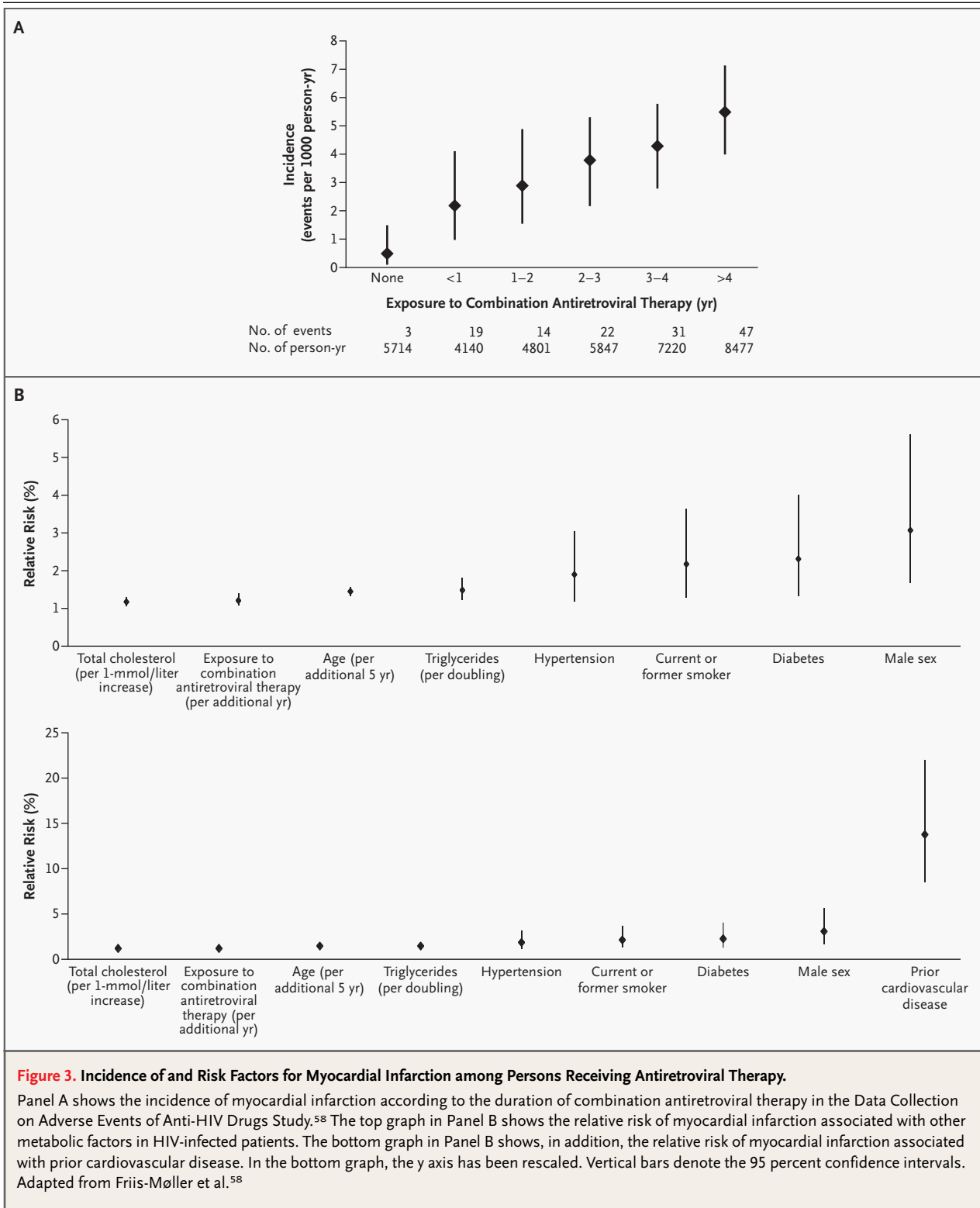
RISK ASSESSMENT AND TREATMENT OPTIONS

RISK-FACTOR MODIFICATION

All potential cardiovascular risk factors, including dyslipidemia, insulin resistance, hypertension, smoking, sedentary lifestyle, weight, and family history, should be assessed. The use of surrogate markers, such as C-reactive protein, to predict vascular disease has not yet been validated in the HIV-infected population. It is recommended that dietary and lifestyle alterations, including appropriate interventions for smoking and hypertension, be initiated first; subsequently, therapy with lipid-lowering medications for hyperlipidemia or changes in antiretroviral therapy can be begun, when clinically possible. Insulin-sensitizing agents are recommended for patients with diabetes mellitus and should be considered for those with marked insulin resistance.

