HIV Therapy, Metabolic Syndrome, and Cardiovascular Risk

Vivian Pao, MD, Grace A. Lee, MD, and Carl Grunfeld, MD, PhD

Corresponding author
Carl Grunfeld, MD, PhD
Department of Veterans Affairs Medical Center, Metabolism Section (Box 111F), 4150 Clement Street, San Francisco, CA 94121, USA.
E-mail: carl.grunfeld@ucsf.edu

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People with HIV infection have metabolic abnormalities that resemble metabolic syndrome (hypertriglyceridemia, low high-density lipoprotein cholesterol, and insulin resistance), which is known to predict increased risk of cardiovascular disease (CVD). However, there is not one underlying cause for these abnormalities and they are not linked to each other. Rather, individual abnormalities can be affected by the host response to HIV itself, specific HIV drugs, classes of HIV drugs, HIV-associated lipoatrophy, or restoration to health. Furthermore, one component of metabolic syndrome, increased waist circumference, occurs less frequently in HIV infection. Thus, HIV infection supports the concept that metabolic syndrome does not represent a syndrome based on a common underlying pathophysiology. As might be predicted from these findings, the prevalence of CVD is higher in people with HIV infection. It remains to be determined whether CVD rates in HIV infection are higher than might be predicted from traditional risk factors, including smoking.

Introduction

Since the introduction of highly active antiretroviral therapy (HAART) for HIV, the decline in morbidity and mortality has been clouded by the emergence of a number of metabolic derangements [1–3]. These disorders include dyslipidemia, insulin resistance, abnormalities of glucose metabolism, and changes in fat distribution [2,3]. Hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), insulin resistance, and increased waist circumference can occur simultaneously in HIV infection and are reminiscent of metabolic syndrome in the general population, which increases the risk of cardiovascular disease (CVD). CVD may be increased in HIV infection, and much of the increased risk may be related to components of metabolic syndrome.

Recently, there has been debate over the extent to which metabolic syndrome represents a coherent syndrome with a major underlying cause, such as insulin resistance, or a group of risk factors that, when occurring together, lead to disproportionately increased risk of CVD. In the context of HIV, the individual metabolic disorders of the syndrome clearly have different identifiable causes and are not associated with one another. In this article, we discuss each metabolic disorder, its associations, and the implications for development of CVD.

Metabolic Syndrome in the General Population

The association of insulin resistance with low HDL-C levels, elevated triglyceride levels, and hypertension was proposed by Reaven [4] in 1988 as "Syndrome X" and later as "insulin resistance syndrome." He noted that patients with this cluster of abnormalities are at higher risk for CVD. The term "metabolic syndrome" came into common use when the World Health Organization (WHO) [5] and the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program [6] proposed criteria by which to identify patients at higher risk for CVD.

Subsequently, several groups have proposed their own definitions of metabolic syndrome that vary in what is required, what is included, and what are the dichotomous cutoffs. In addition to insulin resistance, hypertriglyceridemia, low HDL-C, and hypertension, the syndrome may include abnormalities of glucose metabolism and central obesity.

The WHO definition of metabolic syndrome presumes insulin resistance is the central pathophysiologic lesion, requiring insulin resistance (by hyperinsulinemic, euglycemic clamp) or abnormalities of glucose metabolism (diabetes mellitus, impaired fasting glucose, or impaired glucose tolerance) as prerequisites for the syndrome [5]. It also requires two of three other classes of abnormalities (obesity by body mass index [BMI], waist circumference, or waist-to-hip ratio [WHR]; dyslipidemia by either high triglycerides or low HDL-C; or hypertension) [5].

The ATP III definition [6] does not include insulin resistance at all but gives equal weight to the associated factors, requiring three of five (elevated fasting glucose, central obesity by waist circumference, hypertriglyceridemia, low HDL-C, or hypertension). A definition by the

National Heart, Lung, and Blood Institute/American Heart Association (NHLBI/AHA) [7] is similar but uses different parameters for fasting glucose.

