

ORIGINAL RESEARCH

HIV lipodystrophy: prevalence, severity and correlates of risk in Australia

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Objective

To establish the prevalence, severity and factors associated with the HIV lipodystrophy syndrome.

Methods

Cross-sectional study of lipodystrophy conducted in high HIV caseload primary care sites and HIV outpatient clinics. A subset of patients was examined using dual energy X-ray absorptiometry (DEXA) and single cut abdominal computerized tomography (CT) at the L4 vertebral level to quantify regional and total body fat. Factors associated with lipodystrophy, lipoatrophy and lipohypertrophy were assessed using multiple logistic regression based on assignment of cases and non-cases.

Results

One thousand, three hundred and forty-eight patients (95% male) were surveyed, 20% had AIDS, the mean CD4 lymphocyte count was 486 cells/ μ L, and 55% had <500 HIV-1 RNA copies/mL. Most participants (87%) had previously received or were currently receiving combination antiretroviral therapy, 73% with at least one protease inhibitor (PI) and 14% a non-PI-containing regimen. Lipodystrophy prevalence was 53% and of these, 55% reported both peripheral lipoatrophy and central lipohypertrophy, 31% experienced peripheral lipoatrophy only and 14% had central lipohypertrophy only. The prevalence of any body habitus change was 62% in PI-experienced patients, 33% in PI-naïve patients and 21% in antiretroviral-naïve patients. Lipodystrophy severity was less in antiretroviral-naïve patients and most severe in PI-experienced patients. Increasing severity of lipodystrophy was both positively and significantly correlated with elevated liver enzymes, decreased testosterone levels, decreased skin-fold thickness, lower levels of total and peripheral fat (DEXA) and higher levels of visceral fat (CT). Lipodystrophy was also significantly associated with increasing age, symptomatic HIV disease, effective viral suppression, and increasing duration of therapy with both nucleoside reverse transcriptase inhibitors and PIs.

Conclusions

The prevalence and severity of lipodystrophy reflects both length and type of treatment with antiretroviral therapy and is associated with decreased testosterone, increases in liver enzymes and greater suppression of HIV RNA. The reports of lipodystrophy in a small percentage of antiretroviral-naïve patients suggests that factors other than antiretroviral therapy may be involved in the aetiology of this syndrome or that some conditions, such as wasting or age-associated obesity, may mimic lipoatrophy and lipohypertrophy, respectively.

Keywords: antiretrovirals, HIV, lipodystrophy, prevalence

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Introduction

Combination antiretroviral therapy for HIV infection is frequently associated with lipodystrophy (peripheral lipo-

trophy, central lipohypertrophy, lipomata) and various metabolic abnormalities including hyperlipidemia, insulin resistance and lactic acidemia [1–8]. Lipodystrophy is generally observed months to years after initiation of combination antiretroviral therapy [8]. These changes are often seen in the presence of effective suppression of viral replication and otherwise good health [4]. Some of the

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metabolic abnormalities, such as hypertriglyceridemia, may predate antiretroviral therapy and be exacerbated during therapy [9–11]. Lipodystrophy has been reported more commonly in patients receiving protease inhibitor (PI)-containing combinations [1, 4, 8, 12].

Published studies, to date, have found prevalence rates varying from 18 to 83% and have identified differing potential risk factors [1, 5, 7–9, 13, 14, 14, 15]. These studies have linked lipodystrophy to one or more PI agent, nucleoside analogue reverse transcriptase inhibitors (NRTIs), or effective suppression of HIV replication. The variable prevalence and factors associated with lipodystrophy reported in these studies may have occurred because the studies had relatively small sample sizes and selected cohorts, did not evaluate all potential aetiological factors, did not include all possible treatment options, did not use common diagnostic methods or objective data for quantifying lipodystrophy and were performed at single sites. We conducted a multicentre survey of HIV-infected Australian adults to determine the prevalence and severity of lipodystrophy and potential risk factors associated with lipodystrophy. This survey was conducted using common methodologies and encompassed a broad range of sites, patient groups and assessed a comprehensive range of potential aetiological factors in order to address these potential weaknesses.

Methods

Patient population

The study recruited patients from 15 centres comprising community ($n = 7$), sexual health ($n = 2$) and hospital ($n = 6$) sites in Australia. These sites provide health care for approximately 2200 HIV-infected patients. Consecutive patients greater than 17 years of age with confirmed HIV infection presenting to the study sites over a 6-month period for routine outpatient care were invited to participate. Patients were eligible to participate irrespective of antiretroviral exposure.

