

HAART-Associated Lipodystrophy: A Practical Approach

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Since its emergence in 1981, human immunodeficiency virus (HIV) infection has become a global pandemic.¹ With HIV came the devastating consequences of severe immunodeficiency, including *Pneumocystis jiroveci* (*carinii*) pneumonia, progressive multifocal leukoencephalopathy, and disseminated *Mycobacteria avium* complex (MAC) infection.² The advent of highly-active antiretroviral therapy (HAART) has significantly reduced both HIV-related morbidity and mortality³ but, as life expectancy increased, so did the incidence of chronic disease.⁴ This shift in the pattern of morbidity has highlighted the importance of understanding the effects of HIV and HAART on the cardiovascular (CV) system and metabolism. This issue of *Endocrinology Rounds* presents a practical approach to HIV lipodystrophy and its related conditions – insulin resistance and dyslipidemia – including its definition, epidemiology, pathogenesis, and management.

HIV, HAART, and CV risk

The association between HIV, HAART, and CV risk has been documented, although inconsistently,^{5,6} since 1998.⁷ It remains unclear whether the association is secondary to HIV infection itself, to HAART, or to both. Two recent studies attempted to shed light on this question. A healthcare system-based cohort study⁸ compared the rate of acute myocardial infarction (MI) between HIV and non-HIV-infected patients and found that those with HIV had a significant adjusted relative risk of 1.75 (although not adjusted for smoking). However, because of database constraints, there were no data regarding the risk associated with HAART. To assess the effect of HAART on CV risk, the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group⁹ performed a large, multicentre, prospective, observational study. It found that, during the first 4 to 6 years of use, the incidence of MI increased by 26% with each year of exposure to HAART. The study was insufficiently powered to assess risk with individual agents or classes. However, whether or not the observed association reflects a causal relation can only be answered with a randomized trial.

Case definition

Difficulties with case definitions

Rigorous study of HIV-associated lipodystrophy has been limited by the absence of a universally-applicable and objective case definition which, in turn, has been limited by the marked heterogeneity of the condition, populations, and treatment regimens.¹⁰ Although several groups have attempted to remedy this,¹¹⁻¹⁴ the proposed definitions suffer from lack of generalizability, objective criteria, and external validity. This lack of a universally-applicable definition has resulted in a substantial variation in reports of prevalence, incidence, severity, risk factors, and responses to interventions, and has also limited the evidence base for recommendations regarding screening and management.

The HIV Lipodystrophy Case Definition Study Group

In response, the HIV Lipodystrophy Case Definition Study Group¹⁰ developed a model incorporating demographic, clinical, metabolic, and body composition factors (Table 1). Models for lipotrophy and lipodeposition could not be developed, since pure phenotypes occurred in <10% of patients. Although validated in a prospective study (Table 2), its use is limited by its 80% accuracy rate and, thus, has yet to be adopted into practice.



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Table 1: Lipodystrophy Case Definition Study Group – Case definition				
Category	Criteria	Definition	Score	
Demographic	Age	≤40 years	0	
		>40 years	22	
	Sex	Male	0	
		Female	7	
	Duration of HIV infection	≤4 years	0	
		>4 years	11	
HIV disease stage	CDC A	0		
	CDC B	3		
	CDC C	7		
Clinical	Waist-to-hip ratio		Multiply × 29	
Metabolic	Anion gap		Multiply × 1	
	Serum HDL cholesterol		Multiply × -14	
Body composition*	Trunk-to-peripheral fat ratio		Multiply × 5	
		>21.4%	-16	
		14.5-21.4	-14	
		8.8-14.5	-8	
	Percentage leg fat	<8.8	0	
		Intra-abdominal to extra-abdominal fat ratio	<0.45	0
		0.45-0.83	-2	
		0.83-1.59	3	
>1.59	13			

* assessed by dual energy x-ray absorptiometry (DEXA) and computed tomography (CT)