The International Diabetes Federation (IDF) [8] requires central obesity rather than insulin resistance for the syndrome, plus two of four other factors (hypertriglyceridemia, low HDL-C, hypertension, or elevated fasting glucose). The European Group for the Study of Insulin Resistance (EGIR) [9] excludes diabetes but requires fasting hyperinsulinemia (highest quartile) plus two of four criteria (fasting glucose > 110 mg/dL but < 126 mg/dL, hypertension, central obesity by waist circumference, or dyslipidemia by high triglycerides or low HDL-C).

One response to the burgeoning number of definitions of metabolic system was a critical analysis of whether the components of metabolic syndrome warrant classification as a true syndrome [10]. It has been difficult to show that the metabolic syndrome adds any CVD risk above the sum of its components. Furthermore, treatment of the syndrome is no different from treatment of its individual components.

Prevalence of Metabolic Syndrome in HIV Infection

The prevalence of metabolic syndrome in HIV-infected people has been examined, but different definitions were used (Table 1). Most studies found a prevalence of 11% to 26% in HIV-infected patients, with the exception of three early studies from a single group in Pavia, Italy, whose patients were all on HAART [11–22]. This prevalence of metabolic syndrome may be comparable or slightly less than that in the general population, at least in the United States.

Although some studies with a control group have reported a slightly increased prevalence of metabolic syndrome in HIV-infected patients, others have reported the converse. Jacobson et al. [19] compared 477 HIV-infected patients with 1876 unmatched healthy patients from the National Health and Nutrition Examination Survey (NHANES). The prevalence of metabolic syndrome was lower in HIV-infected patients (24.3%) than controls (34.1%). Mondy et al. [21] compared 471 HIV-infected patients from the midwestern United States to controls from NHANES matched by age, gender, ethnicity, and tobacco use. The prevalence of metabolic syndrome using ATP III guidelines in HIV-infected patients was similar to controls (25.5% vs 26.5%, respectively).

Bonfanti et al. [13] compared 1263 HIV-infected patients from the Sindrome Metabolica ONE (SIMONE) cohort to the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) cohort, a sample of the general Italian population. The group of HIV-infected patients was not matched with the healthy controls and had a higher percentage of men, lower BMI, and higher rate of smoking. By ATP III criteria, the HIV-infected patients had a higher prevalence of metabolic syndrome than the controls (20.8% vs 15.8%), but the difference was smaller using IDF criteria (22.1% vs 20.5%). The difference remained after multivariable adjustment. However, the HIV-negative cohort data were collected 10 years prior to data collection in the HIV cohort, making it likely that the prevalence of metabolic syndrome was underestimated in controls due to the increasing incidence of obesity in recent years.

Three early studies on populations in Pavia, Italy had reported an even higher prevalence of metabolic syndrome in HIV infection, ranging from 33.1% to 45.4% [15,17,18]. Age and gender-matched controls were included in two of the three studies and the prevalence of metabolic syndrome in the healthy population was 2.4% and 6%, respectively, which is clearly lower than the prevalence in the general Italian population, suggesting that the controls in these studies were unusually healthy.

Different Characteristics of Metabolic Syndrome in HIV-infected versus Control Patients

The profile of metabolic syndrome differs between HIV-infected patients and the general population. As is discussed in the next section, the differences can be attributed to the effects of HIV and its therapies. Although different definitions of metabolic syndrome were used in these studies (eg, ATP III, EGIR, NHLBI), the most commonly achieved metabolic criteria for metabolic syndrome in HIV infection were hypertriglyceridemia and low HDL-C [11,14,16,18–21]. In contrast, the most common features contributing to metabolic syndrome in the NHANES cohort by ATP III criterion was abdominal obesity, low HDL-C, and hypertension, followed by hypertriglyceridemia. The opposite was true in HIV infection, where the least common criteria met were increased waist circumference or BMI. In studies with control groups, the HIV-infected cohorts had lower rates of abdominal obesity and BMI than control groups [13,19,21].

Some studies link the presence of metabolic syndrome in the HIV-infected population to the common factors of age, white ancestry, greater BMI, and higher homeostasis model assessment [11,12,14,16,21]. Among the HIV-related factors, higher CD cell count, lipodystrophy, and use of HAART, protease inhibitors (PIs), lopinavir/ritonavir, indinavir, and stavudine have been associated with metabolic syndrome [11,14,16,19–22].

