Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study

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Summary

Background The prevalence and severity of lipodystrophy syndrome with long-term therapy for HIV-1 infection that includes a protease inhibitor is unknown. We studied the natural course of the syndrome to develop diagnostic criteria and identifying markers that predict its severity.

Methods We assessed 113 patients who were receiving HIV-1 protease inhibitors (mean 21 months) and 45 HIV-1-infected patients (28 with follow-up) never treated with a protease inhibitor. Lipodystrophy was assessed by questionnaire (including patients’ rating of severity), physical examination, and dual-energy x-ray absorptiometry. Body composition and fasting lipid and glycaemic variables were compared with data obtained 8 months previously. Oral glucose tolerance was investigated.

Findings There was 98% concordance between patients’ reports of the presence or absence of lipodystrophy (reported by 83% of protease-inhibitor recipients and 4% of treatment-naive patients; p=0.0001) and physical examination. Patients’ ratings of lipodystrophy were significantly associated with declining total body fat (p=0.02). Lower body fat was independently associated with longer duration of protease-inhibitor therapy and lower bodyweight before therapy, and more severe lipodystrophy was associated with higher previous (p=0.03) and current (p=0.01) triglyceride and C-peptide concentrations, and less peripheral and greater central fat (p=0.005 and 0.09, respectively). Body fat declined a mean 1.2 kg over 8 months in protease-inhibitor recipients (p=0.05). The prevalence of hyperlipidaemia remained stable over time (74% of treated patients vs 28% of naive patients; p=0.0001). Impaired glucose tolerance occurred in 16% of protease-inhibitor recipients and diabetes mellitus in 7%; in all but three patients these abnormalities were detected on 2 h post-glucose load values.

Interpretation Diagnosis and rating severity of lipodystrophy is aided by the combination of physical examination, patient’s rating, and measurement of body fat, fasting triglycerides, and C-peptide. Weight before therapy, fasting triglyceride, and C-peptide concentrations early in therapy, and therapy duration seem to predict lipodystrophy severity. Lipodystrophy was common and progressive after almost 2 years of protease inhibitor therapy, but was not usually severe. Hyperlipidaemia and impaired glucose tolerance were also common.

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Introduction

Protease-inhibitor therapy of HIV-1 infection is associated in some cases with a syndrome of peripheral fat wasting, central adiposity, hyperlipidaemia, and insulin resistance, referred to as lipodystrophy syndrome.1,2 Fat deposition in the breasts of women and over the dorsocervical spine (“buffalo hump”) have also been reported.2 Type 2 diabetes mellitus is also a feature of the syndrome but with a reported prevalence of less than 1%.1,10–12 The cause of the syndrome is unknown, partly because the syndrome is occasionally seen in individuals who have not received protease inhibitors. We have proposed that protease inhibitors inhibit proteins involved in lipid metabolism, with the primary event being apoptosis and reduced differentiation of peripheral adipocytes.14 The protease inhibitors indinavir and the ritonavir-saquinavir combination are strongly associated with the syndrome, but there are no published data for nelfinavir.

There are no criteria with which to diagnose or rate the severity of lipodystrophy. The prevalence of lipodystrophy based on self-report by patients was 50% after 10 months of therapy.1 Self-report of fat wasting was associated with significantly lower body-fat mass, but because of the large variability in body fat in general and HIV-1-infected populations, body fat was insufficient for diagnosis. The prevalence of clinically significant hyperlipidaemia related to protease-inhibitor therapy is unknown. The few prevalence data on diabetes mellitus derive from random blood glucose concentrations in small numbers of patients, a flawed approach because hyperglycaemia is in most cases symptomless. A more reliable approach to assess the prevalence of disorders of glucose metabolism is the oral glucose tolerance test.15 Diagnosis of hyperlipidaemia, diabetes mellitus, or impaired glucose tolerance induced by protease inhibitors is important because each increases cardiovascular disease risk,16–19 and because protease-inhibitor therapy would ideally be for an indefinite period.

Our study was undertaken to extend the above findings. We aimed to define the natural course of each feature of lipodystrophy syndrome, to develop useful criteria for assessing the presence, severity of, and risk factors for each component of the syndrome, and to compare abnormalities induced by different protease-inhibitor regimens.
**Methods**

**Patients**

The study population consisted of 116 HIV-1-infected patients receiving at least one HIV protease inhibitor, who were initially investigated cross-sectionally between August and September, 1997, after a mean 13.6 months of therapy, and 45 HIV-1-infected patients who had never received a protease inhibitor (38 of whom were receiving other antiretroviral drugs). Both groups of patients were seen for routine care, and were not selected for any syndrome manifestation. Both groups had no active AIDS-related disorder within 3 months of the first assessment, were not receiving anabolic steroid, corticosteroid, or immune-modulating therapy, and were reassessed between March and June, 1998. The protocol was approved by the Research Ethics Committee of St Vincent's Hospital, and all patients provided written informed consent.