Utility of NCEP ATP-III and IDF definitions of metabolic syndrome

The metabolic syndrome features many of the same metabolic derangements as HIV lipodystrophy, including hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C) levels, and dysglycemia. Although controversial,¹⁵ identifying the metabolic syndrome can be used in CV risk prediction. The prevalence of metabolic syndrome, by the criteria of the International Diabetes Federation (IDF) and the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP)-III, was determined in the above case definition population and found to be 14% and 18%, respectively.¹⁶ However, because waist circumference (WC) is the IDF entry point for metabolic syndrome and with the body fat partitioning disturbances in this population (ie, reduced subcutaneous abdominal fat in combination with excess visceral abdominal fat) result in a “normal” WC, this definition may underestimate the prevalence of metabolic syndrome. Furthermore, in those patients without metabolic syndrome, but with lipodystrophy, their metabolic disturbances (ie, total cholesterol, elevated triglycerides (TG), insulin resistance, blood glucose, C-reactive protein, and HDL-C) were similar to those seen in patients with metabolic syndrome. This suggests that lipodystrophy may be a surrogate marker for the metabolic syndrome in this population. However, the value of either construct, be it metabolic syndrome or lipodystrophy, in predicting CV risk in this population has yet to be determined.

Epidemiology

The prevalence of HAART-associated lipodystrophy – comprising lipoatrophy, lipodeposition, insulin

Table 2: Test characteristics		
	Sensitivity	Specificity
Variables included:		
Demographic, clinical, metabolic, and body composition	79%	80%
Only demographic, clinical, and metabolic	73%	71%
Only demographic and clinical	75%	60%
Score:		
≥ -13	95%	49%
≥ -8	90%	58%
≥ 0	79%	80%
≥ 8	60%	90%
≥ 14	49%	95%

resistance, and dyslipidemia – is variable, with estimates ranging from 10%-80%. This is due to the heterogeneity of the populations studied and the inconsistency in case definitions.¹⁷⁻²⁰ For example, in a cross-sectional study of 1,035 patients with HIV, both treated and untreated, 50% had at least one manifestation, 36% had lipoatrophy, 33% had increased WC, 6% had a dorsocervical fat pad, 10% had hypertriglyceridemia, and 12% had elevated total cholesterol.²⁰ Risk factors for the development of these comorbidities are detailed in the following section and summarized in Tables 3 and 4.

Lipoatrophy refers to the loss of subcutaneous fat that typically affects the face (with a loss of Bichat’s fat pads) and the limbs (with the appearance of prominent veins). Risk factors for its development include higher viral load, older age, lower CD4 counts, co-infection with hepatitis C, and the use of nucleoside reverse transcriptase inhibitors (NRTIs), particularly thymidine analogs (eg, stavudine) and, especially, in combination with protease inhibitors (PIs).^{21,22}

Lipodeposition refers to the accumulation of visceral fat, typically distributed in the abdomen, breast, and dorsocervical spine. Although difficult to differentiate from the current epidemic of obesity, its prevalence ranges from 35%-40%.²²⁻²⁴ Risk factors include older age, female sex, increased duration of HAART, and a low-fibre diet.^{22,25}

Insulin resistance: Dysglycemia occurs in approximately 25%-42% of patients on PIs, with impaired glucose tolerance (IGT) occurring in 16%-35% and type 2 diabetes mellitus occurring in 7%.^{26,27} Risk factors for the development of dysglycemia include not only traditional risk factors – increased WC, hypertriglyceridemia, increased age, and family history – but also NRTI and PI use.²⁸

Dyslipidemia: Although total cholesterol, low-density lipoprotein cholesterol (LDL-C), and HDL-C decrease early in HIV infection, levels of total cholesterol, LDL-C, and TG increase and HDL-C remains low on initiation of HAART.²⁹ For example, the DAD Study Group found that 22% of the cohort (on and off HAART) had total cholesterol ≥6.2 mmol/L, 26% had HDL-C ≥0.9, and 34% had TG ≥2.3 mmol/L.³⁰ Risk factors for elevated total cholesterol include older age, lipodystrophy, higher CD4 counts, lower viral load, as well as NRTI and PI use and

