An objective case definition of lipodystrophy in HIV-infected adults: a case-control study

*HIV Lipodystrophy Case Definition Study Group**

Summary

Background Lipodystrophy (peripheral lipoatrophy, central fat accumulation, and lipomatosis) is a common and disfiguring problem in adult patients with HIV-1 infection on antiretrovirals. However, an objective, validated definition of the disorder does not exist. We aimed to develop an objective, sensitive, specific, and broadly applicable case definition of HIV lipodystrophy.

Methods In a case-control study, 1081 consecutive, HIV-infected, adult outpatients (261 [15%] women) without active AIDS were recruited from 32 sites worldwide. We classed patients with at least one moderate or severe subjective lipodystrophic feature, identified by lipodystrophy-specific physical examination and patient questionnaire, and apparent to both doctor and patient as cases (n=417). We classed patients with no such feature as controls (n=371), and patients without a clear diagnosis as non-assigned. We used objective clinical, metabolic, and body composition measurements to construct a logistic regression model with a subset of randomly selected cases and controls. The model was validated in the remaining patients.

Findings A model including age, sex, duration of HIV infection, HIV disease stage, waist to hip ratio, anion gap, serum HDL cholesterol concentration, trunk to peripheral fat ratio, percentage leg fat, and intra-abdominal to extra-abdominal fat ratio had 79% (95% CI 70–85) sensitivity and 80% (95% CI 71–87) specificity for diagnosis of lipodystrophy. Models that incorporated only clinical, or only clinical and metabolic variables had lower sensitivity and specificity than the inclusive model. Models for lipoatrophy, fat accumulation, and lipomatosis could not be developed since pure phenotypes occurred in fewer than 10% of patients with clinical diagnoses of these disorders.

Interpretation Our objective case definition of HIV-associated lipodystrophy should improve assessment of lipodystrophy prevalence, risk factors, and pathogenesis; prevention and treatment approaches; and assist in diagnosis.

Lancet 2003; **361:** 726–35

*Members listed at end of report
Correspondence to: Dr Andrew Carr, HIV, Immunology, and Infectious Diseases Clinical Services Unit, St Vincent's Hospital, Sydney 2010, Australia
(e-mail: acarr@stvincents.com.au)

Introduction

Lipodystrophy (sometimes referred to as fat redistribution, including peripheral peripheral lipoatrophy, central fat accumulation, or lipomatosis) is common in adults taking protease inhibitors, nucleoside analogue reverse transcriptase inhibitors, or both, for HIV-1 infection.[1–11] Lipodystrophy is disfiguring and potentially stigmatising, and thus can hinder adherence to, and reduce effectiveness of, antiretroviral treatment.[12,13] Furthermore, some associated metabolic features (reduced HDL cholesterol, hypercholesterolaemia, hypertriglyceridaemia, insulin resistance, type 2 diabetes, and lactic acidaemia) might increase the risk of cardiovascular disease.[1,3–7,9,10,14–16] Despite the identification of HIV lipodystrophy 5 years ago,[1] an objective case definition does not exist; this has led to substantial variations in reports of prevalence (20–80%), incidence, severity, risk factors, and responses to interventions. Objective physical or metabolic features that reliably define lipodystrophy have not been identified, perhaps because of the high variability between individuals in metabolic indices and soft-tissue mass and distribution. Five definitions of lipodystrophy have been proposed,[4,17–20] but all were generated from studies done in few sites and with mostly male participants; few included objective body composition data, and none was validated. Development of a case definition has been hampered further by uncertainty about whether lipodystrophy in patients with HIV is more than one syndrome. Is the disease defined by peripheral lipoatrophy, central fat accumulation, or both? And is it caused by either nucleoside analogue HIV reverse transcriptase inhibitors or HIV protease inhibitors?[21–23] In fact, the phenotype is most commonly mixed, almost all patients receive these classes of drugs at some time, and all the physical features have been described in patients receiving only one of the drug classes.

Case definitions of clinically-defined rheumatological syndromes of unknown cause, such as rheumatoid arthritis and systemic lupus erythematosis, have been in existence for more than 30 years.[24,25] Such definitions have allowed workers in industry, regulators, researchers, and clinicians to make improved assessments of disease variables such as: prevalence and incidence across and within populations of patients; potential risk factors; pathogenesis; prevention; and treatment. An objective and standardised case definition of lipodystrophy should yield similar benefits.

In response to the increasing awareness of lipodystrophy after the licensing of antiretroviral drugs, the European Medicines Evaluation Agency convened a working group representing regulatory agencies, academia, antiretroviral manufacturers, and patients with HIV. This study is one of the group's initiatives. The design and analytical approach of this case-control study is similar to that used to develop rheumatological syndrome case definitions.[24,25] Our main aim was to develop an objective, sensitive, specific, and broadly applicable case definition of HIV lipodystrophy.

Methods

Participants

We included patients with documented HIV infection, who were older than 17 years, did not have clinical signs of active AIDS in the 4 weeks before trial entry, and were able to complete all investigations. Since we aimed to address diagnosis of lipodystrophy in HIV-infected adults, we did not include controls who did not have the virus.

We recruited patients from 32 sites in North America (n=13), Europe (n=11), Australia (n=4), Asia (n=2), and South America (n=2), which were chosen by non-industry members of the steering committee before funding for the study was secured. To keep bias to a minimum, we asked consecutive patients in hospital and community-based sites to participate. All patients gave written informed consent and research ethics committees at all study locations gave approval for the study.

Procedures

We recorded patients' age, sex, ethnic origin, and details of HIV infection. Patients completed a lipodystrophy-specific questionnaire and underwent a lipodystrophy-specific physical examination by their doctor (data collection forms available from author). Before the study, all participating doctors underwent training to ensure standardisation of the physical examination, consistent rating of lipodystrophy severity, and that patients were unaware of doctors' assessments when completing their own questionnaires

Patients and physicians independently recorded any lipoatrophy diffuse fat accumulation, in the face, neck, dorso-cervical spine, arms, breasts, abdomen, buttocks, or legs, as well as the presence, site, and number of any lipomata (focal accumulations of fat). The degree of lipoatrophy, diffuse fat accumulation, or lipomatosis at every site on the body was rated as absent (score of 0), mild (noticeable on close inspection, score of 1), moderate (readily noticeable by patient or physician, score of 2), or severe (readily noticeable to a casual observer, score of 3).[8]

All data were entered in a web-based database, which automatically classed patients as ineligible, a case, a control, non-assigned, or as having isolated abdominal obesity. Patients classed as cases had at least one moderate or severe feature of lipoatrophy, diffuse fat accumulation, or lipomatosis that they reported as having arisen since the diagnosis of HIV infection, and that had been independently confirmed by physical examination to be moderate or severe—for example, a patient's report of moderate facial lipoatrophy and severe facial lipoatrophy on physical examination by the physician. There was no requirement for such concordance at more than one site. However, the presence of moderate or severe isolated abdominal obesity was reason for exclusion because we did not want to study patients with age-related central adiposity. Controls were patients who had no lipoatrophy, fat accumulation, or lipomatosis, as judged by both patients and physicians, and no report of change in body fat since HIV diagnosis.

