Human Immunodeficiency Virus and Highly Active Antiretroviral Therapy–Associated Metabolic Disorders and Risk Factors for Cardiovascular Disease

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Abstract

The successful introduction of highly active antiretroviral therapy (HAART), a combination of potent antiretroviral agents, including protease inhibitors, nucleoside reverse transcriptase inhibitors, and nonnucleoside reverse transcriptase inhibitors, has impacted positively on morbidity and mortality among human immunodeficiency virus (HIV)-positive patients. Over time, HAART has been associated with a number of metabolic and anthropometric abnormalities, including dyslipidemia and insulin resistance as well as subcutaneous fat loss and abdominal obesity, potentially contributing to cardiovascular risk. Recent studies have more firmly established that both HIV infection and HAART might increase the risk of clinical cardiovascular events. Furthermore, whereas HIV/HAART is associated with multiple aspects of endocrine dysfunction, there has been less focus on bone disease, although some studies indicate a higher prevalence of osteoporosis among HIV-positive subjects compared to HIV-negative controls. The relationship between bone and fat metabolism under HIV-positive conditions deserves further attention, and available data suggest the possibility of an intriguing connection. In the future, an increasing population of aging HIV-positive patients with a spectrum of antiretroviral therapies and accumulation of endocrine abnormalities and conventional cardiovascular risk factors will present preventive and therapeutic challenges to our health-care system.

Introduction

THE PANDEMIC OF A NEW DISEASE, acquired immune deficiency syndrome (AIDS), was first recognized on June 5, 1981, by the U.S. Centers for Disease Control and Prevention.¹ Since then, the impact of AIDS and/or human immunodeficiency virus (HIV) on demographic, social, and economic conditions has been substantial. At present, about 60 million people have been infected with HIV and 25 million people worldwide have died of the disease. In 2007, an estimated 33 million people were living with HIV/AIDS and 2.5 million people were newly infected.² HIV/AIDS has become a leading cause of mortality worldwide and is the main cause of death in sub-Saharan Africa.

The successful introduction in 1995 of highly active antiretroviral therapy (HAART), a combination of potent antiretroviral agents, including protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and

nonnucleoside reverse transcriptase inhibitors (NNRTIs), has substantially decreased mortality among HIV-positive patients.^{3,4} However, over time HAART has been associated with a number of metabolic and anthropometric abnormalities, including dyslipidemia and insulin resistance as well as subcutaneous fat loss (lipoatrophy) and abdominal obesity (lipomegaly), all of which potentially may contribute to an increased risk of cardiovascular disease (CVD).⁵ Furthermore, in addition to side effects from treatment of HIV, there is a growing recognition that HIV infection by itself, or in combination with genetic and/or environmental factors, may cause metabolic abnormalities as a manifestation of a dynamic relationship between the HIV virus and the host. In view of this, it is noteworthy that increased mortality and morbidity rates from CVD have been reported among HIV-infected patients.⁶ As the HIV-positive population ages, the combination of cardiovascular risk factors commonly seen

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in the general population with presence of HIV infection and its treatment poses significant therapeutic and health-care challenges.

HIV-Associated Dyslipidemia and Metabolic Disorders

Infection with HIV may cause a number of significant anthropometric and metabolic alterations, including cachexia/wasting, dyslipidemia, osteoporosis, hepatic lipogenesis, and changes in the immunologic and cytokine systems (Table 1), even though underlying mechanisms are not completely understood. A common pattern of HIV-associated dyslipidemia seen prior to the advent of antiretroviral therapy was characterized by decreased plasma concentrations of high-density lipoprotein (HDL-C) and low-density lipoprotein cholesterol (LDL-C) and increased triglyceride (TG) levels.⁷⁻¹⁰ Decreased HDL-C levels have been associated with immune activation, and the frequency and extent of decrease in HDL-C levels were greater in HIV-positive patients with a CD4 cell count below median levels, indicative of a more pronounced infection pattern.¹¹ Furthermore, it is proposed that HIV infection might trigger inflammatory reactions of the immune system and enhance β -adrenergic stimulation of adipose tissue and thus advance adipose tissue lipolysis. An increased adipose tissue lipolysis in turn results in an increased potential for a secondary elevation in hepatic fatty acid levels, providing a stimulus for triglyceride synthesis and secretion as very-low-density lipoprotein (VLDL) particles. This notion is supported by studies demonstrating an increased VLDL triglyceride production during HIV-positive conditions.¹²⁻¹⁴