Table 3: Risk factors with HAART-associated lipodystrophy					
Risk factor	Lipo-atrophy	Lipo-deposit.	Insulin resist.	Dyslipidemia	
				↑ Total, ↑ LDL-C	↑ TG, ↓ HDL-C
Patient					
Older age	Yes	Yes	Yes	Yes	
Female sex		Yes			
Disease					
↑ Viral load	Yes			Yes	Yes
↓ CD4 count	Yes			(inverse)	
HAART					
NRTI (esp. stavudine)	Yes	Yes	Yes	Yes	Yes
PI	Yes, in combo with NRTI	Yes	Yes	Yes	Yes (exc. atazanavir)
Duration	Yes	Yes		Yes	
Other					
	HCV	Low-fibre diet	HCV ALT WC		BMI – Trunk/limb fat ratio – Nevirapine protective

ALT = alanine aminotransferase; HAART = highly active antiretroviral therapy; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TG = triglycerides; WC = waist circumference; BMI = body mass index; HCV = hepatitis C virus

duration.³⁰ Risk factors for hypertriglyceridemia and low HDL-C include higher body mass index (BMI), higher trunk-to-limb fat ratio, higher viral load, as well as NRTI and PI use.³¹ NRTI use, especially stavudine, is associated with elevations in TGs, total cholesterol, and LDL-C.^{30,32} PI use, with the exception of atazanavir, is strongly associated with hypertriglyceridemia and low HDL-C; the relative risk of hypertriglyceridemia with PI use (compared with non-PI use) is 4, 9, and 20 times for indinavir, nelfinavir, and ritonavir, respectively.³³ Protective factors include the use of the non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine. Compared with efavirenz, another NNRTI, nevirapine resulted in higher HDL-C levels and less marked hypertriglyceridemia.³⁴

Pathogenesis

Protease inhibitors: PIs are postulated to exert their lipodystrophic effects via 6 possible mechanisms.³⁵⁻³⁸ The first 2 involve inhibition via binding to cytoplasmic retinoic acid-binding protein type 1 (CRABP-1) and cytochrome P450 3a (CYP3a), and of cis-9-retinoic acid

Table 4: Agents with detrimental and beneficial effects on lipodystrophy		
HAART class	Effect on lipodystrophy	
	Detrimental	Beneficial
NNRTI		Nevirapine
NRTI	Stavudine	
PI	Ritonavir Saquinavir Lopinavir	Atazanavir
Fusion inhibitor	No reports in literature	

HAART = highly active antiretroviral therapy; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

signaling and peroxisome proliferator-activated receptor type gamma (PPAR- γ) transcription, thus increasing adipocyte apoptosis and decreasing adipocyte differentiation and proliferation.³⁵ A third mechanism, inhibition of sterol-regulatory element-binding protein-1 (SREBP-1), required for PPAR- γ transcription, also acts on this pathway.³⁶ The fourth mechanism, binding to LDL-receptor-related protein (LRP), inhibits lipoprotein lipase activity, consequently impairing cellular uptake of chylomicrons.³⁵ These 4 mechanisms contribute to the wasting of peripheral fat, increased circulating fat (comprising TGs), and an accumulation of central fat which, in turn, promotes insulin resistance. The fifth mechanism is via the upregulation of TG synthetic enzymes in the liver.³⁷ Finally, certain polymorphisms in apolipoprotein C-III predispose to PI-induced hypertriglyceridemia.³⁸

Nucleotide reverse transcriptase inhibitors: The mechanisms by which the NRTIs cause lipodystrophy are less clear. It is hypothesized that it is via the inhibition of DNA polymerase- γ , the enzyme responsible for replicating mitochondrial DNA.³⁹ The subsequent depletion of mitochondrial DNA results in decreased transcription of mitochondrial enzymes and, finally, mitochondrial dysfunction. This causes the impairment of fatty acid oxidation and disrupts the balance of energy production and storage, with resultant lipodystrophy and insulin resistance. Additional mechanisms include inhibition of adipocyte proliferation and differentiation.⁴⁰

