HIV, Insulin Resistance, and Cardiovascular Disease

Katherine Samaras, MD, PhD

Corresponding author
Katherine Samaras, MD, PhD
Diabetes Program, Garvan Institute of Medical Research, Department of Endocrinology, St Vincent's Hospital, 438 Victoria Street, Darlinghurst, NSW 2010, Australia.
E-mail: k.samaras@garvan.org.au

Current Cardiovascular Risk Reports 2009, **3**:59–64
Current Medicine Group LLC ISSN 1932-9520

Individuals treated for HIV infection are at increased risk for accelerated cardiovascular disease. Treatment of HIV infection confers the significant benefits of improved clinical outcomes, quality of life, and survival. However, a number of metabolic complications have emerged as a consequence of treatment, including often severe, mixed hyperlipidemia, body fat partitioning disorders, and increased risk of type 2 diabetes. Treatment-induced insulin resistance underlies and contributes to these metabolic complications. This review examines the contribution of insulin resistance to increased cardiovascular disease rates in healthy and HIV-infected populations, mechanisms by which treatment of HIV infection exacerbates insulin resistance, and the effect of insulin resistance–modulating interventions on cardiovascular risk factors.

Introduction

Treatment of HIV with highly active antiretroviral therapy (HAART) confers significant benefits in survival and quality of life. A number of metabolic complications of therapy have become apparent, including hyperlipidemia, insulin resistance, and abdominal obesity, associated with the observations of premature or accelerated onset of cardiovascular disease and type 2 diabetes. This article reviews the evidence for increased cardiovascular disease in treated HIV infection and the epidemiologic links between insulin resistance and incident cardiovascular disease. The role of insulin resistance in the pathogenesis of atherosclerosis in treated HIV infection is considered, and the mechanisms by which treated HIV-infection induces insulin resistance are reviewed.

Cardiovascular Disease in HIV Infection

Several recent studies have established that treatment of HIV infection is associated with increased risk of myocardial infarction [1••,2,3]. The American Heart Association has recognized this as a critical area for further investigation and aggressive risk management [4]. The relative risk of myocardial infarction in HIV-infected patients is doubled after adjustment for traditional risk factors [2]. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study of more than 23,000 participants followed for a median of 4.5 years estimated that the risk of myocardial infarction after HAART initiation was 16% per year of exposure to one HAART drug class: protease inhibitors. This effect remained after adjustment for serum lipids, diabetes, and hypertension [1••]. Further recent analyses from the DAD cohort showed that the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir and didanosine were associated with higher myocardial infarction risk, with an increase in relative risk of 1.9 and 1.49, respectively [3]. In a case-control study of 3851 HIV-infected people, the risk of myocardial infarction was increased by 75% after adjustment for age, sex, race, hypertension, diabetes, and dyslipidemia [2]. Limitations of these studies include the lack of reference population data [1••,3] and variable capture of smoking data [2]. Nevertheless, these important end-point studies add to a substantial published literature indicating increased cardiovascular disease risk. Intermediate end-point studies have shown that HAART exposure is an independent predictor of carotid atherosclerosis [5]. In a 1-year prospective case-control study, patients with HIV infection had greater carotid intima-media thickness at baseline, and it increased more rapidly than in controls; traditional risk factors were predictors, as was nadir CD4 count [6]. However, not all studies indicate that HIV treatment affects intima-media thickness. In a 3-year prospective, matched-cohort study, progression of intima-media thickness was no different in people with treated HIV and HIV-negative controls; progression was predicted by traditional risk factors such as low-density lipoprotein cholesterol, nadir CD4 count, and ritonavir exposure [7]. A controlled, cross-sectional study using flow-mediated brachial artery vasodilatation to measure endothelial function found no difference between HIV-

