

A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors

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Objective: To describe a syndrome of peripheral lipodystrophy (fat wasting of the face, limbs and upper trunk), hyperlipidaemia and insulin resistance in patients receiving potent HIV protease inhibitor therapy.

Design: Cross-sectional study.

Setting: Outpatient clinic of a university teaching hospital.

Patients: HIV-infected patients either receiving at least one protease inhibitor (n = 116) or protease inhibitor-naive (n = 32), and healthy men (n = 47).

Interventions and main outcome measures: Lipodystrophy was assessed by physical examination and questionnaire and body composition by dual-energy X-ray absorptiometry. Fasting triglyceride, cholesterol, free fatty acid, glucose, insulin, C-peptide and fructosamine levels, other metabolic parameters, CD4 lymphocyte counts, and HIV RNA load were also assessed.

Results: HIV protease inhibitor-naive patients had similar body composition to healthy men. HIV protease inhibitor therapy was associated with substantially lower total body fat (13.2 versus 18.7 kg in protease inhibitor-naive patients; $P = 0.005$), and significantly higher total cholesterol and triglyceride levels. Lipodystrophy was observed clinically in 74 (64%) protease inhibitor recipients after a mean 13.9 months and 1(3%) protease inhibitor-naive patient ($P = 0.0001$). Fat loss occurred in all regions except the abdomen after a median 10 months. Patients with lipodystrophy experienced a relative weight loss of 0.5 kg per month and had significantly higher triglyceride, cholesterol, insulin and C-peptide levels and were more insulin-resistant than protease inhibitor recipients without lipodystrophy. Patients receiving zidovudine and zalcitabine in combination had significantly lower body fat, higher lipids and shorter time to lipodystrophy than patients receiving didanosine. Three (2%) patients developed new or worsening diabetes mellitus.

Conclusion: A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance is a common complication of HIV protease inhibitors. Diabetes mellitus is relatively uncommon.

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AIDS 1998, 12:F51–F58

Keywords: HIV, protease inhibitors, lipids, diabetes

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Sponsorship: The National Centre in HIV Epidemiology and Clinical Research is supported by the Commonwealth Department of Health and Family Services through the Australian National Council on AIDS and Related Diseases and its Research Advisory Committee; K.S. is supported by a National Health and Medical Research Council Postgraduate Scholarship.

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Date of receipt: 3 February 1998; revised: 23 February 1998; accepted: 24 February 1998.

Introduction

HIV protease inhibitors confer virological, immunological, clinical and survival benefits [1,2]. Protease inhibitors in combination with HIV reverse transcriptase inhibitors are now recommended as standard antiretroviral therapy [3,4]. The potency and sustained effects of combination protease inhibitor therapy have led to its widespread usage.

Known toxicities of HIV protease inhibitors include renal calculi with indinavir, nausea, diarrhoea and perioral paraesthesiae with ritonavir, and diarrhoea with nelfinavir. These adverse effects generally occur early in therapy, are not usually serious and resolve rapidly with discontinuation. Excessive bleeding in haemophiliacs, hepatitis and portal vein thromboses are relatively rare [5,6]. Long-term side effects of protease inhibitors have not been described. Generalized wasting is a common manifestation of HIV infection and is predominantly due to loss of muscle mass [7,8]. However, regional fat wasting as a consequence of any drug therapy has not been reported.

HIV protease inhibitors can cause hyperglycaemia, perhaps a result of insulin resistance [1,9,10]. Insulin resistance correlates closely with abdominal obesity and hypertriglyceridaemia and underlies type 2 (non-insulin-dependent) diabetes mellitus [11,12]. HIV protease inhibitors can also cause hyperlipidaemia [1]. These observations led us to explore the interaction between HIV protease inhibitors, lipids and insulin sensitivity. We report a syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance due to HIV protease inhibitors.

Methods

The aims of this cross-sectional study were to describe and characterize a syndrome of peripheral fat wasting (peripheral lipodystrophy) associated with HIV protease inhibitor therapy. HIV-infected patients who were receiving at least one HIV protease inhibitor were compared with HIV-infected protease inhibitor-naïve patients. A second comparison group comprised healthy men with comparable mean age and body mass index [13]. Patients with recent opportunistic infection or malignancy, receiving anabolic steroids or immunomodulators were excluded. All HIV-infected patients without an exclusion criterion and seen for routine clinical care (A.C., D.A.C.) over a 4-week period in August–September 1997 were included. To avoid recruitment bias, no patient was specifically referred for the study.