Study design and data collection

The study was conducted from November 1998 to July 1999. The following clinical data were obtained cross-sectionally: age, gender, HIV disease stage, personal and family history of diabetes and cardiac disease, smoking, anabolic steroid use, type and duration of all antiretroviral agents and current exercise levels. Fasting lipid (triglycerides, total and HDL cholesterol) and glycaemic parameters (glucose, insulin, C-peptide), liver enzymes, total testosterone, CD4 lymphocyte counts and plasma HIV RNA were

performed at the time of assessment. Local laboratories were used for all assessments.

Lipodystrophy assessments

Height, weight, waist and hip circumference were obtained by standard methods [16]. A targeted physical examination was conducted by the physician to evaluate any changes of lipodystrophy. This included a specific assessment of lipoatrophy in the periphery (face, arms, legs, buttocks and venous prominence), and lipohypertrophy centrally (abdomen, breasts, dorsocervical region as well as the presence of lipomata at any site). Using a standardized questionnaire, physicians subjectively graded any changes present as either mild, moderate or severe, and numerical scores were attached to lipodystrophy reports (0 = none, 1 = mild, 2 = moderate, 3 = severe) for a maximum possible score of 15 peripherally, 12 centrally and 27 overall [1]. At sites where staff were experienced in anthropometry ($n = 8$), triceps, calf, supra-iliac crest and naso-labial fold skin-fold thickness was recorded. The latter assessment, which measures the thickness of the naso-labial fold at its mid-point, is not a validated measure. Every fifth consenting subject also underwent body composition studies using dual X-ray absorptiometry (DEXA; Lunar DPXL, Madison, WI) and single cut abdominal computerized tomography (CT) performed at the mid-L4 level vertebral with a manual calculation to estimate the areas of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and total adipose tissue (TAT). Standard protocols were used for all body imaging studies [1, 2, 4]. All CT and DEXA scans were read at local centres using standardized procedures. If a patient declined body composition studies, the next consenting patient was approached.

Definitions

Lipodystrophy was defined by the physician-assessed presence of lipoatrophy or lipohypertrophy of any severity in one or more body region (face, arms, legs and buttocks, abdomen, breasts, dorsocervical region) or by the presence of lipomata [1, 4]. Clinical HIV disease was categorized using the Centers for Disease Control and Prevention classification system. Assessment of exercise levels was defined as sedentary (light physical activity for <2 h week), low (light physical activity for 2–4 h per week), moderate (light physical activity >4 h per week or vigorous activity for 2–4 h per week), or high (highly vigorous physical activity >4 h per week or regular exercise or competitive sports several times per week) [16].

Approvals

Human Research Ethics Committee approval for the study was obtained for each site. Written, informed consent was obtained from each participant.

Statistics

Comparisons between selected groups used the Mann-Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. Factors associated with lipodystrophy, lipoatrophy and lipohypertrophy were assessed using multiple logistic regression based on assignment of cases and non-cases. Factors assessed included age, HIV disease stage, exercise levels, CD4 lymphocyte count, plasma HIV RNA, and antiretroviral type and duration, steroid use, metabolic and glycaemic parameters.

Relative associations between different antiretrovirals and lipodystrophy were assessed in multivariate analyses. These were analyzed by phenotype (any lipodystrophy, lipoatrophy, lipohypertrophy) and by duration of therapy in months, stratified less than or greater than the median. For analysis, patients were categorized by exposure and duration of exposure to various antiretroviral classes, regardless of whether patients were receiving therapy at the time of survey. The categories used were: (a) antiretroviral naive, (b) past or current treatment with an NRTI with or without an NNRTI, and (c) past or current treatment with a PI in addition to an NRTI with or without an NNRTI.

Results

Study participants

Demographic and treatment data for the 1348 participants are shown in Table 1. The cohort is consistent with the HIV

epidemic in Australia where 92.6% of all HIV infections have occurred in men [17]. The number of survey participants represent 67% of the estimated HIV-infected patients from the participating sites and 11.5% of all known existing HIV-infected adults in Australia at that time [17].