Screening

Since there are no evidence-based recommendations to guide care, it is reasonable to screen for the lipodystrophic and metabolic effects of HAART with serial clinical examinations and selected investigations, ie, prior to HAART initiation, 8 weeks after any change in regimen, then at 6- to 12-month intervals. Although there are no validated techniques to assess facial lipoatrophy, serial thigh circumference and dual-energy x-ray absorptiometry (DEXA) measurements can be used. Objective assessment of lipodeposition, with differentiation of subcutaneous and visceral fat, can be obtained with computed tomography (CT) and magnetic resonance imaging (MRI),⁴¹ but these techniques are limited by radiation exposure and scanning time, respectively and, as a result, are primarily reserved for use in clinical trials. WC or waist-to-hip ratio are economical measures and more easily obtained; although they do not distinguish between subcutaneous or visceral fat. Clinical examination for the presence or absence of subcutaneous fat will often aid in making this distinction. Fasting blood glucose is a useful test to screen for dysglycemia; a subsequent 2-hour oral glucose tolerance test (OGTT) can be performed in individuals with traditional risk factors for diabetes. Finally, screening for dyslipidemia can be done with a fasting lipid profile.

Management

With minimal literature to guide the treatment approach to HAART-associated lipodystrophy, basic

Table 5: Management options for HAART-associated lipodystrophy

Feature	Management options	Comments
Lipoatrophy Facial lipoatrophy	Poly-lactic acid injection	3-5 injections required
Lipodystrophy Dorsocervical fat pad	Exercise Metformin GH, GHRH Change in HAART Liposuction Excision	Safety unknown in those with current lipoatrophy Caution in renal and liver dysfunction and hyperlactemia; monitor during therapy PI → abacavir, (PI → nevirapine) May reaccumulate
Insulin resistance	Metformin Change in HAART	Caution in renal and liver dysfunction and hyperlactemia; monitor during therapy (PI → nevirapine)
Dyslipidemia	Diet and exercise	
↑ TG, ↓ HDL-C	Fibrate	No drug interactions
↓ HDL-C	Change in HAART	PI → abacavir, (PI → nevirapine)
↑ LDL-C	HMG-CoA reductase inhibitor Change in HAART	No drug interactions with pravastatin, fluvastatin, rosuvastatin PI → abacavir, (PI → nevirapine)

GH = growth hormone; GHRH = growth hormone releasing hormone; HAART = highly active antiretroviral therapy; PI = protease inhibitor; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

principles derived from the management of lipodystrophy in the general population can be applied to this population. However, special issues have to be recognized and addressed (eg, drug interactions, toxicity, intolerance, adherence, and lack of outcome data). While a broad approach to CV risk reduction should be taken, including modification of other cardiac risk factors (eg, smoking and hypertension), treatment of specific features of HAART-associated lipodystrophy are discussed below and summarized in Table 5.

Lipoatrophy: Neither lifestyle, nor pharmacologic therapies, are effective in reducing lipoatrophy;⁴² in fact, therapies directed at lipodystrophy and metabolic disturbances, such as exercise, metformin, and growth hormone (GH), may worsen lipoatrophy. Surgical interventions, most notably poly-lactic acid injections, have been reported to improve cosmetic results.⁴³

Lipodystrophy: Exercise and metformin can reduce abdominal girth in this population. For example, metformin can result in a reduction in visceral fat mass of up to 37.5%.⁴⁴ Given NRTI-induced mitochondrial dysfunction and the risk of lactic acidosis with metformin, metformin should be used with caution and with careful monitoring of lactate, as well as renal and liver function. Growth hormone replacement therapy has been found to reduce visceral fat mass;⁴⁵ however, adverse effects include worsening of insulin resistance.