We aimed to recruit about 400 cases and 400 controls (12–13 cases and 12–13 controls per site), such that the number of participants would be roughly five times the number of indices assessed.[26] Because body composition differs between men and women, we planned that control and case groups should have the same sex balance, although we did not stipulate equal numbers of men and women. If recruitment at a site of cases (or controls) was completed before recruitment of all controls (or cases), subsequent obvious cases (or controls) at that site were excluded from screening. We did not replace patients who dropped out before the end of the study.

We gathered more information about cases and controls: personal and family histories of diabetes; current dietary intent; self-assessed physical activity; other possible antiretroviral adverse effects and (for greater specificity) of AIDS-related wasting; and clinical and serological history of chronic hepatitis B and C infections. We recorded history of use of antiretrovirals and of prescribed and non-prescribed agents that might affect body composition, lipids, or glycaemic indices. We did simple anthropometry and recorded blood pressure.

Metabolic variables (serum total and HDL cholesterol, triglycerides, glucose, insulin, C-peptide, lactate, liver enzymes, anion gap, and lactate dehydrogenase) were measured when the patient had had 3 days of regular diet, 24 h without major physical exertion, a minimum 10-h overnight fast, and was well hydrated and had been seated for at least 15 min. If necessary, a tourniquet was applied for up to 2 min, but was removed before blood was taken. We estimated LDL cholesterol using the Friedewald equation and insulin sensitivity with the homoeostasis model assessment. We did CD4 lymphocyte counts and measured plasma HIV-RNA load, if they had not been done in the previous 8 weeks.

Body composition was assessed with whole-body dual-energy X-ray absorptiometry (DEXA), and single-slice abdominal (L4) CT with standard protocols.[1–4,6,9,27] Before DEXA, recent radionucleide or barium tests were avoided for 7 days, jewellery was removed, and arms were placed away from the body. We did not use sandbags or pillows, and we took care to include the whole body. In DEXA analysis, we displayed soft tissue and bone for appropriate allocation of soft tissue; used extended research mode analysis; predefined localisation of the arm, rib, central, pelvic, lumbar, dorsal, and neck cuts; and analysed arms, legs, and trunk. Regular quality control and calibrations were done at all study locations. We measured soft-tissue phantom (ie, composite blocks used for calibration) once at all sites. In CT analysis, each patient was imaged with a conventional helical or non-helical system, with only one CT scanner at every site, and constant soft-tissue imaging parameters. Patients were supine with their head straight, shoulders relaxed, and arms raised above the head; patients' motion was kept to a minimum. All soft tissue was included in the CT field of view. With a mid-L4 vertebral scout film as a guide, a single 10 mm axial slice of the abdomen through the point of the marker was done on a normal setting. Intra-abdominal and subcutaneous extra-abdominal adipose tissue areas were traced manually.

Only one laboratory was used at every site. We did not use a central reading facility, so that any model that we produced could be applied at any site, with any laboratory or imaging equipment.

Statistical analysis

Case definitions were derived from analyses applied to a randomly selected proportion of cases and controls—ie, the training dataset. Models were validated on the basis of remaining cases and controls—ie, the validation dataset.[28] To ensure discrimination between variables, and to avoid overfitting models to the data, the training dataset was designed to include about 250 cases and 250 controls. Random selection of cases and controls for inclusion in the training dataset was made a posteriori, and based on computer-generated random numbers with stratification by site and sex. Rates of agreement between patient and clinician assessment of lipodystrophy were assessed with weighted κ values derived from the total lipodystrophy scores (ie, the sum of accumulation and atrophy at individual sites on the body).

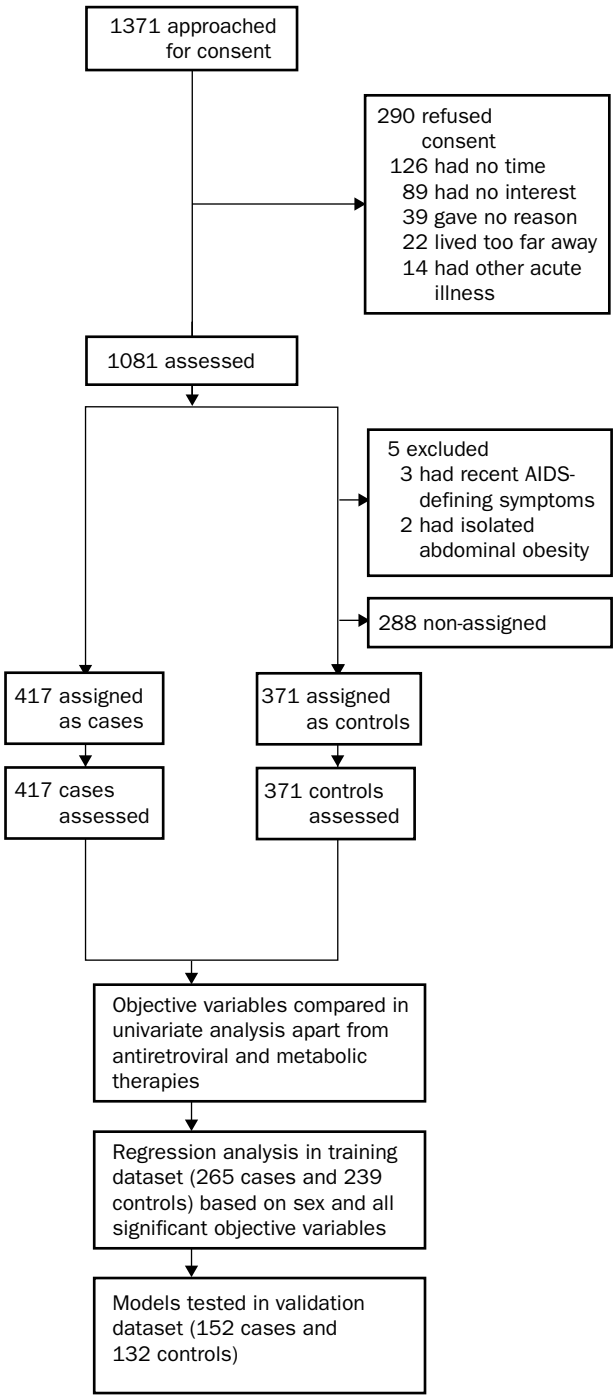

Figure 1 **Study profile**

We included all objective variables (apart from treatments) in the training dataset. We did not include data from lipodystrophy-specific patients' assessments or physical examinations in the primary model because such data were used to assign patients to case and control groups. We also excluded antiretroviral data since the model is intended for use in estimating risk of lipodystrophy with antiretroviral therapy. Subjective patient responses were excluded, since patients' knowledge of the results of this study might lead to biased responses in future studies. On the basis of examination of univariate results, we included continuous variables either single continuous parameters, dichotomous variables, or four-level ordered categorical variables based on quartiles, in accordance with the most appropriate fit for the model. Multivariate case-definition models were developed with forward stepwise logistic regression applied to the training dataset and we included variables that were significant at $p<0·05$. We assessed sensitivity and specificity of these models using the validation dataset. We then reassessed sensitivity and specificity after imputation of missing values from the validation dataset using best-subset linear regression; however, our findings were not much altered and are not shown.

We appraised models on the basis of analyses of prespecified subgroups of cases and controls: only lipoatrophic cases versus all controls; only fat accumulated cases versus all controls; only male cases versus male controls; and only female cases versus female controls.