The lipodystrophy prevalence survey (LPS) data were compared to data from the Australian HIV Observational Database (AHOD) to determine consistency with the broader HIV-affected community [18]. The LPS and AHOD were found to be similar in terms of mean age (39.8 and 40 years, respectively), proportion of males (95% and 96%), mean CD4 lymphocyte count (487 and 521 cells/ μ L), undetectable viral load (55% and 46%), prior AIDS (20% and 16%) and PI use (73% and 67%) [18]. Of those patients who had received treatment with a PI in this survey ($n = 986$), 239 (19%) were not currently taking PIs at the time of the survey, with a median time since discontinuation of 6 months.

Prevalence of lipodystrophy

The overall prevalence of physician-assessed lipodystrophy was 53% (Table 2). A mixed phenotype was most prevalent with 27% of the overall survey having both peripheral lipoatrophy and central lipohypertrophy. Patients with either lipoatrophy only or lipohypertrophy only accounted for 20% and 6%, respectively. The most frequently reported affected site was the face (45%), followed by legs (42%), abdomen (39%), arms (39%), buttocks (36%), dorsocervical region (4%) and lipomata (4%). Lipodystrophy was reported in 21% ($n = 35$) of antiretroviral naive patients in this survey.

Peripheral lipoatrophy

The severity of peripheral lipoatrophy on physical examination was associated with significantly reduced skinfold

Table 1 Characteristics of survey participants

	Total ($n = 1348$)	Male ($n = 1280$)	Female ($n = 68$)
Age (mean, SD)	39.8 (11.5)	40 (12)	35 (7)
CD4 cells/ μ L (mean SD)	487 (434)	486 (441)	491 (272)
HIV RNA			
mean log copies/mL (SD)	4.7 (1.04)	4.7 (1.04)	4.8 (1.02)
≤ 500 copies/mL ($n, \%$)	744 (55)	710 (55)	34 (50)
HIV disease category			
A ($n, \%$)	701 (52)	670 (52)	30 (44)
B ($n, \%$)	376 (28)	345 (27)	30 (44)
C ($n, \%$)	271 (20)	265 (21)	6 (12)
Antiretroviral exposure ($n, \%$)			
naive ($n, \%$)	168 (12)		
no protease inhibitor ($n, \%$)	194 (14)		
protease inhibitor ($n, \%$)	986 (75)		

Table 2 Lipodystrophy prevalence and severity by phenotype and antiretroviral exposure

	None	Lipoatrophy (maximum score = 15)	Lipohypertrophy (maximum score = 12)	Mixed (maximum score = 27)	Any LD (maximum score = 27)
ART Naive					
% (n)	79 (132)	9 (15)	3 (6)	9 (15)	21 (36)
mean severity (SE)	3.6 (2.8)	1.6 (1.0)	7.7 (4.2)	5.0 (4.0)	
NRTI/NNRTI (ever)					
% (n)	68 (132)	16 (31)	6 (11)	10 (20)	32 (62)
mean severity (SE)	3.4 (2.5)	1.2 (0.6)	9.9 (4.8)	5.2 (4.7)	
PI (ever)					
% (n)	38 (375)	23 (225)	6 (63)	33 (326)	62 (611)
mean severity (SE)	4.3 (3.3)	1.7 (1.0)	8.6 (4.6)	6.3 (4.6)	
All					
% (n)	47 (639)	20 (271)	6 (80)	27 (361)	53 (709)
mean severity (SE)	4.1 (3.2)	1.7 (0.9)	8.6 (4.4)	6.1 (4.6)	

Mean severity scores are derived from affected patients only; SE, standard error.