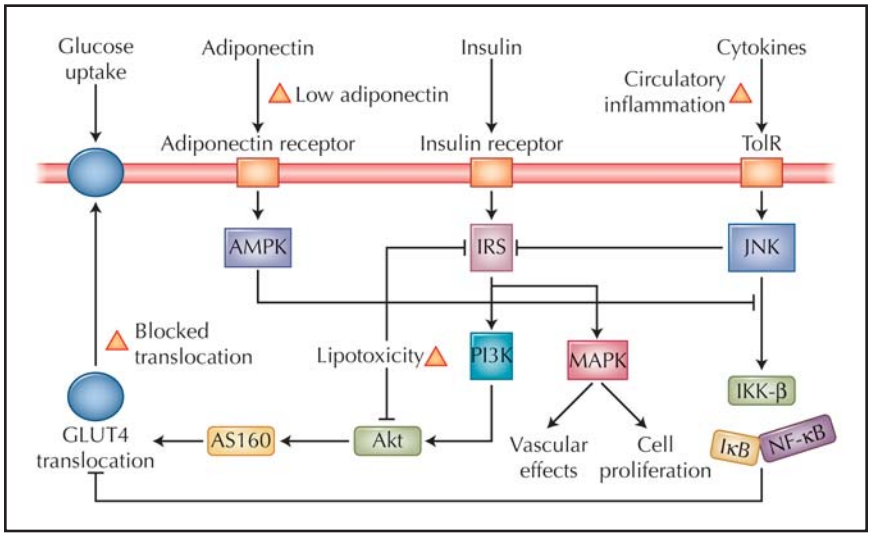

Figure 1. Cell signaling pathways involved in insulin and glucose metabolism and regulation of vascular cytokine synthesis. Crosstalk is present between cytokine and adiponectin signaling pathways with several points of interaction that relate to glucose metabolism. ▲ Points affected in treated HIV infection. AMPK—adenosine monophosphate–activated protein kinase; AS160—Akt substrate of 160 kDa; GLUT4—glucose transporter-4; IκB–inhibitor of nuclear factor–κB (NF-κB); IKK-β—IκB kinase-β; IRS—insulin receptor substrate; JNK—Jun N-terminal kinase; MAPK—mitogen-activated protein kinase; PI3K—phosphoinositol-3 kinase.

infected HAART recipients and matched HIV-negative controls [8]. Insulin resistance was an independent predictor of endothelial dysfunction [8]. The contribution of metabolic and body fat partitioning to cardiovascular risk factors and insulin resistance is summarized in several comprehensive reviews [9–11,12•].

Controversy remains about the degree to which HAART affects cardiovascular disease risk in HIV infection. It is universally accepted, however, that treated HIV infection is associated with a higher prevalence and greater severity of cardiovascular disease risk factors such as hyperlipidemia, insulin resistance, abdominal obesity, metabolic syndrome, and increased circulatory inflammation, superimposed on traditional risks associated with smoking, sociodemographics, and race.

Insulin Resistance and Cardiovascular Disease Risk: Prospective Population Studies

Insulin resistance is considered central to cardiometabolic disease and is present in atherothrombotic cardiovascular disease [13,14]. Insulin resistance is closely associated with the clustering of metabolic disturbances within metabolic syndrome, including abdominal obesity, heart disease, disorders of glucose metabolism, dyslipidemia, and hypertension. In vivo measures of insulin resistance are difficult. The hyperinsulinemic euglycemic clamp is the most accurate measure of insulin action and is considered the gold standard, but it is too expensive and labor-intensive for use in larger studies. Surrogate measures of insulin resistance include the homeostasis model assessment (HOMA) and, for epidemiologic and larger population-based studies, fasting insulin levels.