A simplified lipodystrophy scoring system was developed from the final multivariate case definition model by multiplication of every variable estimate by ten and rounding to the nearest integer.

Role of the funding source

The study sponsors did not participate in study design, site selection, data collection, analysis, or interpretation, or in the decision to submit for publication. The two industry members of the steering committee reviewed the manuscript but did not make material changes to the final report.

Results

Of 1371 patients approached between October, 2000, and June, 2001, 1081 (79%) gave consent to participate (figure 1): 417 were defined as cases, 371 as controls, 288 were non-assigned, and five were ineligible. Table 1 shows patients, baseline and HIV-disease characteristics. A mean of 13 (SD 1·1) cases and 11·6 (3·0) controls were recruited per site during a mean of 9 weeks (4) and 13 weeks (7), respectively. Four sites failed to recruit at least 12 controls, largely because of logistic reasons, but exclusion of these sites from analysis did not affect final results (data not shown). The median number of non-assigned patients per site was eight (range 0–35). Exclusion of sites with high or low numbers of non-assigned patients did not alter the final results (data not shown), and consequently we included all data for cases and controls in the analyses.

On physical examination, 38 (9%) and 23 (6%) cases had only lipoatrophy or only diffuse fat accumulation, respectively (table 2). No case had isolated lipomatosis. Overall, patients, expecially non-assigned patients, rated lipodystrophy as more frequent and severe than did doctors. Of 288 non-assigned patients, 186 (65%) reported moderate or severe lipodystrophy, but had no or mild lipodystrophy on physical examination; 74 (26%) reported no or mild lipodystrophy but were judged by a doctor to have moderate or severe lipodystrophy; and 28 (10%) had only mild features on physical examination, self-report, or both. However, agreement between all patients' reports (cases, controls, and non-assigned) and clinician assessment was substantial (κ 0·65; $p<0·001$). For cases only agreement was moderate (κ 0·43; $p<0·001$), and was poor for non-assigned patients, although it was significant (κ 0·10; $p<0·001$), whereas for controls, the κ by definition was 1.

The training dataset included 265 cases and 239 controls (tables 3 and 4). We noted significant differences between cases and controls for 44 (59%) of 75 variables. Antiretroviral and metabolic treatments used by patients within this group are shown in table 5.

	All patients			Training dataset		
	Cases (n=417)	Controls (n=371)	Non-assigned (n=288)	Cases (n=265)	Controls (n=239)	p*
Age (years, mean [SD])	45 (9)	39 (9)	41 (8)	45 (9)	39 (10)	<0·001
Men	345 (83%)	318 (86%)	237 (82%)	219 (83%)	202 (85%)	0·570
Ethnic group						0·384
White	323 (78%)	264 (71%)	185 (64%)	202 (76%)	173 (72%)	··
Black	34 (8%)	50 (13%)	62 (21%)	24 (9%)	34 (14%)	··
Hispanic	26 (6%)	20 (5%)	20 (7%)	16 (6%)	10 (4%)	··
Asian/Pacific islander	30 (7%)	31 (8%)	12 (4%)	19 (7%)	19 (8%)	··
Other†	4 (1%)	6 (2%)	11 (4%)†	4 (2%)	3 (1%)	··
HIV disease category						<0·001
Asymptomatic (category A)	172 (41%)	225 (61%)	154 (53%)	113 (43%)	148 (62%)	··
Symptomatic (category B)	106 (25%)	78 (21%)	77 (27%)	65 (25%)	53 (22%)	··
AIDS (category C)	139 (33%)	68 (18%)	57 (20%)	87 (33%)	38 (16%)	··
Duration HIV infection (years, mean [SD])	9·0 (4·2)	6·5 (4·7)	8·0 (4·9)	8·9 (4·2)	6·6 (4·8)	<0·001
Duration of care (years, mean [SD])	3·5 (3·5)	2·6 (2·8)	2·9 (3·2)	3·4 (3·4)	2·7 (2·9)	0·131
HIV exposure						0·877
Homosexual	273 (65%)	247 (67%)	161 (56%)	175 (66%)	160 (67%)	··
Heterosexual	97 (23%)	71 (19%)	72 (25%)	60 (23%)	49 (21%)	··
Injecting drug user	18 (4%)	22 (6%)	27 (9%)	13 (5%)	12 (5%)	··
Blood product	12 (3%)	11 (3%)	3 (1%)	7 (3%)	5 (2%)	··
Other/unknown	17 (4%)	20 (5%)	25 (9%)	10 (4%)	13 (5%)	··
CD4 count (cells/mL, mean [SD])						
Current	486 (294)	474 (279)	482 (311)	490 (288)	476 (275)	0·359
Nadir	173 (157)	245 (198)	228 (181)	151 (149)	213 (196)	<0·001
Change from nadir to current	314 (219)	248 (196)	270 (231)	317 (224)	245 (193)	<0·001
HIV-RNA load (log copies/mL)						
Current (mean [SD])	3·17 (0·82)	3·24 (0·89)	3·33 (0·98)	3·16 (0·83)	3·25 (0·91)	0·243
Peak (mean [SD])	4·68 (0·90)	4·80 (0·80)	4·89 (0·76)	4·72 (0·88)	4·81 (0·81)	0·289
Change from peak to current (mean [SD])	1·51 (0·97)	1·63 (1·72)	1·71 (1·00)	1·56 (0·96)	1·62 (1·01)	0·530
Current <500 copies/mL (number [%])	277 (66%)	237 (64%)	175 (61%)	182 (69%)	155 (65%)	0·362

*p values are for cases *vs* controls in the training dataset, calculated with χ^2 test for categorical variables, a *t* test for continuous variables, and test for heterogeneity for sex, ethnic group, HIV disease category, and HIV exposure. †includes one American Indian.