Deconstructing Metabolic Syndrome in the Setting of HIV

A syndrome usually implies that components are associated with one another. Alternatively, the cluster of components confers a risk beyond that of the sum of individual components.

In the general population, there is some evidence for clustering of components in metabolic syndrome. For example, Reaven [4] and others have shown that insulin

resistance is associated with dyslipidemia (low HDL-C and elevated triglyceride levels), hypertension, and a predisposition toward diabetes, which predicts CVD. However, does this association apply to HIV disease?

Due to similar questions arising from a proposed HIV-lipodystrophy syndrome, there has been extensive research dissecting out the relationships among insulin resistance, dyslipidemia, and fat changes in HIV-infected patients. Shortly after the introduction of PIs for HIV, the term "lipodystrophy syndrome" was used to describe a constellation of symptoms that included insulin resistance, dyslipidemia (low HDL-C and higher low-density lipoprotein cholesterol [LDL-C] and triglyceride levels), increased abdominal fat, and decreased peripheral fat [23]. This syndrome had several features reminiscent of metabolic syndrome in the general population. It was rapidly attributed to PI therapy in cross-sectional cohort studies [23] despite earlier research in which individual components of the lipodystrophy syndrome occurred in the absence of PI use [3].

However, recent studies show that these metabolic disorders are not all caused by PIs and are not always associated with one another. The presence of individual components can often be attributed to independent factors, such as specific antiretroviral drugs, HIV disease, and/or restoration of health. In the following sections, each individual component of the syndrome is analyzed in the context of HIV and their contributing factors are reviewed. This analysis shows the independence of components of metabolic syndrome in HIV.

How HIV-related Factors Affect Diagnosis of Metabolic Syndrome

Dyslipidemia: hypertriglyceridemia and low HDL-C

Before the introduction of HAART, HIV infection was associated with dyslipidemia [24]. Early in the course of infection, HDL-C plummets to levels around 25 mg/dL. With progression of HIV, LDL-C decreases slightly. With advanced disease, such as AIDS, triglycerides and very low-density lipoprotein cholesterol (VLDL-C) cholesterol increase. There is a strong negative correlation between HIV RNA levels and HDL-C levels [25•]. The association is weaker with LDL-C levels. Only very high HIV RNA levels are associated with increased triglycerides and VLDL-C. Low CD4 cell count is associated with low HDL-C levels but not with LDL-C, VLDL-C, or triglyceride levels.

Hypertriglyceridemia is thought to be due to decreased clearance of triglycerides and, to a lesser extent, increased production of VLDL. These changes are associated with elevated levels of the cytokine interferon-α, which mediates the host response to viral infection. In contrast, interferon-α is not associated with low HDL-C [24].

These data show clear dissociations of the contributing factors to triglycerides and HDL-C in HIV infection, although triglycerides and HDL-C are tightly linked in the general population. Indeed, in two definitions of metabolic syndrome (WHO and EGIR), the dyslipidemia criteria could even be met by either hypertriglyceridemia or low HDL-C.

The effects of HIV therapy confirm the dissociation of HDL-C and triglycerides. Early cross-sectional cohort studies suggested that PIs were associated with lower HDL-C levels [23], but this has not been substantiated with prospective trials. Studies in healthy volunteers show that treatment with the PIs ritonavir, lopinavir/ritonavir, indinavir, and atazanavir does not change HDL-C levels [25•,26–29]. In HIV infection, some, but not all, trials have found modest increases (13%–21%) in HDL-C levels with atazanavir, nelfinavir, indinavir, and amprenavir [2]. The non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs nevirapine and efavirenz also increase HDL levels [2,30]. None of these drugs restores HDL-C to normal levels in those who begin therapy with HDL-C levels around 25 mg/dL.

In contrast, hypertriglyceridemia is commonly caused by ritonavir-based regimens. Full-dose ritonavir, which is no longer commonly used, can cause a two- to threefold increase in triglyceride levels [29]. When the combination of lopinavir and ritonavir was given to healthy volunteers for 4 weeks, triglyceride and VLDL-C levels increased by 83% and 33%, respectively [26,28]. In the studies of metabolic syndrome in HIV-infected patients, only a ritonavir-based PI regimen has been linked with hypertriglyceridemia [19,20]. Ritonavir has been shown in vitro to inhibit the degradation of apolipoprotein B and increase sterol regulatory element binding proteins in the liver, which may increase VLDL-C production [31].

