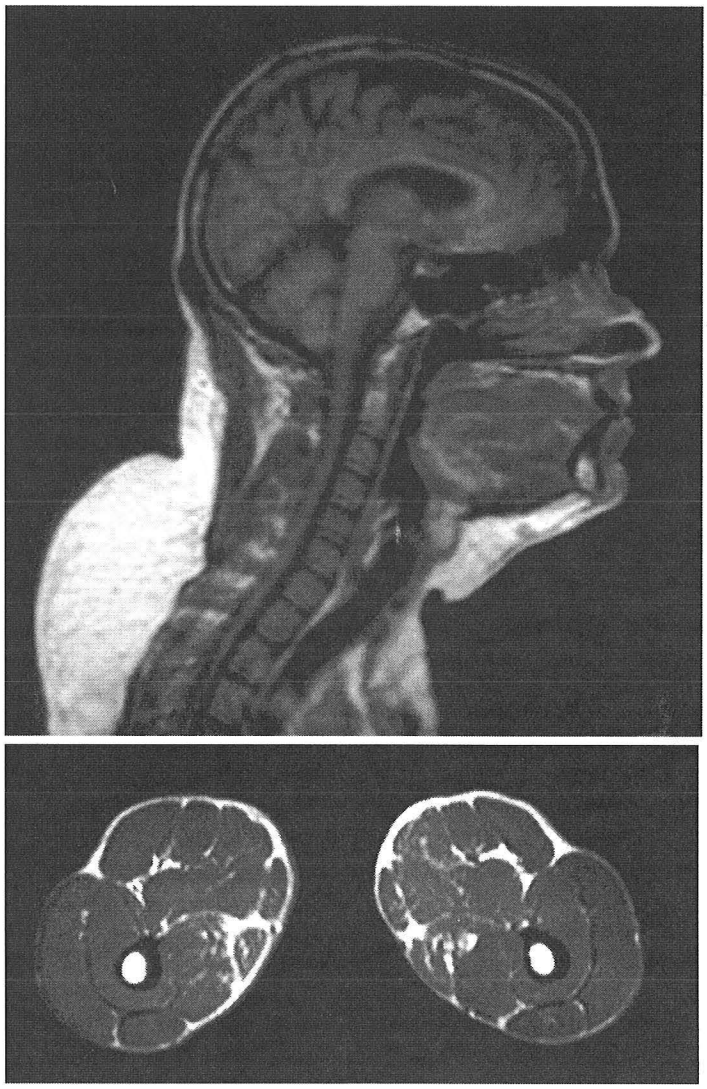
Internal Medicine Grand Rounds

September 28, 2000

LIPODYSTROPHY AND METABOLIC SYNDROME IN HIV-INFECTED PATIENTS



Abhimanyu Garg, M.D.
The University of Texas Southwestern Medical Center,
Dallas, Texas

This is to acknowledge that Abhimanyu Garg, M.D. has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Garg will not be discussing "off-label" uses in his presentation.

Abhimanyu Garg, M.D.
Professor of Internal Medicine
Center for Human Nutrition
Divisions of Human Nutrition and Endocrinology and Metabolism
Associate Program Director
General Clinical Research Center
The University of Texas Southwestern Medical Center at Dallas
Chief, Diabetes Clinic
The Department of Veterans Affairs Medical Center, Dallas, TX.

Special Interests:
Lipodystrophies and other disorders of adipose tissue
Lipoprotein disorders in diabetes
Nutrition in patients with diabetes
Regional obesity, insulin resistance and syndrome 'x'

Cover illustrations:
Upper panel: T1 (TR/TE = 600/17 ms) sagittal magnetic resonance image through the cranium and neck in a 49–year-old HIV-infected male on highly active antiretroviral therapy including indinavir, ritonavir and saquinavir for 2.5 years. Adipose tissue shows as areas with high signal intensity (increased brightness) on t1-weighed images. Excess of adipose tissue is evident in the submental region causing "double chin" and in the posterior cervicothoracic region causing "buffalo hump". The head and face show marked paucity of adipose tissue consistent with lipodystrophy.
Lower panel: Similar T1 (TR/TE = 600/17 ms) image at the level of thighs from the same patient shows marked paucity of subcutaneous fat consistent with lipodystrophy. Bone marrow and intermuscular fat depots are well preserved.

Acknowledgments: I am indebted to Dr. Dali Chen for literature review and collection of data on HIV-infected patients with lipodystrophy, Dr. Dolores Peterson for help with clinical evaluation of HIV patients with lipodystrophy; Dr. Ruth Berggren for providing her unpublished data, Dr. Peter Snell for anthropometric studies; Drs. Saraswathi G. Nair and Manju K. Pillai for literature review; Angela Osborn for illustrations; Dr. Paul Weatherall for MRI studies, Warren Dinges (MS2) and Afua Agaryako (MS1) for image analysis, Jerri Payne and Claudia Quittner for technical assistance; and the nursing and dietetic services of the General Clinical Research Center for patient care support.

Introduction

Recently, great progress has been made in the treatment of human immunodeficiency virus (HIV) infection. Highly active anti-retroviral therapies (HAARTs) that include HIV-1 protease inhibitors (PIs), in particular, result in marked HIV suppression and have dramatically improved the clinical course, prognosis and survival of patients infected with HIV. In the last two years, however, lipodystrophy, characterized by redistribution of body fat and insulin resistance, has been reported in many HIV-infected patients, and its relationship with anti-retroviral drugs and HIV infection per se has become a subject of debate and investigation. This review is intended to discuss the clinical features and possible etiology and pathogenesis of lipodystrophy in HIV-infected patients. Because of the relative paucity of data from complete and in-depth studies, we have included data from preliminary reports of ongoing studies.

Clinical and metabolic characteristics of lipodystrophy in HIV-infected patients (LDHIV)

The first anecdotal report of body fat redistribution in an HIV-infected patient undergoing antiretroviral therapy including a protease inhibitor (indinavir) was published in the medical literature in 1997 (1). In early 1998, Carr and coworkers (2) provided detailed description of a syndrome of peripheral lipodystrophy, dyslipidemia and insulin resistance related to the use of PIs. Subsequently, many more cases have been reported. Currently different names are being used to describe this syndrome, such as pseudo-Cushing's syndrome, fat redistribution or maldistribution syndrome, protease inhibitor-associated or HIV-associated lipodystrophy syndrome. We prefer the term lipodystrophy syndrome in HIV-infected patients (LDHIV).

Body fat redistribution

LDHIV is recognized primarily as loss of subcutaneous (sc) adipose tissue from the facial (sunken cheeks) and peripheral regions, particularly the extremities (2-5) (Table 1). Affected patients appear to be muscular and have prominent superficial veins in the extremities. Some patients have concomitant deposition of excess adipose tissue around neck (double chin), over the dorsocervical spine ("buffalo hump") (6-10), in the upper torso (1) and intra-abdominal region (11-13). Breast enlargement has been observed in both women (12, 14-17) and men (18-20) but whether it is due to excess sc fat or due to glandular hypertrophy or both, is not clear. Compared to men, peripheral fat loss in women with LDHIV is often more subtle, whereas increased truncal adiposity is often the main complaint (12, 21, 22). Acanthosis nigricans and menstrual irregularities in women have not been reported. The majority of patients with LDHIV are clinically well and do not have significant weight loss or opportunistic infections. Their peripheral blood CD4 cell count are relatively high and HIV viral burden low due to effective antiretroviral therapy (3, 7). However, patients affected by severe LDHIV are often troubled by the disfiguring facial and body appearance, altered (stooping) posture, unfit clothes and discomfort from buffalo hump when in a supine position.

A major problem in diagnosing LDHIV currently is the lack of consensus about well-defined diagnostic criteria. Diagnosis is usually based on patient's self-report of regional body fat changes and physical examination. Some investigators consider peripheral sc fat loss as the essential criterion (2). Others, however, have diagnosed LDHIV based on either loss or excess of fat, or both (23-26). We have defined other types of lipodystrophies (familial as well as acquired) as disorders with selective loss of body fat from various regions (27).

Therefore, we consider peripheral fat loss as the primary abnormality and excess fat deposition in other regions as secondary or compensatory.

Several factors may influence the accuracy of patients' self-report and physician's determination of body fat loss in affected individuals. First, since fat loss may occur gradually over months or years, early recognition may be difficult, particularly in obese individuals and in women who have more sc fat than men. Moreover, an individual's awareness and acceptance of body fat loss or gain may be different. For example, an obese person may not be as concerned with mild peripheral fat loss as with increasing central adiposity.

Although a 98% concordance between patients' self-reports and physicians' diagnoses is claimed according to one study (28), significant discrepancy (50%) was reported more recently by the same investigators (29) and others (30, 31). This variability may be related to the type of patient questionnaire used (31). It is important to realize that subjective impression of body fat redistribution may be reported even by significant proportion (10-40%) of healthy subjects (32). The highest specificity of self-reported body fat change in LDHIV patients was the appearance of buffalo hump, but only 19% of them had it. Therefore, the sensitivity and specificity of subjective criteria currently used for LDHIV are poor.

Objective measurement of body fat with dual energy x-ray absorptiometry (DEXA) have confirmed significant reduction of fat in the extremities but preservation or increase of fat in the truncal regions in patients with LDHIV (2, 16, 28, 33). Further, computerized tomography (CT) (9, 11, 34, 35) or magnetic resonance imaging (MRI) studies (13) have shown increased intra-abdominal fat, but not sc fat, in patients with increased abdominal girth. An increased waist to hip circumference ratio and reduced skinfold thickness in the extremities have also been noted in patients with LDHIV (36).

Table 1. Clinical features of HIV-infected patients with body fat redistribution*

Clinical features	PI + NRTI therapy	NRTI only therapy	AIDS wasting
Peripheral and facial fat loss	+	+	+
Prominent superficial veins and muscles	+	?	-
Increase in cervical fat	+	?	-
Buffalo hump	+	+	-
Breast enlargement	+	+	-
Increase in visceral fat	+	+/-	-
Body weight	↑ / -	↓	↓
Lean body mass	-	?	↓

* Peripheral fat loss is necessary in all PI and/or NRTI-treated patients for this analysis. +, present; -, absent or unchanged; ↑, increased; ↓, decreased; ?, not clearly described.