**Assessments**

Lipodystrophy was originally defined by patients’ report of peripheral fat wasting (face, arms, buttocks, or legs) or central abdominal fat accumulation, and confirmed by physical examination. Weight change without peripheral fat wasting or central adiposity was not classified as lipodystrophy. On the basis of data published since our first analysis of these patients, the definition used in this study was expanded to include clinical evidence of fat accumulation in the dorsocervical fat pad. Breast size was not assessed because of the small number of female patients.

Patients’ self-report of lipodystrophy was by questionnaire (available from the authors on request). Patients rated the severity in each of the six regions (face, arms, legs, buttocks, abdomen, neck) as none (score 0), mild (score 1), moderate (score 2), or severe (score 3). Scores for each region (0–3), for peripheral wasting (four sites: face, arms, buttocks, legs; total score 0–12), central accumulation (two sites: abdomen, neck; total score 0–6), and overall (six sites, total score 0–18) were assigned. For overall lipodystrophy, a score of 1–6 arbitrarily defined mild lipodystrophy, 7–12 moderate lipodystrophy, and 13–18 severe lipodystrophy. All scoring definitions were made before data analysis. We chose a patient-rated score in preference to a clinician-rated score for two reasons. First, if valid, a patient-rated score allows the questionnaire to be used widely. Second, a patient’s assessment of the severity of a visible effect is more likely to influence treatment decision. In an attempt to limit reporting bias, patients and investigators were masked to previous questionnaire responses.

Patients were examined by one of two clinicians (AC, DAC) at the time of questionnaire completion for evidence of lipodystrophy. Patients reporting no lipodystrophy but with lipodystrophy on examination were classified as not having lipodystrophy.

Measurement of the duration of HIV infection and AIDS, new AIDS-defining illnesses, weight, height, CD4-lymphocyte counts, HIV RNA load, concentrations of total and HDL cholesterol, triglycerides, glucose, insulin, C-peptide, and free fatty acid (all measured after a 12 h overnight fast), and total body and regional fat measurements were repeated at the follow-up assessment. Oral glucose tolerance tests were done in protease-inhibitor recipients at follow-up to measure blood glucose 2 h after ingestion of 75 g anhydrous glucose except in one patient with longstanding type 1 diabetes. Patients were advised to not alter their normal diet for 3 days before glucose-tolerance testing.

Metabolic variables were measured as in the previous study. Insulin resistance and insulin secretion were estimated by the homeostasis model. Normal and impaired glucose tolerance and diabetes mellitus were defined according to 1998 American Diabetes Association guidelines—fasting blood glucose of less than 6.1 mmol/L, 6.1–7.0 mmol/L, or greater than 7.0 mmol/L, respectively, or blood glucose 2 h after glucose-tolerance test of less than 7.8 mmol/L, 7.8–11.1 mmol/L, or greater than 11.1 mmol/L, respectively (for purposes of clarity, patients with impaired fasting glucose 6.1–7.0 mmol/L were defined as having impaired glucose tolerance). Hypertriglyceridaemia was defined as concentrations above 2.0 mmol/L on the basis of reports of increased risk of cardiac disease with fasting values above 1.6–2.3 mmol/L. Hypercholesterolaemia was defined as concentrations above 5.5 mmol/L and a low HDL-cholesterol concentration as less than 0.9 mmol/L.

Total body and regional fat (kg and percentage) were measured by dual-energy x-ray absorptiometry (DEXA; Lunar DPX-L, Madison, WI, USA) by the same technician. DEXA was done in random subsets of each group (there was no significant difference in any metabolic or demographic variable between those who did or did not have DEXA; data not shown). To compare peripheral lipodystrophy scores, peripheral fat was defined as the sum of arm and leg fat, because these are the only peripheral regions that can be quantified by DEXA. To limit possible reporting bias, DEXA was done after questionnaire completion. A change of more than 5% in total fat mass (for example, a 1 kg change in a patient with 20 kg body fat) between the two DEXA scans was defined as significant on the basis of previous reproducibility studies.

Plasma HIV-1 RNA concentrations were determined by the Amplicor HIV-1 Monitor assay (Roche Molecular Systems, Branchburg, NJ, USA); results below the limit of detection were assigned a value of 2.6 log10 copies/mL. Plasma CD4-lymphocyte counts were measured by three-colour flow cytometry.