Recently, Mujawar et al. demonstrated that HIV impairs adenosine triphosphate (ATP)-binding cassette transporter A1-dependent cholesterol efflux from macrophages, and that this effect was mediated by the HIV Nef protein.¹⁵ If these findings reflect a general reduction in the potential for cholesterol efflux from peripheral tissues, this mechanism could clearly contribute to a reduction in HDL-C levels. Furthermore, elevated tumor necrosis factor- α (TNF- α) levels, attenuating insulin-mediated suppression of lipolysis, have been reported in treatment-naïve HIV patients.¹⁶ Finally, in a recent cohort study of antiretroviral-naïve patients, El-Sadr et al. reported that demographics and HIV disease status influenced lipid and glucose homeostasis and that advanced HIV disease was associated with less favorable profiles.¹⁷

HAART-Associated Dyslipidemia and Metabolic Disorders

HIV-positive subjects undergoing HAART have been reported to have a broad constellation of metabolic side effects, ranging from body composition features to differences in metabolic signatures to conditions associated with an increased cardiovascular risk (Table 1). One of the most characteristic alterations in antiretroviral-treated HIV-infected subjects is the presence of a lipodystrophic pattern, with a loss of facial and truncal subcutaneous fat and an increased abdominal girth or breast size. Although initially these changes in adipose tissue were suggested to be a manifestation of a single process, more recent data indicates that this apparent redistribution pattern is a consequence

of distinct but parallel lipotrophic and lipohypertrophic changes. These morphological changes occur simultaneously with various metabolic changes affecting lipid, carbohydrate, and amino acid metabolic pathways.¹⁸

Protease inhibitors were the first class of antiretroviral drugs associated with lipodystrophy when the initial patients identified as having HIV-associated lipodystrophy were reported in 1997.¹⁹ Since then a number of studies have established an association between the use of PI-class antiretroviral therapy and a wide range of adverse effects; however, clinical end points remain somewhat elusive.^{18,20,21} Results from cross-sectional studies have shown that compared to healthy subjects, HIV-positive patients receiving antiretroviral therapy have increased secretion and decreased clearance of VLDL particles,²² increased synthesis²³ and reduced catabolism of apolipoprotein B,²⁴ the protein backbone of atherogenic lipoproteins, and a diminished lipoprotein lipase activity.²⁵ As a downstream effect of these underlying mechanisms, and in addition to frank hypertriglyceridemia, an increased level of proatherogenic remnant lipoprotein levels has been noted in HIV-positive patients undergoing HAART.^{26,27}

Differences exist between different HAART regimens with respect to the degree and type of dyslipidemia they induce. Results from prospective²⁸ and cross-sectional²⁹ studies show that the NRTI class has the weakest association with dyslipidemia. Among NRTIs, tenofovir may be associated with less aggravation in the lipoprotein profile compared with stavudine.³⁰ Some studies report that NRTI therapy may be related to mitochondrial toxicity, resulting in lactic acidosis.³¹⁻³³ The dyslipidemic pattern has most commonly been reported among patients receiving PIs. For instance, indinavir, nelfinavir, and zidovudine are reported to be associated with a substantial potential for dyslipidemia.³⁴ However, more recent data suggest that the newer PI atazanavir is less likely to induce lipid abnormalities compared with other drugs of the same class.³⁵ Drugs belonging to the class of NNRTIs, in particular nevirapine,³⁶ raise HDL-C levels, although the mechanism remains unknown.