Metabolic abnormalities

Patients with LDHIV often have dyslipidemia, impaired glucose tolerance and insulin resistance (24, 28, 37, 38) (Table 2). Metabolic abnormalities may precede changes in body fat distribution (39). Whether abnormal body fat distribution, dyslipidemia and insulin resistance increase the risk for coronary heart disease in patients with LDHIV on PI therapy is unknown. However, several anecdotal cases of premature and new onset coronary artery disease (40-44), cerebral vascular disease (43) and peripheral vascular disease (41) have been reported in patients on PI-containing therapies.

Table 2. Metabolic features of HIV-infected patients with body fat redistribution

Variables	PI + NRTI therapy	NRTI therapy	AIDS wasting
Plasma lipids/lipoproteins			
Total cholesterol	↑	↓	↓
HDL-Cholesterol	↓	↓	↓
LDL- Cholesterol	↑	↓	↓
VLDL-Cholesterol	↑	↓	↑
Triglycerides	↑	?	↑
Glucose metabolism			
Fasting glucose	↑	↓	↓
Glucose tolerance	↓	Normal	Normal
Insulin	↑	Normal	↓
Insulin resistance	+	-	-

↑, Increased; ↓, decreased; +, present; -, absent; ?, unknown; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein

Dyslipidemia Dyslipidemia in LDHIV is characterized by hypertriglyceridemia, hypercholesterolemia and low serum high-density lipoprotein (HDL)-cholesterol levels. In an early case report (45), a 5-fold increase in serum cholesterol and 15-fold increase in serum triglyceride concentrations were noted in a patient 5 months after initiation of ritonavir therapy, and these values returned towards baseline 5 weeks after cessation of ritonavir. Severe hypertriglyceridemia after starting PI-containing therapy can lead to chylomicronemia, eruptive xanthomas and acute pancreatitis (46, 47). Carr et al. (28) reported dyslipidemia in 67% of patients receiving PI-containing therapy compared to 26% prevalence in PI-naïve patients. Others have also reported similar prevalence (50-70%) of dyslipidemia in patients treated with PI-containing regimen (48, 49).

Dyslipidemia was also noted in pre-PI era in HIV-infected patients, but was characterized by decreased serum levels of total cholesterol, HDL-cholesterol, low-density lipoprotein (LDL)-cholesterol and elevated level of triglycerides (50). Dyslipidemia was associated with low blood CD4 counts and increased plasma levels of interferon-α and was more common in patients with AIDS (51-55).

Impaired glucose tolerance and insulin resistance Impaired glucose tolerance was reported in 62% patients taking PIs (48), and Dube et al. (56) reported a rise in fasting blood glucose level 8 weeks after initiation of indinavir-based therapy. Worsening of preexisting hyperglycemia or new onset of reversible diabetes mellitus with PI therapy is relatively uncommon (57-61). However, Vigouroux et al. (62) reported diabetes occurring in 11/14 (79%) patients with LDHIV, compared to 4/20 (20%) patients on PI-containing HAART without LDHIV. Increased truncal adiposity may be related to higher prevalence of dyslipidemia and insulin resistance (23, 25, 35, 38) but not diabetes (23) in these patients.

Many investigators reported elevation of fasting and/or postprandial serum insulin and C-peptide concentrations in patients on PI therapies and those with LDHIV (2, 3, 28). In an 8-week prospective study of 10 patients receiving indinavir-based therapy, insulin sensitivity assessed by minimal model decreased by 30% (56). Walli and coworkers (63, 64) reported higher prevalence of insulin resistance in patients on PI-containing HAART, compared to those treated with nucleoside transcriptase inhibitors (NRTIs) alone (55% and 27%, respectively), and it was more so in those on prolonged (7-13 months) treatment with PI. In

contrast, HIV-infected patients in the pre-PI era were noted to have increased peripheral insulin sensitivity and lower fasting serum insulin and glucose levels (65, 66).

Prevalence of LDHIV

Over 2000 cases of LDHIV have been reported to date. Due to the differences in diagnostic criteria, selection of study populations and duration of follow-up, considerable differences in the reported prevalence of LDHIV exist, ranging from 1.5% to 84% and averaging 50% in patients treated with PI-containing HAART (Table 3). Despite these differences, however, generally higher prevalence was reported in patients after longer-term therapy. From pooled data, the prevalence of LDHIV is 17% in adults treated with PI-containing therapy for less than one year and 60% in those treated for a year or more (Fig. 1). The prevalence of LDHIV in women is unknown but the cases in women are likely underreported. An increase in the prevalence of LDHIV can be expected in the future with longer follow-up and continued use of current therapies. LDHIV has also been identified in limited number of children receiving antiretroviral medications, including all 4 widely used PIs. The clinical manifestation in affected children appears to be similar to that noted in adults in body fat redistribution and metabolic abnormalities, such as dyslipidemia and hyperinsulinemia (67, 68). There are some reports of abnormal body fat distribution in patients treated with NRTIs alone with a prevalence ranging from 0 to 16%, averaging 7% (Table 3).

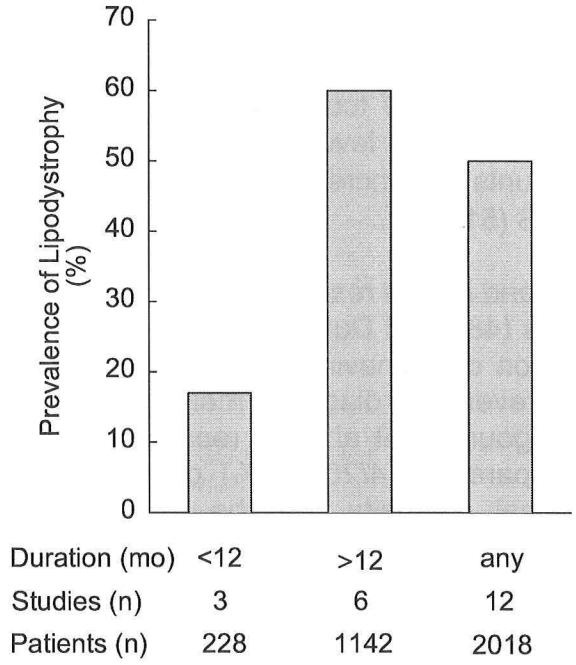


Fig. 1 Prevalence of lipodystrophy in HIV-infected patients treated with protease inhibitor-containing HAART. Prevalence is calculated from the data appropriate for analysis.

Table 3. Prevalence of LDHIV in adult patients on antiretroviral therapies

Source	Cases/total subjects (%)			Duration of therapy[a] (mo.)
	Total	PI-treated	Non-PI-treated	
Duran et al. (148)	18 (9)	18/100 (18)	0/103 (0)	>4
Shaw et al. (4)	12	12/96 (13)	-	6
Viraben et al. (3)	8	8/32 (25)	-	9
Saint-Marc et al. (10)	1	-	1	9
Garcia et al. (166)	2 (0.9)[b]	1/65 (1.5)	1/156 (0.6)	12
Gervasoni et al. (16)	32 (10)	20/144 (14)	12/162 (7)	≥12
Saint-Marc et al. (77)	17	-	17	15
Madge et al. (17)	9	-	9 (4.6)	19
Miller et al. (29)	14	12	2	18
Rozenbaum et al. (26)	524	524/624 (84)	-	18
Vigouroux et al. (62)	14	14	-	20
Viard et al. (167)	44[c]	44/196 (22)	-	20
APROCO study group (168)	?	? (68)	-	20
Carr et al. (28)	93 (66)	92/113 (81)	1/28 (4)	21(PI) 8 (non-PI)
Moyle et al. (78)	5	-	5	24
Carr et al. (71)	14	-	14	61
Lo et al. (30)	8	4	4	?
Roth et al. (8)	8	8/400+	-	?
Renard et al. (169)	28	18	10	?
Ward et al. (170)	529 (49)	?	?	?
Domingo et al. (49)	62	62/159 (39)	-	?
Mercie et al. (171)	220	189	31	?
Mercie et al. (85)	59	46	13	?
Mallal et al. (69)	112 (42)	103/203 (51)	9/66 (14)	?
Galli et al. (73)	31	-	31/188 (16)	?
Dong et al. (12)	21	21/116 (18)		?
Falutz et al. (21)	94	94/170 (55)	-	?
Saint-Marc et al. (25)	73 (53)[d]	?/100	?/39	?
Total cases	2052	1290	160	

[a] Median or mean duration; [b] Early-stage HIV infection; [c] 5 subjects with pure obesity are not included; [d] 9 subjects with pseudo-obesity are not included; ? Information not available.

Risk factors for LDHIV

The direct cause of LDHIV is unknown, but several risk factors have been associated with occurrence of LDHIV. PIs appear to be the strongest link to LDHIV, but interactions among PI and other drugs, HIV virus and the host may all contribute.

Protease Inhibitors

Many case reports (3, 6, 11, 12) and larger observational studies (Table 4) have shown association between LDHIV and PI-based HAART. During a 21-month follow-up of 39 patients on PI therapy, rate of total body fat loss was 0.4 kg per month during the first year and 0.13 kg per month during the second year (28). The fat loss involved all peripheral regions but not the abdomen, while total and extremity lean body masses remained unchanged (28). In contrast, body fat remained essentially unchanged in PI-naïve patients (28). Similarly, 15% fat loss per year from the legs was observed in patients taking PI-containing HAART (69). In addition, PI use is associated with dyslipidemia, impaired glucose tolerance and insulin resistance (Table 5).

PIs were introduced for clinical trials in 1993, and have become widely available since early 1996. It is important to note that LDHIV was not reported before the introduction of PIs when only NRTIs were available and it does not occur in patients naïve to all antiretroviral therapies such as in stable nonprogressors. LDHIV has been associated with all PIs, particularly with combination therapy of ritonavir and saquinavir (28, 70) (2) and with longer duration of PI therapy. Therefore, PIs are strongly linked to occurrence of lipodystrophy in HIV-infected patients.