The relative benefits derived from switching antiretroviral regimens and effecting metabolic and lifestyle changes have not been compared directly. Risk-factor modification must balance the risk of progression of HIV disease against the potential risk of progression of cardiovascular disease with long-term maintenance of antiretroviral therapy (Tables 1 and 2). Although the risk of cardiovascular disease is increasing among HIV-infected patients, it is still low and is unlikely to outweigh the substantial benefits of appropriate administration of antiretroviral medications. Cardiovascular risk may be a lesser concern for patients with advanced HIV disease and those with HIV disease that is resistant to antiretroviral drugs. However, in planning risk-modification strategies, clinicians may do well to consider effective antiretroviral agents with the lowest propensity to increase glucose or lipid levels (Table 3).

LIFESTYLE MODIFICATIONS

Cigarette smoking is the most important modifiable cardiovascular risk factor among HIV-infect-

Figure 3. Incidence of and Risk Factors for Myocardial Infarction among Persons Receiving Antiretroviral Therapy.

Panel A shows the incidence of myocardial infarction according to the duration of combination antiretroviral therapy in the Data Collection on Adverse Events of Anti-HIV Drugs Study.[58] The top graph in Panel B shows the relative risk of myocardial infarction associated with other metabolic factors in HIV-infected patients. The bottom graph in Panel B shows, in addition, the relative risk of myocardial infarction associated with prior cardiovascular disease. In the bottom graph, the y axis has been rescaled. Vertical bars denote the 95 percent confidence intervals. Adapted from Friis-Møller et al.[58]

ed patients. In the DAD Study, more than 50 percent of the enrolled subjects were classified as current or former cigarette smokers, and smoking conferred a greater than twofold risk of myocardial infarction (Fig. 3).[58] Cessation of smoking is more likely to reduce cardiovascular risk than either the choice of antiretroviral therapy or the use of any lipid-lowering therapy.

Exercise alone, in the form of progressive resistance training, has been shown to reduce overall fat and truncal fat in HIV-infected patients who have increased abdominal girth.[73] Combined aerobic and strength programs result in reductions in the waist-to-hip ratio, the amount of visceral fat, and the levels of cholesterol, triglyceride, and LDL cholesterol, in association with a reduction in total fat.[74,75] Combined exercise and metformin therapy decreased truncal fat, the waist-to-hip ratio, muscle adiposity, systolic and diastolic blood pressures, and fasting insulin levels more than metformin therapy alone but did not improve lipid levels.[76] A reduction in muscle adiposity proved to be a strong predictor of improved insulin resistance.[77] In contrast, the effect of conditioning programs on patients with predominant, severe lipoatrophy is unknown, and such programs may be inappropriate or potentially harmful for this group of patients.

Limited data on the effects of dietary modification are available for the HIV-infected population. Use of National Cholesterol Education Program guidelines for reduction of cholesterol and triglyceride levels in HIV-infected patients reduced these levels by 11 percent and 21 percent, respectively, whereas gemfibrozil reduced cholesterol by 32 percent and triglycerides by 57 percent.[66] However, use of the guidelines often failed to normalize lipid levels. Barrios et al. demonstrated that a lipid-lowering diet in HIV-infected patients with combined hyperlipidemia led to 10 percent and 23 percent reductions in total cholesterol and triglyceride levels, respectively, after six months.[78] Thus, though not always effective, dietary counseling is prudent in HIV-infected patients who are at increased cardiovascular risk.

