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## Contribution of Metabolic and Anthropometric Abnormalities to Cardiovascular Disease Risk Factors

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Patients with human immunodeficiency virus (HIV) infection have sustained alterations in metabolism (lipids and insulin/glucose homeostasis) and body composition (fat distribution) that are proatherogenic (the Figure). HIV infection itself and/or its therapies may contribute to these alterations (the Table); although most effects are reversible, there are some possibly irreversible consequences of treatment. With the relative restoration to health seen in the era of highly active antiretroviral therapy (HAART), many traditional risk factors and promoters of dyslipidemia and diabetes also are present; they interact with HIV-specific inducers to worsen dyslipidemia and to increase the prevalence of insulin resistance and diabetes.

These disturbances in lipid and glucose metabolism and renal disease may contribute, at least in part, to the excess cardiovascular disease (CVD) morbidity and mortality observed in HIV-infected individuals (the Figure). However, the relative contribution to excess CVD risk of traditional CVD risk factors, especially smoking, compared with these infection- and treatment-specific complications requires clarification. More prospective data with multivariable modeling are needed.

### Dissecting the Effect of HIV Alone: Metabolic Parameters and Body Composition Before HAART

#### Lipid and Lipoproteins

High-density lipoprotein cholesterol (HDL-C) levels decrease early in HIV infection<sup>1,2</sup> (the Table). Low-density lipoprotein

cholesterol (LDL-C) decreases slightly later.<sup>1,2</sup> Subsequently, triglycerides and very low-density lipoprotein (VLDL) cholesterol (VLDL-C) increase, often at the time when signs and symptoms of AIDS occur.<sup>1,2</sup> The relative proatherogenic effect of reduced HDL may exceed the protective effect of the slight reduction in LDL; the increase in VLDL-C may offset the decrease in LDL-C. HIV infection frequently is characterized by hypertriglyceridemia resulting from increased VLDL. Under those circumstances, non-HDL-C is likely a better predictor of CVD risk than LDL-C.

These lipid changes are related to indexes of HIV disease stage and activity such as increasing HIV RNA levels and decreasing CD4 counts.<sup>1-3</sup> Likely mediators are cytokines involved in the host response to infection. Although multiple cytokines may be involved, the strongest link is between interferon- $\alpha$  levels and the changes in triglyceride metabolism.<sup>4</sup> Triglyceride clearance is slowed and de novo lipogenesis is increased, 2 changes that correlate with interferon- $\alpha$  levels.<sup>1,5</sup> Free fatty acids may rise, but the contribution of increased free fatty acids to the HIV-induced increase in triglycerides is not clear.

Importantly, lipoprotein composition also changes. There are increased concentrations of small dense LDL,<sup>6</sup> which is thought to penetrate vessel walls and undergo oxidation more easily.<sup>7</sup> Oxidized LDL is more atherogenic than nonoxidized LDL.<sup>8</sup> Circulating levels of oxidized LDL may increase.<sup>9,10</sup> Increased levels<sup>11</sup> are seen of the enzyme plasma platelet-activity factor (PAF) acetylhydrolase, which cleaves oxidized