Table 3 Associations with maximal severity of lipodystrophy

	Lipodystrophy					Lipoatrophy					Lipohypertrophy				
	none	mild	mod	sev	P-trend	none	mild	mod	sev	P-trend	none	mild	mod	sev	P-trend
Total															
total fat (%)	18.7	17.5	18.8	14.1	<0.01	19.1	17.4	17.6	14	<0.01	17	18.4	19.2	17.1	0.01
Central															
central fat (%)	21.9	22.6	26	22.5	0.27	22.7	22.6	24	22	0.60	20.1	25.9	26.9	26.7	<0.01
VAT (cm ²)	71	93	121	127	<0.01	78	102	105	126	0.03	70	103	136	154	<0.01
TAT (cm ²)	187	224	227	200	0.76	213	250	215	191	0.29	176	224	231	254	<0.01
waist (cm)	85	85.5	87	87	<0.01	86	85.5	87	84.2	0.89	84	87	90	92	<0.01
Peripheral															
arm (%)	15.2	13.5	14.2	10.3	<0.01	15.7	13.4	13.5	10.0	<0.01	13.7	14.5	14.2	14.7	0.20
leg (%)	18.3	12.4	12.6	8.5	<0.01	18.0	12.3	12.0	8.3	<0.01	14.2	12.4	12.0	10.4	0.05
SAT (cm ²)	104	94	89	63	<0.01	109	95	84	62	<0.01	87	102	86	64	0.46
naso-labial fold (mm)	10	9	9	8	<0.01	10	9	9	7.4	<0.01	9	10	10	8	0.91
tricep (mm)	9	7	7	6	<0.01	9	7	7	6	<0.01	8	8	7	7	0.02
supra-iliac crest (mm)	12	10	11	7.7	<0.01	12	10	10	7.6	<0.01	10	11.3	13	9.5	0.10
calf (mm)	8.6	7.5	5	4	<0.01	10.4	7	4.8	4	<0.01	8	6	5	4.8	<0.01
hip (cm)	94	92	92	91	<0.01	94	92	91.1	90	<0.01	93	92	93	94	0.31
Lipid parameters															
triglyceride (mmol/L)	1.5	1.8	2.3	2.4	<0.01	1.7	1.8	2.4	2.4	<0.01	1.7	2.2	2.5	2.4	<0.01
total cholesterol (mmol/L)	5	5.2	5.4	5.5	0.01	5.1	5.3	5.4	5.4	0.03	5.0	5.4	5.7	5.5	0.01
HDL cholesterol (mmol/L)	1.0	1.1	1.0	0.9	<0.01	1.0	1.0	1.0	0.9	<0.01	1.0	1.0	0.9	1.0	0.01
Glycaemic parameters															
glucose (mmol/L)	4.9	4.8	5.0	5.0	0.25	4.9	4.8	5.0	5.0	0.99	4.9	5.0	5.0	5.2	0.02
insulin (mIU/L)	6.0	9.0	8.0	10.9	<0.01	7.0	9.0	8.4	9.0	0.01	7.0	9.0	9.7	14.2	<0.01
C-peptide (µg/L)	1.1	1.2	1.5	2.4	<0.01	1.2	1.2	2	2.3	<0.01	1.2	1.3	2.36	4.1	<0.01
Other parameters															
ALT (IU/L)	28	28	28	33	<0.01	28	29	29	32	<0.01	28	29	31	41	<0.001
AST (IU/L)	25	29	28	32	<0.01	26	27	29	31	<0.01	26	29	28	34	<0.001
testosterone (nmol/L)	22.5	22.0	19.2	18.3	<0.01	22.1	21.5	19.4	18.3	<0.01	21.9	21.0	18.3	17.2	<0.01

Data are means. VAT, visceral adipose tissue; TAT, total adipose tissue; SAT, subcutaneous adipose tissue; HDL, high-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

thickness, decreased hip circumference, and lower levels of abdominal subcutaneous abdominal adipose tissue, total fat and limb fat (Table 3). Patients with and without peripheral lipoatrophy had similar levels of visceral adipose tissue.

Central lipohypertrophy

Lipohypertrophy on physical exam was associated with significantly greater waist circumference and visceral adipose tissue (Table 4), but no differences were seen in subcutaneous

adipose tissue. DEXA demonstrated an increase in the total percentages of body fat and central fat, while no significant differences were seen in limb fat between those with and those without central lipohypertrophy.

Lipodystrophy severity

While lipodystrophy was frequently observed, the majority of cases were mild to moderate (Tables 4 and 5). Severe lipodystrophy, lipoatrophy or lipohypertrophy in at least one site was observed in 25%, 16% and 9% of patients, respectively. When numerical scores were attached to lipodystrophy reports (0 = none, 1 = mild, 2 = moderate, 3 = severe), the mean total severity rating for patients with any lipodystrophy was 6.1 (Table 2). Differences were seen between treatment groups for overall severity scores. Naive patients had the lowest overall lipodystrophy severity ratings and PI-treated patients had the highest overall rating as well as the highest ratings for lipoatrophy only and lipohypertrophy only. Of the naive patients with lipohypertrophy (21/168), 20 had abdominal lipohypertrophy, and of these only four were of severe intensity. Similarly, in naive patients with lipoatrophy, either alone or as part of a mixed phenotype (30/168), 15 patients had two or less affected sites with the majority of the affected sites being of mild intensity.