HOMA estimates of insulin resistance reliably predict subsequent cardiovascular events across a number of populations [15–19]. The Bruneck Study, which followed an Italian population for 15 years, found that insulin resistance increased the relative risk of an incident cardiovascular event to 2.2 after adjustments were made for age, smoking, sex, body mass index, lipids, C-reactive protein (CRP), and novel risk factors [15]. HOMA predicted incident fatal and nonfatal cardiovascular events over 8 years in the San Antonio Heart Study, with age-, sex-, and ethnicity-adjusted risk ratios of 2.5 reduced to 1.9 after adjustment for lipids, smoking, physical activity, and waist size [16]. The Malmö Study found that insulin resistance increased the relative risk of a coronary event to 2.1 after adjustment of metabolic syndrome covariates, including lipids, blood pressure, and obesity [17]. The Veterans Affairs HDL Intervention Trial reported that insulin resistance predicted incident cardiovascular events in subjects with and without diabetes [18]. In contrast, insulin resistance did not predict incident cardiovascular events in the Framingham Offspring Study, when the covariates of metabolic syndrome and other traditional risk factors were included [19]. Thus, traditional risk factors and composites of metabolic syndrome are an excellent clinical marker of the insulin-resistance phenotype that increases cardiovascular risk across different populations. Insulin resistance per se may even be associated with a small, incremental cardiovascular disease risk beyond composite risk factors.

Insulin Resistance in the Pathogenesis of Atherosclerosis

Insulin is a critical and essential hormone with pleiotropic effects on multiple organ systems. It is the fundamental hormonal regulator of glucose metabolism, where it induces glucose uptake following stimulation of cell surface insulin receptors, establishing a signaling cascade of phosphorylation in key cellular substrates. Activation of the pivotal node of phosphoinositol-3 kinase (PI3K) results in a number of cellular events, one of which results in translocation of glucose transporter-4 (GLUT4) from the cell cytosol to the cell surface, where it facilitates glucose entry into the cell (Fig. 1).

Insulin action may encounter interference at numerous points within this complex network, resulting in insulin resistance. Possible mechanisms by which treated HIV infection can interfere with insulin signaling pathways are indicated in Figure 1. They include lipotoxicity, direct protease inhibitor effects on GLUT4 translocation, effects of NRTIs on mitochondrial function, and disturbed adipocyte function and inflammation.

Beyond the node of PI3K, insulin signaling diversifies into separate pathways pertaining to cellular growth, proliferation and, importantly, pathways relevant to atherogenesis. Insulin resistance appears to be confined to the part of the postinsulin receptor cell signaling pathway involved in glucose uptake. Other pathways retain sensitivity, and the compensatory hyperinsulinemia of insulin resistance results in increased signaling down proliferative and proatherogenic pathways [20]. This may explain a direct link between insulin resistance and atherogenesis independent of associated disturbances in circulating lipids, inflammation, and adipocyte function.

In addition to proatherogenic effects mediated specifically through insulin signaling pathways, the links between insulin resistance and cardiovascular risk may be mediated through indirect or intermediate pathways. Insulin resistance is closely associated with visceral obesity, a proinflammatory circulatory milieu, endothelial dysfunction, oxidative stress, and procoagulation. The common link between these is considered insulin resistance but may also be related to dysregulated adipocyte function as a consequence of visceral obesity and other factors.

Metabolic Syndrome in HIV

Metabolic syndrome refers to the long-observed clustering of the clinical phenotypes of hyperlipidemia, abdominal obesity, elevated fasting glucose, and hypertension; vigorous debate continues to interrogate whether, as a composite of risk factors, it predicts a multiplicative or additive increase in cardiovascular disease.

The prevalence of metabolic syndrome in treated HIV-infected patients varies among populations. A prevalence rate of 17% was found in Spain, where body mass index and past or present exposure to protease inhibitors were predictors [21]. The US Nutrition for Healthy Living Study reported the prevalence of metabolic syndrome at 24%, associated with higher viral load, higher body mass index, higher trunk-to-limb fat ratio, and the use of the protease inhibitors lopinavir-ritonavir and the NRTI didanosine [22]. This study reported the incidence of metabolic syndrome at 1.2 per 100 person-months, predicted by viral load, weight gain, and use of lopinavir-ritonavir or didanosine [22]. The multinational HIV Lipodystrophy Case Definition Study found a prevalence of metabolic syndrome of up to 17% [23]. Higher levels of the inflammatory marker CRP and lower levels of the anti-inflammatory molecule adiponectin were found in those with metabolic syndrome [23].