Table 1: **Patients' age, sex, ethnic origin, and HIV disease characteristics**

	Cases (n=417)				Non-assigned (n=288)			
	Physician		Patient		Physician		Patient	
	n (%)	Mean severity score*	n (%)	Mean severity score*	n (%)	Mean severity score*	n (%)	Mean severity score*
No fat abnormality	0	··	0	··	89 (31%)	··	22 (8%)	··
Lipoatrophy	394 (94%)	7·2 (3·3)	394 (94%)	8·6 (4·2)	123 (43%)	3·1(2·5)	200 (69%)	4·3 (3·8)
Face	325 (78%)	2·1 (0·8)	325 (78%)	2·2 (0·7)	81 (28%)	1·5(0·5)	116 (40%)	1·4 (0·7)
Neck	66 (16%)	1·4 (0·6)	89 (21%)	1·6 (0·7)	9 (3%)	1·2(0·4)	42 (15%)	1·3 (0·6)
Dorso-cervical spine	13 (3%)	1·6 (0·9)	42 (10%)	1·7 (0·7)	4 (1%)	1·0(0·0)	24 (8%)	1·3 (0·4)
Arms	290 (70%)	1·7 (0·7)	290 (70%)	1·9 (0·7)	54 (19%)	1·3(0·5)	96 (33%)	1·4 (0·6)
Breasts	30 (7%)	1·5 (0·6)	77 (18%)	1·8 (0·7)	12 (4%)	1·4(0·7)	32 (11%)	1·4 (0·7)
Abdomen	41 (10%)	1·5 (0·6)	94 (23%)	1·8 (0·7)	12 (4%)	1·1(0·3)	63 (22%)	1·5 (0·6)
Buttocks	334 (80%)	2·1 (0·7)	338 (81%)	2·3 (0·7)	66 (23%)	1·3(0·5)	115 (40%)	1·5 (0·7)
Legs	350 (84%)	2·1 (0·7)	343 (82%)	2·3 (0·7)	67 (23%)	1·3(0·5)	110 (38%)	1·4 (0·6)
Fat accumulation	379 (91%)	4·3 (2·9)	384 (92%)	4·7 (3·3)	164 (57%)	2·1 (1·6)	209 (73%)	3·3 (2·9)
Face	40 (10%)	2·0 (0·7)	51 (12%)	1·9 (0·1)	13 (5%)	1·2 (0·6)	41 (14%)	1·5 (0·7)
Neck	58 (14%)	1·8 (0·7)	68 (16%)	1·9 (0·8)	13 (5%)	1·2 (0·6)	30 (10%)	1·3 (0·5)
Dorso-cervical spine	102 (24%)	1·7 (0·7)	100 (24%)	2·0 (0·8)	21 (7%)	1·2 (0·4)	22 (8%)	1·2 (0·4)
Arms	20 (5%)	1·8 (0·7)	30 (7%)	1·7 (0·8)	2 (1%)	1·0 (0·0)	23 (8%)	1·5 (0·8)
Breasts	108 (26%)	1·8 (0·7)	116 (28%)	1·9 (0·7)	29 (10%)	1·2 (0·4)	69 (24%)	1·4 (0·6)
Abdomen	263 (63%)	1·9 (0·7)	237 (57%)	2·1 (0·7)	116 (40%)	1·4 (0·6)	138 (48%)	1·6 (0·7)
Buttocks	20 (5%)	1·9 (0·7)	26 (6%)	2·0 (0·8)	6 (2%)	1·0 (0·0)	39 (14%)	1·6 (0·7)
Legs	12 (3%)	1·7 (0·7)	24 (6%)	1·9 (0·7)	4 (1%)	1·0 (0·0)	33 (11%)	1·5 (0·6)
Lipomata	44 (11%)	1·6 (0·6)	83 (20%)	NR	12 (4%)	1·0 (0·0)	33 (11%)	NR

*Maximum severity score is 3 for lipoatrophy or diffuse fat accumulation per region. Mean total severity scores are the sum of each score for each of the 8 regions. Severity scores are mean values for patients reporting a fat abnormality in a given region. NR=not recorded.

Table 2: **Body composition abnormalities in cases and non-assigned patients**

	Missing data	Cases (n=265)	Controls (n=239)	p
Diabetes mellitus	2			
Diagnosed prior to study		18 (7%)	6 (3%)	0·032
Family history type 1 diabetes		13 (5%)	9 (4%)	0·546
Family history type 2 diabetes		56 (21%)	51 (21%)	0·916
Dietary intent*	2			0·185
Aim to increase weight		62 (23%)	30 (13%)	..
Aim to lose weight		35 (13%)	21 (9%)	..
Aim to maintain current weight		168 (63%)	188 (79%)	..
Alcohol consumption (units per week)*	2			0·001
7		227 (86%)	175 (73%)	..
7–14	..	26 (10%)	38 (16%)	..
>14	..	11 (4%)	24 (10%)	..
Physical activity*	3			0·288
Sedentary	..	84 (32%)	71 (30%)	..
Low	..	75 (28%)	61 (26%)	..
Moderate	..	75 (28%)	70 (29%)	..
High	..	30 (11%)	35 (15%)	..
Other symptoms and signs				
Dry skin	3	133 (50%)	79 (33%)	<0·001
Dry lips	3	113 (43%)	64 (27%)	<0·001
Ingrown nails	3	30 (11%)	8 (3%)	0·001
Peripheral neuropathy	3	68 (26%)	23 (10%)	<0·001
Unexplained fever	3	14 (5%)	5 (2%)	0·071
Unexplained diarrhoea	3	40 (15%)	21 (9%)	0·033
Increased bleeding tendency	3	18 (7%)	3 (1%)	0·006
Abdominal bloating	4	93 (35%)	24 (10v)	<0·001
Body hair				
loss	3	36 (14%)	18 (8v)	0·014†
gain	3	28 (11%)	8 (3%)	0·002†
Libido				
loss	3	79 (30%)	46 (19%)	0·007†
gain	3	10 (4%)	9 (4%)	0·759†
Energy				
loss	3	72 (27%)	46 (19%)	0·041†
gain	3	16 (6%)	16 (7%)	0·988†
Weight change >3 kg				
loss	3	42 (16%)	19 (8%)	0·004†
gain	3	36 (14%)	21 (9%)	0·042†
Appetite				
loss	3	40 (15%)	19 (8%)	0·007†
gain	3	25 (9%)	9 (4%)	0·008†
Abnormal menstruation	2	9 (4%)	2 (1%)	0·254†
Blood pressure (mm Hg)‡	3			
Systolic	..	125 (16)	122 (15)	0·087
Diastolic	..	77 (10)	76 (11)	0·042
Anthropometry‡				
Height (cm)	4	172 (9)	174 (9)	0·491
Weight (kg)				
Baseline	4	72·1 (12·8)	71·8 (12·5)	0·976
Peak	110	77·2 (13·3)	76·0 (13·7)	0·487
Nadir	117	64·9 (11·9)	65·9 (11·4)	0·365
Change peak to baseline	110	–5·6 (4·7)	–4·2 (4·3)	<0·001
Change nadir to baseline	117	7·0 (6·6)	5·8 (5·4)	0·119
Body mass index (kg/m^2)	4	24·1 (3·7)	23·8 (3·8)	0·454
Waist circumference (cm)	8	87·6 (10·1)	85·0 (10·5)	0·002
Hip circumference (cm)	8	91·9 (8·6)	93·2 (9·2)	0·088
Waist/hip circumference ratio	8	0·95 (0·09)	0·91 (0·07)	<0·001
DEXA derived measurements‡	24			
Total fat (kg)	..	12·6 (7·7)	14·2 (8·9)	0·007
Total fat (%)	..	19·2 (9·5)	21·6 (9·6)	0·001
Arm fat (%)	..	17·6 (10·5)	20·0 (11·3)	0·013
Leg fat (%)	..	13·7 (9·8)	20·2 (10·2)	<0·001
Limb fat (%)	..	14·9 (9·8)	20·2 (10·1)	<0·001
Limb fat (kg)	..	4·59 (3·68)	6·45 (4·60)	<0·001
Trunk fat (%)	..	21·7 (10·2)	21·6 (9·5)	0·727
Trunk/limb fat percent ratio	..	1·89 (3·00)	1·16 (0·46)	<0·001
Trunk fat % minus limb fat %	..	6·8 (7·2)	1·4 (7·4)	<0·001
Total lean tissue (kg)	..	51·4 (9·6)	49·6 (9·2)	0·011
CT derived measurements‡				
Extra-abdominal fat (cm^2)	56	123 (115)	144 (107)	<0·001
Intra-abdominal fat (cm^2)	41	138 (88)	97 (71)	<0·001
Intra/extra-abdominal fat ratio	58	3·21 (9·87)	0·90 (1·16)	<0·001

p values for continuous variables from rank sum test and for categorical variables from χ^2 test. *In 3 months before questionnaire. †Versus patients with no loss or gain. ‡Data are mean (SD).