Table 4. Risk factors for LDHIV *

N	(+) Association	(-) Association	Source
171	PIs		Shevitz et al. (33)
269	PIs, stavudine, zidovudine		Mallal et al. (69)
158	Duration of PIs, duration of HIV infection	Age, HIV viral load, AIDS	Carr et al. (28)
220 *	PI and NRTI duration, stavudine		Carr et al. (71)
196	Durations of PI-HAART, NRTI before HAART, and HIV infection	Age, sex, CD4, HIV viral load	Viard et al. (167)
1077	Indinavir, saquinavir, lamivudine, stavudine, duration of HIV infection, age, lowest CD4, CD4 rebound from nadir		Lichtenstein et al. (172)
306	Duration of any antiretroviral therapy, previous HIV viral load, lamivudine	PI, zidovudine	Gervasoni et al. (16)
154	Stavudine		Saint-Marc et al (25)
60	Stopping stavudine for 6 m → ↑ sc fat		Saint-Marc et al. (136)

- Factors that are associated with increasing regional adiposity only are not included. Abbreviations: CD4, CD4 lymphocyte count; NRTI, nucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; sc, subcutaneous.

Table 5. Risk factors of metabolic abnormalities in patients on antiretroviral therapies

N		(+) Association	(-) Association	Source
182 5	↑ TG	PI duration, AIDS stage, male sex, age, positive virological response	NRTI	Thiebaut et al. (75), Daucourt et al. (22)
196	↑ TG, TC	PIs	Lipodystrophy	Viard et al. (167)
221	↑ TG, TC, glucose	PIs, age, baseline lipids	Non-PI drugs, HIV viral load, weight, steroids	Tsiodras et al. (74)
105[a]	↑ TG, insulin	Duration of PI use, HIV infection,	PI, truncal adiposity (for TG)	Hadigan et al. (173)
190	↑ TG, TC	PIs	Stavudine	Wit et al. (76)
154	↑ TG, FFA, insulin	Lipodystrophy, ↓ HIV viral load, stavudine		Saint-Marc et al. (25)
60	↓ TG	Stopping stavudine for 6 m		Saint-Marc et al. (174)

[a] Study in women only. Abbreviations: CD4, CD4 lymphocyte count; DM, diabetes mellitus; FFA, free fatty acids; HLP, hyperlipidemia; NRTI, nucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; TC, total cholesterol; TG, triglyceride.

NRTIs

Fat loss has also been reported in PI-naive patients treated with NRTIs alone (Table 3). Lamivudine (3TC) (16) and stavudine (d4T) (25, 69, 71, 72) as well as various combinations of NRTI therapies (73) have been implicated to cause body fat redistribution (Table 1,4). A preliminary report suggested that the features of body fat loss in 14 patients

treated with NRTI alone were indistinguishable from those of PI-induced lipodystrophy (71). These patients also presented with recent weight loss, fatigue, nausea, hepatomegaly, hepatic dysfunction and high plasma concentrations of lactic acid (71).

Data are inconsistent as to the effects of NRTIs on glucose and lipid metabolism (Table 2). While some investigators have found dyslipidemia in patients treated with NRTIs alone (17, 72), negative relationship between metabolic abnormalities characteristic of insulin resistance and NRTI therapy has been reported by others (74-76) (Table 5). In fact, patients with NRTI-associated body fat redistribution had either low or normal blood lipids, glucose and insulin levels (71, 77, 78).

It is possible, therefore, that the fat loss in patients treated with NRTIs alone represents a different disorder than the lipodystrophy syndrome in patients treated with PI-containing HAART and is complicated by organ toxicity or failure and AIDS wasting. Whether a particular NRTI causes more fat loss than others is not yet clear. Long duration of NRTI therapy may be required to observe significant fat loss as no significant body fat changes were noted in 151 patients participating in a randomized, controlled trial of combination NRTI therapy for 6 months period (79). It is speculated that NRTIs may cause slow fat loss, which is accelerated with the addition of PIs (69).

HIV infection

Duration of HIV infection, previous HIV viral load and CD4 lymphocyte count have been associated with development and severity of LDHIV in various studies (Table 4). However, how these factors play a role in determining or modifying the development of LDHIV remains unclear.

Nutritional status, age and adiposity

Body adiposity before receiving PI-containing HAART may also affect features of LDHIV. For example, a cross-sectional study suggested that overweight men and women (body mass index>28 kg/M^2) had higher prevalence of buffalo hump and breast enlargement (women) but lower prevalence of facial and gluteal fat loss compared to underweight subjects (body mass index<20 kg/M^2) (80). Older people tend to have greater body fat mass, particularly intra-abdominal fat (81-84) which may contribute or modulate body fat changes seen in LDHIV (22, 85).

Disproportionately higher gain in fat mass relative to lean tissue is observed during refeeding after malnutrition and weight loss although there is substantial individual variation (86). HIV-infected patients with wasting syndrome (weight loss > 10% of baseline body weight) lose more fat than lean body mass (87). Thus, during recovery from wasting, body fat may accumulate disproportionately in certain areas. However, LDHIV can occur in patients without a previous history of wasting.

Pathogenesis of LDHIV

The precise mechanisms by which PIs or NRTIs cause body fat changes are not known. However, various speculations and hypotheses have been proposed. Recently some data are emerging about effects of PIs on adipocyte differentiation and glucose metabolism, which may help elucidate the mechanisms involved.

Mechanisms of PI-induced metabolic syndrome and lipodystrophy

Some similarities in body fat distribution between patients with LDHIV and Cushing's syndrome prompted examination of the hypothalamic-pituitary-adrenal (HPA) axis in patients with LDHIV (1, 6-9, 88, 89). Only a few patients with LDHIV had mildly increased serum cortisol concentration or 24-hour urinary excretion of free cortisol, but they all had preserved cortisol circadian rhythm and normal response to dexamethasone. Thus, overt hypercortisolism is essentially ruled out.

However, cortisol may be locally produced in adipose tissue from conversion of biologically inactive cortisone by the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1). The expression of this enzyme and glucocorticoid receptors is significantly higher in omental fat than in sc fat (90-92). Therefore, regional adiposity may possibly be induced by locally increased glucocorticoid concentration or action without systemic hypercortisolism, but whether this mechanism contributes to development of LDHIV has not been assessed.

Carr et al. (93) identified a 60% (7 amino acids) homology between a 12-amino acid sequence of the catalytic domain of HIV-1 protease and regions of two human proteins related to lipid metabolism --- retinoic acid binding domain of cytoplasmic retinoic acid binding protein (CRABP)-1 and lipid binding domain of low density lipoprotein receptor-like protein (LRP). CRABP-1 carries retinoic acid (94) which when isomerized to cis-9-retinoic acid activates nuclear retinoid X receptor (RXR) α - peroxisome proliferator-activated receptor γ (PPARγ) complex known to regulate adipocyte proliferation and differentiation (95, 96). Thus, PIs by inhibiting CRABP-1 may inhibit adipocyte differentiation and result in adipocyte apoptosis. However, preliminary results of *in vitro* studies do not support this hypothesis. For instance, 3-dimensional crystal analyses of CRABP-1 and HIV-1 protease showed no structural similarity (97). More importantly, western blot analysis failed to detect CRABP-1 in adipocytes, suggesting that this protein may not be constitutively expressed in adipose tissue (97). Furthermore, none of the PIs binds to RXRα or PPARγ directly (98, 99). Although not proven, inhibition of LRP by PIs was hypothesized to contribute to dyslipidemia due to diminished clearance of circulating chylomicrons by the liver and metabolism of triglycerides by LRP-lipoprotein lipase complex.

Other investigators propose that non-specific inhibition of human proteins, such as insulin degrading enzymes or cathepsins (aspartyl proteases) by PIs can cause primary hyperinsulinemia (37, 39, 100, 101). However, this mechanism cannot explain loss of body fat.

Recent *in vitro* studies with C3H10T1/2 murine mesenchymal stem cells (102) and 3T3-L1 preadipocytes (99) as well as human breast preadipocytes (103) show that several PIs inhibit adipocyte differentiation. However, whereas Zhang et al. (99) showed that PIs reduced aP2 expression in 3T3-L1 cells, Wentworth et al. (103) were not able to confirm it in human breast preadipocytes. Indinavir may also effects on retinoid signaling. Indinavir stimulates activity of alkaline phosphatase (a retinoid-regulated protein) in the presence of all-trans-retinoic acid in C3H10T1/2 cells. This effect seems to be mediated through retinoic acid receptor (RAR) and CRABP (104).

Similarities with familial partial lipodystrophy (Dunnigan variety; FPLD)

Interestingly, there are several similarities in clinical features as well as in associated metabolic disturbances in patients with FPLD and lipodystrophy syndrome in HIV-infected patients (Table 6). Extreme lack of sc adipose tissue in both upper and lower extremities but accumulation of excess fat in submental region and neck (causing double chin and prominent

supraclavicular fat pads) characterize both the disorders. However, HIV-infected patients with lipodystrophy syndrome do lose fat from the face and develop buffalo hump. These features are not seen in patients with FPLD. Furthermore, both type of patients have increased propensity to develop insulin resistance and associated complications such as premature diabetes mellitus, hypertriglyceridemia and low HDL cholesterol levels.

Table 6. Characteristics of lipodystrophy syndrome in HIV-infected patients and familial partial lipodystrophy (Dunnigan variety)

Affected Region	Lipodystrophy Syndrome in HIV-Infected Patients	Familial Partial Lipodystrophy (Dunnigan variety)
Face	Reduced fat	Normal or increased fat
Neck	Increased fat	Increased fat
Buffalo hump	Present	Occasional
Extremities	Marked loss of fat	Marked loss of fat
Trunk	Increased fat	Reduced fat anteriorly
Mechanical fat	Well preserved	Well preserved

Although purely speculative, it is possible that the underlying mechanisms of lipodystrophy in the two disorders may also be related. Using genome-wide linkage analysis in 5 well-characterized families, we localized the gene for FPLD to chromosome 1q21-22 (105).