Lipodystrophy was defined clinically by physical examination and by patient report of fat wasting in the face,

arms or legs with or without central obesity. Because data on lipodystrophy were collected retrospectively, patients were initially asked a general question about any changes in body appearance (without reference to protease inhibitor therapy), followed by questions with specific reference to the regions mentioned above, month of onset for change in each region, and whether the changes had resolved. Patients with weight change but without peripheral fat wasting were not defined as having lipodystrophy. Lipodystrophy was attributed to one or more protease inhibitors if lipodystrophy appeared during, but not before, protease inhibitor therapy. For those receiving sequential protease inhibitors, cause was attributed to the protease inhibitor(s) prescribed at onset of lipodystrophy, as long as the duration of therapy exceeded 3 months. Patients completed a validated questionnaire detailing physical activity over the preceding 12 months [14].

Demographic data collected for each HIV-infected patient were as follows: duration of HIV infection and AIDS, duration and types of all antiretroviral therapies and antimicrobial prophylactic therapies, and family history of diabetes mellitus.

The following measurements were recorded for each HIV-infected patient: weight prior to protease inhibitor therapy and current weight, height, total and high density lipoprotein (HDL) cholesterol, triglyceride, glucose, insulin (Access immunoassay, Beckman, Australia), C-peptide (Linco, St Charles, Missouri, USA), free fatty acid (NEFA, Wako, Osaka, Japan), fructosamine, testosterone, sex hormone-binding globulin (SHBG), prolactin, cortisol, C3, leptin (Linco), and tumour necrosis factor (TNF)- α (Quantikine, R&D Systems, Minneapolis, Minnesota, USA) levels (all measured after a 12 h overnight fast), liver enzymes (total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), CD4+ lymphocyte counts and HIV RNA levels (also recorded prior to protease inhibitor therapy) and, in a randomly selected subgroup, total body and regional fat levels. Total and HDL cholesterol, triglyceride, glucose, fructosamine, liver enzyme, testosterone, SHBG, prolactin, cortisol and C3 levels were determined using routine methods, and insulin resistance was estimated using the homeostasis model [15]. For healthy men, anthropometry, fasting glucose, insulin, C-peptide levels and body fat were determined.

Changes in body weight were expressed as kg per month of protease inhibitor therapy. Total body and regional fat and lean masses and percentages were measured by dual-energy X-ray absorptiometry (DEXA; Lunar DPXL, Madison, Wisconsin, USA). Central abdominal fat measured by DEXA correlates strongly with insulin sensitivity [12] and with measures of abdominal fat by computed tomography [16]. DEXA

was chosen in preference to computed tomography because DEXA precisely measures total body and regional fat levels, except in the face.

HIV infection was confirmed by enzyme-linked immunosorbent assay and immunoblotting. CD4 cell counts were determined by three-colour flow cytometry. Plasma HIV RNA levels were determined by the Amplicor HIV-1 Monitor assay (Roche Molecular Systems, Branchburg, New Jersey, USA); results below the assay's limit of detection were assigned a value of $2.6 \log_{10}$ copies/ml plasma.

Statistical analysis

Continuous variables were analysed by analysis of variance methods. Leptin levels were adjusted for total fat levels using residuals from simple linear regressions. Time to lipodystrophy was estimated by the Kaplan–Meier method. Risk factors for development of lipodystrophy were assessed using Cox regression models.

Results

Clinical and laboratory findings in study subjects

Three groups were studied: 116 HIV-infected subjects currently receiving at least one protease inhibitor for a mean 13.6 months (range, 1–39 months; 77 receiving indinavir, 25 receiving ritonavir plus saquinavir, nine receiving nelfinavir plus saquinavir, four receiving nelfinavir, and one receiving saquinavir); 32 HIV-infected subjects who were protease inhibitor-naïve; and 47 healthy men (Table 1). There was no significant difference in age, weight, body mass index or albumin levels between the groups. HIV-infected patients had significantly higher C-peptide and lower HDL levels than healthy men. Fasting total cholesterol ($P = 0.0001$) and triglyceride ($P = 0.003$) levels were significantly greater in protease inhibitor recipients than in protease inhibitor-naïve patients, and leptin ($P = 0.004$) and HIV RNA ($P = 0.002$) levels were significantly greater in the protease inhibitor-naïve patients than in protease inhibitor recipients.