After initiation of HAART in treatment-naive HIV-infected patients, the prevalence of metabolic syndrome increased from 16% to 25% after 2 years of HAART, with an incidence of 14 cases per 100 patient-years [24]. Wand et al. [25•] found similar incidence rates: 12 per 100 patient-years after 3 years of HAART in previously treatment-naive subjects. Importantly, this study demonstrated an increase in the relative risk of cardiovascular disease to 2.76 in incident cases of metabolic syndrome [25•]. Further prospective studies of the progression from metabolic syndrome to cardiovascular outcomes are required.

Mechanisms of Insulin Resistance in HIV

Chronic infection and illness are usually associated with increased insulin resistance. Detailed studies of HIV-infected subjects prior to the HAART era found insulin sensitivity was not altered, using the definitive measure of the hyperinsulinemic euglycemic clamp [26]. In the HAART era, insulin resistance, again measured by clamp, was found to be double that of controls [27].

One mechanism by which HAART can exacerbate insulin resistance is the classic pathway of lipotoxicity [28••]. Treated HIV is associated with elevated fatty acids and circulating lipids [29], which interfere with postinsulin receptor signaling pathways by generating ceramide [28••]. Elevated fatty acids are also found in abdominal or visceral obesity. HAART in HIV infection induces abdominal obesity [9–11,12•]. HAART-induced metabolic effects would be superimposed on population-wide trends for obesity and metabolic syndrome, which has reached epidemic proportions in some countries.

Separate from the effects of lipotoxicity on the insulin signaling cascade are the effects of HAART components themselves on insulin resistance. There are distinctive effects that appear to be class specific (ie, specific to protease inhibitors or NRTIs) and drug specific within class, with certain drugs being more potent in inducing insulin resistance.

Protease Inhibitors

In vivo and in vitro studies subsequently showed insulin resistance in HIV-infected subjects receiving HAART, with protease inhibitors being identified early as the cause. More recently, NRTIs also have been implicated.

Administration of single drugs to HIV-negative healthy controls has best informed the research on drug effects. Effective suppression of HIV replication and its effects necessarily requires multiple drugs. Even in prospective studies of HAART initiation in HIV-infected treatment-naive patients, there may be confounding by the multiple drugs used. In healthy, HIV-negative subjects, a single dose of the protease inhibitor indinavir induced a

30% increase in insulin resistance, measured by hyperinsulinemic euglycemic clamp [30]. In similarly designed studies using a clamp, single-dose ritonavir increased insulin resistance by 15%, whereas amprenavir had no effect [31•], establishing acute and hierarchical protease inhibitor effects on accurate in vivo measures of insulin resistance in humans.

Protease inhibitors have multiple direct effects on cellular insulin resistance, demonstrated in elegant in vitro studies. In experiments using insulin-responsive cell lines, all protease inhibitors induced an acute reduction of insulin-stimulated glucose uptake, reducing GLUT4 translocation independently of insulin signaling pathways [32]. Noncompetitive and reversible binding of the drug moiety to GLUT4 has been reported [33].

Human studies following surrogate measures of insulin resistance indicate differences between protease inhibitors; for example, amprenavir does not appear to exacerbate or induce insulin resistance by 24 weeks of therapy [34].

The intense scrutiny of effects of protease inhibitors has revealed system effects additional to the cellular effects described above. Protease inhibitors reduce adipocyte differentiation, interfering with key molecules involved in adipogenesis: sterol regulatory element-binding protein-1 (SREBP-1) and peroxisome proliferator-activated receptor-γ (PPAR-γ) [35]. SREBP-1 and PPAR-γ are critical to adipocyte differentiation, adipocyte function, and secretion of the insulin-sensitizing adipokine, adiponectin. Dysregulation of these molecules, adipocyte function, and secretion with hypoadiponectinemia are acknowledged to contribute to insulin resistance.