Recently gene encoding, lamin A/C (*LMNA*) was described as a candidate for FPLD on the basis of a novel mis-sense mutation, R482Q in five Canadian probands (106). Subsequently, our group and others reported missense mutations in the gene in affected subjects, both sporadic and belonging to various pedigrees (107,108)

Lamin A/C (*LMNA*) gene:

This gene, lamin A/C, encodes a component of the nuclear lamina; a polymeric structure intercalated between chromatin and the inner membrane of the nuclear envelope. The coding region spans ~ 24 kilobases and contains 12 exons (Fig. 2). Alternative splicing within exon 10 gives rise to two different mRNAs that code for prelamin A and lamin C (109). Human lamins A and C are identical for the first 566 amino acids. Lamin C has 6 unique carboxy-terminal amino acids and lamin A has 80 unique carboxy-terminal amino acids. Usually, alternative splicing produces approximately equal amounts of the two respective mRNAs within the same cell. However, different splice variants of lamin A may be expressed at different levels depending on the cell types (110). Prelamin A has a CAAX box at the carboxy terminus, which undergoes isoprenylation, specifically farnesylation, which is, required for conversion of prelamin A to lamin A. In contrast, lamin C does not undergo isoprenylation. A specific prelamin A endoprotease (65 kDa serine protease) cleaves carboxy terminus 18 amino acids to from lamin A from prelamin A (111).

LMNA is a member of the intermediate filament multigene family and lamins A and C have primary and secondary structures similar to cytoplasmic intermediate filament proteins. Two other lamins, B1 and B2 are products of two different genes. These proteins have a central α-helical rod, an amino-terminal head, and carboxy terminal tail domains (112). They dimerize through their rod domain to form 10-nm diameter filaments and bind and assemble on the surface of mitotic chromosomes at specific sites on the rod (113). Both homodimers and heterodimers can form between various lamins i.e. A, B1, B2 and C (114). Lamins B1 and B2 are expressed widely in tissues whereas lamins A and C are expressed mainly in differentiated non-proliferating cells. Lamins A and C bind to DNA, histones and retinoblastoma gene product (which controls cell cycle and gene expression) and thus play a role in organization of DNA transcription in cells. Lamins B bind to nuclear membrane and are

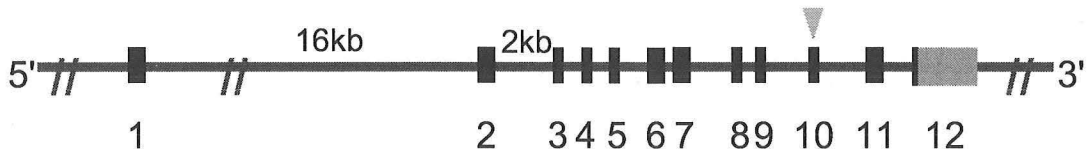


Fig. 2 Lamin A/C (*LMNA*) gene structure. Numbers under the boxes denote the exons and the arrow indicates the site at which alternate splicing occurs to form Lamin A or C.

associated with replicating chromatin in mammalian cells. Lamins A and C also associate with integral proteins of the nuclear envelope such as lamin associated polypeptides (LAPs) 1A and 1B and emerin whereas lamins B associate with LAP1 and LAP2 and lamin B receptor (115). Whether, PIs cause disruption on Lamin A/C gene or other proteins interacting with it, remains to be investigated.

Similarities with transgenic mouse model of lipodystrophy

Transgenic mice that overexpressed SREBP-1c exclusively in fat using the fat-specific aP2 promoter to drive the transgene developed lipodystrophy (116). The transgenic mice (aP2-SREBP-1c) had very little omental or sc fat but developed an enlarged interscapular fat pad ("buffalo hump") that was histologically similar to white adipose tissue. The histology of the epididymal fat from transgenic mice showed small immature appearing adipocytes, suggesting SREBP-1c overexpression caused an alteration in adipocyte differentiation. The mice also developed severe hyperinsulinemia and hypertriglyceridemia with no change in plasma FFA levels (116). Thus, the phenotype in transgenic mice (aP2-SREBP-1c) not only resembles congenital generalized lipodystrophy (extreme lack of omental and sc fat), but also shares some features with lipodystrophy syndrome in HIV-infected patients (extreme lack of sc fat in the limbs and presence of buffalo hump).

We believe the phenotypic similarities between the SREBP-1c transgenic mouse model and lipodystrophy in HIV-infected patients suggest that changes in adipocyte-related gene expression may occur in HIV-infected patients developing lipodystrophy syndrome. It is conceivable that the administration of PIs results in either: 1) An increase in a general transcription factor such as SREBP-1c or Pref-1 that causes de-differentiation of adipocytes or 2) A reduction or inhibition of a key transcription factor such as C/EBPα or PPARγ that results in significant changes in adipocyte gene expression.

Mechanisms of PI-induced metabolic changes

Recently, Murata et al. (117) have shown a dose-dependent inhibition of insulin-mediated glucose disposal in 3T3-L1 adipocytes by protease inhibitors. This inhibition was not due to effects on insulin signaling events or translocation of glucose transporters (GLUTs) to the cell surface. In *Xenopus* oocytes heterologously expressing GLUT1 and GLUT4, protease inhibitors only inhibited GLUT4 activity.

In a recent study, Purnell and co-workers (118) reported hypertriglyceridemia in healthy subjects after 2 week of ritonavir therapy, which was associated with 20% reduction in hepatic lipase activity. Lipoprotein lipase activity remained unchanged. In another study in healthy volunteers, indinavir caused no increase in serum triglyceride concentrations but caused hyperinsulinemia (personal communication Carl Grunfeld, M.D.).

Mechanisms of NRTI induced body fat changes

Recently, Brinkman et al. (119) have emphasized the similarity in body fat distribution in patients with LDHIV and multiple symmetric lipomatosis (MSL), which is characterized by marked accumulation of non-encapsulated adipose tissue around the neck ("horse collar" and "buffalo hump"), shoulders and upper torso regions (120). Although heavy ethanol intake causes MSL in most patients, point mutations in mitochondrial DNA (121-124) and mitochondrial dysfunction (125) have been identified in four families and seven sporadic cases, who had associated peripheral neuropathy, myopathy, cerebellar ataxia, myoclonus or hearing loss. Mitochondrial DNA mutations A-to-G and G-to-A transitions at nucleotides 8344 and 8363, respectively and deletions in the $tRNA^{Lys}$ were reported. However, most of these patients had multiple, discrete and encapsulated lipomas in the neck and trunk unlike typical patients of multiple symmetric lipomatosis in whom adipose tissue growth is not encapsulated and insinuates along fascial planes. Mitochondrial DNA mutations have not been found in many other patients who consumed ethanol.

Interestingly, NRTIs inhibit DNA polymerase-γ and thus replication of mitochondrial DNA (126,127). Mitochondrial toxicity, including reduced cytochrome *c* oxidase activity and impaired β-oxidation of fatty acids, is a recognized side effect of NRTIs and is implicated in hepatotoxicity, myopathy and neuropathy. NRTIs increase lactate production and can cause lactic acidemia (71, 128) and, in a few cases, severe lactic acidosis (129-133). Some investigators speculate that, as in familial MSL, mitochondrial dysfunction by NRTIs can induce body fat changes (119,134). However, patients with MSL do not have facial fat loss and reduction in sc fat in the extremities distal to the mid-arms and mid-thighs is relatively mild. Furthermore, most MSL patients with mitochondrial DNA mutations had multiple, discrete and encapsulated lipomas in the neck and trunk. It should also be noted that patients with MSL usually do not develop metabolic abnormalities associated with insulin resistance and instead have high levels of serum HDL cholesterol (120, 135-139). Therefore, whether mitochondrial toxicity of NRTIs is related to body fat changes remains controversial. Whether lactic acidemia is an integral component of NRTI-induced body fat changes is also unclear.

Differential diagnosis

Several disorders, which cause loss or redistribution of body fat, need to be differentiated from LDHIV. First of all, generalized body fat loss is commonly seen in HIV-infected patients with AIDS wasting syndrome (Tables 1 and 2). These individuals often are clinically ill due to high viral burden. Such patients lose significant weight and body fat mass and lean body mass, as opposed to LDHIV in which lean body mass is preserved. Furthermore, patients with AIDS wasting syndrome do not have impaired glucose tolerance or hyperinsulinemia, although they may have hypertriglyceridemia (50). Poorly controlled diabetes can also present with severe weight loss. MSL should be considered if there is a history of heavy ethanol intake. History of steroid or megesterol use should be inquired as Cushing's syndrome is associated with central obesity and dorsocervical fat deposition.

Testosterone therapy can cause muscular appearance of the limbs requiring differentiation from lipodystrophy.

Management

Observation

Most patients with LDHIV have only mild symptoms. It is unclear how frequent and to what extent LDHIV is reversible, either spontaneously or with intervention. Since PIs provide superior HIV suppression and, at present, are the most effective treatment for long-term survival of HIV-infected patients, benefit from continued use of PIs likely may outweigh the side effects in many patients.

Diet and Exercise

Increased physical activity reduces insulin resistance and therefore should be encouraged. Resistance exercise has been shown to be beneficial in reducing truncal fat as well as total body fat in a 16-week pilot study (140). Dyslipidemic patients should reduce dietary intake of saturated and trans fats and replace them with either carbohydrates or unsaturated fats such as monounsaturated or polyunsaturated fats. This should reduce plasma LDL cholesterol levels. Severely hypertriglyceridemic patients should be advised to take very low fat diets and avoid ethanol consumption to prevent chylomicronemia and acute pancreatitis. N-3 polyunsaturated fatty acids from fish oils may lower plasma triglyceride concentrations if taken in large doses (5-10 g of n-3 polyunsaturated fatty acids per day).

Cessation and alteration of antiretroviral therapies

In patients with severe LDHIV syndrome unable to continue current therapy, improvement in fat loss after cessation of PI from therapy has been observed by some investigators (141) but not by others (3, 8). PI withdrawal may also improve dyslipidemia, insulin resistance or hyperglycemia in such patients (47, 58, 59, 142). Since the severity of adverse effects of PIs on lipids may be different (2, 44, 143,144), switching PIs (such as from ritonavir/saquinavir combination to indinavir or nelfinavir) may also result in improvement in lipid profile in certain patients.