Body composition in study subjects

DEXA was performed in 61 HIV-infected patients and all healthy men. There was no significant difference in any biochemical or clinical parameter between those HIV-infected patients who did or did not have DEXA performed (data not shown). Patients receiving protease inhibitors had comparable body weight and fat-free mass but significantly lower fat mass overall and in each body region except the central abdomen than both protease inhibitor-naïve patients and healthy men (Table 2). Although abdominal distension was reported commonly, mean central abdominal fat mass was not

Table 1. Characteristics of HIV-infected patients receiving protease inhibitors compared with those not receiving protease inhibitors and healthy men.

	HIV-infected		
	Protease inhibitor (n = 116)	No protease inhibitor (n = 32)	Healthy men (n = 47)
Age (years)	40.4 ± 0.8	38.2 ± 1.5	41.3 ± 1.3
Sex (% male)	98	100	100
Duration HIV infection (years)	8.0 ± 0.3	5.6 ± 0.7 [‡]	NA
AIDS (%)	26	19	NA
Activity score (mets)	151 ± 7	167 ± 21	ND
Weight (kg)	74.8 ± 1.0	74.8 ± 2.8	77.5 ± 1.5
Body mass index (kg/m ²)	23.9 ± 0.2	24.7 ± 0.4	24.6 ± 0.4
Family history diabetes (%)	27	14	ND
CD4 cell count (× 10 ⁶ /l)	450 ± 29	581 ± 128	NA
HIV RNA (log ₁₀ copies/ml)	3.1 ± 0.1	3.6 ± 0.2 [†]	NA
Total cholesterol (mmol/l)	5.9 ± 0.2	4.5 ± 0.2 [‡]	4.9 ± 0.2 [¶]
HDL cholesterol (mmol/l)	1.11 ± 0.03	1.12 ± 0.06	1.30 ± 0.06 ^{§**}
Triglycerides (mmol/l)	3.3 ± 0.4	1.6 ± 0.2 [†]	1.2 ± 0.1 [§]
Glucose (mmol/l)	4.9 ± 0.1	4.9 ± 0.2	5.1 ± 0.1
Insulin (mIU/l)	9.1 ± 0.6	7.2 ± 0.8	5.1 ± 0.4 [§]
C-peptide (mmol/l)	2.6 ± 0.1	2.1 ± 0.2	1.1 ± 0.1 ^{¶††}
Fructosamine (µmol/l)	226 ± 3	220 ± 4	ND
Free fatty acids (µmol/l)	542 ± 34	496 ± 59	ND
Albumin (g/l)	44.5 ± 0.3	44.5 ± 0.6	ND
Leptin (ng/ml)	2.6 ± 0.4	7.8 ± 4.9*	ND
Insulin resistance (mmol ² /l ²)	2.00 ± 0.15	1.66 ± 0.24	1.13 ± 0.10 [§]

Data are means ± SE, unless otherwise indicated. HIV-infected protease inhibitor recipients versus naïve patients: * $P < 0.05$, [†] $P < 0.01$, [‡] $P < 0.0001$. HIV-infected protease inhibitor recipients versus controls: [§] $P < 0.01$, [¶] $P < 0.0001$. HIV-infected non-protease inhibitor recipients versus controls: ** $P < 0.01$, ^{††} $P < 0.0001$. NA, Not applicable; ND, not done.

different in protease inhibitor recipients. HIV protease inhibitor-naïve recipients had similar total and central fat mass to healthy men.

Features and prevalence of lipodystrophy and diabetes mellitus

Lipodystrophy was observed in 74 (64%) patients receiving a protease inhibitor and in one (3%) protease inhibitor-naïve HIV-infected patient (χ^2 test, $P = 0.0001$). Lipodystrophy occurred with equal frequency in all body regions, including the trunk, except the abdomen (data not shown) where patients reported relative abdominal obesity (Fig. 1). Lipodystrophy was attributed to indinavir in 41 patients and to ritonavir–saquinavir in 25 patients. Kaplan–Meier analysis estimated the median time to lipodystrophy to be 10 months (Fig. 2a). This interval was shorter in patients who received ritonavir–saquinavir than in those receiving indinavir (8 and 12 months, respectively; $P = 0.013$, Fig. 2b). Lipodystrophy was

Table 2. Body composition in a subgroup of HIV-infected patients and healthy men.