METABOLIC INTERVENTIONS

Lipid-Lowering Drugs

In general, a hydroxymethylglutaryl–coenzyme A reductase inhibitor (statin) should be used to treat isolated hypercholesterolemia, and a fibrate should be used to treat isolated hypertriglyceridemia. Combined statin–fibrate therapy can be consid-

ered when the response is incomplete, provided that there is appropriate safety monitoring, including periodic measurement of creatine kinase and aminotransferase levels. In one study, gemfibrozil therapy in conjunction with a low-fat diet lowered triglyceride levels by 18 percent over a 16-week pe-

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Table 1. Suggested Cardiovascular and Body-Composition Assessments for Adults Receiving Antiretroviral Therapy.*

Cardiovascular assessment — Assess cardiovascular risk factors before initiation of antiretroviral therapy and annually during stable therapy or at the time of changes to antiretroviral therapy†

Fasting metabolic assessments
  Cholesterol (total,‡ HDL,‡ and LDL) and triglycerides
  Glucose
  Oral glucose tolerance§

Other assessments
  Age‡
  Sex‡
  Smoking status‡
  Blood pressure and use or nonuse of antihypertensive therapy‡
  Family history of cardiovascular disease

Body-composition assessment — Assess body composition before the initiation of antiretroviral therapy and annually during stable therapy or at the time of changes to antiretroviral therapy

  Weight
  Waist and hip circumferences
  Lipoatrophy and fat accumulation, with use (by patient or physician) of standardized data-collection form¶
  Limb fat mass and percentage by dual-energy x-ray absorptiometry, if available‖

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* HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

† Overall cardiovascular risk in HIV-infected patients[60] can be determined from specific risk factors (indicated by double daggers) by using the Framingham equation (hin.nhlbi.nih.gov/atpiii/calculator.asp).[61] The validity of the Framingham equation to determine long-term cardiovascular risk among young patients with changing lipid levels and medication regimens requires further study; as such, the equation can provide only a relative estimate of cardiovascular risk. The Framingham equation may be less accurate in HIV-infected women than in HIV-infected men and has not been validated for use in adults with prior myocardial infarction. The estimate should be adjusted according to national rates of cardiovascular disease. The risk of cardiovascular disease with or without antiretroviral therapy should be compared with the benefits of antiretroviral therapy in terms of the risk of progression of HIV disease or HIV-related death, before the initiation of antiretroviral therapy and after therapy has been established, as described by the ART Cohort Collaboration (www.art-cohort-collaboration.org).

‡ Total cholesterol, HDL cholesterol, age, sex, smoking status, and use or nonuse of antihypertensive therapy are variables that may be used in the Framingham equation to determine overall cardiovascular risk.

§ Use of the oral glucose-tolerance test should be considered in patients with risk factors for type 2 diabetes, other cardiovascular risk factors, or severe lipoatrophy, but the test result is not used in the calculation of the Framingham equation.

¶ This form is available as Supplementary Appendix 1 with the full text of this article at www.nejm.org.

‖ Dual-energy x-ray absorptiometry should be performed by positioning the patient in the center of the scanning table with the arms separated from the sides of the body and the feet strapped together. Regional fat distribution may then be analyzed, as described by the National Centre in HIV Epidemiology and Clinical Research (www.ti3m.com/hiv/pdf/dexa_instructions.pdf).

Table 2. Estimated Risks of Myocardial Infarction at 10 Years and of AIDS or Death at 3 Years among Men Initiating Highly Active Antiretroviral Therapy, According to Cardiovascular Risks and HIV Disease Status.*