In one of the more severe metabolic complications of treated HIV infection, lipoatrophy associated with abdominal obesity, the degree of insulin resistance can be severe [27,29,36]. Studies of protease inhibitor–treated HIV-infected subjects with this pattern of body fat partitioning have insulin resistance (as measured by clamp) double that of HIV-infected protease inhibitor–naive controls matched for age, body mass index, and waist [27].

Thus, effects of protease inhibitors on adipocyte function may affect insulin resistance and risk of cardiac disease. Hypoadiponectinemia has been shown in several studies to be a predictor of cardiovascular disease [37]. In treated HIV infection, the contribution of dysregulated adipocyte function remains associative, with early data reporting links among low adiponectin levels, insulin resistance, and abnormal body fat partitioning [23,38].

Nucleoside Reverse Transcriptase Inhibitors

NRTIs also contribute to insulin resistance, via separate mechanisms than those described for protease inhibitors. Recent work in healthy, HIV-negative subjects has shown that treatment with the NRTI stavudine for 4 weeks increased insulin resistance (by clamp) [39•]. Importantly, this elegant study showed that the deteriorated insulin resistance was associated with reduced muscle mitochondrial DNA and reduced mitochondrial function, assessed by ^{31}P magnetic resonance spectroscopy [39•]. The reduced mitochondrial function implies that there may be a mitochondrial oxidative defect that may explain the findings of earlier studies of intramyocellular lipid accumulation (by magnetic resonance spectroscopy) in treated HIV infection that was strongly associated with insulin resistance [27]. Beyond effects having an impact on metabolic pathways on muscle metabolism, NRTIs also influence adipocyte functioning and may further influence insulin resistance via separate mechanisms. The expression of adipocyte mitochondrial genes involved in metabolism is reduced after short-term stavudine treatment in HIV-negative subjects [40].

Thus, studies published to date indicate that NRTIs induced effects on skeletal muscle and adipocyte mitochondrial function, contributing to insulin resistance. Relatively little is known about direct mitochondrial effects in the myocardium, a tissue characterized by reliance on fatty acid metabolism. Whether mitochondrial dysfunction within the myocardium exists—and thus adds to cardiovascular disease pathogenesis independent of the effects of insulin resistance and hyperlipidemia—is worthy of investigation.

Other Drug Classes

The existing drug class of non-NRTIs does not appear to have adverse effects on inulin resistance. Two novel classes of HAART are expected to be in use in the near future: entry inhibitors (fusion inhibitors and CCR5 inhibitors) and integrase inhibitors. There are little data on metabolic effects of these newer drug classes.

Pleiotropic Factors in Accelerated Insulin Resistance and Atherogenesis in Treated HIV Infection: The Role of Inflammation

The contribution of inflammation to insulin resistance and the pathogenesis of cardiovascular disease is well recognized. Cardiovascular disease is predicted by higher circulating levels of CRP [41,42]. Adiponectin, an antiatherogenic, antidiabetic adipokine, is reduced in obesity, insulin resistance, metabolic syndrome, and diabetes, and it identifies individuals at higher risk for myocardial infarction [37]. Proinflammatory adipokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are also implicated in the pathogenesis of insulin resistance and cardiovascular disease. Increased circulating inflammatory markers contribute to insulin resistance [43], through a number of possible mechanisms. Interaction of proinflammatory cytokines with the toll-like receptor induces cell signaling events that interfere with insulin signaling (Fig. 1).