Table 3: **Physical characteristics of cases and controls in training dataset**

	Missing data	Cases n=265	Controls n=239	p
Lipids				
Triglyceride (mmol/L)	10	3·4 (3·9)	2·0 (1·7)	<0·001
Total cholesterol (mmol/L)	10	5·6 (1·8)	5·1 (1·6)	0·04
HDL cholesterol (mmol/L)	10	1·1 (0·3)	1·2 (0·3)	<0·001
Total/HDL cholesterol ratio	10	5·6 (2·0)	4·5 (2·0)	<0·001
Estimated LDL cholesterol (mmol/L)*	50	3·1 (1·2)	3·0 (1·0)	0·113
Glycaemic				
Glucose (mmol/L)	15	5·3 (1·4)	5·0 (0·9)	0·033
Insulin (pmol/L)	26	117 (188)	77 (107)	<0·001
C-peptide (mmol/L)	44	1·5 (1·7)	1·2 (1·6)	<0·001
Glucose/insulin ratio	30	0·78 (1·17)	0·88 (1·15)	<0·001
Insulin resistance (mmol-1mIU-1L-2)	30	4·5 (8·9)	2·6 (4·1)	<0·001
Mitochondrial and hepatic characteristics				
Lactate (mmol/L)	29	1·8 (1·6)	1·4 (0·8)	<0·001
Anion gap (mmol/L)	35	17 (5)	14 (5)	<0·001
Lactate dehydrogenase (mmol/L)	41	325 (171)	304 (146)	0·221
Alanine aminotransferase (IU/mL)	10	49 (137)	35 (45)	0·001
Alkaline phosphatase (IU/mL)	9	102 (54)	102 (58)	0·485
Hepatitis B surface antigen detected	1	19 (7%)	15 (6%)	0·712
Hepatitis B e antigen detected	1	9 (3%)	3 (1%)	0·116
Chronic symptomatic hepatitis B	1	5 (2%)	1 (<1%)	0·168
Hepatitis C antibody detected	1	24 (9%)	31 (13%)	0·175
Hepatitis C RNA detected	1	20 (8%)	13 (5%)	0·584
Chronic symptomatic hepatitis C	1	12 (5%)	6 (3%)	0·233

Date are mean (SD) or number (%). *Estimated using the Friedewald equation in 229 cases and 225 controls with available data and with triglycerides <4 mmol/L.

Table 4: **Biochemical charectoristics of cases and controls in training data set**

The validation dataset consisted of the remaining 152 cases and 132 controls. From analysis of this dataset, variables included in the case definition for HIV lipodystrophy were age, sex, duration of HIV infection, HIV disease clinical stage, ratio of waist to hip circumference, anion gap, HDL cholesterol, ratio of trunk to limb fat, intra-abdominal to extra-abdominal fat ratio, and percentage leg fat (table 6; panel). The model had 79% (95% CI 70–85) sensitivity and 80% (71–87) specificity.

We derived a total lipodystrophy score from the model by adding individual scores for every variable, and then subtracting 43 (the constant). A final score of at least zero indicates the presence of lipodystrophy, and a score less than zero, no lipodystrophy. This scoring system is available at http://www.med.unsw.edu.au/ nchecr.

The sensitivity and specificity of the model changed with the cutoff score (table 7).

With use of clinical and metabolic data, but not body composition data, a model that incorporated age, sex, duration of HIV infection, clinical stage of HIV disease, waist to hip ratio, anion gap, lactate, HDL cholesterol, estimated LDL cholesterol, and triglyceride had somewhat lower sensitivity (73% [64–81] and specificity (71% [62–79]) than the model that included body composition variables. With only clinical data, the best model incorporated age, duration of HIV infection, HIV disease clinical stage, change in CD4+ count from nadir, and waist circumference, and had a sensitivity of 75% (66–82) but specificity of only 60% (50–69) (figure 2). Scoring systems for these incomplete models are also available at the website http://www.med.unsw. edu.au/ nchecr.

We compared cases that the case-definition model defined as lipodystrophic or non-lipodystrophic. Proportions of men and women in these two groups were the same, but cases without objective lipodystrophy were younger, less likely to have AIDS, had had HIV for a substantially shorter time, and had fewer abnormal metabolic and body composition parameters (data not shown). Cases defined as not having the disorder also had significantly fewer sites with lipodystrophy than did those with lipodystrophy on physical examination (2·7 [1·8] *vs* 3·7 [1·3], respectively; p=0·004), a lower overall lipodystrophy severity score on physical examination (8·4 [4·1] *vs* 10·1 [3·9], respectively; p<0·001) and lower mean lipodystrophy model-derived scores (–9 [5] and 21 [10], respectively; p<0·001).

We did not develop models for pure lipoatrophy and pure fat accumulation because of the small numbers of patients who were classified as cases with these phenotypes. A model for lipoatrophy including cases with only lipoatrophy or with lipoatrophy and only mild fat accumulation by self-report or physician assessment contained the same variables and had similar sensitivity and specificity as the overall lipodystrophy model (data not shown).

Because some variables in the case definition probably differ between men and women, analyses were done to assess models that include interaction terms between sex and each of the other variables. Results of these analyses suggested interactions between sex and percentage leg fat, and ratios of intra-abdominal to extra-abdominal fat, although the interaction term was significant only for the ratio of trunk to peripheral fat. Furthermore, model sensitivity and specificity were not improved with use of interaction terms. Results of cross-tabulations between sex and these other variables showed that inclusion of sex in the case-definition model allow for the between-sex differences in variables.

We also constructed separate case-definition models for men and women. A model for men included duration of HIV infection, HIV disease stage, waist circumference, anion gap, HDL cholesterol, percentage leg fat, and intra-abdominal to extra-abdominal fat ratio. The model had 75% sensitivity (95% CI, 66–83) and 74% specificity (64–82). A model for women (derived from a small number of cases) included only trunk to peripheral fat ratio and anion gap, and had 76% sensitivity (55–91) and 81% specificity (54–96).

We tested whether there was an association between the prevalence of lipodystrophy defined by the model and exposure to antiretroviral drugs. One (5%) of 19 antiretroviral-naive patients were classed by the model as cases in the validation dataset, as were 19 (39%) of 49 who had received such treatment, but never taken a protease inhibitor, and 109 (59%) of 185 patients who had ever received a protease inhibitor. The proportions of cases and controls who met consensus criteria for metabolic syndrome (syndrome X) were 17% (13–21) and 7% (5–10), respectively (p<0·001).[29]