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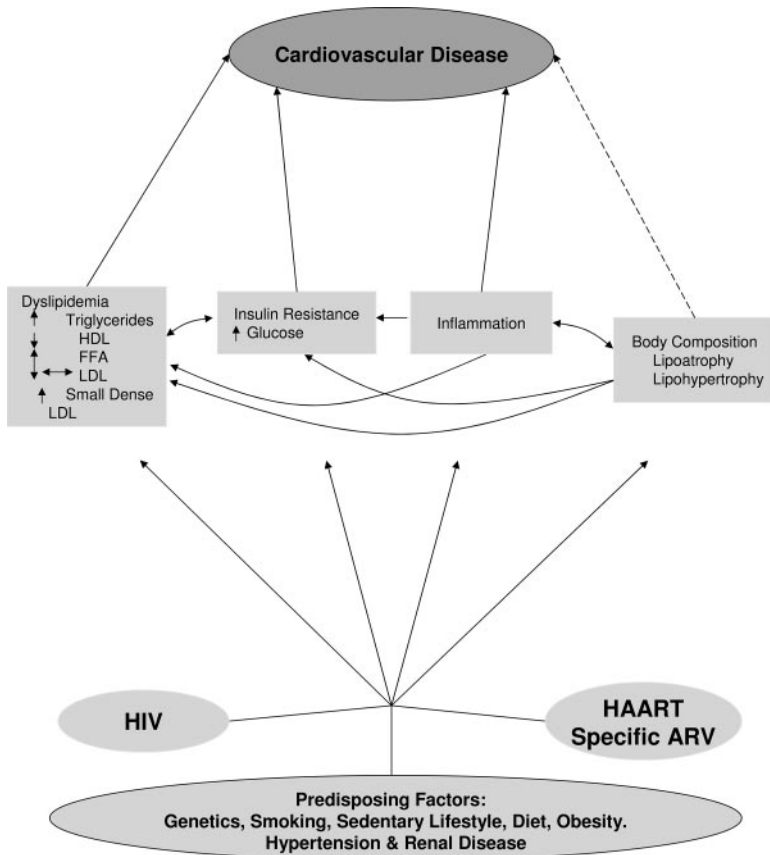
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**Figure.** Overview of the effects of HIV and its therapies on CVD risk. The contribution of traditional risk factors must be kept in mind, and they may occur with increased prevalence in people with HIV infection (eg, smoking). HIV, likely through the inflammatory response, and antiretroviral therapies independently affect many of the mediators of CVD risk. The effects on lipids are a prominent but complex example; HIV infection lowers LDL levels, but antiretroviral therapy raises LDL back up to normal levels. The bidirectional arrows indicate associations, but there is not yet adequate proof of causality. The dotted arrow between body composition and CVD indicates that body fat is known to affect the mediators such as dyslipidemia and insulin resistance but may also have a direct effect. FFA indicates free fatty acids; ARV, antiretroviral.

phosphatidylcholine to lysophosphatidylcholine, a lipid that promotes macrophage recruitment into the vessel wall.<sup>8</sup> More study is needed on the fine structure of lipoproteins that might influence atherosclerosis risk independently of lipoprotein levels. Early evidence suggests that HIV-infected macrophages may be more susceptible to foam cell formation, an early step in atherosclerosis.<sup>12</sup>

Although many of these changes might be predicted to increase atherosclerosis, in aggregate, there is little evidence to permit estimation of the contribution of individual alterations to atherosclerotic disease. Indeed, the contribution of untreated HIV infection to CVD is debated. For example, of the 2 largest studies, 1 study found that the incidence of CVD events decreased at the time of introduction of effective HAART, and the other found an increase.<sup>13,14</sup> In a randomized trial of treatment to suppress HIV RNA compared with intermittent therapy to maintain CD4 cell counts, intermittent therapy had more complications, including increased CVD, suggesting that sustained therapy reduced CVD.<sup>15</sup>

**Glucose Metabolism and Insulin Resistance**

Interpreting published studies to provide a unifying summary of the effects of HIV infection per se on insulin sensitivity is difficult because there are conflicting results from current studies of antiretroviral-naïve subjects and earlier studies of naïve or ineffectively treated subjects (the Table). In early studies before the availability of effective HAART when AIDS wasting was common, patients were not insulin resistant, and evidence of disturbances of glucose metabolism was

unusual.<sup>16,17</sup> More recently, insulin resistance may be seen before the initiation of HAART.<sup>18</sup>

Explanations for this discrepancy may relate to differences in the body composition characteristics of the 2 eras (see the Body Composition section below). In early studies before HAART, patients were cachectic or had a body mass index (BMI) <25 kg/m<sup>2</sup> and thus did not have a phenotype prone to insulin resistance and disorders of glucose metabolism.<sup>19</sup> In the current era, there may be a greater prevalence of visceral adipose tissue (VAT) and even obesity at the time of HIV diagnosis or initiation of treatment<sup>20</sup>; obesity is associated with insulin resistance.<sup>21</sup>

**Body Composition**

As discussed above, historically, many HIV-infected patients became cachectic or at least had lower BMIs (<25 kg/m<sup>2</sup>) than their non-HIV-infected counterparts<sup>19</sup> (the Table). Negative energy balance (decreased energy intake resulting from opportunistic infection or gastrointestinal disease plus inappropriately increased resting energy expenditure resulting from HIV) caused weight loss, followed by failure to return to preillness weight.<sup>22–25</sup>