Other antiviral therapies, including efavirenz and the nucleoside reverse transcriptase inhibitor (NRTI) stavudine, may be associated with hypertriglyceridemia [32–34]. It should be emphasized that ritonavir, efavirenz, and stavudine induce hypertriglyceridemia without the decrease in HDL-C expected from studies of hypertriglyceridemia in patients without HIV.

PIs do not induce hypertriglyceridemia by inducing insulin resistance. The PI most effective in inducing insulin resistance in healthy volunteers, indinavir, does not induce hypertriglyceridemia [27]. Lopinavir/ritonavir induces significant hypertriglyceridemia under conditions where it has little effect on insulin resistance [26].

Insulin resistance, glucose metabolism, and diabetes

Consistent with early studies linking insulin resistance with other components of metabolic syndrome [4], insulin resistance or disturbances in glucose metabolism are included as criteria in each of the syndrome definitions [5]. Insulin resistance is a required criterion in the WHO and EGIR definitions [5]. Elevated glucose is required for the IDF definition [8].

In the setting of HIV, insulin resistance has a number of causes, including antiretroviral therapy (certain PIs

Table 1. Studies of the prevalence of metabolic syndrome in HIV infection

Study / year	Prevalence	Criteria	Study population	Comments
Gazzaruso et al. [18] / 2002	45.4% HIV+	NCEP-ATP III	553 Italian HIV+, all on HAART (regimens not described)	
Bruno et al. [15] / 2002	39.8% HIV+	EGIR	201 Italian HIV+, all on HAART (regimens not described)	Italian HIV-negative patients in this study have an unusually low prevalence of metabolic syndrome
	6% HIV-negative controls		201 HIV-negative were matched by age and gender	
Gazzaruso et al. [17] / 2003	33.1% HIV+	EGIR	287 Italian HIV+ on HAART	Italian HIV-negative patients in this study have an unusually low prevalence of metabolic syndrome
	2.4% HIV-negative controls		HIV-negative were matched by age and gender	
Jerico et al. [20] / 2005	17% HIV+ overall	NCEP-ATP III	710 HIV+, Barcelona, Spain	Associated with stavudine and lopinavir/ritonavir
	5.1% < 30 y			
	27.0% 50–59 y			
Bonfanti et al. [14] / 2006	22% HIV+	NCEP-ATP III	1243 Italian HIV+ from SIMONE multicenter study	Associated with age, BMI, lipodystrophy, and indinavir use
	23.8% men			
	17.4% women			
Jacobson et al. [19] / 2006	24% NFHL HIV+	NHLBI/AMA	477 HIV+ patients in NFHL Study (of US HIV+) compared with 1876 HIV-negative patients in NHANES	Associated with lopinavir/ritonavir
	34% NHANES HIV-negative			
Bergersen et al. [11] / 2006	13.3% of all HIV+ patients	Essentially NCEP-ATP III*	357 patients: 56 HIV+ HAART naive	Associated with HAART, age, and lipodystrophy
	1.8% of HAART naive		207 HIV+ on HAART (regimens not described)	
	16.4% of HAART therapy		94 HIV-negative controls in Scandinavia	
	16.0% of controls			
	In non-overweight patients:			
	15% in HAART HIV+			
	2% in HAART naive			
	2% controls			

*Participants having 3 or more of the following criteria were defined as having the metabolic syndrome: 1) abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women); 2) high level of fasting glucose (≥ 6.1 mmol/L or on antidiabetic medication); 3) low level of high-density lipoprotein cholesterol (< 1.0 mmol/L in men and < 1.3 mmol/L in women); 4) hypertriglyceridemia (> 1.7 mmol/L); and 5) elevated blood pressure (≥ 130 / ≥ 85 mm Hg [both] or on antihypertensive medication).
AMA—American Medical Association; BMI—body mass index; EGIR—European Group for the Study of Insulin Resistance; HAART—highly active antiretroviral therapy; HOMA—homeostasis model assessment; IDF—International Diabetes Federation; NCEP-ATP III—2003 National Cholesterol Education Program Adult Treatment Panel III; NFHL—Nutrition for Healthy Living; NHANES—National Health and Nutrition Examination Survey; NHLBI—National Heart, Lung, and Blood Institute; PI—protease inhibitor.