HIV/HAART-Associated Metabolic Syndrome

A common lipoprotein pattern associated with HIV/HAART is characterized by decreased HDL-C, increased TG, and a relatively modest increase in LDL-C levels (Table 1). The lipid abnormalities associated with this constellation have similarities with the lipoprotein phenotype observed in patients with metabolic syndrome. Although these abnormalities were seen more often in subjects with advanced disease, they may also occur in patients with asymptomatic HIV disease.³⁷ The overall prevalence and incidence of metabolic syndrome in HIV-infected patients in the United States is unknown. A recent cross-sectional study among 788 HIV-infected adults examined the prevalence of the metabolic syndrome using International Diabetes Federation (IDF) and National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. The authors showed that prevalence of the metabolic syndrome was 14% by IDF criteria and 18% by ATP III criteria, much lower in prevalence than reported for the general population.³⁸ Furthermore, the metabolic syndrome was more common in those currently receiving PI; subjects with metabolic syndrome showed disturbances in inflammatory markers and adipokines.³⁸ In the

Nutrition for Healthy Living (NFHL) study, the incidence and components of the metabolic syndrome among 477 HIV-infected adults were compared to the data from National Health and Nutrition Examination Survey (NHANES), 1999–2002.³⁹ The unadjusted prevalence of metabolic syndrome in the NFHL study was 24%, and the syndrome was mostly diagnosed through low HDL-C and high TGs plus ≥ 1 additional abnormality. Interestingly, the HAART users in the NFHL had significantly higher odds of having low HDL-C (odds ratio [OR] = 1.6; confidence interval [CI], 1.1–2.1) or high TGs (OR = 2.5, CI, 1.9–3.4) compared to the NHANES participants.³⁹ In the INITIO randomized trial, the incidence of metabolic syndrome, but not baseline prevalence, was significantly associated with an increased risk of CVD (hazard ratio [HR] = 2.73; CI, 1.07–6.96) among HIV-infected patients receiving HAART.⁴⁰ Taken together, a growing body of evidence demonstrates that HAART regimens, especially those including PIs, have been shown to cause a high prevalence of metabolic syndrome in HIV-infected patients and a subsequent increase in the risk of developing CVD.⁴¹

Pathogenesis of Antiretroviral-Induced Metabolic Disorders

The mechanisms responsible for HIV/HAART-related metabolic disorders are not fully understood, but the etiology is likely multifactorial, involving various drug-induced effects in combination with genetic predisposition and environmental factors.^{42,43} As described above, abnormal lipid and lipoprotein concentrations have been reported among HIV-positive patients prior to initiation of HAART, which may be exacerbated after treatment initiation. The fundamentally proatherogenic lipoprotein changes, with increased plasma TG, increased total and LDL-C, and decreased HDL-C,^{26,44–47} can be further underscored by other potentially proatherogenic changes such as increases in the levels of small, dense LDL particles,⁴⁸ lipoprotein(a),^{26,49,50} and apolipoproteins B,^{51,52} C-III,^{52,53} E,⁵⁴ and H.⁵⁵

A number of studies have addressed mechanisms for the dyslipidemic pattern in HIV/HAART. *In vivo* lipoprotein turnover studies have shown that an increase in circulating VLDL apolipoprotein B levels during HAART is caused by either impaired VLDL apolipoprotein B clearance or a treatment-mediated increase in VLDL apolipoprotein B secretion.⁵⁶ Furthermore, in a stable isotope kinetic study, Petit et al. demonstrated that PI-treated HIV-positive patients had higher VLDL and intermediate-density lipoprotein (IDL) apolipoprotein B pool sizes and production rates compared to PI-naïve HIV-positive patients.⁵⁷ Under postprandial conditions, HAART results in increased peripheral lipolysis of TG-rich lipoproteins,^{58,59} disrupts fatty acid and lipoprotein catabolism,^{14,60} and increases proatherogenic remnant lipoprotein levels.²⁷ Studies from cell culture and animal models have shown that PI administration may result in an increased hepatic *de novo* lipogenesis and cholesterol synthesis through suppression of sterol regulatory element binding protein 1 (SREBP-1).⁶¹ Protease inhibitor treatment may also prevent apolipoprotein B degradation with an ensuring potential for increased secretion of apolipoprotein B-containing lipoproteins.