Inflammatory markers are increased in treated HIV and are related to insulin resistance [44,45]. A recent study reported that circulating inflammatory markers including CRP, TNF-α, IL-6, and adiponectin in treated men with HIV were similar to those found in obese sedentary men; insulin resistance (by hyperinsulinemic clamp) was predicted by hypoadiponectinemia and increased TNF-α levels [45]. In treated HIV infection, circulating IL-6 levels predicted the traditional cardiovascular risk factors of total cholesterol, high-density lipoprotein cholesterol, triglycerides, and CRP [45].

HIV itself and the immunologic and inflammatory response of the host was examined in the Strategies for Management of Antiretroviral Therapy (SMART) study, which tested the effects of interrupted therapy (to limit drug exposure and adverse events) versus virologic suppression with continuous therapy. Interrupted HAART was associated with a number of worsened outcomes, including an increase in the relative risk of major cardiovascular disease to 1.6 [46].

Conclusions

Treatment of HIV infection is associated with a number of metabolic disturbances—including hyperlipidemia, insulin resistance, altered body fat partitioning, and increased circulatory inflammation—that contribute to the increased risk of cardiovascular disease. Strategies to reduce cardiovascular disease in HIV infection include early screening for metabolic disturbances with aggressive risk factor management, including optimization of healthy weight, diet and physical activity, smoking cessation and, where indicated, pharmacologic intervention. Ongoing interrogation of drug therapies with careful scrutiny for adverse cardiometabolic effects is required in the era of virologic remission and (anticipated) lifelong therapy.

Disclosure

Dr. Samaras is supported by a National Health and Medical Research Council Career Development Award (Australia).

References and Recommended Reading

Papers of particular interest, published recently,
have been highlighted as:

- • Of importance
- •• Of major importance

1.•• DAD Study Group, Friis-Moller N, Reiss P, et al.: **Class of antiretroviral drugs and risk of myocardial infarction.** *N Engl J Med* 2007, **356:**1723–1735.

This large, international observational study found that treatment with the protease inhibitors increased subsequent development of myocardial infection, independent of known cardiovascular risk factors.

2. Triant VA, Lee H, Hadigan C, Grinspoon SK: **Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease.** *J Clin Endocrinol Metab* 2007, **92:**2506–2512.
3. D:A:D Study Group, Sabin CA, Worm SW, et al.: **Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration.** *Lancet* 2008, **371:**1417–1426.
4. Grinspoon SK, Grunfeld C, Kotler DP, et al.: **State of the science conference: initiative to decrease cardiovascular risk and increase quality of care for patients living with HIV/AIDS: executive summary.** *Circulation* 2008, **118:**198–210.
5. Jericó C, Knobel H, Calvo N, et al.: **Subclinical carotid atherosclerosis in HIV-infected patients: role of combination antiretroviral therapy.** *Stroke* 2006, **37:**812–817.
6. Hsue PY, Lo JC, Franklin A, et al.: **Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection.** *Circulation* 2004, **109:**1603–1608.
7. Currier JS, Kendall MA, Henry WK, et al.: **Progression of carotid artery intima-media thickening in HIV-infected and uninfected adults.** *AIDS* 2007, **21:**1137–1145.
8. Mondy K, Overton ET, Grubb J, et al.: **Metabolic syndrome in HIV-infected patients from an urban, midwestern US outpatient population.** *Clin Infect Dis* 2007, **44:**726–734.
9. Grinspoon S, Carr A: **Cardiovascular risk and body-fat abnormalities in HIV-infected adults.** *N Engl J Med* 2005, **352:**48–62.
10. Florescu D, Kotler DP: **Insulin resistance, glucose intolerance and diabetes mellitus in HIV-infected patients.** *Antivir Ther* 2007, **12:**149–162.
11. Bradbury RA, Samaras K: **Antiretroviral therapy and the human immunodeficiency virus--improved survival but at what cost?** *Diabetes Obes Metab* 2008, **10:**441–450.

12.• Grunfeld C, Kotler DP, Arnett DK, et al.: **Contribution of metabolic and anthropometric abnormalities to cardiovascular disease risk factors.** *Circulation* 2008, **118:** e20–e28.