Insulin resistance: Metformin has been found to reduce insulin resistance in this population⁴⁴ but, as noted above, must be used with caution. Thiazolidinediones, although effective in reducing insulin resistance, have no effect on either lipoatrophy or lipodystrophy and may have adverse effects on serum lipids.⁴⁶ Management of type 2 diabetes in this popu-

lation is similar to that in the general population, with the above caveats.

Dyslipidemia: In general, lipid disorders in patients on HAART are managed using the same principles as in the general population. Although controversial,⁴⁷ CV risk can be estimated with the Framingham risk calculator, and NCEP guidelines can be adopted in the absence of evidence for this population. Lifestyle interventions, namely dietary modification and exercise, remain important. For lipid disturbances that primarily constitute LDL-C elevations, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) continue to be most effective.⁴⁸ However, most statins are metabolized by CYP450 3A4, which is inhibited by many drugs, including the PIs, NRTIs, itraconazole, and fluconazole. Inhibition of this cytochrome results in decreased metabolism and, thus, potentially toxic levels of statins. For example, the use of ritonavir or saquinavir will result in serum levels of atorvastatin and simvastatin that are 3 and 30 times higher, respectively.⁴⁹ Three statins that are not metabolized via CYP450 3A4 are fluvastatin, pravastatin, and rosuvastatin (although the latter has not been studied in this population). Ezetimibe (not yet studied in this population) is also effective in lowering LDL-C and is not metabolized through CYP450 3A4. In lipid disturbances that are primarily elevations of TG, fibrates are the most effective.⁵⁰ Because fibrates are not metabolized by CYP450 3A4, there are no drug interactions with HAART. For mixed lipid disturbances, combination therapy with pravastatin and fenofibrate has proven to be safe and effective.⁵¹

Change in HAART: Despite the limited and mostly discordant literature, there is some evidence that

changing the HAART regimen may result in improvements in lipodystrophy. In all of the following changes, there were no adverse effects on virologic or immunologic control.

PI to nevirapine: Although there have been discrepancies in the results from studies on the effects on lipid redistribution, insulin resistance, and dyslipidemia, improvements in dyslipidemia of up to 27% reductions in total cholesterol, LDL-C, and triglycerides have been consistently observed.⁵²⁻⁵⁷

PI to efavirenz: Lipodeposition, insulin resistance, and hypertriglyceridemia are improved;⁵⁸ the effect on total and LDL cholesterol was inconsistent.⁵⁷⁻⁵⁸

PI to abacavir: Studies examining this change were more consistent, with all studies reporting improvements in dyslipidemia;^{57,59-61} for example, reports found TG reductions of up to 39% and total cholesterol reductions of up to 17%. However, few studies reported improvement in lipodeposition⁶⁰ or insulin resistance.⁵⁹

Summary

Despite the lack of a standard definition of HAART-associated lipodystrophy and the marked heterogeneity of the population, there is a clear syndrome of lipotrophy, lipodeposition, insulin resistance, and dyslipidemia associated with HIV and HAART use. With this clustering of CV and metabolic risk factors, there are concerns about increased CV risk in this population. This association has been demonstrated in prospective studies, but their causal relation has yet to be confirmed in a randomized setting. Risk factors include patient characteristics (older age), disease characteristics (CD4 count and viral load), HAART characteristics (NRTI and PI use and duration), and other factors (eg, hepatitis C coinfection). Agents that are particularly detrimental include stavudine, ritonavir, saquinavir, and lopinavir, while more favourable agents include nevirapine and atazanavir.

The pathogenesis of HAART-associated lipodystrophy is complex, with PIs impairing the PPAR- γ pathway, and NRTIs impairing mitochondrial function. The final common pathway for both agents appears to involve inhibition of adipocyte proliferation and differentiation, resulting in peripheral fat wasting, increased circulating fat, and central fat accumulation with resultant insulin resistance.

Screening should be done at baseline, upon initiation or change in HAART, and every 6 to 12 months thereafter and consists of anthropometric measurements (WC, waist-to-hip ratio, thigh circumference), bloodwork (fasting blood glucose \pm 2-hour OGTT fasting lipid profile), and selected imaging (DEXA).