While substituting PI with a NRTI may improve insulin sensitivity (63), non-NRTI (NNRTI) class of antiretroviral drugs may be other alternatives. Replacing PI with nevirapine in combination antiretroviral therapy for 6-12 months has been reported to improve and even normalize dyslipidemia, glycemia and insulin resistance, while HIV suppression was maintained (145,146). Quality of life and subjective perception of lipodystrophy were also improved after switching PI to nevirapine during 6-12 month follow-up (20,145,147). However, lipodystrophy associated with nevirapine (148) and failure of HIV suppression after switching PI to nevirapine in some patients (149) have been reported. The incidence of developing lipodystrophy was reported to be lower in patients treated with efavirenz than with indinavir-containing regimens during a 24 to 88-week follow-up (150). However, conflicting effects of efavirenz on dyslipidemia are reported (34, 151). Although substitution of stavudine with other NRTIs for 6 months was reported to increase total body fat in patients on PI-containing and other regimen (152), further prospective, controlled studies are needed before such recommendation can be made.

Recombinant human growth hormone (rhGH) and anabolic steroids

Therapy with rhGH for 3-6 months caused noticeable reduction in the size of buffalo hump and truncal adiposity in small number of patients with LDHIV in two studies, but there was no improvement in peripheral lipodystrophy and dyslipidemia (153, 154). In another study, rhGH therapy for 3 months decreased visceral fat and fasting serum triglycerides concentration but increased fasting blood glucose in 30 HIV-infected patients (155). Nandrolone therapy for 8 weeks had no significant effects on body fat redistribution (156). The effects of testosterone therapy on LDHIV have not been studied but it may reduce intra-abdominal fat accumulation.

Surgical correction

Liposuction has been used to remove excess cervical and truncal fat (157, 158). Chances of recurrence of fat deposition after such treatment vary according to our own observation and others (6, 8). Limited information of histopathology of fine needle biopsy or surgical specimens of the adipose deposition reveals nonencapsulated mature adipose tissue (6, 8), some with fibrotic changes (159), ruling out dysplastic or neoplastic pathology.

Drug therapy for dyslipidemia

Whether HIV-infected patients should be managed as aggressively as in non-infected patients, remains controversial. The recent Preliminary Guidelines for the Evaluation and Management of Dyslipidemia in HIV-infected Adults Receiving Antiretroviral Therapy by the Adult ACTG Cardiovascular Disease Focus Group (160) suggest the same guidelines for managing HIV-infected patients as recommended by the Adult Treatment Panel of the National Cholesterol Education Program. However, since HIV-infected patients are usually on multiple antiretroviral and other drugs, the relative safety and efficacy of lipid-lowering drugs for prevention of coronary heart disease in them remains unknown. Patients with extreme hypertriglyceridemia definitely should be treated to reduce their risk of acute pancreatitis.

The drugs of choice for the treatment of HAART-associated hypertriglyceridemia are fibrates (gemfibrozil or fenofibrate) (161-163) and hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) (161). Protease inhibitors (indinavir, nelfinavir, saquinavir and ritonavir) inhibit cytochrome P450 (CYP) 3A4 enzyme (160). Indinavir appears to be a less potent inhibitor of CYP 3A4. Interestingly, many statins, namely, simvastatin, atrovastatin and lovastatin are metabolized by CYP 3A4 pathway. Fluvastatin is metabolized by the CYP 2C9 pathway and cerivastatin is metabolized by dual 2C9 (or 2C8) and 3A4 pathways. Pravastatin is not metabolized by the CYP pathway. Furthermore, fibrates such as gemfibrozil and fenofibrate are also metabolized by CYP 3A4 pathway. Thus concomitant use of CYP 3A4 inhibitors such as PIs in patients taking some statins and fibrates may increase the risk of myopathy. Therefore, pravastatin and fluvastatin may be the preferred statins in HIV-infected patients with PI-induced dyslipidemia. Combination of statins and fibrates can also increase the risk of myopathy and therefore should be tried only in carefully selected patients without abnormal liver and renal function tests. Recently, Berggren et al. (personal communication) noted myopathy in 2 patients on PIs and statins.

Women with LDHIV and hypertriglyceridemia should avoid estrogen therapy either as oral contraceptives or as postmenopausal hormone replacement therapy as estrogens can accentuate hypertriglyceridemia. Niacin therapy should be avoided as it can induce insulin resistance and can induce hyperglycemia in those with abnormal glucose tolerance or

diabetes. Bile acid sequestrants are also not the drugs of choice because these drugs can accentuate hypertriglyceridemia.

Drug therapy for diabetes

Treatment of diabetes with common hypoglycemic medications (58, 60, 61) are effective. In a pilot study of 6 patients with PI-associated diabetes, treatment with troglitazone, a PPAR-γ activator, improved insulin sensitivity, glucose homeostasis and dyslipidemia (64, 164). A recent study reported that metformin therapy 500 mg twice daily was effective in reducing postprandial hyperinsulinemia in HIV-infected patients with impaired glucose tolerance on combination antiretroviral therapy (165).

Future directions

The first step in studying LDHIV is to establish reliable diagnostic criteria. Large scale epidemiological studies and, ultimately, prospective, randomized and controlled clinical trials are needed to establish risk factors of LDHIV and to assess whether associated metabolic complications pose a risk of atherosclerotic vascular disease. The underlying molecular basis of LDHIV needs to be elucidated and the genetic predisposition, if any, for developing LDHIV should be identified. This knowledge may lead to the discovery of new antiretroviral agents that are low risk for lipodystrophy and may provide insight into mechanisms of insulin resistance in other adipose tissue disorders.

References:

1. **Hengel RL, Watts NB, Lennox JL.** 1997 Benign symmetric lipomatosis associated with protease inhibitors. Lancet.350:1596.
2. **Carr A, Samaras K, Burton S, et al.** 1998 A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS.12:F51-8.
3. **Viraben R, Aquilina C.** 1998 Indinavir-associated lipodystrophy.AIDS.12:F37-9.
4. **Shaw AJ, McLean KA, Evans BA.** 1998 Disorders of fat distribution in HIV infection. Int J STD AIDS.9:595-9.
5. **Kotler DP, Rosenbaum K, Wang J, Pierson RN.** 1999 Studies of body composition and fat distribution in HIV-infected and control subjects. J Acquir Immune Defic Syndr Hum Retrovirol. 20:228-237.
6. **Lo JC, Mulligan K, Tai VW, Algren H, Schambelan M.** 1998 "Buffalo hump" in men with HIV-1 infection. Lancet.351:867-70.
7. **Miller KK, Daly PA, Sentochnik D, et al.** 1998 Pseudo-Cushing's syndrome in human immunodeficiency virus-infected patients. Clin Infect Dis.27:68-72.
8. **Roth VR, Kravcik S, Angel JB.** 1998 Development of cervical fat pads following therapy with human immunodeficiency virus type 1 protease inhibitors. Clin Infect Dis.27:65-7.
9. **Striker R, Conlin D, Marx M, Wiviott L.** 1998 Localized adipose tissue hypertrophy in patients receiving human immunodeficiency virus protease inhibitors. Clin Infect Dis.27:218-20.
10. **Saint-Marc T, Touraine JL.** 1998 "Buffalo hump" in HIV-1 infection. Lancet.352:319-20.
11. **Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J.** 1998 Visceral abdominal-fat accumulation associated with use of indinavir. Lancet.351:871-5.
12. **Dong KL, Bausserman LL, Flynn MM, et al.** 1999 Changes in body habitus and serum lipid abnormalities in HIV-positive women on highly active antiretroviral therapy (HAART). J Acquir Immune Defic Syndr Hum Retrovirol.21:107-113.
13. **Engelson ES, Kotler DP, Tan YX, et al.** 1999 Fat distribution in HIV-infected patients reporting truncal enlargement quantified by whole-body magnetic resonance imaging. Am J Clin Nutr.69:1162-1169.
14. **Herry I, Bernard L, de Truchis P, Perronne C.** 1997 Hypertrophy of the breasts in a patient treated with indinavir. Clin Infect Dis.25:937-8.
15. **Lui A, Karter D, Turett G.** 1998 Another case of breast hypertrophy in a patient treated with indinavir. Clin Infect Dis.26:1482.