The catalytic region of HIV-1 protease, to which PIs bind, has homologies at the protein level (~60%) with a region within two proteins involved in lipid metabolism: low-

TABLE 1. HIV/HAART-RELATED METABOLIC AND CLINICAL ABNORMALITIES

<i>HIV-related metabolic consequences</i>	
1. Cachexia/wasting	Weight loss Chronic weakness Diarrhea Intermittent or constant fever
2. Dyslipidemia	Increased triglyceride Decreased HDL-C Decreased LDL-C Increased VLDL
3. Increased TNF- α	
4. Osteoporosis	
5. Changes in glucose homeostasis	
6. Changes in immune and cytokine system	
<i>HAART-related metabolic consequences</i>	
1. Lipodystrophy syndrome	Fat atrophy (lipoatrophy) Fat accumulation (lipohypertrophy)
2. Dyslipidemia	Increased triglyceride Decreased HDL-C Increased total and LDL-C Increased VLDL Increased hepatic <i>de novo</i> lipogenesis Increased small dense LDL particles Increased lipoprotein(a) Increased apolipoprotein B, C-III, E, H
3. Glucose tolerance and insulin resistance	Impaired glucose tolerance Increased fasting insulin and proinsulin Increased proinsulin to insulin ratio Increased C-peptide
4. Mitochondrial toxicity	
5. Endothelial dysfunction	
6. Endocrine system dysfunction	Bone and mineral metabolism: osteoporosis or osteopenia Thyroid: hypothyroidism or hyperthyroidism Adrenal: mineralocorticoid, glucocorticoid, or adrenal androgen dysfunction Hypogonadism: primary and secondary Pituitary: hypercortisolemia or glucocorticoid resistance

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL, very-low-density lipoprotein; TNF- α , tumor necrosis factor- α .

density lipoprotein receptor-related protein (LRP) and cytoplasmic retinoic-acid-binding protein type 1 (CRABP-1).⁶² This has prompted suggestions that inhibition of LRP and CRABP-1 might contribute to the observed dyslipidemic pattern. Thus, PI binding to LRP could interfere with endothelial LRP-lipoprotein lipase complex formation and increase plasma TG-rich lipoproteins.^{63,64} Moreover, PIs might be able to stimulate hepatic TG synthesis directly,⁶⁵ as CRABP-1 binds *cis*-9-retinoic acid, a key activator of the retinoid X

receptor and peroxisome proliferator-activated receptor type- γ (RXR-PPAR γ) heterodimer, potentially promoting reduced differentiation and increased apoptosis of peripheral adipocytes. Protease inhibitors, particularly ritonavir, are potent inhibitors of cytochrome P450 3A that convert retinoic acid to *cis*-9-retinoic acid, resulting in decreased activity of RXR-PPAR γ .⁸ However, the extent to which these mechanisms may contribute to the dyslipidemic pattern remains to be established.

Genetic predispositions have been also shown to be associated with HAART-related dyslipidemia. Recent studies have demonstrated a potential interaction of lipoprotein genes with PI therapy in promoting lipid abnormalities in HIV patients. Thus, rare apolipoprotein C-III promoter polymorphisms -455C, -482T, or SstI-S2(G) were associated with higher TG and apolipoprotein B and lower HDL-C in HIV patients.^{52,66} The combined effect of apolipoprotein E and apolipoprotein C-III genotypes on change in lipids on HAART in HIV patients was also studied.⁶⁷ Patients with the -1131T→C promoter polymorphism were shown to be predisposed to a more pronounced hyperlipidemia during PI treatment.⁴³ Other DNA polymorphisms have also been associated with various responses to antiretroviral treatment.^{66–68}