	Cases (n=265)			Controls (n=239)		
	Ever use	Current use	Total use (months) (mean [SD])	Ever use	Current use	Total use (months) (mean [SD])
Antiretroviral therapy	264 (100%)	253 (95%)	71 (35)	205 (86%)	195 (82%)	44 (32)
Nucleoside analogues						
Any	264 (100%)	246 (93%)	70 (34)	205 (86%)	192 (82%)	44 (32)
Only	217 (82%)	21 (8%)	37 (30)	107 (45%)	31 (13%)	34 (29)
Lamivudine	249 (94%)	184 (69%)	40 (18)	181 (76%)	149 (63%)	30 (19)
Zidovudine	233 (83%)	74 (28%)	39 (29)	161 (68%)	99 (42%)	35 (28)
Stavudine	224 (85%)	133 (50%)	35 (18)	115 (48%)	75 (32%)	22 (16)
Abacavir	74 (28%)	56 (21%)	15 (10)	33 (14%)	30 (13%)	15 (10)
Didanosine	156 (59%)	54 (20%)	23 (18)	75 (32%)	32 (13%)	20 (19)
Zalcitabine	84 (32%)	5 (2%)	22 (17)	37 (16%)	6 (3%)	23 (20)
Osther	2 (1%)	1 (<1%)	24 (3)	2 (1%)	2 (1%)	2 (3)
Non-nucleoside analogues						
Any	172 (61%)	113 (43%)	19 (13)	105 (44%)	83 (35%)	16 (13)
Nevirapine	106 (40%)	55 (21%)	16 (12)	54 (23%)	36 (15%)	19 (16)
Efavirenz	86 (32%)	52 (20%)	15 (10)	59 (25%)	47 (20%)	11 (8)
Delavirdine	15 (6%)	7 (3%)	14 (11)	2 (1%)	0	23 (16)
Protease inhibitors						
Any	235 (89%)	159 (60%)	40 (16)	133 (56%)	93 (39%)	32 (18)
Only	22 (8%)	2 (1%)	10 (8)	17 (7%)	2 (1%)	3 (5)
Indinavir	163 (62%)	48 (18%)	25 (16)	65 (27%)	26 (11%)	27 (19)
Nelfinavir	115 (43%)	46 (17%)	21 (14)	66 (28%)	30 (13%)	17 (13)
Saquinavir hard-gel	92 (35%)	12 (5%)	18 (15)	31 (13%)	10 (4%)	22 (17)
Ritonavir <400 mg/day	77 (29%)	50 (19%)	11 (11)	34 (14%)	29 (12%)	12 (14)
Ritonavir >400 mg/day	69 (26%)	22 (8%)	18 (14)	32 (13%)	11 (5%)	18 (16)
Saquinavir soft-gel	47 (18%)	25 (9%)	19 (17)	18 (8%)	8 (3%)	22 (18)
Lopinavir/ritonavir	36 (14%)	34 (13%)	6 (4)	16 (7%)	16 (7%)	7 (4)
Amprenavir	26 (10%)	18 (7%)	11 (7)	8 (3%)	7 (3%)	13 (8)
Metabolic agents						
Lipid-lowering*	NR	45 (17%)	NR	NR	5 (2%)	NR
Hypoglycaemic†	NR	14 (5%)	NR	NR	2 (1%)	NR
Glucocorticosteroid‡	NR	31 (12%)	NR	NR	43 (18%)	NR
Appetite suppressing§	NR	77 (29%)	NR	NR	86 (36%)	NR
Appetite stimulanting¶	NR	7 (3%)	NR	NR	3 (1%)	NR
Anabolic‖	NR	34 (13%)	NR	NR	6 (3%)	NR

NR=not recorded. Use and duration of antiretroviral therapy (ever or current) based upon at least one 4-week period of continuous treatment. Previous use and duration of metabolic therapies not recorded. Use of metabolic drugs refers to regular use in the 30 days before the questionnaire. *One or more of bile salt sequestrants, fibrates, nicotinic acid, statins, or other lipid-lowering agent (dextrothyroxine, fish oils, olestra, plant sterols, probucol). †One or more of biguanides, insulin, sulphonylureas, thiazolidinediones, or other hypoglycaemic agent (acarbose, miglitol, repaglinide). ‡Oral or parenteral treatment at pharmacologic doses (eg, prednisolone >7·5 mg daily). §One or more of amphetamines, cocaine, opiates, or tobacco. ¶One or more of cannabinoids or megestrol acetate. ‖One or more of growth hormone, nandrolone, oxandrolone, oxymetholone, stanazolol, or testosterone.

Table 5: **Antiretroviral and metabolic drug use in training dataset**

Discussion

We have objectively defined HIV lipodystrophy by locally-derived and readily available clinical, metabolic, and body-composition data. Our syndromic case definition is a substantial advance on the approach of subjective diagnoses made by doctors, patients, or both, because the definition contains only objective indices and so is unbiased. Our definition should lead to improvements in the study of lipodystrophy prevalence, incidence, risk factors, pathogenesis, prevention, and treatment.

The final model contains several overlapping body composition indices: namely waist to hip ratio, intra-abdominal to extra-abdominal fat ratio, percentage leg fat, and trunk to peripheral fat ratio. This result might be an effect of variability secondary to local body composition assessment.

In studies sponsored by the pharmaceutical industry, reading of body composition by one centre to adjust for differences in scanners and technicians has become increasingly common. Indeed, central reading of our imaging data could provide a more sensitive and specific model. Use of more accurate body composition measures, such as total body MRI, might simplify the model, but because such measures are rarely available we did not include them in our study.

Anion gap rather than plasma lactate (for which anion gap is likely to be a surrogate) was included in the model, possibly because of the inherent difficulties associated with collection and transport of plasma for lactate measurement. Although centrally measured lactate might be a better marker of lipodystrophy, a case definition that included lactate measured in this way would not be practical.

Although our case definition contains ten parameters, it is not more complex than those developed for many rheumatological syndromes such as systemic lupus erythematosis and rheumatoid arthritis.[24,25] Furthermore, availability of the model on a website, into which individual patient data can be entered (as per the Framingham equation)[30] should allow for rapid use in research and clinical settings. Although the model's primary purpose is for research, the study website also contains simpler, albeit less sensitive and specific, models for clinicians who do not have access to imaging or metabolic data.

We did not design the study to establish whether HIV lipoatrophy and HIV fat accumulation are more than one syndrome or disease. To define pure lipoatrophy and fat accumulation, greater numbers of patients with pure phenotypes than we included will need to be assessed. Nevertheless, such definitions will be helpful only if they have greater sensitivity or specificity than the overall lipodystrophy case definition and if they are applicable to a large number of patients. However, we saw pure lipoatrophy or fat accumulation in only 15% of cases and provisional models to assess these disorders had no greater sensitivity or specificity.

We did not include HIV-uninfected adults as controls for two reasons. First, the clinical dilemma is not how to distinguish between HIV-infected patients with

	OR (95% CI)	p	p trend	Lipodystrophy score
Demographic				
Sex				
Male	1·0			0
Female	9·33 (3·86–22·52)	<0·001		22
Age				
≤40 years	1·0			0
>40 years	2·02 (1·20–3·40)	0·008		7
Duration HIV				
≤4 years	1·0			0
>4 years	3·11 (1·69–5·71)	<0·001		11
CDC category				
A	1·0			0
B	1·32 (0·73–2·39)	0·361		3
C	1·92 (1·02–3·61)	0·043	0·042	7
Clinical				
Waist/hip Circumference ratio (0·1)	1·34 (1·06–1·69)	0·014		Multiply by 29
Metabolic				
HDL cholesterol (0·1 mmol/L)	0·87 (0·81–0·94)	<0·001		Multiply by –14
Anion gap (1 mmol/L)	1·101 (1·040–1·166)	0·001		Multiply by 1
Body composition				
VAT/SAT ratio				
<0·45	1·0			0
0·45–0·83	0·82 (0·38–1·76)	0·613		–2
0·83–1·59	1·40 (0·62–3·18)	0·416		3
>1·59	3·70 (1·44–9·55)	0·007	0·003	13
Trunk/limb fat ratio (1·0)	1·72 (1·12–2·66)	0·014		Multiply value by 5
Leg fat (%)				
>21·4	1·0			–16
14·5–21·4	1·27 (0·57–2·87)	0·559		–14
8·8–14·5	2·32 (1·00–5·40)	0·051		–8
<8·8	5·04 (1·90–13·35)	0·001	<0·001	0

VAT=intra-abdominal adipose tissue (visceral fat). SAT=subcutaneous adipose tissue (subcutaneous fat).