Characteristic	Average Risk of Cardiovascular Disease		Increased Risk of Cardiovascular Disease	
	Before Antiretroviral Therapy	After Antiretroviral Therapy	Lipodystrophy	No Lipodystrophy
Age (yr)	36	36	50	50
AIDS illness	No	No	No	No
Time relative to initiation of antiretroviral therapy that includes a protease inhibitor	Before	>6 mo after	>6 mo after	>6 mo after
Lipodystrophy	No	No	Yes	No
Injection-drug user	No	No	No	No
Smoker	Yes	Yes	Yes	Yes
Blood pressure (mm Hg)	120/80	120/80	120/80	120/80
Antihypertensive therapy	No	No	No	No
CD4+ lymphocyte count (per mm³)	200–350†	>350	>350	>350
HIV-1 RNA load (copies/ml of plasma)	<100,000†	<500	<500	<500
Cholesterol (mg/dl)				
Total	171	217	250	217
HDL	39	39	30	39
Absolute risk of AIDS or death at 3 yr (%)‡	4.7§	2.4	4.1	4.1
Absolute risk of myocardial infarction at 10 yr (%)¶				
No cardiovascular-risk intervention	3	7	23	14
Use of a statin or switch in protease inhibitor‖	—	3	14	8
Smoking cessation	—	1	9	6
Use of a statin or switch in protease inhibitor plus smoking cessation	—	<1	5	3

* AIDS denotes acquired immunodeficiency syndrome, and HDL high-density lipoprotein. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
† Values are based on data from patients more than 16 years of age.[9,11,29,36,37,39,59]
‡ The three-year risk of progression to AIDS or death is calculated according to the method of the ART Cohort Collaboration (www.art-cohort-collaboration.org). The 10-year risk of progression to AIDS or death is not known.
§ If antiretroviral therapy is not initiated, the risk of progression to AIDS or death at three years is approximately 40 percent.
¶ The risk of myocardial infarction at 10 years applies to male patients and is calculated according to the Framingham equation (hin.nhlbi.nih.gov/atpiii/calculator.asp).[61]
‖ A reduction in the risk of myocardial infarction is based on a 25 percent decline in total cholesterol.[66-72]

riod, but it did not lower cholesterol levels.[67] In contrast, pravastatin combined with dietary advice reduced cholesterol levels by 17 percent (a significant reduction) over a 24-week period, without changing triglyceride levels.[68] An open-label study reported that atorvastatin lowered cholesterol and triglyceride levels,[66] suggesting that the drug may be beneficial in adults with combined hyperlipidemia. In an open-label study involving 113 adults with hypertriglyceridemia who were receiving HAART, fibrates (bezafibrate, fenofibrate, and gemfibrozil) were more beneficial than statins in decreasing triglycerides (a reduction of 41 percent vs. 35 percent) but were less beneficial in reducing total cholesterol (22 percent vs. 25 percent) over a 12-month period.[69] Fenofibrate alone resulted in a 40 percent reduction in triglycerides and a 14 percent reduction in cholesterol in a three-month study of HIV-infected adults with hypertriglyceridemia.[79] Until more specific recommendations become available, National Cholesterol Education Program guidelines should be used when lipid-lowering therapy is initiated in HIV-infected patients. Drug interactions, especially between spe-

Table 3. Potential Interventions for Anthropometric and Metabolic Abnormalities in HIV-Infected Patients.*