Early studies of cachexia suggested that lean mass was lost preferentially.<sup>19,26,27</sup> In later studies, weight loss was accompanied by more loss of fat than of lean.<sup>28,29</sup> However, in retrospect, one cannot rule out nucleoside reverse transcriptase inhibitor (NRTI)-induced fat loss as a contributor to the later results.<sup>30</sup>

Extrapolation from studies in other diseases and limited studies in HIV suggests conservation of VAT relative to subcu-

**Table. Effects of HIV Treatment**

	Effects of Untreated or Ineffectively Treated HIV	Changes Associated With Viral Suppression	Changes With Specific Antiretroviral Therapy	Role of Body Shape Changes
<b>Lipid metabolism</b>				
HDL-C	Decreases early in infection	Increases modestly but not to premorbid levels	Greater increases seen with NNRTI and possibly atazanavir than other PI	Increased VAT and upper trunk fat associated with low HDL-C
LDL-C	Decreases later in infection	Increases modestly	No evidence of direct drug effects	
Triglycerides	Increases in late infection	Decreased in early study of AZT monotherapy	No decrease or even further increase with HAART regimens containing ritonavir and other (but not all) PIs; increases also may be seen with stavudine and efavirenz	Increased VAT and upper trunk fat but lower leg fat associated with increased triglyceride levels
<b>Glucose metabolism</b>				
Insulin sensitivity	Some early evidence of increase; recent data find decrease	Overall trend to decreased insulin sensitivity independently of regimen; some insulin resistance represents restoration to health	Some PIs decrease; NRTIs (particularly stavudine) also may contribute to decreases	Increased VAT and upper trunk fat and lower limb fat associated with insulin resistance
Insulin secretion	No evidence of an effect	No evidence of an effect	Some PIs may decrease insulin secretion	
Fasting glucose	No evidence of an effect		Increased in some studies; some PIs increase endogenous glucose production	
Glucose tolerance	No evidence of an effect		Higher rates of IGT	
Diabetes	No evidence of differences in incidence or prevalence	Possibly higher prevalence of diabetes	Higher prevalence and incidence of type 2 diabetes; associated with some PI (especially indinavir, ritonavir) and NRTI (especially stavudine)	
<b>Body composition</b>				
Lean body mass	Decreases disproportionately with severe wasting	Increases modestly with initiation of effective HAART	No consistent evidence of direct drug effects	
Peripheral fat	Decreases proportionally with wasting	Initially increases with initiation of effective HAART	Subsequent preferential depletion of subcutaneous fat in face, arms, legs, and buttocks more than upper trunk associated with some NRTIs (especially, thymidine analogues); role of different PIs and NNRTIs unclear	
Visceral fat	Decreased but possibly relatively preserved; effect of weight cycling during episodic weight loss and regain unknown	Increases with initiation of effective HAART	Preserved or increased visceral fat in some patients on HAART; association with specific drugs or drug classes unclear	
<b>Renal function</b>				
Renal disease	HIVAN	Decreased HIVAN	Some impaired renal function with tenofovir	
	Microalbuminuria and elevated cystatin C	Microalbuminuria and elevated cystatin C remain common in current era		

PI indicates protease inhibitors; AZT, azidothymidine; IGT, impaired glucose tolerance; and HIVAN, HIV-associated nephropathy.

taneous adipose tissue before treatment with HAART.<sup>20,31,32</sup> Many studies in HIV infection include young and female subjects who have little VAT, making depletion or conservation of VAT hard to assess. Weight loss in obesity may have preferential VAT loss, which is accompanied by improvements in metabolic CVD risk factors.<sup>21,33</sup> However, when total fat is significantly depleted in any disease, VAT may be relatively preserved compared with subcutaneous adipose

tissue during weight loss.<sup>31,32</sup> The metabolic and health consequences of depot-specific fat loss in the context of diminished lean tissue mass are not yet fully understood. Little is known about the interaction of aging with these disease-related changes.