Table 6: **HIV lipodystrophy case definition and scoring system**

lipodystrophy and HIV-uninfected patients without lipodystrophy, but whether HIV-infected adults do or do not have lipodystrophy. Second, identification of appropriate controls without HIV infection would have been extremely difficult, especially in an international study; a major risk category for HIV infection (injecting drug user) being also associated with altered body composition. If our controls had been matched for these variables, their contribution to the case definition would have been difficult or impossible to determine.

Central adiposity and buffalo hump might not be HIV-specific.[31] However, exclusion of the 6% of clinical cases from our analysis with isolated diffuse fat accumulation (none had isolated lipomatosis), or the 19% of clinical cases with predominant fat accumulation, did not alter our final

Variables included in case definition

Demographic	Sex Age Duration of HIV infection HIV disease clinical stage
Clinical	Waist/hip circumference ratio
Metabolic	Anion gap HDL cholesterol
Body composition	Leg fat Trunk/limb fat ratio Intra-abdominal/subcutaneous abdominal fat ratio

Score	Sensitivity	Specificity
≥–13	95%	49%
≥–8	90%	58%
≥0	79%	80%
≥8	60%	90%
≥14	49%	95%

Table 7: **Model sensitivity and specificity according to lipodystrophy score**

model (data not shown). Similarly, separate case definitions for men and women did not improve the sensitivity and specificity of the case-definition model, suggesting that one case definition including an interaction term for sex is most appropriate. However, these adapted models were necessarily based on subsets of the data (for example, only 15% of participants were women) and so there was limited power to identify the need for separate models for lipoatrophy and fat accumulation, or for men and women. Inclusion of female sex as a positive parameter in the model might thus seem paradoxical. However, the sex term in the model is substantially offset by body composition variables, because women have much more total and peripheral fat than do men. Furthermore, the model was not designed to distinguish lipodystrophy from AIDS-associated wasting, although clinically this distinction is not common.

Other caveats should be acknowledged. The probable exclusion of some mild cases and the inclusion of only very definite cases and controls might have reduced the model's specificity, although it is probably less important to accurately diagnose very mild cases. Our clinical definitions of cases and controls were deliberately more stringent than those in many studies, so as to have minimum risk of

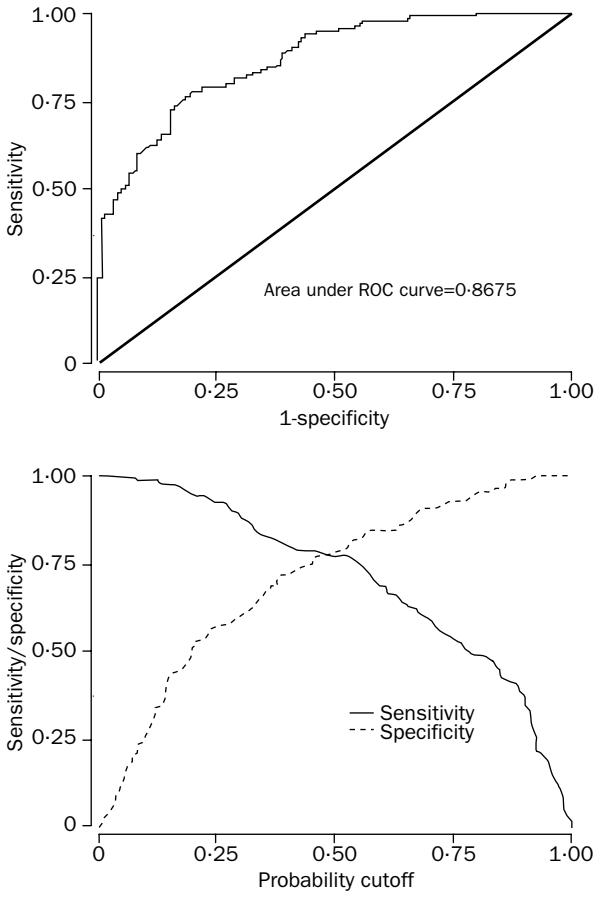

Figure 2 **Receiver operator characteristic and sensitivity-specificity curves**

patients with non-lipodystrophic body fat changes being incorrectly assigned clinically to the case group.

The 80% accuracy of the model is not ideal, but is good in view of the high variability in body composition. This accuracy could actually be greater; the 80% accuracy rate is based on the assumption that clinical assignment was 100% accurate. Further analysis is needed to establish whether the associations between many of the symptoms and lipodystrophy are direct or indirect, and whether the lipodystrophy case definition differs between adults and children.

Implementation of our findings in studies of HIV disease will allow for more reliable estimates of lipodystrophy prevalence, incidence, cause, and responses to prevention or treatment strategies. Our study serves as a model for the development of objective measures for other common, subjectively defined, adverse events associated with antiretroviral treatment, such as peripheral neuropathy, symptomatic lactic acidaemia, sexual dysfunction, and clinical hepatitis.[32]

Lipodystrophy case definition. study group

Writing committee—A Carr (St Vincent's Hospital, Sydney, Australia; principal investigator); S Emery, M Law, R Puls (National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia); J D Lundgren (Hvidovre University Hospital, Copenhagen, Denmark); W G Powderly (Washington University School of Medicine, St Louis, USA).
Steering committee—A Carr; D Barr (Forum for Collaborative HIV Research, Baltimore, USA; to September, 2001); D A Cooper (National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia); S Emery; S Grinspoon (Massachusetts General Hospital, Boston, USA); J Ioannidis (University of Ioannina, Ioannina, Greece); R Lewis (Agouron Pharmaceuticals, San Diego, USA); M Law; K Lichtenstein (HIV Outpatient Study/Centres for Diseases Control and Prevention, Denver, USA); J Murray (US Department of Health and Human Services Food and Drug Administration, Washington, DC, USA); D Pizzuti (Bristol-Myers Squibb, Princeton, USA, representing the European Medicines Evaluation Agency Oversight Committee); W G Powderly; W Rozenbaum (Agence Nationale du Researche sur le SIDA; Hôpital Rothschild, Paris, France); M Schambelan (University of California, San Francisco, USA; to September 2000).
Coordinating committee—R Puls, S Emery, A Moore, J Miller, A Carr (National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia).