Lipodystrophy-associated factors

Multivariate analyses demonstrated significant associations between physician-assessed lipodystrophy, lipoatro-

phy, lipohypertrophy and a range of demographic, disease and treatment factors (Table 3). Factors significantly associated with the presence of any lipodystrophy, regardless of phenotype, were older age, CDC HIV disease category B or C, undetectable levels of HIV RNA, extended treatment exposure to NRTIs and any exposure to PIs. Associated factors were similar for lipoatrophy and lipohypertrophy; females, however, were 50% less likely to have lipoatrophy and participants who had higher exercise levels had a reduced likelihood of central lipohypertrophy.

The relative associations between different antiretroviral classes and lipodystrophy were assessed in multivariate analyses. Increased exposure to both NRTIs and PIs was significantly associated with significant increases in risk for lipodystrophy, while no effect was seen with NNRTI use, although the median length of exposure to this drug class was relatively short (Table 6). In patients with lipoatrophy, significant trends were seen with increased duration of therapy with saquinavir, indinavir (IDV), nelfinavir, zalcitabine and stavudine (d4T). Lipohypertrophy was significantly associated with increased duration of therapy with IDV, d4T and lamivudine.

Discussion

This survey of a broad cross-section of people with HIV in Australia has provided a comprehensive assessment of lipodystrophy and its associated factors. The survey is the largest published to date and, based on comparisons with

Table 4 Lipodystrophy by phenotype and severity (%)

	Lipohypertrophy Severity	None	Mild	Moderate	Severe	Total
Lipoatrophy	None	40	3.1	1.1	0.5	44.7
	Mild	10.7	8.4	2.4	0.3	21.8
	Moderate	7.9	6.3	5.1	1.5	20.8
	Severe	2.5	2.8	2.8	4.5	12.9
	Total	61.1	20.6	13.1	5.3	100

Figures are rounded to nearest 0.1 decimal point. Patients classified by the maximal severity rating attained for peripheral lipoatrophy and/or central lipohypertrophy using the severity grading system described in the Methods section.

Table 5 Per cent of patients with lipodystrophy – regions affected by maximum recorded severity

	Abdomen	Breast	Dorsocervical	Lipoma	Face	Arms	Legs	Buttocks
None	61	93	96	96	55	61	58	64
Mild	21	4	2	3	23	22	21	16
Moderate	13	2	1	1	14	13	15	14
Severe	5	1	1	<1	8	4	6	6

All percentages rounded to nearest whole number.