16. **Gervasoni C, Ridolfo AL, Trifiro G, et al.** 1999 Redistribution of body fat in HIV-infected women undergoing combined antiretroviral therapy. AIDS.13:465-471.
17. **Madge S, Kinloch-de-Loes S, Mercey D, Johnson MA, Weller IVD.** 1999 Lipodystrophy in patients naive to HIV protease inhibitors. AIDS.13:735-737.
18. **Schurmann D, Bergmann F, Ehrenstein T, Padberg J.** 1998 Gynaecomastia in a male patient during protease inhibitor treatment for acute HIV disease. AIDS.12:2232-3.
19. **Toma E, Therrien R.** 1998 Gynecomastia during indinavir antiretroviral therapy in HIV infection. AIDS.12:681-2.
20. **Donovan B, Bodsworth NJ, Mulhall BP, Allen D.** 1999 Gynaecomastia associated with saquinavir therapy. Int J STD AIDS.10:49-50.
21. **Falutz J, Turcot D.** 1999 Considerations in the development of a case definition for HIV/HAART-associated lipodystrophy syndrome. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 21.
22. **Daucourt V, Thiebaut R, Mercie P, et al.** 1999 Prevalence of lipodystrophy and relation with clinical, anthropometric data and treatment, Aquitaine cohort, 1999. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 16.
23. **Thiebaut R, Daucourt V, Malvy D, et al.** 1999 Lipodystrophy, glucose and lipid metabolism dysfunctions, Aqutain cohort, 1999. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 17.
24. **Gharakhanian S, Salhi Y, Nguyen TH, et al.** 1999 Frequency of lipodystrophy and factors associated with glucose/lipid abnormalities in a cohort of 650 patients treated by protease inhibitors. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, IL:Abstract 642.
25. **Saint-Marc T, Partisani M, Poizot-Martin I, Bruno F, Rouviere O.** 1999 Changes in body fat distribution in 154 HIV-infected male patients treated with combined antiretroviral therapy. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 25.
26. **Rozenbaum W, Gharakhanian S, Salhi Y, et al.** 1999 Clinical and laboratory characteristics of lipodystrophy in a French cohort of HIV-infected patients treated with protease inhibitors. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 12.
27. **Garg A.** 2000 Lipodystrophy. Am J Med.108:143-152.
28. **Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA.** 1999 Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. Lancet.353:2093-2099.
29. **Miller J, Smith D, Grey P, et al.** 1999 Lipodystrophy in patients with primary HIV infection on long term antiretroviral therapy. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 46.
30. **Lo JC, Mulligan K, Tai VW, Algren H, Schambelan M.** 1998 Body shape changes in HIV-infected patients. J Acquir Immune Defic Syndr Hum Retrovirol.19:307-8.
31. **Pettit R, Nuurahainen N, Falutz J, et al.** 1999 HIV-related truncal obesity: a comparison of physician and patient diagnoses in the SALSA (self-ascertained lipodystrophy syndrome assessment) questionnaire. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, IL:Abstract 651.
32. **Muurahainen N, Falutz J, Santos G, et al.** 1999 The SALSA (self-ascertained lipodystrophy syndrome assessment) cohort: abnormalities in cases compared to controls. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 22.
33. **Shevitz A, McDermott AY, Knox T, Roubenoff R, Kehayias J, Gorbach S.** 1999 DXA analysis of the association between protease inhibitor use and fat distribution in HIV-infected adults. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 27.
34. **Moyle GJ, Baldwin C, Comitis N, Dent N, Gazzard BG.** 1999 Changes in visceral adipose tissue and blood lipids in persons reporting fat redistribution syndrome switched from PI therapy to efavirenz. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 54.
35. **Kosmiski L, Kuritzkes D, Lichtenstein K, Greenburg K, Ehrlich J, Eckel RH.** 1999 An increase in abdominal girth on protease inhibitor therapy is associated with visceral obesity and metabolic disturbances that closely resemble syndrome X. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 56.
36. **Romeu J, Bonjoch A, Arno A, et al.** 1999 Lipodystrophy index by anthropometric parameters (LIAP): an approach to the diagnosis of lipodystrophy by measurable parameters in patients taking protease inhibitors. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, IL:Abstract 652.
37. **Martinez E, Casamitjana R, Conget I, Gatell JM.** 1998 Protease inhibitor-associated hyperinsulinaemia. AIDS.12:2077-9.

38. **Falutz J.** 1999 Lipid abnormalities and body composition alterations in progressive stages of the HIV/HAART associated lipodystrophy. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, IL:Abstract 646.
39. **Martinez E, Gatell JM.** 1999 Metabolic abnormalities and body fat redistribution in HIV-1 infected patients: the lipodystrophy syndrome. Current Opinion Infect Dis.12:13-19.
40. **Henry K, Melroe H, Huebsch J, et al.** 1998 Severe premature coronary artery disease with protease inhibitors. Lancet.351:1328.
41. **Behrens G, Schmidt H, Meyer D, Stoll M, Schmidt RE.** 1998 Vascular complications associated with use of HIV protease inhibitors. Lancet.351:1958.
42. **Gallet B, Pulik M, Genet P, Chedin P, Hiltgen M.** 1998 Vascular complications associated with use of HIV protease inhibitors. Lancet.351:1958-9.
43. **Vittecoq D, Escaut L, Monsuez JJ.** 1998 Vascular complications associated with use of HIV protease inhibitors. Lancet.351:1959.
44. **Stocker DN, Meier PJ, Stoller R, Fattinger KE.** 1998 "Buffalo hump" in HIV-1 infection. Lancet.352:320-1.
45. **Sullivan AK, Nelson MR.** 1997 Marked hyperlipidaemia on ritonavir therapy. AIDS.11:938-9.
46. **Di Perri G, Del Bravo P, Concia E.** 1998 HIV-protease inhibitors. N Engl J Med.339:773-4; discussion 774.
47. **Perry RC, Cushing HE, Deeg MA, Prince MJ.** 1999 Ritonavir, triglycerides, and pancreatitis. Clin Infect Dis.28:161-162.
48. **Behrens GMN, Dejam A, Schmidt HHJ, Brabant G, Stoll M, Schmidt RE.** 1999 Lipid evaluation and glucose metabolism in HIV-1 positive patients treated with protease inhibitors. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, IL:Abstract 647.
49. **Domingo P, Perez A, Torres OH, Montiel JA, Vazquez G.** 1999 Lipodystrophy in HIV-1-infected patients. Lancet.354:868.
50. **Sellmeyer DE, Grunfeld C.** 1996 Endocrine and metabolic disturbances in human immunodeficiency virus infection and the acquired immune deficiency syndrome. Endocr Rev.17:518-32.
51. **Grunfeld C, Kotler DP, Hamadeh R, Tierney A, Wang J, Pierson RN.** 1989 Hypertriglyceridemia in the acquired immunodeficiency syndrome. Am J Med.86:27-31.
52. **Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR.** 1992 Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. J Clin Endocrinol Metab.74:1045-52.
53. **Shor-Posner G, Basit A, Lu Y, et al.** 1993 Hypocholesterolemia is associated with immune dysfunction in early human immunodeficiency virus-1 infection. Am J Med.94:515-9.
54. **Constans J, Pellegrin JL, Peuchant E, et al.** 1994 Plasma lipids in HIV-infected patients: a prospective study in 95 patients. Eur J Clin Invest.24:416-20.
55. **Zangerle R, Sarcletti M, Gallati H, Reibnegger G, Wachter H, Fuchs D.** 1994 Decreased plasma concentrations of HDL cholesterol in HIV-infected individuals are associated with immune activation. J Acquir Immune Defic Syndr.7:1149-56.
56. **Dube MP, Aqeel R, Edmondson-Melancon H, Johnson D, Buchanon TA.** 1999 Effect of initiating indinavir therapy on glucose metabolism in HIV-infected patients: results of minimal model analysis. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 28.
57. **Lumpkin M.** 1997 Protease inhibitors may raise blood glucose levels. Am J Health Syst Pharm.54:1575.
58. **Eastone JA, Decker CF.** 1997 New-onset diabetes mellitus associated with use of protease inhibitor. Ann Intern Med.127:948.
59. **Dube MP, Johnson DL, Currier JS, Leedom JM.** 1997 Protease inhibitor-associated hyperglycaemia. Lancet.350:713-4.
60. **Visnegarwala F, Krause KL, Musher DM.** 1997 Severe diabetes associated with protease inhibitor therapy. Ann Intern Med.127:947.
61. **Paterson DL, Singh N.** 1998 Exacerbated hyperglycemia associated with nelfinavir. Ann Pharmacother.32:609-10.
62. **Vigouroux C, Gharakhanian S, Salhi Y, et al.** 1999 Diabetes, insulin resistance and dyslipidaemia in lipodystrophic HIV-infected patients on highly active antiretroviral therapy (HAART). Diabetes & Metabolism.25:225-232.
63. **Walli R, Herfort O, Michl GM, et al.** 1998 Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1-infected patients. AIDS.12:F167-73.

64. **Goebel FD, Walli R.** 1999 ART-associated insulin resistance: frequency, potential cause and possible therapeutic interventions. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 5.
65. **Hommes MJ, Romijn JA, Endert E, Eeftinck Schattenkerk JK, Sauerwein HP.** 1991 Insulin sensitivity and insulin clearance in human immunodeficiency virus-infected men. Metabolism.40:651-6.
66. **Heyligenberg R, Romijn JA, Hommes MJ, Endert E, Eeftinck Schattenkerk JK, Sauerwein HP.** 1993 Non-insulin-mediated glucose uptake in human immunodeficiency virus-infected men. Clin Sci (Colch).84:209-16.
67. **Babl FE, Regan AM, Pelton SI.** 1999 Abnormal body-fat distribution in HIV-1-infected children on antiretrovirals. Lancet.353:1243-1244.
68. **Jaquet D, Levine M, Ortega E, Polak M, Levy-Marchal C.** 1999 Evidence for lipodystrophic syndrome in HIV-infected children. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 62.
69. **Mallal S, John M, Moore C, James I, Mckinnon E.** 1999 Protease inhibitors and nucleoside analogue reverse transcriptase inhibitors interact to cause subcutaneous fat wasting in patients with HIV infection. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 19.
70. **Flexner C.** 1998 HIV-protease inhibitors. N Engl J Med.338:1281-92.
71. **Carr A, Miller J, Law M, Cooper DA.** 1999 A syndrome of lipodystrophy (LD), lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue reverse transcriptase inhibitor therapy: contribution to PI-related LD syndrome. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 11.
72. **Saint-Marc T, Partisani M, Poizot-Martin I, et al.** 1999 A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. AIDS.13:1659-1667.
73. **Galli M, Ridolfo AL, Gervasoni C, Ravasio L, Adorni F, Moroni M.** 1999 Incidence of fat tissue abnormalities in protease inhibitor-naive patients treated with NRTI combinations. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 20.
74. **Tsiodras S, Mantzoros C, Hammer SM, Samore M.** 1999 Effects of protease inhibitor use on hyperglycemia and hyperlipidemia: a five year analysis. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, IL:Abstract 643.
75. **Thiebaut R, Malvy D, Mercie P, Daucourt V, Marimoutou C, Dabis F.** 1999 Factors influencing the evolution of plasma triglyceride in the era of HAART, Aquitaine cohort, 1996-1998. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 15.
76. **Wit FWNM, Gisolf EH, Oostweegel LMM, et al.** 1999 Stavudine use is not associated with an incremental risk of hyperlipidaemia during treatment with HIV-1 protease inhibitors. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 65.
77. **Saint-Marc T, Poizot-Martin I, Partisani M, Fabre J, Touraine JL.** 1999 A syndrome of lipodystrophy in patients receiving a stable nucleoside-analogue therapy. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, IL:Abstract 653.
78. **Moyle G, Dent N, Baldwin C.** 1999 Body fat redistribution in persons on non-PI-containing regimens. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 53.
79. **Molina JM, Chene G, Ferchal F, et al.** 1999 The ALBI trial: A randomized controlled trial comparing stavudine plus didanosine with zidovudine plus lamivudine and a regimen alternating both combinations in previously untreated patients infected with human immunodeficiency virus. J Infect Dis.180:351-358.
80. **Muurahainen N, Pettit R, Kotler D, et al.** 1999 Abnormalities in HIV-associated lipodystrophy syndrome that vary by weight status. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 63.
81. **Shimokata H, Tobin JD, Muller DC, Elahi D, Coon PJ, Andres R.** 1989 Studies in the distribution of body fat: I. Effects of age, sex, and obesity. J Gerontol.44:M66-73.
82. **Kehayias JJ, Fiatarone MA, Zhuang H, Roubenoff R.** 1997 Total body potassium and body fat: relevance to aging. Am J Clin Nutr.66:904-10.
83. **Borkan GA, Hults DE, Gerzof SG, Robbins AH.** 1985 Comparison of body composition in middle-aged and elderly males using computed tomography. Am J Phys Anthropol.66:289-95.
84. **Zamboni M, Armellini F, Harris T, et al.** 1997 Effects of age on body fat distribution and cardiovascular risk factors in women. Am J Clin Nutr.66:111-5.
85. **Mercie P, Tchamgoue S, Dabis F, Pellegrin JL.** 1999 Lipodystrophy in HIV-1-infected patients. Lancet.354:867-868.
86. **Dulloo AG, Jacquet J, Girardier L.** 1996 Autoregulation of body composition during weight recovery in human: the Minnesota Experiment revisited. Int J Obes Relat Metab Disord.20:393-405.