	HIV-infected patients				Healthy men (n = 47)
	Protease inhibitor (n = 45)	No protease inhibitor (n = 16)	P*		
			Unadjusted	Adjusted [†]	
Fat-free mass (kg)	60.1 ± 1.9	58.7 ± 1.9	0.681	0.865	59.6 ± 0.9
Total fat (%)	18.1 ± 0.9	24.3 ± 1.7	0.001	0.005	23.6 ± 0.7 [‡]
Total fat mass (kg)	13.2 ± 0.8	18.7 ± 1.9	0.003	0.009	17.9 ± 0.8 [‡]
Arm fat mass (kg)	1.56 ± 0.13	2.60 ± 0.38	0.002	0.012	2.25 ± 0.15 [‡]
Leg fat mass (kg)	3.20 ± 0.29	5.45 ± 0.62	< 0.001	0.005	4.94 ± 0.22 [‡]
Trunk fat mass (kg)	7.56 ± 0.39	9.59 ± 0.83	0.017	0.021	9.40 ± 0.56 [‡]
Central abdominal fat mass (kg)	1.45 ± 0.12	1.41 ± 0.13	0.830	0.890	1.42 ± 0.08

Data are means ± SE, unless otherwise indicated. *P values for comparison of HIV-infected patients receiving or not receiving protease inhibitors. [†]P values adjusted for family history of diabetes mellitus, duration of HIV infection (< or >8 years), prior AIDS, current CD4 cell count < or > 350 × 10⁶/l, and current plasma HIV RNA detectable or undetectable. [‡]Healthy men versus HIV-infected protease inhibitor recipients: P < 0.0001; healthy men versus HIV-infected protease inhibitor-naive patients: P > 0.2.

attributed to nelfinavir in three patients and to saquinavir in one patient, but patient numbers were too small to calculate median time to development. Lipodystrophy did not resolve in any patient but improved in three patients who switched from ritonavir-saquinavir to indinavir.

Patients with lipodystrophy had significantly lower fat in all regions except the central abdomen as well as significantly higher triglyceride, insulin and C-peptide levels, and greater insulin resistance than those without lipodystrophy (Table 3). Patients who developed lipodystrophy experienced a relative weight loss of 0.5 kg per month compared with those without lipodystrophy (P = 0.0005).

Three (2%) protease inhibitor recipients had worsening (n = 1) or new (n = 2) diabetes mellitus. For the long-standing, type 1 (insulin-dependent) diabetic patient, daily insulin requirements increased by 70%. In the two new diabetics, one required insulin for symptomatic hyperglycaemia after 4 weeks of indinavir at which time lipodystrophy was noted. The second patient had asymptomatic hyperglycaemia 4 weeks after switching from indinavir to ritonavir-saquinavir that required no therapy and had noted increased fat wasting after 9 months of indinavir.

Risk factors for lipodystrophy

Patients with protease inhibitor-induced lipodystrophy had significantly longer duration of protease inhibitor



Fig. 1. (a) Facial lipodystrophy in a patient after 2 years of therapy with ritonavir and saquinavir. (b) A photograph of the patient taken 3 years prior to therapy shows no facial wasting. (c) There is relative central abdominal distension and fat wasting on the arms. The patient has asymptomatic HIV infection, a CD4⁺ lymphocyte count of 800 × 10⁶/l and undetectable HIV viral load.