Management should not only address each of these features, but also encompass comprehensive CV risk factor modification. Polylactic acid injections

remain the only successful therapy for facial lipotrophy. Exercise and growth hormone replacement therapy have been used with some success for visceral abdominal fat deposition. Metformin has been used in this setting, as well as for insulin resistance and type 2 diabetes. Caution must be exercised given the risk of lactic acidosis in this population on concurrent NRTI. Diet, exercise, statins, and fibrates remain the cornerstones of therapy for dyslipidemia, with care taken to minimize drug-drug interactions. Finally, although changes in HAART have had mixed results with respect to lipotrophy and lipodeposition, improvements in dyslipidemia were consistently seen, especially with PI regimens switched to nevirapine or abacavir, and virologic and immunologic control were maintained.

References

1. The Global HIV/AIDS pandemic, 2006. *MMWR Morb Mortal Wkly Rep* 2006 Aug 11;55(31):841-4.
2. Jones JL, Hanson DL, Dworkin MS, et al. Surveillance for AIDS-defining opportunistic illnesses, 1992-1997. *MMWR CDC Surveill Summ* 1999 Apr 16;48(2):1-22.
3. Beck EJ, Mandalia S, Williams I, et al. Decreased morbidity and use of hospital services in English HIV-infected individuals with increased uptake of antiretroviral therapy 1996-1997. National prospective monitoring system steering group. *AIDS* 1999;13(15):2157-2164.
4. Gilden DE, Kubisiak JM, Gilden DM. Managing medicare's HIV caseload in the era of suppressive therapy. *Am J Public Health* 2007;97(6):1053-1059.
5. Holmberg SD, Moorman AC, Williamson JM, et al; HIV Outpatient Study (HOPS) investigators. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet* 2002;360(9347):1747-1748.
6. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med* 2003;348(8):702-710.
7. Henry K, Melroe H, Huebsch J, et al. Severe premature coronary artery disease with protease inhibitors. *Lancet* 1998;351(9112):1328.
8. 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(7):2506-2512.
9. Friis-Moller N, Sabin CA, Weber R, et al; Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003;349(21):1993-2003.
10. Carr A, Emery S, Law M, et al. An objective case definition of lipodystrophy in HIV-infected adults: A case-control study. *Lancet* 2003;361(9359):726-735.
11. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipotrophy, lactic acidemia and liver dysfunction associated with HIV nucleoside analogue therapy: Contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* 2000;14(3):F25-32.
12. Saint-Marc T, Partisani M, Poizot-Martin I, et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: Preliminary results of the LIPOCO study. *AIDS* 2000;14(1):37-49.
13. Belloso WH, Quiros RE, Ivalo S, et al. Agreement analysis of variables involved in lipodystrophy syndrome definition in HIV-infected patients. *J Acquir Immune Defic Syndr* 2003;32(1):104-111.
14. Martinez E, Bianchi L, Garcia-Viejo MA, Bru C, Gatell JM. Sonographic assessment of regional fat in HIV-1-infected people. *Lancet* 2000;356(9239):1412-1413.
15. Grundy SM. Does the metabolic syndrome exist? *Diabetes Care* 2006;29(7):1689-1692.
16. Samaras K, Wand H, Law M, Emery S, Cooper D, Carr A. Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using international diabetes foundation and adult treatment panel III criteria: Associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and corrected hypoadiponectinemia. *Diabetes Care* 2007;30(1):113-119.
17. Mallon PW, Miller J, Cooper DA, Carr A. Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. *AIDS* 2003;17(7):971-979.
18. Leitz G, Robinson P. The development of lipodystrophy on a protease inhibitor-sparing highly active antiretroviral therapy regimen. *AIDS* 2000;14(4):468-469.
19. Lo JC, Mulligan K, Tai VW, Algren H, Schambelan M. Body shape changes in HIV-infected patients. *J Acquir Immune Defic Syndr Hum Retroviral* 1998;19(3):307-308.

