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Severe Weight Gain, Lipodystrophy, Dyslipidemia, and Obstructive Sleep Apnea in an HIV-Infected Patient Following Highly Active Antiretroviral Therapy

Zachariah Dorey-Stein[a], **Valerianna K. Amorosa**[a], **Jay R. Kostman**[a], **Vincent Lo Re III**[a,b], and **Richard P. Shannon**[c]

[a] Division of Infectious Diseases, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

[b] Department of Biostatistics and Epidemiology and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

[c] Division of Cardiovascular Medicine, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

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Human immunodeficiency virus infection; antiretroviral therapy; lipodystrophy

INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) has led to reductions in morbidity associated with opportunistic infections and has significantly decreased mortality among patients living with human immunodeficiency virus (HIV) infection [1]. However, the emergence of long-term drug-related adverse effects has become a major concern to patients with HIV, and a challenge to HIV practitioners. A variety of treatment-related metabolic changes have been observed since the introduction of HAART, including dyslipidemia, insulin resistance, and diabetes mellitus [2]. In addition, changes in body fat distribution, often referred to as “lipodystrophy,” have also been recognized [3] and can have deleterious effects on HIV-infected patients’ quality of life [4,5]. Collectively, these metabolic changes may place HIV-infected patients at increased risk for developing cardiovascular disease. In this report, we describe a case of HIV-associated lipodystrophy accompanied by dramatic weight gain, dyslipidemia, and obstructive sleep apnea following initiation of HAART.

CASE REPORT

A 50-year-old African-American man was diagnosed with *Pneumocystis jiroveci* pneumonia and HIV in February 1999. His primary risk factor for HIV was unprotected sex with men. His social history was also notable for a 30 pack-year history of tobacco and a remote history of intranasal cocaine use. He did not drink alcohol. At the time of HIV diagnosis, his CD4 T lymphocyte count was 145 cells/mm^3, and his HIV RNA level was 86,423 copies/mL. He was tested for hepatitis B and C virus infections, and he had no serological evidence of prior

Address Correspondence to: V. Lo Re III, M.D., M.S.C.E., Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, 711 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104, vincent.lore@uphs.upenn.edu, Tel: 215-573-5964, Fax: 215-349-5111.

exposure to either virus. His pulmonary infection was treated with trimethoprim-sulfamethoxazole, and after its resolution, he was prescribed a HAART regimen consisting of nevirapine (non-nucleoside reverse transcriptase inhibitor) as well as stavudine and abacavir (two nucleoside reverse transcriptase inhibitors).

By April 2001 his CD4 T lymphocyte cell count was 672 cells/mm^3, and his HIV RNA level was undetectable (<75 copies/mL). However, he acknowledged an increase in appetite on antiretroviral therapy and gained 9 kilograms of body weight. He also developed elevations in total serum cholesterol (201 mg/dL, increased from 180 mg/dL) and triglycerides (500 mg/dL, increased from 165 mg/dL; see Table 1). His fasting serum glucose level was normal (90 mg/dL). Results of serum cortisol and testosterone were normal. An electrocardiogram was performed and showed no abnormalities. He was recommended to exercise daily and reduce his caloric intake. In addition, he was prescribed atorvastatin 10 mg daily.

In September of 2002, the patient's HIV RNA level rose to 1,100 copies/mL, and his HAART regimen was intensified with the addition of tenofovir (nucleotide reverse transcriptase inhibitor) to promote HIV virologic suppression. Despite the addition of this antiretroviral, the HIV RNA level rose to 4,353 copies/mL by February 2003. Based on HIV genotypic resistance testing, the patient was switched to a new regimen consisting of fosamprenavir/ritonavir ("boosted" protease inhibitor) as well as abacavir, didanosine, and lamivudine (three nucleoside reverse transcriptase inhibitors). His atorvastatin was switched to pravastatin 20 mg daily due to concern regarding drug interaction between the atorvastatin and protease inhibitor. The new antiretroviral regimen resulted in HIV virologic suppression.

In July 2004, the patient's weight increased an additional 12 kilograms. In particular, he developed severe abdominal obesity as well as noticeable loss of extremity fat. His serum lipids increased further, and his total cholesterol was now 220 mg/dL and triglycerides were 820 mg/dL (Table 1). The fasting serum glucose remained normal (81 mg/dL). Fenofibrate 48 mg daily was prescribed. He was referred to a dietician, who noted that the patient's meal patterns were irregular, his intake of saturated fats high, and his physical activity limited. He was recommended to reduce his caloric intake and begin daily cardiovascular exercises.

Along with his body weight gain, he reported frequent arousals from sleep, excessive daytime somnolence, and increased fatigue. Physical examination was notable for increased adipose tissue around the neck. He was referred for overnight polysomnography, which identified obstructive sleep apnea. He also underwent an echocardiogram, which showed normal left ventricular size and systolic function (ejection fraction, 65%), a mildly dilated right ventricle with depressed right ventricular systolic function, and elevated pulmonary arterial pressures (65 mm Hg). The patient began nighttime nasal continuous positive airway pressure, which improved his symptoms.