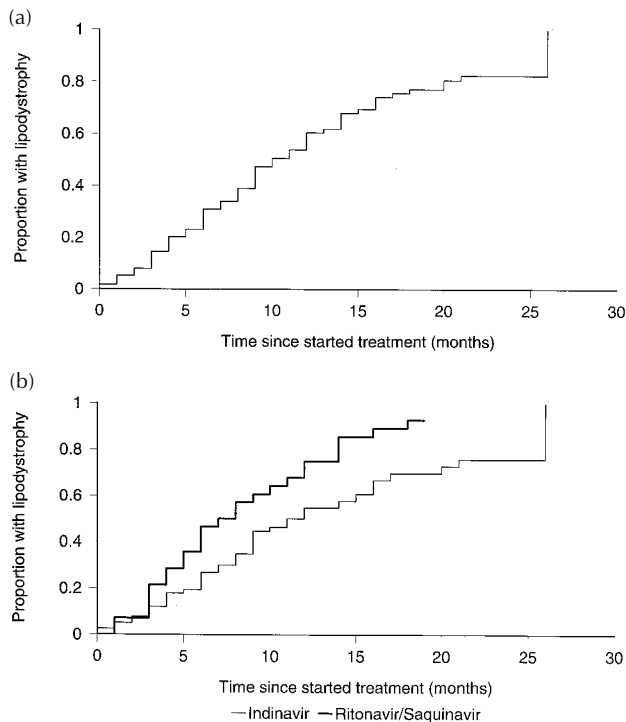


Fig. 2. Times to development of lipodystrophy for (a) all patients receiving protease inhibitors and (b) those receiving indinavir or ritonavir-saquinavir. Lipodystrophy developed significantly earlier in those receiving ritonavir-saquinavir ($P = 0.013$).

therapy than those without lipodystrophy (15.2 and 10.9 months, respectively; $P = 0.0001$). Lipodystrophy was more common in patients receiving ritonavir-saquinavir than in those receiving indinavir (relative

risk, 1.70; $P = 0.038$; Table 4). Lipodystrophy was also more severe in ritonavir-saquinavir patients than in indinavir patients, as shown by less total body fat (8.4 and 14.4 kg, respectively; $P = 0.008$), and higher insulin (11.4 and 8.4 mIU/l, respectively; $P = 0.004$), triglyceride (6.7 and 2.2 mmol/l, respectively; $P = 0.0001$) and total cholesterol (7.0 and 5.6 mmol/l, respectively; $P = 0.0008$) levels.

Lipodystrophy was not more likely in those with a family history of diabetes mellitus. Other clinical variables, CD4+ lymphocyte counts and HIV RNA levels were also not independent risk factors for lipodystrophy (Table 4). Neither the use of protease inhibitors nor the presence of lipodystrophy was associated with significant differences in levels of liver function, testosterone, SHBG, prolactin, cortisol, C3 or TNF- α (data not shown). Leptin levels were significantly related to total fat mass ($r = 0.35$; $P = 0.008$), but were not related to lipodystrophy after adjustment for total fat mass.

Discussion

Patients receiving HIV protease inhibitors frequently develop a syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance, which is common with prolonged therapy but occurrence of secondary diabetes mellitus is relatively rare. This syndrome was more frequent and profound in those receiving ritonavir-saquinavir than those receiving indinavir. This might be because protease inhibitors have differential capacities to cause this syndrome or

Table 3. Body composition and metabolic parameters in protease inhibitor recipients with or without lipodystrophy.

	No lipodystrophy (n = 42)	Lipodystrophy		
		Any protease inhibitor (n = 74)	Indinavir (n = 41)	Ritonavir-saquinavir (n = 25)
Duration therapy (months)	10.9 \pm 1.2 [†]	15.2 \pm 0.7	14.7 \pm 0.9	17.1 \pm 1.3
Weight (kg)	76.2 \pm 1.6	74.0 \pm 0.9	75.1 \pm 1.2	73.0 \pm 1.5
Body mass index (kg/m ²)	24.0 \pm 0.5	23.9 \pm 0.3	23.9 \pm 0.3	24.1 \pm 0.5
Fat-free mass (kg)	60.1 \pm 2.0	62.6 \pm 1.0	62.8 \pm 1.4	62.2 \pm 1.2
Total fat (%)	24.1 \pm 1.8 [‡]	15.3 \pm 0.6	16.5 \pm 0.7	12.1 \pm 0.9 [¶]
Total fat mass (kg)	18.2 \pm 1.8 [‡]	10.9 \pm 0.47	11.8 \pm 0.52	8.4 \pm 0.68 [¶]
Arm fat (kg)	2.29 \pm 0.28 [‡]	1.24 \pm 0.09	1.34 \pm 0.11	0.83 \pm 0.12 [¶]
Leg fat (kg)	5.23 \pm 0.60 [‡]	2.28 \pm 0.15	2.50 \pm 0.17	1.75 \pm 0.23 [§]
Trunk fat (kg)	9.62 \pm 0.95 [‡]	6.62 \pm 0.24	7.08 \pm 0.27	5.28 \pm 0.32 [¶]
Central abdominal fat (kg)	1.52 \pm 0.16	1.42 \pm 0.15	1.61 \pm 0.21	0.99 \pm 0.08
Triglycerides (mmol/l)	1.8 \pm 0.2*	4.1 \pm 0.7	2.5 \pm 0.3	5.3 \pm 0.8 [¶]
Total cholesterol (mmol/l)	5.5 \pm 0.2	6.1 \pm 0.2	5.5 \pm 0.2	7.1 \pm 0.6 [¶]
Glucose (mmol/l)	4.8 \pm 0.1	5.0 \pm 0.1	5.0 \pm 0.1	4.9 \pm 0.1
Fructosamine (μ mol/l)	226 \pm 3	226 \pm 3	227 \pm 3	231 \pm 5
Insulin (mIU/l)	7.5 \pm 0.8*	10.1 \pm 0.8	9.2 \pm 0.9	11.5 \pm 1.8
Insulin resistance (mmol ² /l ²)	1.58 \pm 0.20*	2.23 \pm 0.20	2.07 \pm 0.21	2.55 \pm 0.45
Leptin (ng/ml)	4.59 \pm 1.9	2.60 \pm 0.47	2.77 \pm 0.47	2.28 \pm 0.48
C-peptide (mmol/l)	2.14 \pm 0.16 [†]	2.87 \pm 0.16	2.81 \pm 0.21	3.01 \pm 0.27
Free fatty acids (μ mol/l)	462 \pm 52	589 \pm 43	602 \pm 65	612 \pm 61