Table 1. Studies of the prevalence of metabolic syndrome in HIV infection (*Continued*)

Study / year	Prevalence	Criteria	Study population	Comments
Estrada et al. [16] / 2006	15.8% HIV+ on therapy	NCEP-ATP III	146 HIV+ patients in Madrid, Spain	Associated with elevated HOMA and lipodystrophy
	3.2% HIV-negative		159 HIV-negative patients matched by BMI	
Samaras et al. [22] / 2007	14% HIV+	IDF	788 HIV+ (451 with clinical lipodystrophy) from Lipodystrophy Case Definition Cohort (international multicenter)	Associated with PI use
	12% all men			
	25% all women			
	18% HIV+	NCEP-ATP III		
Bernal et al. [12] / 2007	11.4% HIV	IDF	210 HIV+ from Mediterranean Spain	Associated with age and BMI
Mondy et al. [21] / 2007	25.5% HIV+	NCEP-ATP III	471 HIV+ from US	Associated with age, white ancestry, greater BMI, and higher CD4
	26.5% HIV-		NHANES (2001–2002) matched for age, gender, ethnicity, tobacco use	
Bonfanti et al. [13] / 2007	20.8% HIV+	NCEP-ATP III	1243 Italian HIV+ from SIMONE	
	15.8% HIV-negative ($P < 0.0001$)		922 HIV-negative unmatched Italian controls from PAMELA	
	22.1% HIV+	IDF		
	20.5% HIV– ($P < 0.0001$)			

*Participants having 3 or more of the following criteria were defined as having the metabolic syndrome: 1) abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women); 2) high level of fasting glucose (≥ 6.1 mmol/L or on antidiabetic medication); 3) low level of high-density lipoprotein cholesterol (< 1.0 mmol/L in men and < 1.3 mmol/L in women); 4) hypertriglyceridemia (> 1.7 mmol/L); and 5) elevated blood pressure (≥ 130 / ≥ 85 mm Hg [both] or on antihypertensive medication).
AMA—American Medical Association; BMI—body mass index; EGIR—European Group for the Study of Insulin Resistance; HAART—highly active antiretroviral therapy; HOMA—homeostasis model assessment; IDF—International Diabetes Federation; NCEP-ATP III—2003 National Cholesterol Education Program Adult Treatment Panel III; NFHL—Nutrition for Healthy Living; NHANES—National Health and Nutrition Examination Survey; NHLBI—National Heart, Lung, and Blood Institute; PI—protease inhibitor.

and to a lesser extent certain NRTIs). The mechanism of induction by these PIs is partially understood and differs from insulin resistance in the general population. HIV-related insulin resistance does not seem to be associated with other aspects of the syndrome.

The PI indinavir has the most dramatic effect on insulin-mediated glucose disposal. Indinavir given for 4 weeks to healthy normal volunteers caused a 17% decrease in insulin-mediated glucose disposal (insulin sensitivity) [27]. A single dose of indinavir induced a greater (34%) decrease in insulin-mediated glucose disposal [35]. A single dose of full-dose ritonavir, which is no longer used, decreased insulin-mediated glucose disposal by 15%; the effect of chronic administration is unknown [36]. Lopinavir/ritonavir has less of an effect on insulin sensitivity, but the magnitude of this effect is not clear. In healthy volunteers, a single dose of lopinavir/ritonavir decreased insulin-mediated glucose disposal by 13% [37], but 4 weeks of lopinavir/ritonavir had no effect on insulin sensitivity [26]. Several PIs (amprenavir, atazanavir, and tipranvir) have no effect on insulin sensitivity [28,36].

PIs induce insulin resistance by a novel mechanism that does not resemble the insulin resistance found in patients with type 2 diabetes or obesity, which involves most aspects of insulin action. Rather, PIs acutely block transport of glucose by the insulin-sensitive glucose transporter GLUT4 [38]. In vitro studies have shown that PIs selectively inhibit glucose transport in adipocytes without affecting early insulin-signaling events or translocation of intracellular GLUT4 transporters to the cell surface.