The current patterns of body composition found in research studies differ from the pattern in the pre-HAART era for a variety of reasons, particularly changing demographics. Pa-

tients are starting HAART with higher BMI and body fat mass, if not obesity.<sup>20</sup> HIV-infected people may be healthier and heavier at initiation of HAART, whereas earlier research studies often focused on people with recent opportunistic infections who had illness-related wasting and included predominantly middle class, homosexual white men. Now, studies of HIV infection include individuals of both genders and all races and within various social classes who have genetic and/or environmental factors (socioeconomic status, diet, smoking, sedentary lifestyle) that predispose to obesity, increased VAT, and insulin resistance.<sup>34</sup> On the other hand, women more often have gluteofemoral fat accumulation rather than the abdominal/truncal accumulation that is the typical pattern found in men.<sup>35</sup> More gluteofemoral fat also is found in blacks among both men and women, in contrast to whites and Hispanics.<sup>35</sup> Abdominal truncal fat is more associated with metabolic abnormalities. It should be recognized that in Asians, higher levels of VAT are present for corresponding lower weight, BMI, and waist circumference than found in other ethnic groups.<sup>36</sup> Obesity, especially upper body obesity, is associated with insulin resistance, higher triglycerides, and lower HDL<sup>37</sup> in HIV-infected patients.

The contribution of illicit drug use and anabolic steroids to fat distribution is not understood and difficult to interpret in the clinical context. As a wider variety of patients undergo study and treatment, it must be recognized that genetic and environmental factors<sup>38</sup> may add to the superimposed HIV- and antiretroviral drug-induced changes now occurring in the era of HAART.

### Renal Disease

Renal disease is associated with increased CVD. In the era before HAART, the major renal disease was HIV-associated nephropathy characterized by proteinuria.<sup>39</sup> HIV-associated nephropathy leads to end-stage renal disease requiring dialysis.<sup>39</sup> End-stage renal disease currently is the fourth-leading cause of death in HIV infection.<sup>40</sup> The prevalence of proteinuria ranged from 19% to 34% in the pre-HAART era. Risk factors include black race, high HIV RNA, and low CD4 count.<sup>41</sup>

### The Effect of HAART and Specific Antiretrovirals

In evaluating the evidence available, we must consider 2 factors. First, early studies were conducted in HIV-infected patients receiving ineffective single or dual therapies. Second, it is difficult to distinguish the separate contributions of individual drugs and drug classes in HAART. Some changes may be induced by only some drugs in a class, whereas other changes may be induced by all drugs in the class. In addition to randomized trials, informative data come from studies of antiretroviral administration to HIV-negative healthy volunteers.

### Lipids and Lipoproteins

Historically, the sentinel signal of disturbed lipid metabolism caused by antiretroviral therapy itself was the paradoxical change in triglycerides. Whereas azidothymidine therapy decreased the elevated triglycerides found in advanced HIV

infection<sup>42</sup> (the Table), the addition of another drug class, the protease inhibitors (PIs), increased triglycerides.<sup>43–45</sup> PI drugs also increased LDL-C with little or no change in HDL-C.<sup>45</sup> These changes in lipid metabolism occur before any observable change in body composition.<sup>45</sup>

These changes may occur less often with the newer drugs now available to treat HIV.<sup>46</sup> In the current era, when patients are healthier at the time of HIV diagnosis, it also must be recognized that dyslipidemias are common in the general population and are due to genetic and environmental causes (eg, diet, obesity, sedentary lifestyle). Preexisting dyslipidemia may be exacerbated by HIV treatment. Those with underlying genetic predisposition may have worse lipids during antiretroviral treatment.<sup>47</sup>

#### *Factors Associated With Increases in Triglycerides*

Ritonavir-based PI regimens induce the greatest increase in triglycerides in a dose-dependent manner.<sup>43,48–51</sup> As studies in HIV-infected and HIV-negative subjects show, most other PIs have little effect.<sup>51,52</sup> Efavirenz and stavudine also may increase triglycerides in patients with HIV infection.<sup>53–55</sup> Severe lipoatrophy (see below), increased VAT, and increased upper trunk fat are associated with elevated triglycerides.<sup>56,57</sup>

#### *Factors Associated With Increases in LDL-C*

The increase in LDL-C with HAART is modest because it represents mainly the consequence of effective treatment of HIV, reversing the small decrease in LDL-C caused by HIV.<sup>45,48,58</sup> (the Table). Most HAART regimens, whether they contain PI or non-NRTI (NNRTI) drugs, raise LDL-C, except perhaps for some atazanavir-based regimens.<sup>46,55,58,59</sup> LDL-C elevations after HAART may be due to modulation of the immune response to HIV, restoration of health, or both. These changes are unlikely to move an individual from low or moderate CVD risk to a high-risk category. Significantly elevated LDL in the context of HIV is likely due to other causes, including genetics and diets high in saturated and *trans* fats (which may be more common in the HIV-infected population).<sup>60</sup>

#### *Factors Associated With Decreased HDL*

The ability of PIs to increase HDL is modest at best (the Table).<sup>45,48,58</sup> Effects of NNRTIs and perhaps atazanavir in increasing HDL are more impressive.<sup>46,55,58,59</sup> Increased VAT and upper trunk fat are associated with low HDL. Nevirapine induces the largest increase.<sup>53</sup> The persisting decreased levels of HDL-C may be a key mechanism by which HIV promotes CVD in the era of HAART.