Data are means \pm SE. Body composition data (fat free mass, total fat percentage, total fat mass, arm fat, leg fat, trunk fat, and central abdominal fat) were from a subgroup of 45 patients, 31 with and 14 without lipodystrophy. Lipodystrophy versus non-lipodystrophy: * $P < 0.05$, [†] $P < 0.01$, [‡] $P < 0.0001$. Lipodystrophy in indinavir versus ritonavir-saquinavir recipients: [§] $P < 0.05$, [¶] $P < 0.01$.

Table 4. Potential risk factors for lipodystrophy in protease inhibitor recipients.

	Univariate analysis			P
	No. patients	Events	RR (95% CI)	
Age prior to protease inhibitor (years)				
<40	55	34	1.0	
≥40	61	40	0.96 (0.61–1.53)	0.875
Duration of HIV infection (years)				
<8.0	54	26	1.0	
≥8.0	60	46	1.06 (0.65–1.73)	0.826
Not known	2	2		
AIDS prior to protease inhibitor				
No	86	52	1.0	
Yes	30	22	1.31 (0.79–2.17)	0.301
Family history of diabetes mellitus				
No	78	52	1.0	
Yes	29	17	0.92 (0.53–1.60)	0.778
Not known	9	5		
Weight prior to protease inhibitor (kg)				
No	60	37	1.0	
Yes	55	36	0.85 (0.53–1.35)	0.485
Not known	1	1		
Body mass index prior to protease inhibitor (kg/m ²)				
<23.7	51	30	1.0	
≥23.7	56	37	1.10 (0.68–1.75)	0.700
Not known	9	7		
CD4 cell count prior to protease inhibitor (×10 ⁶ /l)				
<200	52	34	1.0	
≥200	58	34	1.10 (0.68–1.75)	0.700
Not known	6	6		
HIV RNA level prior to protease inhibitor (log ₁₀ copies/ml plasma)				
<4.71	45	31	1.0	
≥4.71	46	24	1.02 (0.60–1.76)	0.932
Not known	25	19		
Protease inhibitor(s)				
Indinavir	77	41	1.0	
Ritonavir–saquinavir	28*	26	1.70 (1.03–2.80)	0.038
Other	11	7	1.04 (0.46–2.32)	0.931
Antiretroviral therapy since commencing protease inhibitors [†]				
Zidovudine				
No	84	56	1.0	
Yes	31	17	0.99 (0.56–1.74)	0.969
Lamivudine				
No	12	6	1.0	
Yes	103	67	0.63 (0.27–1.46)	0.278
Didanosine				
No	98	64	1.0	
Yes	17	9	1.06 (0.53–2.13)	0.878
Stavudine				
No	21	10	1.0	
Yes	94	63	1.58 (0.78–3.20)	0.200
Nevirapine				
No	95	57	1.0	
Yes	20	16	1.45 (0.83–2.53)	0.192
Concomitant antimicrobial prophylactic therapy [†]				
Trimethoprim–sulphamethoxazole				
No	52	29	1.0	
Yes	63	44	1.07 (0.67–1.72)	0.774
Aciclovir				
No	80	44	1.0	
Yes	35	29	1.32 (0.82–2.13)	0.247
Fluconazole				
No	92	55	1.0	
Yes	23	18	1.23 (0.72–2.10)	0.460
Azithromycin				
No	101	62	1.0	
Yes	14	11	1.01 (0.53–1.93)	0.971
Rifabutin				
No	110	69	1.0	
Yes	5	4	0.92 (0.33–2.54)	0.870