20. Heath KV, Hogg, RS, Chan KJ, et al. Lipodystrophy-associated morphological, cholesterol and triglyceride abnormalities in a population-based HIV/AIDS treatment database. *AIDS* 2001;15(2):231-239.
21. Lichtenstein KA, Ward DJ, Moorman AC, et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS* 2001;15(11):1389-1398.
22. Jacobson DL, Knox T, Spiegelman, D, et al. Prevalence of, evolution of, and risk factors for fat atrophy and fat deposition in a cohort of HIV-infected men and women. *Clin Infectious Dis* 2005;40(12):1837-1845.
23. Bacchetti P, Giphshover B, Grunfeld C, et al. Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). (2005). Fat distribution in men with HIV infection. *J Acquir Immune Defic Syndr* 2005;40(2):121-131.
24. Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). Fat distribution in women with HIV infection. *J Acquir Immune Defic Syndr* 2006;42(5), 562-571.
25. Hendricks KM, Dong KR, Tang AM, et al. High-fiber diet in HIV-positive men is associated with lower risk of developing fat deposition. *Am J Clin Nutr* 2003;78(4):790-795.
26. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: A cohort study. *Lancet* 1999;353(9170):2093-2099.
27. Hadigan C, Meigs JB, Corcoran, C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis* 2001;32(1):130-139.
28. Jones CY, Wilson IB, Greenberg AS, et al. Insulin resistance in HIV-infected men and women in the nutrition for healthy living cohort. *J Acquir Immune Defic Syndr* 2005;40(2):202-211.
29. Riddler SA, Smit E, Cole SR, et al. Impact of HIV infection and HAART on serum lipids in men. *JAMA* 2003;289(22):2978-2982.
30. Friis-Moller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients – association with antiretroviral therapy. results from the DAD study. *AIDS* 2003;17(8):1179-1193.
31. 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(4):458-466.
32. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: A 3-year randomized trial. *JAMA* 2004;292(2):191-201.
33. Periard D, Telenti A, Sudre P, et al. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. the swiss HIV cohort study. *Circulation* 1999;100(7):700-705.
34. van Leth F, Phanuphak P, Stroes E, et al. Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naïve patients infected with HIV-1. *PLoS Medicine / Public Library of Science* 2004;1(1):e19.
35. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998;351(9119):1881-1883.
36. Caron M, Auclair M, Vigouroux C, Glorian M, Forest C, Capeau J. The HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation, and induces insulin resistance. *Diabetes* 2003;50(6):1378-1388.
37. Lenhard JM, Croom DK, Weiel JE, Winegar DA. HIV protease inhibitors stimulate hepatic triglyceride synthesis. *Arteriosclerosis Thromb Vasc Biol* 2000;20(12):2625-2629.
38. Fauvel J, Bonnet E, Ruidavets JB, et al. An interaction between apo C-III variants and protease inhibitors contributes to high triglyceride/low HDL levels in treated HIV patients. *AIDS* 2001;15(18):2397-2406.
39. Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. *Lancet* 1999;354(9184):1112-1115.
40. Pace CS, Martin AM, Hammond EL, Mamotte CD, Nolan DA, Mallal SA. Mitochondrial proliferation, DNA depletion and adipocyte differentiation in subcutaneous adipose tissue of HIV-positive HAART recipients. *Antivir Ther* 2003;8(4):323-331.
41. Bodasing N, Fox R. HIV-associated lipodystrophy syndrome: Assessment and management. *J Infection* 2003;46(2), 87-93.
42. Carr A. Treatment strategies for HIV lipodystrophy. *Curr Opin HIV & AIDS* 2007;2(4):332-338.
43. Moyle GJ, Brown S, Lysakova L, Barton SE. Long-term safety and efficacy of poly-L-lactic acid in the treatment of HIV-related facial lipodystrophy. *HIV Med* 2006;7(3):181-185.