This state-of-the-science article reviews the metabolic and body fat partitioning abnormalities observed in treated HIV infection with regard to known cardiovascular risk factors.

13. Eckel RH: **Mechanisms of the components of the metabolic syndrome that predispose to diabetes and atherosclerotic CVD.** *Proc Nutr Soc* 2007, **66:**82–95.
14. Meigs JB, Rutter MK, Sullivan LM, et al.: **Impact of insulin resistance on risk of type 2 diabetes and cardiovascular disease in people with metabolic syndrome.** *Diabetes Care* 2007, **30:**1219–1225.
15. Bonora E, Kiechl S, Willeit J, et al.: **Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in Caucasian subjects from the general population.** *Diabetes Care* 2007, **30:**318–324.
16. Hanley AJ, Williams K, Stern MP, Haffner SM: **Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study.** *Diabetes Care* 2002, **25:**1177–1184.
17. Hedblad B, Nilsson P, Engstrom G, et al.: **Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death.** *Diabet Med* 2002, **19:**470–475.
18. Robins SJ, Rubins H, Faas FH, et al.: **Insulin resistance and cardiovascular events with low HDL cholesterol: the Veteran Affairs HDL Intervention Trial (VA-HIT).** *Diabetes Care* 2003, **26:**1513–1517.
19. Rutter MK, Meigs JB, Sullivan LM, et al.: **Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham Offspring Study.** *Diabetes* 2005, **54:**3252–3257.