Intervention	Anthropometric Changes		Metabolic Changes			Comments
	Lipoatrophy	Central Fat Accumulation	Hyperlipidemia	Low HDL Cholesterol	Insulin Resistance	
Changes in antiretroviral therapy						
tNRTI cessation, without switch to abacavir	Improvement	No effect	No effect	No effect	No effect	High risk of virologic failure without substitution; no excess risk of virologic failure with switch to abacavir. Risk of hypersensitivity to abacavir in about 4% of patients
Protease inhibitor switched to NNRTI or abacavir	No effect	Possible improvement	Improvement	No effect	Possible improvement, if no lipoatrophy	Reduced visceral abdominal fat in one randomized study; risks of virologic failure or resistance with use of new antiretroviral drug
Protease inhibitor switched to atazanavir or saquinavir	Unknown	Unknown	Improvement	No effect	Improvement or no effect	Unknown whether different protease inhibitors incur different risks of lipodystrophy
Metabolic interventions						
Lifestyle changes (diet and exercise)	Unknown	Improvement with exercise	Possible improvement	No effect	Improvement	Diet should not affect meals necessary for absorption of antiretroviral therapy; exercise reduces blood pressure
Fibrate	No effect	No effect	Decrease in triglycerides by 20% to 25%; possibly greater decrease with fenofibrate	Improvement	No effect	Minimal effect on total and LDL cholesterol but possible improvement in LDL particle size. May be less effective than in adults without HIV infection
Statins	No effect	No effect	Decrease in total and LDL cholesterol by about 25%	Improvement	No effect	Pravastatin or fluvastatin preferred, since they have no significant cytochrome P-450–mediated interaction with antiretroviral therapy; may be less effective than in adults without HIV infection
Metformin	Possible worsening; associated weight loss	Improvement	Possible improvement in hypertriglyceridemia	No effect	Improvement	Also reduces plasminogen-activator inhibitor 1 and blood pressure; theoretical risk of lactic acidosis
Thiazolidinediones	No effect on lipoatrophy alone; potential benefit for adults with lipoatrophy and insulin resistance	No effect	Increase in triglycerides and LDL cholesterol	No effect	Improvement	Increase in serum adiponectin levels and reduction in liver fat; no significant improvement in arterial endothelial reactivity; possible reduction in blood pressure
Growth hormone (4–6 mg/day)	Possible worsening at higher doses	Improvement	No effect on triglyceride levels; improvement in total and LDL cholesterol	Possible improvement	Worsens, at least initially	Risks of fluid retention and arthralgias. Maintenance therapy required to sustain effect on intraabdominal fat
Growth hormone–releasing hormone	Possible improvement	Improvement	Possible improvement	No effect	No effect	Minimal safety risk with achievement of physiologic growth hormone levels

* tNRTI denotes thymidine-based nucleoside analogue reverse-transcriptase inhibitor (generally stavudine or zidovudine), NNRTI nonnucleoside analogue reverse-transcriptase inhibitor (efavirenz or nevirapine).

cific protease inhibitors and statins, should always be considered (Table 3).[80]

Insulin-Sensitizing Drugs

In HIV-infected adults with central obesity and hyperinsulinemia, metformin (500 mg twice daily) improved insulin sensitivity and decreased visceral adiposity, levels of cardiovascular risk markers (tissue plasminogen activator and plasminogen-activator inhibitor 1), and blood pressure.[81,82] Metformin, like all biguanides, can theoretically precipitate lactic acidosis; but this adverse interaction has not been reported.[82-84] Greater reductions in visceral fat may be seen with larger doses of metformin[84] but may increase the risk of toxic effects. Metformin may also be useful as an initial treatment for type 2 diabetes mellitus in HIV-infected adults who have increased truncal adiposity and are overweight, but lactate levels and hepatic and renal function must be monitored. Initiation of metformin therapy may be associated with gastrointestinal upset, but this effect is usually transient. Use of metformin should be avoided in patients with creatinine levels above 1.5 mg per deciliter (132.6 μmol per liter), increased aminotransferase levels, or hyperlactatemia. It is unknown whether the use of metformin in HIV-infected patients with impaired glucose tolerance prevents the development of diabetes mellitus. Because metformin may reduce subcutaneous fat,[85] its use should be avoided in patients with clinically significant lipoatrophy who have no increase in truncal adiposity.

Thiazolidinediones are antidiabetes drugs with PPARγ-agonist properties that increase subcutaneous fat in persons with diabetes and adults with congenital lipoatrophy.[86] Three randomized studies have investigated the effects of thiazolidinediones in HIV-infected adults. In a 24-week study of rosiglitazone, no benefit in patients with lipoatrophy was observed with respect to total or subcutaneous fat, but there was improvement in hepatic steatosis.[87] By contrast, in a 12-week study of rosiglitazone in HIV-infected patients with insulin resistance and fat atrophy there was a 24 percent improvement in fat in the legs, as assessed by CT. The study also found statistically significant improvements in lipoatrophy, as assessed by physicians and by the patients themselves.[88] A larger, 48-week study in adults receiving a protease inhibitor, a thymidine nucleoside analogue, or both reported that rosiglitazone did not improve limb fat or total fat distribution.[89] However, all three studies found beneficial effects on insulin resistance, possibly as a result of increased adiponectin levels.[87-89] Two small, nonrandomized studies of thiazolidinediones found increased amounts of abdominal subcutaneous fat in HIV-infected patients who had insulin resistance.[90,91] Rosiglitazone was associated with increased total cholesterol and LDL cholesterol levels in all three of the randomized studies[87-89] and with increased triglyceride levels in one of them.[89] Rosiglitazone cannot be recommended for general treatment of lipoatrophy at this time, but it may be useful in patients with insulin resistance.