Despite interventions to reduce his hyperlipidemia, the patient's total cholesterol increased further to 244 mg/dL, and his triglycerides rose to 1501 mg/dL by January 2005. He failed to comply consistently with the prescribed dietary and exercise recommendations. The dosage of fenofibrate was increased to 145 mg daily, pravastatin was increased to 40 mg daily, and fish oil was added. This regimen resulted in a reduction in the serum cholesterol to 188 mg/dL and serum triglycerides to 174 mg/dL by February 2007. Continued efforts at body weight loss have been unsuccessful, and further modification of the HAART regimen has been limited by the extensive drug resistance on HIV genotypic resistance testing.

DISCUSSION

This case highlights the variety of metabolic changes associated with use of antiretroviral therapy for HIV infection. The patient in this report developed weight gain after the initiation

of both antiretroviral regimens. Body weight gain after the initiation of HAART is likely a multifactorial process and may be due to fat accumulation caused by these medications [3] as well as increases in body weight due to the successful reversal of HIV-associated wasting. Obesity has become more common among those with HIV. One recent cross-sectional study examined body mass indices within a large U.S. urban cohort of HIV-infected individuals and found a 45% prevalence of overweight and obesity in this population [6]. The prevalence and risk factors for overweight and obesity in this group paralleled that of the urban population in general and was not associated with specific antiretroviral agents, suggesting that the obesity observed among patients receiving treatment for HIV is in large part due to factors seen in the overall population rather than due to antiretrovirals specifically.

Beyond weight gain, our patient had prominent abdominal/neck adiposity and peripheral lipoatrophy, findings consistent with lipodystrophy. Lipodystrophy is a heterogeneous syndrome that is clinically characterized by accumulation of fat in the trunk, neck, and abdomen (lipohypertrophy) as well as loss of subcutaneous fat from the face, limbs, and buttocks (lipoatrophy) [3]. Patients on antiretroviral therapy can develop lipohypertrophy, lipoatrophy, or both. The diagnosis depends on subjective findings from the physical examination and/or patient report of central fat accumulation (including fat deposition in the dorso-cervical area causing a “buffalo hump”) and/or peripheral lipoatrophy. Metabolic features associated with the lipodystrophy syndrome include those of the metabolic syndrome in general: hypercholesterolemia, hypertriglyceridemia, low levels of high-density lipoprotein, insulin resistance, type 2 diabetes mellitus, hepatic transaminitis, and lactic acidemia [7]. Observational studies among HIV-infected patients have identified a number of potential risk factors for lipodystrophy, including increasing age, female sex, low body weight pre-antiretroviral treatment, chronic hepatitis C virus infection, current use and total duration of antiretroviral therapy, thymidine analogue use (especially stavudine and zidovudine), and use of dual protease inhibitors [3,8]. The body changes associated with HIV lipodystrophy can be recognizable and stigmatizing and may lead to reduced adherence to antiretroviral therapy [4].

The development of body weight gain and lipodystrophy (especially with neck fat accumulation) due to antiretroviral therapy may lead to disturbances in sleep, particularly the obstructive sleep apnea (OSA) syndrome, as was observed in the case patient. One recent observational study characterized HIV-infected patients with OSA as confirmed by overnight polysomnography [9]. More than 90% of the subjects with OSA in this study were overweight or obese, and 58% had HIV-associated lipodystrophy. Thus, both lipodystrophy specifically and general body weight gain attributed to HAART initiation may increase the risk of OSA. Epidemiologic studies also suggest that individuals with OSA have a high prevalence of hypertension and an increased risk of coronary artery disease, cardiac arrhythmias, and heart failure [10].

Receipt of HAART has also been associated with insulin resistance, worse hyperglycemia, and an increased risk of diabetes mellitus in several large cohort studies [11]. Regimens containing protease inhibitors, particularly the protease inhibitor indinavir (now rarely used), and regimens containing nucleoside reverse transcriptase inhibitors, chiefly stavudine, have been associated with the development of insulin resistance [11]. While indinavir has been demonstrated *in vitro* to have a direct effect on glucose metabolism and may induce insulin resistance by inhibiting glucose movement through the GLUT4 transporter [12], the emergence of insulin resistance during antiretroviral therapy is a complex process that is not completely understood. Improvement in insulin resistance has been reported after switching from a protease inhibitor-based HAART regimen to a non-nucleoside reverse transcriptase inhibitor-based regimen in some studies [13].

The adverse metabolic effects associated with HIV-infection and HAART may place infected people at increased risk of developing premature cardiovascular disease. A recent observational cohort study among 23,468 HIV-infected patients in the U.S., Europe, and Australia revealed that HAART was independently associated with a 26 percent relative increase in the rate of myocardial infarction per year of exposure (during the first four to six years of use) [14]. However, the annual rate of myocardial infarction, even among those exposed to HAART for four to six years, was less than 0.6 percent, and only a portion of the apparent excess risk could be attributed to antiretroviral therapy. Although newer antiretrovirals with more favorable metabolic profiles than those used by the majority of patients in this large cohort are increasingly being used in the U.S., additional data are needed to determine whether substantial increases in cardiovascular morbidity and mortality from cumulative HAART exposure will continue to emerge.