Because PIs do not block insulin signaling, they may have little effect on fatty acid (FA) metabolism. Indeed, indinavir, which induces the most insulin resistance, has no effect on FA levels, insulin suppression of FA, or triglyceride levels [27]. Lopinavir/ritonavir induces hypertriglyceridemia under conditions where insulin still fully suppresses FAs [26]. Thus, the HIV drug–specific effects do not link insulin resistance to other intermediary derangements observed in metabolic syndrome.

NRTIs, specifically stavudine, may have an effect on insulin sensitivity [39]. Less is known about the mechanisms.

There are other effects of PIs on glucose metabolism that are not fully understood. Chronic administration of indinavir induces small increases in fasting glucose and insulin levels, which are not easily attributed to an effect on GLUT4. Indinavir also increases endogenous glucose production and blunts insulin suppression of endogenous glucose production in healthy volunteers [40]. The mechanism by which indinavir affects endogenous glucose production is not known. No other PI has been shown to increase fasting glucose.

There may be other independent effects of PI on glucose tolerance. When healthy volunteers with normal glucose tolerance were given indinavir for 4 weeks, three of 10 developed impaired glucose tolerance or diabetes [27]. Even when PIs have little or no effect on insulin-mediated glucose disposal (atazanavir/ritonavir or lopinavir/ritonavir), they may still induce deterioration in glucose tolerance [26,41]. The mechanism by which PIs impair glucose tolerance is not fully understood.

Fat distribution in HIV infection: implications for metabolic syndrome

All definitions of metabolic syndrome include central obesity. Central obesity is required to meet the IDF definition, which uses different waist circumferences for ethnic groups as well as for gender. An alternative view of metabolic syndrome is that visceral obesity is the driving mechanism for insulin resistance, hypertriglyceridemia, low HDL-C, and hypertension. Changes in fat distribution that occur in HIV infection were first thought to be similar, but as is discussed in the following text, the HIV-specific change may actually lead to underestimation of the prevalence of metabolic syndrome.

Early after the introduction of HAART, reports appeared of facial lipoatrophy (fat loss), increased upper trunk fat (buffalo hump), lipoatrophy of the arms and legs, and abdominal obesity. They were rapidly synthesized into a single syndrome of peripheral lipoatrophy with central lipohypertrophy that was attributed to PIs [23]. Peripheral lipoatrophy was different from the cachexia previously seen in HIV infection. Many felt that the peripheral lipoatrophy resulted in compensatory central lipohypertrophy, which would lead to metabolic syndrome with increased CVD.

Because patients with both lipoatrophy and central obesity looked so striking, a link was presumed. Diagnosis of HIV-associated lipodystrophy was based on clinical criteria, not measurements. Those criteria initially only looked for peripheral lipoatrophy or central lipohypertrophy (unidirectional clinical scales), presuming the link.

More recent studies objectively assessed fat with bidirectional scales and clinical measurements [42••,43••]. These studies found that the HIV-specific lesion was subcutaneous lipoatrophy, with the upper trunk least affected. Lipoatrophy was mostly associated with thymidine analogue NRTI drugs, especially stavudine. PIs, and to a lesser extent NNRTIs, may contribute. Visceral fat levels were found to be independent of subcutaneous fat (not inversely increased) and not affected by those drugs. The major determinants of visceral fat were restoration to health, age, male gender, and white ancestry [42••,43••].

While the leg was the depot most affected by lipoatrophy, lower trunk (abdominal and back) subcutaneous adipose tissue was another site greatly affected by lipoatrophy [42••,43••]. Hence, it is not proper to use the term central lipohypertrophy, because only visceral fat is not affected by lipoatrophy. The lipoatrophy of abdominal and leg subcutaneous fat has great importance for the diagnosis of metabolic syndrome. Diagnostic criteria use waist circumference or WHR for central obesity [5–9]. Waist circumference includes abdominal subcutaneous fat as well as visceral fat. If waist

circumference is a surrogate for visceral fat, then the loss of abdominal subcutaneous fat might miss visceral obesity in HIV-infected patients with lipoatrophy.

Even the use of WHR is problematic. With HIV-associated lipoatrophy, patients can have loss of hip fat that causes an increase in WHR without increased visceral fat [42••,43••]. Although severe congenital and acquired lipoatrophy patients without HIV have metabolic disorders, the metabolic disorders are more severe than those seen in HIV, which mostly has less lipoatrophy.