HIV/HAART and CVD

The relationship between HIV infection and CVD has evoked growing interest since mid-1990s, with publications of case reports of myocardial infarction (MI) in young patients infected with HIV. Recent studies have more firmly established that HIV infection might significantly increase the risk of MI and clinical CVD events.^{4,69–72} Thus, a report from a large Northern California clinical database from the Kaiser Permanente Medical Care Program demonstrated that HIV-infected patients had a significantly higher rate of MI than HIV-negative controls.⁷³ Further, data from the California Medicaid program showed that younger HIV-infected men and women had a significantly higher coronary heart disease (CHD) risk compared to HIV-negative subjects.⁷⁰ The large prospective observational Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study has published several reports on the association between HIV infection, antiretroviral therapy, and CVD. In an initial report published in 2003, a positive association between HAART and MI was found.⁴ This was recently followed by a report showing an association between PI use and cardiovascular disease.^{72,74} Notably, the observation time for non-PI-based treatment, mainly NNRTIs, was considerably shorter than for PIs, potentially precluding an ability to detect a positive association. In addition, use of the NRTIs didanosine and abacavir was associated with increased rates of MI after adjustment for the predicted 10-year risk of CHD.⁷² Another large prospective observational study, the French Hospital Database on HIV study, showed that administration of PIs resulted in a 2.5-fold increased risk of MI compared with patients not taking PIs.⁷⁵

Several studies have examined the relationship between HIV infection and surrogate markers of atherosclerosis such as endothelial dysfunction or carotid intima-media thickness.^{76,77} In a cohort of 168 HIV-infected patients, a high prevalence of atherosclerotic plaques of femoral and carotid arteries was observed. However, the presence of atherosclerosis was

not associated with PI use.⁷⁸ Similarly, case-control studies by Hsue et al.⁷⁷ and Currier et al.⁷⁹ have shown that traditional risk factors may contribute to atherosclerosis in HIV-infected patients independent of PI treatment. In addition, a study by Maggi et al. reported a higher than expected prevalence of premature carotid lesions among PI-treated compared to PI-naïve patients.⁸⁰ Furthermore, the presence of HIV infection may activate inflammatory pathways and induce cytokine production, including TNF- α , transforming growth factor- β (TGF- β), nuclear factor- κ B (NF- κ B), interleukin-6, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and endothelial cell adhesion molecule-1.⁴² It is tempting to suggest that these chemokines may initiate the atherosclerotic process, induce fatty streak formation, disrupt the fibrous cap, and contribute to cap rupture and possibly MI.

However, contradictory results have also been reported regarding HAART and cardiovascular risk. Thus, no relationship between the use of PI or NNRTI and risk for cardiovascular and cerebrovascular events was observed in a large retrospective study of patients receiving care for HIV infection at Veterans Affairs facilities.⁷¹ Another retrospective data analysis from the Kaiser Permanente Medical Care Program of Northern California found no association between PI use and rates of hospitalization for CHD or MI among HIV-infected individuals.⁷³ Furthermore, a retrospective analysis of 30 phase II/III industry-sponsored randomized clinical trials revealed that, compared to NRTI-only therapy, patients receiving PI-containing therapy did not have a significantly higher rate of MI.⁸¹

Lipid and Bone Metabolism in HIV/HAART

It is now well established that dysfunction in the endocrine system, as a result of HIV infection, impacts adrenal,^{82–86} thyroid,^{85,87,88} pituitary,^{89–95} and gonadal function (Table 1),^{85,91,96,97} and endocrinopathies in HIV-positive patients have been the subject of a number of excellent review articles.^{86,88,93–99} Many aspects of the endocrine dysfunction can be attributed to opportunistic infections as well as to HIV infection.⁸² Recent research has investigated the effects of HIV and HAART on bone and further defined their influence on lipids. However, the connections between lipid abnormalities and low bone mineral density (BMD) have not received as much attention. The possibility of a relationship between lipid and bone metabolism in this patient population is intriguing.