Established guidelines for management of the metabolic changes induced by HAART are based on expert opinion and extrapolated from existing data in non-HIV-infected patients with these disorders. Limited data among HIV-infected patients with lipodystrophy suggest that dietary modification and exercise may reduce body weight and improve insulin resistance and dyslipidemia. Two pilot studies examined the effect of a combination of aerobic and resistance training among patients with HIV-associated lipodystrophy and demonstrated improvements in exercise tolerance, body fat, and blood lipid profiles [15,16]. In addition, Roubenoff and colleagues [17] recently published preliminary data examining the efficacy of a combination of exercise and a low-fat/high-fiber diet to treat HIV-associated lipodystrophy and showed improvements in body weight, fat redistribution, and lipid parameters with such a regimen. Modifying the antiretroviral regimen may be of benefit. Several studies have demonstrated that substitution of a non-nucleoside reverse transcriptase inhibitor for a protease inhibitor may decrease fasting glucose, improve insulin resistance, and reduce hyperlipidemia while preserving HIV virologic suppression and CD4 response [13,18,19]. However, abnormal fat redistribution, particularly fat loss, was not readily reversible in the majority of patients. When protease inhibitor therapy becomes necessary, the protease inhibitor atazanavir should be considered if resistance to this drug is not present because it appears less likely to induce hyperlipidemia and insulin resistance [20].

When lipid-lowering therapy is required in an HIV-infected person receiving HAART, as it was in this case, practitioners must be aware of important interactions between the antiretroviral and lipid-lowering medications. HMG-CoA reductase inhibitors, or statins, have been studied in protease inhibitor-treated, HIV-infected subjects [21]. HIV protease inhibitors variably inhibit the function of cytochrome P450 (CYP) isoforms, particularly CYP3A4. Since the primary route of metabolism for most statins is via oxidation using CYP3A4, the concentrations of certain statins, including simvastatin and lovastatin, may be substantially elevated during protease inhibitor therapy and should not be used because of the increased risk for toxicity [21]. The concentration of atorvastatin may also be increased but may be used if administered at the lowest starting dose. However, pravastatin is safe for use with HIV protease inhibitors. As such, when the case patient was switched to a protease inhibitor-based antiretroviral therapy, his atorvastatin was discontinued and he was switched to pravastatin. When triglyceride levels are elevated (especially over 500 mg/dL, as in this patient), treatment with fibrates should be considered [21]. Niacin has been shown to decrease LDL levels while increasing HDL levels, but it may induce insulin resistance and so should be avoided as first-line therapy for patients receiving protease inhibitors or who have lipodystrophy [22]. Fish oils may also be of benefit [23].

In conclusion, a number of treatment-related metabolic changes have been observed after the initiation of antiretroviral therapy, including lipodystrophy, obesity, dyslipidemia, insulin resistance, and diabetes mellitus. These adverse effects may increase the risk of sleep disorders

and premature cardiovascular disease. Additional research is needed to ascertain the long-term clinical outcomes of antiretroviral therapy and determine the most appropriate therapeutic interventions to reduce the risk of these adverse effects.

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Table 1

Case patient's changes in metabolic parameters over time.

Metabolic Parameter	3/7/2000	4/3/2001 Atorvastatin begun	2/3/2003	7/22/2004 Pravastin/fenofibrate begun	1/27/2005 Pravastin/fenofibrate increased	7/11/2006	2/22/2007
Body Weight (kg)	77.6	86.6	86.1	98.8	105.2	101.2	102.5
Body Mass Index (kg/m^2)	23.2	25.8	25.7	29.5	31.4	30.2	30.6
Heart Rate (beats/minute)	68	84	82	72	72	66	74
Blood Pressure (mm Hg)	130/70	108/80	130/90	132/88	118/74	120/82	106/70
Antiretroviral Regimen	Indinavir Lamivudine Zidovudine	Nevirapine Abacavir Stavudine	Nevirapine Abacavir Stavudine Tenofovir	Fosamprenavir Ritonavir Abacavir Lamivudine Didanosine	Fosamprenavir Ritonavir Abacavir Lamivudine Didanosine	Fosamprenavir Ritonavir Abacavir Emtricitabine Didanosine	Didanosine Epzicom Abacavir Emtricitabine Didanosine
CD4 Cell Count (cells/mm^3)	493	672	735	1285	794	787	938
HIV RNA Level (copies/mL)	36811	<75	4353	<75	<75	2025	993
Fasting Glucose (mg/dL)	90	90	91	81	119	127	93
Total Cholesterol (mg/dL)	180	201	126	220	244	142	188
LDL (mg/dL)	NR	Not calculated*	39	Not calculated*	Not calculated*	53	117
Triglycerides (mg/dL)	165	500	298	820	1501	258	174

HIV=human immunodeficiency virus; HDL=high density lipoprotein; LDL=low-density lipoprotein; NR=not reported

*LDL is unable to be calculated when serum triglyceride level exceeds 400 mg/dL.