#### **Glucose Metabolism and Insulin Resistance**

PI-induced increases in glucose and insulin resistance occur before observable changes in body composition (the Table).<sup>45,52,61</sup> Newer PI drugs appear to have less effect.<sup>62–64</sup> Specific NRTIs, particularly thymidine analogues, also may contribute to insulin resistance by an independent effect possibly related to mitochondrial dysfunction.<sup>18,65,66</sup> Insulin resistance in HIV-infected patients also occurs late after initiation of HAART therapy, which may not be a direct drug toxicity.<sup>67</sup>

**Factors Associated With Increased Insulin Resistance**

Direct effects of PI drugs have been demonstrated in HIV-negative volunteers. Indinavir induces the greatest insulin resistance, followed by ritonavir, with little effect of other PIs.<sup>50,52,61,63,64,68,69</sup> Some data support the induction of insulin resistance by NRTI, particularly stavudine and zidovudine.<sup>18,65,66</sup> Insulin resistance increases with time after initial drug effects and occurs on most regimens; restoration to health or subsequent changes in body fat composition may mediate this phenomenon.<sup>67</sup> Increased VAT and trunk fat are associated with insulin resistance; lipoatrophy also may contribute in HIV-infected patients.<sup>37,70</sup>

**Factors Associated With Increased Prevalence of IGT and Diabetes**

Although an increased prevalence of diabetes and, to a lesser extent, impaired glucose tolerance has been found in HIV infection, the studies of the associated causes are less consistent or have not been repeated. Early reports invoked the PI indinavir as a cause of diabetes, but more recently, diabetes has been associated with use of ritonavir, NRTIs, especially stavudine, and HAART itself.<sup>17,71–75</sup> Some studies link PIs to defects in insulin secretion, a necessary step in the development of diabetes.<sup>74,76–78</sup> Ethnic and genetic predisposition plays a role.

**Body Composition**

Lipoatrophy is an HIV-specific change that occurs with certain antiretrovirals (the Table). Lipoatrophy affects all subcutaneous adipose tissue depots, with the least loss of fat in the upper trunk.<sup>54,79–83</sup> The major culprits in lipoatrophy are thymidine analogue NRTI drugs (especially stavudine).<sup>30,65,80,81,84–89</sup> The effects of NNRTIs and PIs are less clear, if not controversial: Some PIs may worsen lipoatrophy (eg, indinavir), others may not, whereas there may be an effect of some NNRTIs (eg, efavirenz).<sup>80,81,85,88,90</sup> The relative sparing of upper trunk fat likely contributes to the appearance of “buffalo hump.”

Lipohypertrophy refers to increases in adipose tissue, in particular depots including VAT and upper trunk, especially in the breasts and dorsocervical fat pads. High levels of VAT may occur in HIV infection despite subcutaneous lipoatrophy.<sup>79–83</sup> The presence of lipohypertrophy is not linked to or the result of lipoatrophy in other depots. Indeed, most evidence indicates that lipohypertrophy is disassociated from lipoatrophy. The drug factors that contribute to lipoatrophy are not associated with lipohypertrophy. Effective viral suppression, restoration to health, and weight gain play significant roles in lipohypertrophy.<sup>79–83</sup>

Increased VAT is associated with increased inflammation even in the absence of HIV.<sup>21,91</sup> HIV infection itself is associated with inflammation. It is not known whether inflammation from HIV infection leads to increased VAT. Other evidence suggests that HIV lipoatrophy is associated with inflammation in adipose tissue.<sup>92</sup>

**Terminology Does Not Describe What Is Happening in Adipose Tissue**

Lipohypertrophy is a term that refers to a measurable increase in fat volume. However, it is not known whether at a cellular

level this represents adipocyte hypertrophy (increase in cell size) or hyperplasia (increase in cell number). Some data suggest that fat cell size, not merely fat mass, predicts a worse metabolic profile.<sup>93–95</sup>