The potential effects of HIV and HAART medications on bone metabolism and BMD have been subject to a number of recent investigations. For example, Triant et al. described an increased fracture prevalence in HIV-positive men and women, and reported a significant increase in fracture risk at the hip and wrist for HIV-positive subjects compared to HIV-negative controls.¹⁰⁰ Notably, the difference between the groups was accentuated with age. Multiple reports have been published on the association between HAART and low BMD in HIV-positive patients.^{101–108} Protease inhibitors have been suggested as causative agents for a low BMD,¹⁰⁹ although other studies have not been able to support this finding.^{101,103–108,110} A meta-analysis of osteoporosis in HIV-positive patients examining data from 20 cross-sectional studies showed a 15% increased prevalence of osteoporosis among HIV-positive subjects compared to HIV-negative controls. Compared to HAART-naïve HIV-positive subjects,

patients on HAART had a 2.4 times higher OR of having osteoporosis. Studies examining patients on PI-based regimens also demonstrate increased risks of developing osteoporosis (OR, 1.6) as compared to PI-naïve patients. However, although many of the studies used dual-energy X-ray absorptiometry (DXA) measurements as end points, adjustment for potential confounders that might affect bone density were not always done.¹⁰² At present, the relationship between HAART, osteoporosis, and fracture risk warrants further study. It is interesting to posit a relationship between the lipid abnormalities that have been previously reported with PIs and NRTIs and their more recently described effects on the bone.

A factor contributing to the variation seen in bone density studies is the heterogeneity within the various drug classes used in the treatment of HIV, illustrated by a recent *in vitro* study of thymidine analogues on mitochondrial function.¹¹¹ Investigators examined the effects of NRTI-treated and untreated fibroblasts and preadipocytes obtained from healthy subjects. Stavudine and zidovudine reduced mitochondrial membrane potential in the cultured fibroblasts, increased cellular production of reactive oxygen species (ROS), and reduced fibroblast replication and proliferation. In contrast, abacavir, didanosine, lamivudine, and tenofovir did not exhibit these negative effects. Additionally, subcutaneous adipocytes collected from 4 HIV-positive patients with lipodystrophy on NRTI-based regimens (and not on PIs) containing either stavudine or zidovudine also demonstrated mitochondrial dysfunction and increased expression of markers of cellular senescence.¹¹¹ In view of these results, it is tempting to suggest that NRTI effects on the mitochondria might provide a connection between lipid abnormalities and osteoporosis. A small cohort of HIV-negative men with severe osteoporosis was found to have mitochondrial DNA deletions. One of the subjects studied in this cohort had multiple mitochondrial DNA deletions and a very high lactic acid level.¹¹² In HIV-positive patients, lactic acidemia has been associated with NRTIs and mitochondrial toxicity.^{113,114} Carr et al. explored the question of mitochondrial toxicity with use of NRTIs, as measured by lactic acid levels, on the development of osteopenia or osteoporosis in over 200 HIV-positive men.¹¹⁴ Total-body BMD, *t*-scores, and *z*-scores were reported rather than the corresponding measurements of the hip or spine. Lactic acidosis was defined as a serum lactate level greater than 2.0 mmol/L. In this analysis, osteopenia and osteoporosis were independently associated with both symptomatic and asymptomatic lactic acidosis. Patients taking stavudine had higher risk (OR, 2.90; 95% CI, 1.25–6.71; *P* = 0.013) of developing lactic acidosis. Low BMD was independently associated with longer use of stavudine, older age, and lower lean body mass.¹¹⁴ Additionally, zidovudine has been associated with lactic acidosis, hepatic steatosis, and fat deposition in skeletal muscle.¹¹³

In addition to cellular changes, body composition may impact BMD. Low body weight has been cited as a causative factor for low BMD in HIV patients.^{105–107} Conversely, central obesity, as a result of lipodystrophy and associated lipid abnormalities, could play a role in the development of low BMD in HIV-positive patients receiving HAART. A study in HIV-positive men with lipodystrophy demonstrated significant associations between postprandial hyperglycemia and low BMD. Additionally, a relationship between increased markers of bone resorption and elevated non-HDL-C levels

was found.¹¹⁰ Furthermore, a higher degree of visceral obesity was strongly associated with lower trabecular bone density at the lumbar spine, as detected by quantitative computed tomography.¹¹⁵ This raises the issue of whether a low BMD could result from HIV infection, metabolic complications during antiretroviral therapy, or a combination thereof.