Abdominal subcutaneous lipoatrophy explains why HIV-infected patients less frequently meet the waist circumference criteria for metabolic syndrome. Lipoatrophy also leads to lower BMI, so substituting BMI does not help. Nevertheless, despite the lower waist circumference and BMI of HIV-infected patients compared with controls, BMI remains a strong quantitative predictor of metabolic syndrome in several studies [19–21].

Thus, the parameters for waist and hip circumference need to be recalibrated for HIV, similar to what is done for gender and ethnicity in the IDF definition [8,19–21]. However, HIV-associated lipoatrophy is not universal, so a simple recalibration is not likely to work.

Associations of body fat with metabolic parameters

Because of HIV lipodystrophy, the correlation between individual body fat depots and metabolic disturbances has been studied in detail with comparisons to controls. However, it should be noted that the metabolic effects described here for specific antiretroviral drugs occur before any change in body composition and are independent of the associations with body fat depots using multivariable analysis in cross-sectional studies.

Increased visceral fat is associated with insulin resistance, higher triglycerides, and lower HDL-C in both HIV-infected and control men and women [44••]. There is little difference in the effect in HIV-infected and control populations.

Upper-trunk fat is a strong independent predictor of insulin resistance in HIV-infected and control patients and of triglyceride levels in control and, to a lesser extent, HIV-infected women [44••]. In contrast, the amount of trunk fat is not associated with HDL-C, emphasizing that each metabolic parameter may have different contributors.

On the other hand, leg fat seems protective. More leg fat is associated with lower triglycerides in control and HIV-infected men and women. Although there is little difference in the association of the amount of fat with triglycerides in HIV-infected patients compared with controls, there is a high prevalence of lipoatrophy in HIV due to thymidine-based NRTI, contributing to the hypertriglyceridemia of HIV infection. There is no apparent association of leg fat with low HDL-C or insulin resistance.

Hypertension

There are very few studies of hypertension in the HIV-infected population and little evidence for a significant increase compared with controls. Prospective studies of PIs or NRTIs in healthy volunteers, including those that are associated with induction of hypertriglyceridemia or insulin resistance, did not find increases in blood pressure [26–28,41]. However, blood pressure rises when HIV-infected patients are treated with effective antiretroviral therapy [45–48]. No specific antiretroviral drug has been linked to hypertension, but, as in control populations, age and BMI are linked to hypertension.

Components of Metabolic Syndrome and CVD Risk in HIV Infection

Another reason to group findings into a syndrome is to determine whether the cluster leads to a disproportionate outcome. There currently is debate over whether the risk of CVD in people with metabolic syndrome in the absence of HIV is greater than the sum of the components (Table 2). Regardless, those who have metabolic syndrome are at greater risk than those without.

There is no reason to believe that components of metabolic syndrome in HIV pose less risk for CVD, perhaps with one exception. As discussed previously, the insulin resistance of PIs is limited to insulin-mediated glucose disposal and not other aspects of insulin action [27,38]. Therefore, it is not clear whether the insulin resistance of PIs conveys the same risk of CVD as other forms of insulin resistance and hyperinsulinemia. Nevertheless, there are other causes of insulin resistance in HIV, and although their mechanisms are unknown, they likely involve more insulin pathways and convey the same risk as insulin resistance in the general population.

The hypertriglyceridemia of HIV resembles that of metabolic syndrome. It is also accompanied by increased prevalence of small dense LDL-C, which is thought to be more atherogenic than large LDL-C [49]. Small dense LDL-C penetrates the vessel wall easier and is more susceptible to oxidation. There is debate as to whether, in the absence of therapy, HIV infection is accompanied by increased circulating oxidized LDL-C and whether PIs increase LDL-C oxidation.

However, most oxidation is thought to occur in the vessel wall. LDL-C in HIV infection has higher levels of the platelet-activating factor acetylhydrolase, which cleaves oxidized phosphatidylcholine to the highly atherogenic lipid mediator lysophosphatidycholine [50]. Treatment with PIs does not decrease levels of this enzyme; hence, oxidized LDL from patients with HIV may generate more lysophosphatidycholine.