Lipoatrophy is a term that refers to a measurable decrease in fat volume. Again, it is not known whether this is due to smaller fat cells or fewer fat cells (eg, apoptosis). There is evidence that lipoatrophy is accompanied by abnormalities of fat cell regulation that do not occur with decreased fat mass as a result of negative caloric balance.<sup>92,96</sup> Among non-HIV-infected patients, evidence suggests potentially significant genetic contributions to fat loss in lipodystrophy syndromes. Less is known regarding the genetic contributions to fat loss in HIV-infected patients and whether genetic influences, viral factors, inflammatory mediators, and antiretroviral effects may interact to contribute to lipoatrophy in HIV-infected patients. Studies to determine potential genetic predictors of lipoatrophy in HIV-infected patients are ongoing.

**Metabolic Syndrome**

A number of the changes seen with HIV infection, restoration to health, and treatment with HAART, including dyslipidemia, diabetes, and increased BMI and waist circumference, may present simultaneously in HIV-infected patients. These factors are part of the metabolic syndrome.<sup>97,98</sup> There is debate as to whether the prevalence of the metabolic syndrome is increased among HIV-infected patients.<sup>99</sup> Furthermore, it remains unknown whether the presence of the metabolic syndrome per se confers increased risk for CVD disease in HIV-infected patients beyond that associated with individual risk factors.<sup>99,100</sup>

**Renal Disease**

Treatment with HAART has led to a reduction in HIV-associated nephropathy, but renal disease remains prominent in HIV-infected people. Microalbuminuria, a marker of both renal and CVD, is 5-fold more common in HIV infection even after adjustment for known factors associated with microalbuminuria.<sup>101</sup> Although microalbuminuria is still associated with low CD4 count, high HIV RNA, and black race, in the era of HAART, microalbuminuria also is associated with potential CVD risk factors, including age, blood pressure, insulin resistance, glycosuria, and triglyceride levels.

Cystatin C is a measure of glomerular function that, unlike creatinine-based estimates of glomerular filtration (including equations for estimated glomerular filtration rate), is not affected by body composition. Elevated cystatin C levels predict renal failure but, in addition, strongly predict CVD and all-cause mortality in the general population. People with HIV infection are 9.8-fold more likely to have elevated cystatin C levels, even after adjustment for the known associated factors.<sup>102</sup> Elevated cystatin C levels are associated with traditional risk factors of hypertension, low HDL, uric acid levels, albuminuria, or proteinuria but not with impaired fasting glucose or diabetes. Elevated cystatin C levels were strongly associated with low CD4 count and coinfection with hepatitis C. There is debate over the extent to which tenofovir use leads to decreased renal function as measured by creatinine, creatinine clearance, and cystatin C levels.<sup>103–107</sup> The

implications of these findings for end-stage renal disease and CVD are not yet known.

### Controversial Issues, Gaps in Knowledge, and Future Research Priorities

- To understand how HIV infection and the host response to it affects metabolism and body composition, patients with newly diagnosed HIV infection need to be studied with measurements of lipids, lipoproteins, glucose metabolism, insulin resistance, body composition, and renal function in the window before HAART is required. Research is needed into the aspects of the host response to infection that cause these changes.
- To understand how HAART affects metabolism, body composition, and renal function, the effects of new and emerging antiretroviral drugs and HAART regimens need to be studied with measurements of lipids, lipoproteins, glucose metabolism, insulin resistance, body composition, and renal function.
- What are the contributions of mitochondrial toxicity/mitochondrial dysfunction, intramyocellular fat, lean body mass, fatty liver, and hepatitis C virus coinfection to metabolic and body fat distribution?
- How should obesity be assessed in patients with HIV-associated lipodystrophy, and what are the implications of obesity for cardiovascular risk in HIV infection?
- What are the contributions of antiretroviral-induced diabetes to CVD?
- Do markers of renal disease predict CVD and mortality in HIV infection similar to their predictive ability in noninfected populations?
- Those studied should include all groups in the current HIV epidemic (women, blacks, Asians, and the elderly) because there are indications of differences in response to HIV infection and HAART.
- Longer-term research should assess the contribution of these HIV- and HAART-induced changes to atherosclerosis.

### Disclosures

Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary, which is available online at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189622>.

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