87. **Mulligan K, Tai VW, Schambelan M.** 1997 Cross-sectional and longitudinal evaluation of body composition in men with HIV infection. J Acquir Immune Defic Syndr Hum Retrovirol.15:43-8.
88. **Williamson K, Reboli AC, Manders SM.** 1999 Protease inhibitor-induced lipodystrophy. J Am Acad Dermatol.40:635-6.
89. **Yanovski JA, Miller KD, Kino T, et al.** 1999 Endocrine and metabolic evaluation of human immunodeficiency virus-infected patients with evidence of protease inhibitor-associated lipodystrophy. J Clin Endocrinol Metab.84:1925-1931.
90. **Bujalska IJ, Kumar S, Stewart PM.** 1997 Does central obesity reflect "Cushing's disease of the omentum"? Lancet.349:1210-3.
91. **Bujalska IJ, Kumar S, Hewison M, Stewart PM.** 1999 Differentiation of adipose stromal cells: the roles of glucocorticoids and 11beta-hydroxysteroid dehydrogenase. Endocrinology.140:3188-96.
92. **Rebuffe-Scrive M, Bronnegard M, Nilsson A, Eldh J, Gustafsson JA, Bjorntorp P.** 1990 Steroid hormone receptors in human adipose tissues. J Clin Endocrinol Metab.71:1215-9.
93. **Carr A, Samaras K, Chisholm DJ, Cooper DA.** 1998 Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. Lancet.351:1881-3.
94. **Li E, Norris AW.** 1996 Structure/function of cytoplasmic vitamin A-binding proteins. Annu Rev Nutr.16:205-34.
95. **Chambon P.** 1996 A decade of molecular biology of retinoic acid receptors. Faseb J.10:940-54.
96. **Tontonoz P, Hu E, Spiegelman BM.** 1995 Regulation of adipocyte gene expression and differentiation by peroxisome proliferator activated receptor gamma. Curr Opin Genet Dev.5:571-6.
97. **Stevens GJ, Chen M, Grecko R, et al.** 1999 Investigations into proposed mechanisms of HIV-associated peripheral lipodystrophy, hyperlipidemia and insulin resistance. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 29.
98. **Lenhard JM, Weiel JE, Paulik MA, et al.** 1999 HIV protease inhibitors block adipogenesis and increase lipolysis in vitro. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, IL:Abstract 666.
99. **Zhang B, MacNaul K, Szalkowski D, Li ZH, Berger J, Moller DE.** 1999 Inhibition of adipocyte differentiation by HIV protease inhibitors. J Clin Endocrinol & Metab.84:4274-4277.
100. **Martinez E, Gatell J.** 1998 Metabolic abnormalities and use of HIV-1 protease inhibitors. Lancet.352:821-2.
101. **Stricker RB, Goldberg B.** 1998 Fat accumulation and HIV-1 protease inhibitors. Lancet.352:1392.
102. **Lenhard J, Furfine E, Paulik M, Croom D, Spaltenstein A, Weiel J.** 1999 Effect of HIV protease inhibitors on in vitro adipogenesis and in vivo fat deposition. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 1.
103. **Wentworth JM, Burris TP, Chatterjee VK.** HIV protease inhibitors block human preadipocyte differentiation, but not via the PPARgamma/RXR heterodimer. *Journal of Endocrinology*. 2000;164(2):R7-R10.
104. **Lenhard JM, Weiel JE, Paulik MA, Furfine ES.** 2000 Stimulation of vitamin A1 acid signaling by the HIV protease inhibitor Indinavir. Biochem Pharmacol 59: 1063-68.
105. **Peters JM, Barnes R, Bennett L, Gitomer WM, Bowcock AM, Garg A.** Localization of the gene for familial partial lipodystrophy (Dunnigan variety) to chromosome 1q21-22. *Nat Genet*. 1998;18(3):292-5.
106. **Cao H, Hegele RA.** Nuclear lamin A/C R482Q mutation in Canadian kindreds with Dunnigan-type familial partial lipodystrophy. *Hum Mol Genet*. 2000;9(1):109-12.
107. **Shackleton S, Lloyd DJ, Jackson SN, et al.** LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. *Nat Genet*. 2000;24(2):153-6.
108. **Speckman R, Garg A, F Du, et al.** Mutational and haplotype analyses in families with familial partial lipodystrophy (Dunnigan variety) reveal recurrent mis-sense mutations in the globular C-terminal domain of Lamin A/C. *Am J Human Genet*. 2000;66:1192-1198.
109. **Lin F, Worman HJ.** Structural organization of the human gene encoding nuclear lamin A and nuclear lamin C. *J Biol Chem*. 1993;268(22):16321-6.
110. **Machiels BM, Zorenc AH, Endert JM, et al.** An alternative splicing product of the lamin A/C gene lacks exon 10. *J Biol Chem*. 1996;271:9249-53.
111. **Kilic F, Johnson DA, Sinensky M.** Subcellular localization and partial purification of prelamin A endoprotease: an enzyme which catalyzes the conversion of farnesylated prelamin A to mature lamin A. *FEBS Letters*. 1999;450(1-2):61-5.
112. **Fisher DZ, Chaudhary N, Blobel G.** cDNA sequencing of nuclear lamins A and C reveals primary and secondary structural homology to intermediate filament proteins. *Proc Natl Acad Sci USA*. 1986;83(17):6450-4.
113. **Glass CA, Glass JR, Taniura H, Hasel KW, Blevitt JM, Gerace L.** The alpha-helical rod domain of human lamins A and C contains a chromatin binding site. *EMBO Journal*. 1993;12(11):4413-24.