Table 6 Factors associated with lipodystrophy

	<i>n</i>	Any lipodystrophy			Abdominal adiposity			Lipoatrophy		
		OR	(95% CI)	<i>p</i>	OR	(95% CI)	<i>p</i>	OR	(95% CI)	<i>p</i>
Age (years)										
<35	331	1.0			1.0			1.0		
35–39	297	1.55	(1.08, 2.22)	0.019	1.72	(1.14, 2.59)	0.010	1.34	(0.94, 1.92)	0.110
40–49	387	1.89	(1.33, 2.67)	<0.001	2.50	(1.71, 3.66)	<0.001	1.93	(1.37, 2.72)	<0.001
≥50	188	3.20	(2.04, 5.00)	<0.001	5.08	(3.26, 7.92)	<0.001	2.24	(1.47, 3.42)	<0.001
Gender										
male	1192	1.0			1.0			1.0		
female	67	0.53	(0.29, 0.98)	0.043	1.46	(0.79, 2.72)	0.232	0.44	(0.23, 0.82)	0.009
HIV disease category										
A	662	1.0			1.0			1.0		
B	356	2.22	(1.61, 3.07)	<0.001	1.80	(1.32, 2.47)	<0.001	1.99	(1.46, 2.71)	<0.001
C	249	1.82	(1.26, 2.62)	<0.001	1.84	(1.28, 2.64)	<0.001	1.76	(1.23, 2.51)	0.002
CD4 (cells/μL)										
<200	194	1.0			1.0			1.0		
200–499	508	0.90	(0.59, 1.38)	0.639	0.87	(0.57, 1.32)	0.505	0.99	(0.66, 1.49)	0.959
≥500	546	0.97	(0.62, 1.52)	0.896	0.76	(0.48, 1.19)	0.228	0.96	(0.62, 1.48)	0.845
HIV RNA (log/mL)										
>10 000	280	1.0			1.00			1.0		
501–10 000	225	1.56	(1.02, 2.39)	0.039	2.12	(1.34, 3.37)	0.001	1.52	(1.00, 2.32)	0.049
≤500	619	2.28	(1.62, 3.23)	<0.001	3.07	(2.10, 4.48)	<0.001	2.04	(1.45, 2.87)	<0.001
Exercise level										
sedentary	158	1.0			1.0			1.0		
low	381	1.12	(0.71, 1.76)	0.626	0.89	(0.57, 1.40)	0.626	1.25	(0.80, 1.93)	0.325
moderate	472	1.13	(0.73, 1.75)	0.586	0.79	(0.51, 1.23)	0.300	1.42	(0.93, 2.19)	0.106
high	201	0.94	(0.57, 1.56)	0.812	0.60	(0.35, 1.01)	0.054	1.11	(0.68, 1.82)	0.678
Steroid use										
no	1164	1.0			1.0			1.0		
yes	52	1.22	(0.60, 2.49)	0.587	0.84	(0.43, 1.65)	0.620	1.46	(0.73, 2.90)	0.286
NRTI use (months)										
0	157	1.0			1.0			1.0		
≤57	559	1.27	(0.76, 2.13)	0.358	1.18	(0.63, 2.20)	0.607	1.47	(0.86, 2.52)	0.155
>57	543	3.11	(1.84, 5.28)	<0.001	1.90	(1.41, 2.56)	<0.001	3.41	(1.98, 5.88)	<0.001
<i>didanosine</i>										
0	672	1.0			1.0			1.0		
≤12	256	1.40	(0.98, 2.01)	0.64	1.02	(0.72, 1.45)	0.906	1.36	(0.97, 1.92)	0.078
>12	207	1.26	(0.86, 1.84)	0.240	1.43	(0.98, 2.10)	0.065	1.36	(0.94, 1.95)	0.099
<i>lamivudine</i>										
0	188	1.0			1.0			1.0		
≤19	447	0.93	(0.57, 1.50)	0.753	0.95	(0.58, 1.55)	0.830	0.68	(0.44, 1.04)	0.076
>19	500	1.15	(0.70, 1.87)	0.588	1.60	(0.97, 2.65)	0.066	1.03	(0.65, 1.61)	0.907
<i>stavudine</i>										
0	556	1.0			1.0			1.0		
≤17	365	1.91	(1.31, 2.79)	0.001	1.50	(0.97, 2.31)	0.069	1.48	(1.02, 2.14)	0.040
>17	414	4.28	(3.00, 6.12)	<0.001	1.72	(1.15, 2.58)	0.008	2.50	(1.74, 3.59)	<0.001
<i>zalcitabine</i>										
0	933	1.0			1.0			1.0		
≤9	153	1.10	(0.73, 1.67)	0.652	1.27	(0.85, 1.90)	0.243	1.29	(0.87, 1.92)	0.208
>9	149	0.84	(0.55, 1.29)	0.425	1.12	(0.74, 1.69)	0.604	1.63	(1.07, 2.47)	0.021
<i>zidovudine</i>										
0	334	1.0			1.0			1.0		
≤20	406	1.16	(0.81, 1.66)	0.429	0.75	(0.51, 1.12)	0.158	0.68	(0.48, 0.97)	0.035
>20	391	1.81	(1.26, 2.59)	<0.001	1.17	(0.78, 1.12)	0.445	1.11	(0.75, 1.63)	0.598
NNRTI use (months)										
0	798	1.0			1.0			1.0		
≤9	228	1.29	(0.89, 1.87)	0.187	1.40	(0.98, 1.99)	0.066	1.43	(1.00, 2.05)	0.052
>10	232	0.87	(0.60, 1.26)	0.472	0.70	(0.48, 1.02)	0.064	1.04	(0.73, 1.49)	0.822
<i>delavirdine</i>										
0	1072	1.0			1.0			1.0		
≤11	23	0.99	(0.37, 2.62)	0.979	1.33	(0.50, 3.56)	0.571	2.41	(0.86, 6.75)	0.094
>11	20	3.16	(1.10, 9.10)	0.032	1.63	(0.59, 4.52)	0.344	1.09	(0.37, 3.19)	0.880