HDL-C in other inflammatory diseases may be more atherogenic than levels indicate [50]. For example, inflammatory HDL-C is less active at preventing LDL-C oxidation and at removing cholesterol from macrophage foam cells. Indeed, inflammatory HDL may recruit macrophages to the vessel intima and may actually load macrophages with cholesterol.

Table 2. The influence of HIV-related factors on components of metabolic syndrome

	HIV-specific effects	Traditional factors that may be influenced by HIV
Lipid metabolism		
HDL-C	Increases early in infection	Decreases with increased visceral fat
	Increases modestly with HAART	
	Increases more with NNRTI (and possibly atazanavir) than other PIs	
LDL-C	Decreases later in infection	
	Increases modestly with HAART	
Triglycerides	Increases in late infection	Increases with increased visceral fat
	Decreases in early study of zidovudine monotherapy	Increases with increased trunk fat but decreases with lower leg fat
	No change with some HAARTs	
	Increases with regimens containing ritonavir	
	Increases may be seen with stavudine and efavirenz	
	Increases with HIV-associated lipoatrophy	
Glucose metabolism		
Insulin sensitivity	Some early evidence of increases due to HIV itself	Increases with increased VAT and upper trunk fat
	Recent data find decreases in untreated HIV	
	Decreases with some PIs	
	Decreases with some NRTIs	
Waist circumference	Decreases with HIV-associated lipoatrophy; may underestimate visceral fat	Increases with increased VAT

HAART—highly active antiretroviral therapy; HDL-C—high-density lipoprotein cholesterol; LDL-C—low-density lipoprotein cholesterol; NRTI—nucleoside reverse transcriptase inhibitor; NNRTI—non-nucleoside reverse transcriptase inhibitor; PI—protease inhibitor; VAT—visceral adipose tissue.

Atherosclerosis in HIV

Given the increased prevalence of various metabolic disorders in HIV infection, it is not surprising that several studies have shown that HIV-infected patients have an increased prevalence or incidence of CVD compared with the general population [51,52]. Smoking, an unrelated risk factor, is twice as common in HIV-infected populations.

There is debate over whether the risk of CVD is higher in HIV patients after accounting for traditional risk factors and, if so, what the causes are. Two large studies published seemingly opposite results. A study by Bozzette et al. [51] found that CVD admissions or deaths decreased progressively after the introduction of HAART (1.7 to 0.9 per 100 patient-years from 1995 to 2001) at a time when death from AIDS decreased by more than 75% (21.3% to 5.0% per year). However, a study by Friis-Moller et al. [53] found that duration of HAART exposure was associated with an increased risk of myocardial infarction (1.26 per year of exposure, with an overall rate of 0.35 per 100 patient-years). In a follow-up study, PIs were identified as conferring increased risk (1.16 per year of exposure), whereas the use of NNRTIs was not significant (1.05 per year of exposure) [54••]. Although other small studies often did not find a significant increase in CVD events with PI use, the trend was for increased risk [52,55]. A pooled analysis of randomized trials undertaken by pharmaceutical companies for licensing estimated the risk of myocardial infarction from PIs to be low (0.077 per 100 patient-years, which was not significant) [55]. However, whether the PIs directly confer increased risk of atherosclerosis via their effects on metabolism (such as insulin resistance or dyslipidemia which varies among PIs) or through another pathway is not known [54].

There are no reports on the risk of CVD in HIV-infected patients with metabolic syndrome. Thus, it is unclear if recognizing metabolic syndrome in HIV-infected patients is useful compared with identifying and treating the individual components.

Conclusions

Although HIV infection is accompanied by an increased prevalence of metabolic syndrome, it provides perspective on the limitations of metabolic syndrome itself. For

each component, different causes can be identified, supporting the concept that metabolic syndrome as currently described does not have a common underlying pathology. These causes include the host response to HIV infection, specific HIV drugs, classes of drugs, and HIV-associated lipoatrophy. Furthermore, restoration to health allows metabolic syndrome to be manifest in those who were genetically predisposed. As a consequence, the rates of CVD are increased in those with HIV infection. Future research is needed to determine if the risk of CVD is greater than the sum of traditional risk factors.

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Disclosures

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