114. **Georgatos SD, Stournaras C, Blobel G.** Heterotypic and homotypic associations between the nuclear lamins: site-specificity and control by phosphorylation. *Proc Nat Acad Sci USA*. 1988;85(12):4325-9.
115. **Wilson K.** The nuclear envelope, muscular dystrophy and gene expression. *Trends Cell Biol*. 2000;10:125-129.
116. **Shimomura I, Hammer RE, Richardson JA, et al.** Insulin resistance and diabetes mellitus in transgenic mice expressing nuclear SREBP-1c in adipose tissue: model for congenital generalized lipodystrophy. *Genes & Development*. 1998;12(20):3182-94.
117. **Murata H, Hruz PW, Mueckler M.** The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *Journal of Biological Chemistry*. 2000;275(27):20251-4.
118. **Purnell JQ, Zambon A, Knopp RH, et al.** Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. *AIDS*. 2000;14(1):51-7.
119. **Brinkman K, Smeitink JA, Reiss P.** 1999 Mitochondria toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. Lancet.354:1112-5.
120. **Enzi G.** 1984 Multiple symmetric lipomatosis: an updated clinical report. Medicine (Baltimore).63:56-64.
121. **Klopstock T, Naumann M, Seibel P, Shalke B, Reiners K, Reichmann H.** 1997 Mitochondrial DNA mutations in multiple symmetric lipomatosis. Mol Cell Biochem.174:271-5.
122. **Campos Y, Martin MA, Navarro C, Gordo P, Arenas J.** 1996 Single large-scale mitochondrial DNA deletion in a patient with mitochondrial myopathy associated with multiple symmetric lipomatosis. Neurology.47:1012-4.
123. **Naumann M, Kiefer R, Toyka KV, Sommer C, Seibel P, Reichmann H.** 1997 Mitochondrial dysfunction with myoclonus epilepsy and ragged-red fibers point mutation in nerve, muscle, and adipose tissue of a patient with multiple symmetric lipomatosis. Muscle Nerve.20:833-9.
124. **Gamez J, Playan A, Andreu AL, et al.** 1998 Familial multiple symmetric lipomatosis associated with the A8344G mutation of mitochondrial DNA. Neurology.51:258-60.
125. **Klopstock T, Naumann M, Schalke B, et al.** 1994 Multiple symmetric lipomatosis: abnormalities in complex IV and multiple deletions in mitochondrial DNA. Neurology.44:862-6.
126. **Dalakas MC, Illa I, Pezeshkpour GH, Laukaitis JP, Cohen B, Griffin JL.** 1990 Mitochondrial myopathy caused by long-term zidovudine therapy. N Engl J Med.322:1098-105.
127. **Chen CH, Vazquez-Padua M, Cheng YC.** 1991 Effect of anti-human immunodeficiency virus nucleoside analogs on mitochondrial DNA and its implication for delayed toxicity. Mol Pharmacol.39:625-8.
128. **Brinkman K.** 1999 Mitochondrial toxicity of nucleoside analogue reverse transcriptase inhibitors. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 9.
129. **Mhiri C, Baudrimont M, Bonne G, et al.** 1991 Zidovudine myopathy: a distinctive disorder associated with mitochondrial dysfunction. Ann Neurol.29:606-14.
130. **Gopinath R, Hutcheon M, Cheema-Dhadli S, Halperin M.** 1992 Chronic lactic acidosis in a patient with acquired immunodeficiency syndrome and mitochondrial myopathy: biochemical studies. J Am Soc Nephrol.3:1212-9.
131. **Bissuel F, Bruneel F, Habersetzer F, et al.** 1994 Fulminant hepatitis with severe lactate acidosis in HIV-infected patients on didanosine therapy. J Intern Med.235:367-71.
132. **Sundar K, Suarez M, Banogon PE, Shapiro JM.** 1997 Zidovudine-induced fatal lactic acidosis and hepatic failure in patients with acquired immunodeficiency syndrome: report of two patients and review of the literature. Crit Care Med.25:1425-30.
133. **Roy PM, Gouello JP, Pennison-Besnier I, Chennebault JM.** 1999 Severe lactic acidosis induced by nucleoside analogues in an HIV-infected man. Ann Emergency Med.34:282-284.
134. **Kakuda TN, Brundage RC, Anderson PL, Fletcher CV.** 1999 NRTI-induced mitochondrial toxicity as an aetiology for fat redistribution syndrome. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 41.
135. **Ruzicka T, Vieluf D, Landthaler M, Braun-Falco O.** 1987 Benign symmetric lipomatosis Launois-Bensaude. Report of ten cases and review of the literature. J Am Acad Dermatol.17:663-74.
136. **Greene ML, Glueck CJ, Fujimoto WY, Seegmiller JE.** 1970 Benign symmetric lipomatosis (Launois-Bensaude adenolipomatosis) with gout and hyperlipoproteinemia. Am J Med.48:239-46.
137. **Enzi G, Favaretto L, Martini S, et al.** 1983 Metabolic abnormalities in multiple symmetric lipomatosis: elevated lipoprotein lipase activity in adipose tissue with hyperalphalipoproteinemia. J Lipid Res.24:566-74.
138. **Deiana L, Pes GM, Carru C, Campus GV, Tidore MG, Cherchi GM.** 1993 Extremely high HDL levels in a patient with multiple symmetric lipomatosis. Clin Chim Acta.223:143-7.
139. **Enzi G, Martini S, Baggio G, Baldo G, Digito M, Zanella A.** 1985 Lipoprotein metabolism in patients with elevated lipoprotein-lipase activity in adipose tissue. Int J Obes.9:173-6.

140. **Roubenoff R, Weiss L, McDermott A, et al.** 1999 A pilot study of exercise training to reduce trunk fat in adults with HIV-associated fat redistribution. AIDS.13:1373-1375.
141. **O'Mahony C, Price LM, Nelson M.** 1998 Lipodystrophy despite anabolic steroids. Int J STD AIDS.9:619.
142. **Sullivan AK, Feher MD, Nelson MR, Gazzard BG.** 1998 Marked hypertriglyceridaemia associated with ritonavir therapy. AIDS.12:1393-4.
143. **Roge BT, Katzenstein TL, Gerstoft J.** 1999 Alterations in plasma triglycerides levels during treatment with three different protease inhibitor regimens: a randomized study. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 33.
144. **Skolnik P, Siemon-Hryczyk P, Drake J, Duff F, Buss N.** 1999 Serum lipid levels in HIV-positive adults during saquinavir-containing combination therapy. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 35.
145. **Martinez E, Conget I, Lozano L, Casamitjana R, Gatell JM.** 1999 Reversion of metabolic abnormalities after switching from HIV-1 protease inhibitors to nevirapine. AIDS.13:805-810.
146. **Gatell JM, Conget I, Lozano L, Casamitjana R, Martinez E.** 1999 One year effects of switching from HIV-1 PIs to nevirapine on metabolic abnormalities. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 40.
147. **Ruiz L, Negredo E, Bonjoch A, et al.** 1999 A multicentre, randomized open-label, comparative trial of the clinical, immunological and virological benefit of switching the PI by nevirapine in HAART-experienced patients suffering lipodystrophy. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 31.
148. **Aldeen T, Wells C, Hay P, Davidson F, Lau R.** 1999 Lipodystrophy associated with nevirapine-containing antiretroviral therapies. AIDS.13:865-867.
149. **Carr A, Thorisdottir A, Samaras K, R. KG, Chisholm DJ, Cooper DA.** 1999 Reversibility of protease inhibitor (PI) lipodystrophy syndrome on stopping PIs or switching to nelfinavir. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, IL:Abstract 668.
150. **Stryker R, Skiest D, Tashima K, et al.** 1999 Lack of clinical lipodystrophy in patients receiving efavirenz plus NRTIs in study 006. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 39.
151. **Harris M, Larsen G, Bell M, Montaner JSG.** 1999 Replacing a PI with efavirenz for management of PI toxicity. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 51.
152. **Saint-Marc T, Touraine JL.** 1999 The effects of discontinuing stavudine therapy on clinical and metabolic abnormalities in patients suffering from lipodystrophy. AIDS.13:2188-2189.
153. **Torres R, Unger K.** 1999 The effect of recombinant human growth hormone on protease-inhibitor-associated fat maldistribution syndrome. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, IL:Abstract 675.
154. **Wanke C, Gerrior J, Kantaros J, Coakley E, Albrecht M.** 1999 Recombinant human growth hormone improves the fat redistribution syndrome (lipodystrophy) in patients with HIV. AIDS.13:2099-2103.
155. **Engelson ES, Glesby M, Sheikhan J, et al.** 1999 Effect of recombinant human growth hormone in the treatment of visceral fat accumulation in HIV infection: interim analysis. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 6.
156. **Gold J, Batterham M.** 1999 Nandrolone decanoate; use in HIV-associated lipodystrophy syndrome: a pilot study. Int J STD AIDS.10:558.
157. **Rohrich RJ, Kenkel JM.** 1999 Suction-assisted lipectomy for lipodystrophy syndromes attributed to HIV-Protease inhibitor use - Discussion. Plastic & Reconstructive Surgery.104:1821-1822.
158. **Wolfort FG, Cetrulo CL, Nevarre DR.** 1999 Suction-assisted lipectomy for lipodystrophy syndromes attributed to HIV-protease inhibitor use. Plastic & Reconstructive Surgery.104:1814-1820.
159. **Schindler JT, Spooner KM, Decker CF.** 1998 "Buffalo humps" associated with protease inhibitors. Ann Intern Med.129:164.
160. **Dube MP, Sprecher D, Henry WK, et al.** 2000 Preliminary guidelines for the Evaluation and Management of Dyslipidemia in HIV-Infected Adults Receiving Antiretroviral Therapy. Recommendations of the Adult ACTG Cardiovascular Disease Focus Group. Clin Infect Dis. (in press).
161. **Henry K, Melroe H, Huebesch J, Hermundson J, Simpson J.** 1998 Atrovastatin and gemfibrozil for protease-inhibitor-related lipid abnormalities. Lancet.352:1031-2.
162. **Hewitt RG, Shelton MJ, Esch LD.** 1999 Gemfibrozil effectively lowers protease inhibitor-associated hypertriglyceridemia in HIV-1-positive patients. AIDS.13:868-869.

163. **Lee D, Mathews WC, Hsia S, Basinger S, Barber E.** 1999 Effect of fenofibrate on hyperlipidemia in HIV-infected patients. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 44.
164. **Walli RK, Michl GM, Bogner JR, Goebel FD.** 1999 Effects of the PPAR-gamma activator troglitazone on protease inhibitor associated peripheral insulin resistance. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, IL:Abstract 673.
165. **Duran A, Flaster N, Keszberg E, Sequeira G, Losso M.** 1999 Prevalence of lipodystrophy and metabolic abnormalities in relation with antiretroviral regimens for the treatment of HIV infection. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 49.
166. **Garcia F, Ortega M, Cruceta A, et al.** 1999 Incidence of metabolic changes and lipodystrophy in two trials comparing double versus triple antiretroviral therapy in early HIV disease. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 58.
167. **Viard JP, Rakotoambinina B.** 1999 Lipodystrophic syndromes in a cohort of HIV-1-infected patients receiving HAART with a protease inhibitor. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 26.
168. **APROCO study group on metabolic complications 1** 1999 A cross-sectional study of metabolic disorders and lipodystrophy in HIV-infected patients treated with antiretroviral combination therapy including protease inhibitors (PI) within a phase IV cohort study of PI: APROCO-ANRS EP11. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 23.
169. **Renard E, Fabre J, Paris F, Reynes J, Bringer J.** 1999 Syndrome of body fat redistribution in HIV-1-infected patients: relationships to cortisol and catecholamines. Clin Endocrin.51:223-230.
170. **Ward DJ, Delaney KM, Moorman AC, et al.** 1999 Description of lipodystrophy in the HIV outpatient study (HOPS). First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 14.
171. **Mercie P, Malvy D, Daucourt V, et al.** 1999 Case report of lipodystrophy observations in patients naive of protease inhibitor treatment, Aquitaine cohort, 1999. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 18.
172. **Lichtenstein K, Ward D, Delaney K, et al.** 1999 Clinical factors related to the severity of fat redistribution in the HIV outpatient study (HOPS). First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 71.
173. **Hadigan C, Miller K, Corcoran C, Anderson E, Basgoz N, Grinspoon S.** 1999 Fasting hyperinsulinemia and changes in regional body composition in human immunodeficiency virus-infected women. J Clin Endocrinol & Metab.84:1932-1937.
174. **Saint-Marc T, Touraine JL.** 1999 Reversibility of peripheral fat wasting (lipodystrophy) on stopping stavudine therapy. First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Diego, USA:Abstract 24.