Table 6 (Continued)

	n	Any lipodystrophy			Abdominal adiposity			Lipoatrophy		
		OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p
<i>efavirenz</i>										
0	1071	1.0			1.0			1.0		
≤3	36	0.91	(0.42, 1.93)	0.797	0.80	(0.35, 1.79)	0.584	1.75	(0.73, 4.20)	0.209
>3	28	1.54	(0.64, 3.76)	0.334	1.07	(0.45, 2.54)	0.344	0.97	(0.34, 2.74)	0.955
<i>nevirapine</i>										
0	769	1.0			1.0			1.0		
≤9	187	1.25	(0.85, 1.84)	0.266	1.23	(0.83, 1.80)	0.298	0.94	(0.63, 1.39)	0.748
>9	177	1.07	(0.72, 1.58)	0.752	0.68	(0.45, 1.04)	0.074	1.05	(0.73, 1.53)	0.777
PI use (months)										
0	407	1.0			1.0			1.0		
≤22	451	1.82	(1.29, 2.58)	0.001	1.78	(1.24, 2.57)	0.002	1.71	(1.21, 2.43)	0.002
>22	401	3.57	(2.41, 5.28)	<0.001	3.07	(2.09, 4.50)	<0.001	3.08	(2.10, 4.50)	<0.001
<i>indinavir</i>										
0	641	1.0			1.0			1.0		
≤15	248	1.11	(0.78, 1.58)	0.550	1.19	(0.81, 1.73)	0.373	1.23	(0.87, 1.74)	0.240
>15	246	2.38	(1.67, 3.39)	<0.001	1.55	(1.07, 2.23)	0.020	3.51	(2.41, 5.09)	<0.001
<i>nelfinavir</i>										
0	854	1.0			1.0			1.0		
≤7	136	0.96	(0.62, 1.49)	0.850	1.36	(0.87, 2.11)	0.171	1.01	(0.67, 1.52)	0.965
>7	145	1.49	(0.98, 2.26)	0.059	1.00	(0.65, 1.55)	0.994	1.73	(1.14, 2.64)	0.010
<i>ritonavir</i>										
0	870	1.0			1.0			1.0		
≤12	129	1.84	(1.19, 2.85)	0.006	1.40	(0.89, 2.21)	0.140	1.92	(1.20, 3.08)	0.007
>12	136	1.08	(0.70, 1.69)	0.721	1.46	(0.90, 2.37)	0.123	1.03	(0.63, 1.69)	0.892
<i>saquinavir</i>										
0	636	1.0			1.0			1.0		
≤15	254	0.85	(0.57, 1.25)	0.405	1.18	(0.78, 1.78)	0.424	1.66	(1.16, 2.37)	0.005
>15	245	1.20	(0.81, 1.79)	0.359	1.27	(0.75, 2.14)	0.374	2.84	(1.97, 4.11)	<0.001

All variables were included in the analysis, statistically significant variables (in bold) were included in the final model.

the Australian HIV Observational Database, the sample is representative of the HIV epidemic in Australia in terms of gender, age, treatment exposure and disease stage [18]. The data provide a clearer picture of this phenomenon, including a comprehensive analysis of associated factors by phenotype (Table 6).

While the prevalence of lipodystrophy was higher in those patients taking PIs, it was also seen in patients who had been treated for HIV, but who were PI-naïve and also, albeit less frequently, in treatment-naïve patients. While these findings in treatment-naïve patients may be somewhat reflective of the subjective nature of the definition of lipodystrophy used, their extent suggests that causative mechanisms apart from antiretroviral therapy, may need to be considered, or that some conditions such as wasting or age-associated obesity may mimic some aspects of lipoatrophy and lipohypertrophy, respectively.

The correlates established in this survey between clinician assessment and body composition assessment using DEXA, single cut abdominal CT and skin fold measurements provide added support for their use in determining lipodystrophy presence and severity. Similarly, physician assessment of the presence and severity of

lipodystrophy using a subjective tool correlated with differences in body fat quantity and patterns of fat deposition.

Limitations to study

There are inherent limitations in this study. While the proportion of caucasians and women included is representative of the HIV epidemic in Australia, interpretation of the results must be kept within the context of white males. The large number of geographically diverse recruiting sites and personnel involved in the patient assessment increases the prospect of operator differences in the assessment of the severity of body fat changes, questionnaire administration, anthropometry and laboratory methods. The lipodystrophy questionnaire used in this study has been tested in previous surveys, but severity results must be interpreted with a degree of caution in an observational study like this due to the subjective nature of the rating process. Some other researchers have utilized a more objective severity grading system than that used in this study. While there would appear to be merit in this approach, the superiority of either method is yet to be

established [5]. Further, the questionnaire utilized was designed to assess one directional fat changes, specifically, peripheral lipodystrophy and central lipohypertrophy. This design was based on observations made up to that time about the fat changes seen with the syndrome. While provision was made within the questionnaire for the clinician to make comment about changes seen, we were not able to examine in detail any instances where there may have been fat gain peripherally or fat loss centrally. While anecdotally these events are rarely seen in this syndrome, it is clear that in future studies, bi-directional measures should be included.