44. Saint-Marc T, Touraine JL. Effects of metformin on insulin resistance and central adiposity in patients receiving effective protease inhibitor therapy. *AIDS* 1999;13(8):1000-1002.
45. Grunfeld C, Thompson M, Brown SJ, et al. Recombinant human growth hormone to treat HIV-associated adipose redistribution syndrome: 12 week induction and 24-week maintenance therapy. *J Acquir Immune Defic Syndr* 1999;45(3), 286-297.
46. Carr A, Workman C, Carey D, et al. No effect of rosiglitazone for treatment of HIV-1 lipodystrophy: Randomised, double-blind, placebo-controlled trial. *Lancet* 2004;363(9407):429-438.
47. Behrens GM. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med* 2005;352(16):1721-1722.
48. Moyle GJ, Lloyd M, Reynolds B, Baldwin C, Mandala S, Gazzard BG. Dietary advice with or without pravastatin for the management of hypercholesterolaemia associated with protease inhibitor therapy. *AIDS* 2001;15(12):1503-1508.
49. Fichtenbaum CJ, Gerber JG, Rosenkranz SL, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG study A5047. *AIDS* 2002;16(4):569-577.
50. Calza L, Manfredi R, Chioldo F. Use of fibrates in the management of hyperlipidemia in HIV-infected patients receiving HAART. *Infection* 2002;30(1):26-31.
51. Aberg JA, Zackin RA, Brobst SW, et al. A randomized trial of the efficacy and safety of fenofibrate versus pravastatin in HIV-infected subjects with lipid abnormalities: AIDS clinical trials group study 5087. *AIDS Res Human Retroviruses* 2005;21(9):757-767.
52. Barreiro P, Soriano V, Blanco F, Casimiro C, de la Cruz JJ, Gonzalez-Lahoz J. Risks and benefits of replacing protease inhibitors by nevirapine in HIV-infected subjects under long-term successful triple combination therapy. *AIDS* 2000;14(7):807-812.
53. Ruiz L, Negredo E, Domingo P, et al. Antiretroviral treatment simplification with nevirapine in protease inhibitor-experienced patients with HIV-associated lipodystrophy: 1-year prospective follow-up of a multicenter, randomized, controlled study. *J AIDS* 2001;27(3):229-236.
54. Martinez E, Conget I, Lozano L, Casamitjana R, Gatell JM. Reversion of metabolic abnormalities after switching from HIV-1 protease inhibitors to nevirapine. *AIDS* 1999;13(7):805-810.
55. Negredo E, Ribalta J, Paredes R, et al. Reversal of atherogenic lipoprotein profile in HIV-1 infected patients with lipodystrophy after replacing protease inhibitors by nevirapine. *AIDS* 2002;16:1383-1389.
56. Calza L, Manfredi R, Colangeli V, et al. Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidaemia. *AIDS* 2005;19:1051-1058.
57. Fisac C, Fumero E, Crespo M, et al. Metabolic benefits 24 months after replacing a protease inhibitor with abacavir, efavirenz or nevirapine. *AIDS* 2005;19:917-925.
58. Martinez E, Garcia-Viejo MA, Blanco JL, et al. Impact of switching from human immunodeficiency virus type 1 protease inhibitors to efavirenz in successfully treated adults with lipodystrophy. *Clin Infect Dis* 2000;31(5):1266-1273.
59. Walli R, Michl M, Bogner JR, Goebel FD. Improvement of HAART-associated insulin resistance and dyslipidaemia after replacement of protease inhibitors with abacavir. *Eur J Med Res* 2001;6:413-421.
60. Carr A, Workman C, Smith DE, Hoy J, Hudson J, Doong N, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipodystrophy: A randomized trial. *JAMA* 2002;288(2):207-215.
61. Keiser PH, Senson MG, DeJesus E, et al. Substituting abacavir for hyperlipidemia-associated protease inhibitors in HAART regimens improves fasting lipid profiles, maintains virologic suppression, and simplifies treatment. *BMC Infect Dis* 2005;5:2.

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