20. Wang CC, Goalstone ML, Draznin B: **Molecular mechanisms of insulin resistance that impact cardiovascular biology.** *Diabetes* 2004, **53:**2735–2740.
21. Jerico C, Knobel H, Montero M, et al.: **Metabolic syndrome among HIV-infected patients: prevalence, characteristics, and related factors.** *Diabetes Care* 2005, **28:**132–137.
22. Jacobson DL, Tang AM, Spiegelman D, et al.: **Incidence of metabolic syndrome in a cohort of HIV-infected adults and prevalence relative to the US population (National Health and Nutrition Examination Survey).** *J Acquir Immune Defic Syndr* 2006, **43:**458–466.
23. Samaras K, Wand H, Law M, et al.: **Metabolic syndrome in HIV-infected patients using IDF and ATPIII criteria: prevalence, discordance and clinical utility.** *Diabetes Care* 2007, **30:**113–119.
24. Palacios R, Santos J, Gonzalez M, et al.: **Incidence and prevalence of the metabolic syndrome in a cohort of naive HIV-infected patients: prospective analysis at 48 weeks of highly active antiretroviral therapy.** *Int J STD AIDS* 2007, **18:**184–187.
25.• Wand H, Calmy A, Carey DL, et al.: **Metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus after initiation of antiretroviral therapy in HIV-infection.** *AIDS* 2007, **21:**2445–2453.
This study reports the incidence of metabolic syndrome in a large cohort of treatment-naive HIV-infected subjects who began antiretroviral therapy. It found that development of metabolic syndrome during treatment was associated with increased risk of heart disease and type 2 diabetes.
26. Hommes MJ, Romijn JA, Endert E, et al.: **Insulin sensitivity and insulin clearance in human immunodeficiency virus-infected men.** *Metabolism* 1991, **40:**651–656.
27. Gan SK, Samaras K, Thompson CH, et al.: **Altered myocellular and abdominal fat partitioning predict disturbance in insulin action in HIV protease inhibitor-related lipodystrophy.** *Diabetes* 2002, **51:**3163–3169.
28.•• Kraegen EW, Cooney GJ: **Free fatty acids and skeletal muscle insulin resistance.** *Curr Opin Lipidol* 2008, **19:**235–241.
A review of the cellular and biochemical basis for development of insulin resistance in states of lipid excess.
29. Carr A, Samaras K, Burton S, et al.: **A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance due to HIV protease inhibitors.** *AIDS* 1998, **12:**F51–F58.
30. Noor MA, Seneviratne T, Aweeka FT, et al.: **Indinavir acutely inhibits insulin-stimulated glucose disposal in humans: a randomized, placebo-controlled study.** *AIDS* 2002, **16:**F1–F8.
31.• Lee GA, Rao M, Mulligan K, et al.: **Effects of ritonavir and amprenavir on insulin sensitivity in healthy volunteers.** *AIDS* 2007, **21:**2183–2190.
This interventional study gave two different protease inhibitors to healthy volunteers without HIV infection and found that ritonavir acutely reduced insulin sensitivity.
32. Murata H, Hruz PW, Mueckler M: **The mechanism of insulin resistance caused by HIV protease inhibitor therapy.** *J Biol Chem* 2000, **275:**20251–20254.
33. Hertel J, Struthers H, Horj CB, Hruz PW: **A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity.** *J Biol Chem* 2004, **279:**55147–55152.
34. Dube MP, Qian D, Edmondson-Melancon H, et al.: **Prospective, intensive study of metabolic changes associated with 48 weeks of amprenavir-based antiretroviral therapy.** *Clin Infect Dis* 2002, **35:**475–481.
35. Caron M, Auclair M, Vigouroux C, et al.: **The HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation and induces insulin resistance.** *Diabetes* 2001, **50:**1378–1388.
36. Carr A, Samaras K, Thorisdottir A, et al.: **Natural history, diagnosis and prediction of HIV protease inhibitor-induced lipodystrophy, hyperlipidaemia and diabetes mellitus.** *Lancet* 1999, **353:**2094–2099.
37. Pischon T, Girman CJ, Hotamisligil GS, et al.: **Plasma adiponectin levels and the risk of myocardial infarction in men.** *JAMA* 2004, **291:**1730–1737.
38. Tong Q, Sankale JL, Hadigan CM, et al.: **Regulation of adiponectin in human immunodeficiency virus-infected patients: relationship to body composition and metabolic indices.** *J Clin Endocrinol Metab* 2003, **88:**1559–1564.
39.• Fleischman A, Johnsen S, Systrom DM, et al.: **Effects of a nucleoside reverse transcriptase inhibitor, stavudine, on glucose disposal and mitochondrial function in muscle of healthy adults.** *Am J Physiol Endocrinol Metab* 2007, **292:** E1666–E1673.
Stavudine given to healthy HIV-negative volunteers for 1 month reduced insulin sensitivity and was associated with changes in muscle mitochondrial function.
40. Mallon PWG, Unemori P, Sedwell R, et al.: **In vivo, nucleoside reverse transcriptase inhibitors alter expression of both mitochondrial and lipid metabolism genes in the absence of mitochondrial DNA depletion.** *J Infect Dis* 2005, **191:**1686–1696.
41. Ross R: **Atherosclerosis--an inflammatory disease.** *N Engl J Med* 1999, **340:**115–126.
42. Cao JJ, Arnold AM, Manolio TA, et al.: **Association of carotid artery intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality: the Cardiovascular Health Study.** *Circulation* 2007, **116:**32–38.
43. De Luca C, Olefsky JM: **Inflammation and insulin resistance.** *FEBS Lett* 2008, **582:**97–105.
44. Vigouroux C, Maachi M, Nguyên TH, et al.: **Serum adipocytokines are related to lipodystrophy and metabolic disorders in HIV-infected men under antiretroviral therapy.** *AIDS* 2003, **17:**1503–1511.
45. Samaras K, Gan SK, Peake P, et al.: **Proinflammatory markers, insulin sensitivity, and cardiometabolic risk factors in treated HIV infection.** *Obesity* 2008 Nov 13 (Epub ahead of press).
46. Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren JD, et al.: **CD4+ count-guided interruption of antiretroviral treatment.** *N Engl J Med* 2006, **355:**2283–2296.