Growth Hormone

Growth hormone at high doses (e.g., 6 mg per day) appears to be effective in reducing visceral fat, but it also reduces subcutaneous fat and is associated with side effects, including joint swelling, fluid retention, and worsening of glucose tolerance.[92] Furthermore, it is expensive. Lower, but nonetheless supraphysiologic, doses of growth hormone may also be effective in reducing visceral fat and may have fewer side effects.[93] Growth hormone levels are reduced in HIV-infected men who have excess visceral adiposity, and growth hormone secretagogues (including growth hormone–releasing hormone) may prove useful for increasing growth hormone levels to within the physiologic range and for restoring the distribution of body fat toward normal.[94]

SURGERY AND OTHER STRATEGIES TO RESTORE BODY CONTOURS

Injection of various agents has been investigated as therapy for facial lipoatrophy. The most widely used is polylactic acid, a resorbable molecule that promotes collagen formation and appears to improve the appearance of facial soft tissue,[95] with few complications. Surgery (excision or liposuction) has been performed on some patients who have marked dorsocervical fat accumulation, although fat may reaccumulate within a few months.

CHANGES IN ANTIRETROVIRAL THERAPY

Cessation of therapy with the thymidine nucleoside analogue stavudine or zidovudine generally leads to substantial improvements in limb fat mass. However, if another drug is not substituted, virologic failure is likely. In one study, virologic control was unaffected two years after stavudine or zidovudine was replaced by abacavir.[27] Limb fat mass in-

creased by about 36 percent but remained well below normal levels and was not clearly associated with clinically evident improvement in lipoatrophy. Substitution of thymidine nucleoside analogues has not been shown to improve central adiposity, insulin resistance, or dyslipidemia.[27,96]

Replacement of a protease inhibitor with nevirapine, efavirenz, or abacavir can effectively reduce total cholesterol,[70,71,97,98] LDL cholesterol,[97,98] and triglyceride levels[71,97] and increase HDL cholesterol levels.[98] Limited data suggest that insulin resistance may also improve in response to replacement of a protease inhibitor by nevirapine.[71] Protease-inhibitor cessation has not been shown to improve lipoatrophy. In one randomized study, body-fat changes tended to improve six months after a switch from a protease inhibitor to nevirapine.[72]

PREVENTION

Few studies have been performed to determine whether strategies such as lifestyle modification, diet, or medications might be used to prevent metabolic and body-composition abnormalities in HIV-infected adults. Furthermore, specific studies have not investigated whether the timing of antiretroviral therapy would effect such changes. Use of the nucleoside analogues abacavir and lamivudine together with the nonnucleoside analogue efavirenz may not result in decreased limb fat for up to three years after the start of treatment.[99] Tenofovir combined with lamivudine and efavirenz is associated with less limb fat loss and a better lipid profile than stavudine in a similar combination in patients who have not taken any antiretroviral drugs.[36]

CONCLUSIONS

Metabolic and body-fat abnormalities are common among HIV-infected adults receiving nucleoside-analogue and protease-inhibitor therapy. There is preliminary evidence that suggests that such patients have an increased risk of cardiovascular disease. Diet, lifestyle modification, and use of lipid-lowering and insulin-sensitizing regimens may be useful in specific situations. Clinicians caring for HIV-infected adults should assess cardiovascular risk factors and target risk reduction, though not at the expense of successful treatment of the underlying HIV disease.

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