If an association between HIV and low BMD could be substantiated to be due to HAART-associated metabolic complications, it would seem reasonable that a low BMD might be seen in HIV-negative conditions with similar metabolic characteristics, such as insulin resistance. In the HIV-negative population, the association between the metabolic syndrome and low BMD has been explored, and results from the Rancho Bernardo Study support the presence of an association between low BMD and metabolic syndrome.¹¹⁶ In this cohort, a low HDL-C level in men was associated with a low BMD in the total hip, whereas in women, a high TG level was associated with low BMD in the total hip and lumbar spine. Overall, when adjusted for BMI, low BMD was associated with the metabolic syndrome.¹¹⁶ However, Ahmed et al. found that patients with more features of metabolic syndrome in the Tromsø cohort had decreased nonvertebral fracture risk, although BMD was not measured and fracture incidence data was collected by survey.¹¹⁷ Furthermore, a meta-analysis of fracture risk in type 1 and type 2 diabetics revealed a significant positive association between presence of diabetes and risk of hip fracture.¹¹⁸

Beyond BMD, Huang et al. demonstrated a relationship between decreased amounts of bone marrow fat measured by magnetic resonance spectroscopy (MRS) and the presence of lipodystrophy in HIV-positive men.¹¹⁹ Another group investigated intravertebral bone fat content with MRS and BMD with DXA in relation to total cholesterol levels. Patients on HAART had lower intravertebral bone fat, but not lower BMD, and this small cross-sectional study did not find an association between a low BMD and total cholesterol levels.¹²⁰ Interestingly, osteoblasts and adipocytes share common embryonic progenitor lineage because they are both derived from mesenchymal cells, and the osteoclastic lineage can be traced back to lymphoid precursors.¹²¹ The question arises whether the metabolism of these cell lines could be affected by similar external influences. An *ex vivo* study of the effect of PIs on the differentiation of human mesenchymal stem cells demonstrated a substantial heterogeneity among this drug class, similar to that described above within the NRTI drug class. Nelfinavir, saquinavir, and lopinavir were each found to inhibit adipogenesis and osteogenesis. Additionally, nelfinavir, but not lopinavir, stimulated osteoclast activity.¹²¹ Nelfinavir was also associated with reduced intravertebral bone marrow fat and low BMD in a cross-sectional study of HIV-positive men taking PIs.¹¹⁹ While these findings highlight the differential effects of this drug class, further studies to explore mechanisms related to the role of antiretroviral therapy and bone effects are warranted. The relationship between bone and fat metabolism under HIV-positive conditions deserves further attention; nonetheless, available data suggest the possibility of an intriguing connection.

Summary

Over the very short time span of two and half decades, the HIV/AIDS pandemic has emerged as a major worldwide

medical and health concern. During the last decade, an increasing frequency of metabolic abnormalities, including dyslipidemia and endocrinopathies, has been observed among HIV-positive patients. Underlying pathogenic mechanisms have proven to be complex and to date are not fully understood, but likely include effects of the HIV infection, toxic effect of antiretroviral drugs on key metabolic pathways, and a combination of both in association with genetic predisposition and environmental factors. It remains challenging to determine to which degree HIV infection constitutes an independent cardiovascular risk factor, and whether an increased cardiovascular risk is due to solely to antiretroviral therapy or to a synergistic effect of disease and therapy. However, whatever the mechanism, the balance of studies favors the conclusion that cardiovascular risk is increased in HIV/HAART patients. Reflecting this, a recent executive summary by the American Heart Association entitled "Initiative to decrease cardiovascular risk and increase quality of care for patients living with HIV/AIDS" underscores the importance of assessing cardiovascular risk in HIV-positive patients.¹²² Faced with an increasing population of aging HIV-positive patients with a spectrum of antiretroviral therapies and accumulation of conventional cardiovascular risk factors requiring attention, we must take this advice to heart.

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