*Includes three patients who switched to nelfinavir or nelfinavir–saquinavir prior to the study. [†]Data not available for one patient. RR, Relative risk; CI, confidence interval.

may merely represent the use of more than one protease inhibitor. Differentiating the relative contributions of ritonavir and saquinavir was not possible, although ritonavir monotherapy frequently causes hyperlipidaemia [1]. Whether the new formulation of saquinavir with greater bioavailability (about 12%) will cause lipodystrophy as monotherapy is not known.

The study was cross-sectional and relied on a subjective clinical definition, although the clinical data were supported by body composition data obtained by DEXA. The cross-sectional design may have excluded those who had stopped protease inhibitors and therefore a fully representative population was not studied. Prior to this study, however, patients were not ceasing protease inhibitors because of fat wasting. Prospective studies are in progress to further assess the syndrome's incidence and severity, and to determine whether any clinical or biochemical parameter predicts the syndrome. Studies of lipodystrophy in women and children receiving protease inhibitors and its reversibility upon ceasing or switching antiretroviral regimens are required.

The pathogenesis of this syndrome is unclear. Published data on the metabolic effects of HIV protease inhibitors are lacking. Peripheral fat wasting may be due to abnormal lipid release or storage perhaps via adipocyte apoptosis. Fat mobilization leads to elevated circulating fatty acids that can interfere with insulin signalling [17] or provide oxidative substrate competition between glucose and fatty acid cycles [18,19]. Nevertheless, this study could not determine the sequence of biochemical events or why central fat mass was unchanged. HIV protease inhibitors have high affinity for the catalytic site (Asp-Thr-Gly) of HIV protease, and may bind and alter the function of an homologous human protein(s) involved in lipid metabolism or insulin signalling. It is possible that altered cytochrome P450 metabolism of a substance involved in lipid regulation could also be involved.

Type 2 diabetes generally results from both insulin resistance and impaired insulin secretion. This may explain why lipodystrophy was common but hyperglycaemia relatively rare.

The protease inhibitor-naïve patients had slightly increased C-peptide levels and insulin resistance than controls, suggesting that HIV disease may have an effect on insulin sensitivity, although a smaller study did not demonstrate this [20]. However, lipodystrophy was rarely reported in our protease inhibitor-naïve patients, and these patients did not have hyperlipidaemia. Any role of HIV infection in the pathogenesis of this syndrome remains to be determined.

Patients with advanced HIV disease clearly benefit from protease inhibitors in terms of disease progression, survival [2] and reversal of some opportunistic infections

[21]. However, any survival advantage in early HIV disease is unproven, although biologically plausible and widely advocated [5,6]. Alternative strategies for complete suppression of HIV replication, such as combining two nucleoside analogues with a non-nucleoside reverse transcriptase inhibitor [22], although less reliable, might be appropriate, particularly for those with low HIV viral load. Cessation of protease inhibitors should be considered for patients who have failed therapy if there is evidence of lipodystrophy or diabetes mellitus. Furthermore, several patients with lipodystrophy were mistakenly assumed to have HIV wasting syndrome with its psychological, social and economic consequences.

Longer term follow-up is required to assess whether vascular complications of insulin resistance and hyperlipidaemia will develop and whether there is significant morbidity associated with long-term, severe fat depletion, especially for those with HIV-associated wasting. Any role for dietary modification or lipid-lowering drugs for the treatment or prevention of lipodystrophy should be explored.

Newer HIV protease inhibitors that do not cause lipodystrophy, hyperlipidaemia and insulin resistance are required. Proteases from other pathogenic viruses including hepatitis C virus and cytomegalovirus have been proposed as targets for antiviral therapy. These proteins are serine proteases, which are more numerous than aspartyl proteases in humans. The present study highlights the need for more thorough interpretation of prelicensing data and post-marketing surveillance as part of the development of antiprotease agents.

Acknowledgements

The authors thank the patients who participated in this study, C. Satchell for performing leptin and TNF- α assays, G. Howard for recruitment of the control subjects, and J. Eisman and L. Campbell for review of the manuscript.

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