Local laboratories were used for all metabolic parameters. Although all conformed to national laboratory accreditation standards, some intralaboratory differences may result. Calculations for abdominal fat assessed by CT were performed locally using standardized methods by staff experienced in this methodology. While all of these facilities were experienced in the techniques required for the study and all used a standardized protocol, no central reading facilities were utilized and it is likely that some interoperator differences may have occurred.

Comparisons with other studies

This study has demonstrated similar lipodystrophy prevalence rates for the overall cohort and for the protease inhibitor-experienced group to those seen in other published cohorts. The identification of lipodystrophy in treatment-naive patients within a survey of this type is new, however. The identification of lipodystrophy in this group is somewhat surprising given the wealth of data linking lipodystrophy with antiretroviral therapy. It is unclear whether this group represent another aspect of the syndrome or whether it, in fact, either reflects the sensitivity and specificity of the diagnostic methods used, or is a manifestation of the age or stage of HIV disease of this group. As most previous lipodystrophy prevalence surveys have specifically studied patients already taking antiretrovirals, this finding may simply stem from a difference in study designs.

This study also provides support for a clinical diagnosis of both the presence and severity of lipodystrophy using DEXA, CT and anthropometry to quantify lipodystrophic changes, especially when examining specific phenotypes, although the results in antiretroviral-naive subjects may provide an estimate of the magnitude of false positive rates for these tests if this syndrome is truly related to drug toxicity. There have been limited published data, to date, examining the impact of lipodystrophy on central fat, measured by CT. In patients with increasing severity of central lipohypertrophy increased levels of visceral adipose

tissue were seen alongside increased umbilical waist circumference. Conversely, diagnosis of lipodystrophy was associated with diminished levels of subcutaneous tissue and decreased skin-fold thickness. All clinician diagnoses of lipodystrophy in this survey were based on criteria that included an assessment of both phenotype and severity. This is the largest study to examine associations with increasing severity of lipodystrophy rather than the presence or absence of the condition. Disturbingly, the survey demonstrated strong associations between visceral adiposity, increased age and increased lipid and glycaemic parameters, suggesting that factors associated with accelerated coronary artery disease, while perhaps not syndrome specific, may be phenotype specific as this clustering of associated factors was not seen to the same extent in patients with lipodystrophy. This is the first time that an association has been made between lipodystrophy and elevated alanine aminotransferase, aspartate aminotransferase and decreased testosterone levels. It has been established that hepatotoxicity, usually independent of immune status is associated with long-term exposure to antiretroviral medications. Drugs implicated include the NRTIs, the NNRTI nevirapine, and certain PIs. Given the lack of congruence between the drugs associated with lipodystrophy in this survey and those associated with hepatotoxicity in the literature, it is clearly beyond the scope of this study to speculate on issues of causality, but it is clear that studies of lipodystrophy and hepatocyte function are warranted. Given the established role of sex hormones in lipid regulation, these findings support the notion that factors other than, or in addition to, mitochondrial toxicity may be relevant in the aetiology of this syndrome. It may be of significance that this study and others have identified disparities in lipodystrophy prevalence between gender groups, increased age and lipodystrophy. In addition, lower levels of HIV RNA have been described for the first time in all lipodystrophy phenotypes. This finding supports the purported link with antiretroviral therapy and lipodystrophy.

Conclusion

This large survey of demonstrates that lipodystrophy is a common phenomenon in patients with HIV, overwhelmingly more frequent in those who have been treated with antiretrovirals. The majority of cases of lipodystrophy were either mild or moderate in severity with a mixed phenotype being the predominant presentation.

Lipodystrophy is significantly associated with increased age, symptomatic HIV disease, effective viral suppression, and increased duration of therapy with both NRTIs and PIs. These findings are suggestive of a multifactorial aetiology for lipodystrophy. This study also suggests relationships

between different lipodystrophy phenotypes and specific ARV agents, although definitive associations cannot be deduced from this type of survey.

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