Investigators

Argentina—W H Belloso, S A Ivalo, L O Clara, L A Barcan, L D Stern, A M Galich, M I Perman (Hospital Italiano de Buenos Aires, Buenos Aires); M Losso, A Duran, J Toibaro (Hospital J M Ramos Mejía, Buenos Aires).
Australia—D Baker, R Vale, R McFarlane, H MacLeod, J Kidd, B Genn (407 Doctors, Sydney); A Carr, R Fielden (St Vincent's Hospital, Sydney); S Mallal, M French, A Cain, J Skett, D Maxwell (Royal Perth Hospital, Perth); A Mijch, J Hoy, A Pierce, C McCormick, B De Graaf (Alfred Hospital and Monash University, Melbourne).
Canada—J Falutz, J Vatistas, L Dion (Montreal General Hospital, Montreal); J Montaner, M Harris, P Phillips, V Montessori, M Valyi, W Stewart (St Paul's Hospital, Vancouver); S Walmsley, L Casciaro (Toronto Hospital, Toronto).
Denmark—J Lundgren, O Andersen, A Gronholdt (Hvidovre University Hospital, Copenhagen).
France—I Beguinot (Hôpital Robert Debré, Reims); P Mercié, G Chêne (Hôpital Haut-Lévêque, Bordeaux); J Reynes, L Cotte (Hôpital Gui de Chauliac, Montpellier); W Rozenbaum, L Nait-Ighil, L Slama, T H Nguyen, C Rousselle (Hôpital Rothschild, Paris); J-P Viard, L Roudière, A Maignan, M Burgard (Hôpital Necker, Paris).
Germany—S Mauss, G Schmutz, S Scholten (Gemeinschafts Praxis, Dusseldorf).
Japan—S Oka, H Fraser, M Ishihara, K Itoh (International Medical Centre of Japan, Tokyo).
Netherlands—P Reiss, M van der Valk, P Leunissen, M Nievaard, B van Eck-Smit, C can Kujik (Academic Medical Centre, University of Amsterdam and International AIDS Therapy Evaluation Center, Amsterdam).
Singapore—N Paton, B Peperstraete, F Karim, C Y Khim, S Ong (Tan Tock Seng Hospital, Singapore).
Spain—J Gatell, E Martinez, A Milinkovic (Hospital Clinic Provincial de Barcelona);
UK—D Churchill, C Timaeus, T Maher, N Perry, A Bray (Sussex Hospital, Brighton); G Moyle, C Baldwin, C Higgs, B Reynolds (Chelsea and Westminster Hospital, London).
USA—C Carpenter, L Bausserman, T Fiore, M DiSpigno (Miriam Hospital, Providence, RI); C Cohen, J Hellinger, K Foy, S Hubka, B Riccio (Community Research Initiative of New England, Brookline, MA); W El-Sadr, S Raghavan, N Chowdury, B de Vries, S Miller (Harlem Hospital Center, New York, NY); S Hammer, M Crawford, S Chang, J Dobkin, B Quagliarello, D Gallagher, M Punyanitya (Columbia University, New York, NY); H Kessler, A Tenorio, S Kjos (Rush Presbyterian St Luke's Medical Center, Chicago, IL); J Falloon, H C Lane, D Rock, L Ehler (National Institute of Allergy and Infectious Diseases, Bethesda, MD); K Lichtenstein, T McClain (Denver Infectious Disease Consultants, Denver, CO); R Murphy, P Milne (Northwestern Memorial Hospital, Chicago, IL); W Powderly, J Aberg, M Klebert, M Conklin (Washington University School of Medicine, St Louis, MO); D Ward, L Green, B Stearn III (Dupont Circle Physician's Group, Washington, DC).

Conflict of interest statement

Some members of the writing committee (A Carr, S Emery, J D Lundgren, and W Powderly) have held advisory positions, or received research grants, funding, honoraria, consultancy fees, or lecture sponsorships from pharmaceutical companies including Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, DuPont, Gilead Sciences, Chiron, GlaxoSmithKline, Pfizer-Agouron, Roche, Schering Plough, Pharmacia and UpJohn, Merck, Sharpe and Dohme, and Triangle.

Contributors

A Carr conceived and helped design the study, enrolled patients, analysed data, secured funding, drafted the manuscript, and oversaw the study. S Emery participated in study design, analysed data, prepared the manuscript, and oversaw the study. M Law participated in study design, did statistical analyses, and prepared the manuscript. R Puls oversaw site initiations, established the study website, monitored data, and participated in manuscript preparation. J Lundgren participated in study design,enrolled patients, analysed data, secured funding, prepared the manuscript, and oversaw the study. W Powderly participated in study design, enrolled patients, analysed data, prepared the manuscript, and oversaw the study. All members of the steering committee contributed to study design and supervision, and reviewed the final manuscript. All investigators contributed to study design, patients' recruitment, and reviewed the final manuscript.

Acknowledgments

We thank Janet Darbyshire, Donald Kotler, Orjan Mortimer, Bob Munk, Kathy Mulligan, Andrew Phillips, Alexander Walker, and Ian Weller for their input and guidance; and the patients for their time and commitment. The study was sponsored in equal parts by an unrestricted grant from Abbott Laboratories, Boehringer-Ingelheim, Bristol-Myers Squibb, DuPont, GlaxoSmithKline, Merck, Pfizer-Agouron, Pharmacia-Upjohn and Roche. The Australian National Centre in HIV Epidemiology and Clinical Research is funded by the Commonwealth Department of Health and Ageing.

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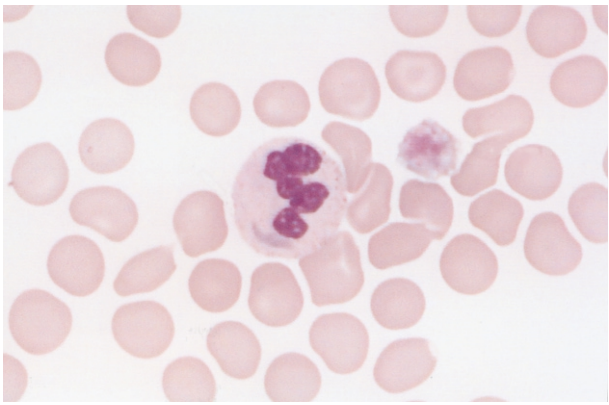
Clinical picture

Thrombocytopenia or giant platelets?

U Fabry, F Lammert, R Osieka

A 67-year-old woman was referred for risk assessment before treatment with I^{131} for benign thyroid disease because of her history of persistent thrombocytopenic purpura. Electronic blood counts showed a normal packed cell volume and white blood count, but only 8×10^9 platelets per L. However, we manually recounted the thrombocytes and found only slightly lowered values (100×10^9/L). Peripheral blood smears showed giant platelets almost as large as erythrocytes and elliptic cytoplasmic inclusion bodies in nearly all granulocytes (figure). These findings established the diagnosis of May-Hegglin anomaly, which was confirmed by diagnosis of thrombocytopenia in the patient's son and her sister. The combination of granulocyte inclusion bodies and enlarged platelets was described in 1909 by May. 36 years later Hegglin observed the autosomal-dominant inheritance of the anomaly in two generations of a family. It took another 55 years to relate this anomaly to mutations in the *MYH9* gene encoding the non-muscle myosin heavy chain 9. The mutations probably affect myosin filament self-assembly and cause the non-assembling structures to aggregate into paracrystalline inclusion bodies.



Inclusion bodies in granulocytes

Department of Internal Medicine (U Fabry MD, F Lammert MD, R Osieka MD) **Medical Faculty of the Technical University of Aachen, 52074 Aachen, Germany**