**Statistical analysis**

The protease-inhibitor group and the protease-inhibitor-naïve group were compared at baseline and at follow-up for demographic, metabolic, and body-composition measures by ANOVA. Comparison of these variables between baseline and follow-up visits within each group was by paired t tests for protease-inhibitor recipients, who remained on therapy between visits, and protease-inhibitor-naïve patients, who remained protease-inhibitor-naïve throughout (inclusion of protease-inhibitor recipients who ceased therapy before the current assessment did not affect the results; data not shown). The magnitude of change in measured variables was also compared between the two groups by ANOVA. Changes in immunological status, metabolic variables, and body composition within individuals in each group were investigated by repeated-measures ANOVA.

Because HIV infection duration was longer in the protease-inhibitor group, the relation between HIV infection duration and body composition was examined in protease-inhibitor recipients by simple regression analysis (r=0.35, p=0.03). The proportion of body fat was therefore adjusted for duration of infection and standardized residuals used in repeated-measures ANOVA to ensure there was no confounding of the prospective analyses by duration of infection. The relation between total fat mass at the second assessment and age, duration of HIV infection, weight before protease-inhibitor therapy, CD4-cell count, viral load, duration of therapy, and AIDS status was tested in a multiple regression analysis.

Clinical, metabolic, and body composition variables were compared (ANOVA) by lipodystrophy-severity grouping in protease-inhibitor recipients and by type of protease inhibitor (data not shown). The prevalence of hypertriglyceridaemia and hypercholesterolaemia in the two groups was compared by reports of χ2 test. Comparison of all variables at baseline and severity of lipodystrophy at follow-up was by ANOVA. Two-sided p values less than 0.05 were defined as significant.

**Results**

**Patients**

113 (98%) protease-inhibitor recipients were reassessed after a mean 21 months (SD 8) total therapy (table 1). 14 (12%) patients had ceased protease-inhibitor therapy a mean of 3 months (range 1–6) previously, two patients because of lipodystrophy, and 12 because of pill burden,
other adverse events, or antiretroviral failure. In 28 of 45 protease-inhibitor-naïve patients, repeat measurements were made after a mean 8 months (SD 1); of those who did not have repeat measurements, 11 had started protease-inhibitor therapy and were excluded from follow-up but had lipodystrophy on examination. Two protease-inhibitor recipients reporting no lipodystrophy had the disorder on physical examination. No patient received any lipid-lowering diet or drug.

Diagnosis of lipodystrophy and glucose intolerance

Overall, there was 98% concordance for lipodystrophy diagnosis between patients’ report and physical examination, with lipodystrophy being reported by 92 (83%) protease-inhibitor recipients and one (4%) protease-inhibitor-naïve patient (p=0·0001). All patients reporting lipodystrophy had the disorder on physical examination. One patient with lipodystrophy at baseline who continued protease-inhibitor therapy and were excluded from follow-up had lipodystrophy on examination. Two protease-inhibitor recipients reporting no lipodystrophy had lipodystrophy on physical examination. Total adiposity was lower in protease-inhibitor recipients than in protease-inhibitor-naïve patients (15·9% vs 23·3%; p=0·0001; table 2) but did not differ significantly between protease-inhibitor recipients with mild or no lipodystrophy. Among protease-inhibitor recipients, those with mild lipodystrophy had significantly higher central abdominal fat mass than those reporting no lipodystrophy (p=0·04; table 3); this difference was not explained by any other variables (which were similar in the two subgroups; data not shown). Protease-inhibitor recipients with mild lipodystrophy also had significantly higher triglyceride and C-peptide concentrations than those reporting no lipodystrophy (p=0·05 for both comparisons).

Diabetes mellitus was diagnosed in 7% of protease-inhibitor recipients and impaired glucose tolerance in a further 16%. Most abnormalities were found in 2 h post-glucose values; diabetes mellitus was diagnosed in 2% and impaired glucose tolerance in 7% by fasting blood glucose load values. No protease-inhibitor recipient had symptoms of hyperglycaemia. Patients with abnormal glucose tolerance had greater insulin resistance (3·71 vs 2·13 mIU mmol L$^{-2}$, respectively; p=0·0005) and fatty-
acids were stable over time in protease-inhibitor naïve patients. According to the predefined criteria (>5% change in total body fat mass), lipodystrophy worsened significantly in 58% and improved in 26% of protease-inhibitor recipients. No risk factor for either change could be identified, including cessation or switching of protease-inhibitor therapy (data not shown).

Triglyceride and total cholesterol concentrations were abnormal in a greater proportion of protease-inhibitor recipients than protease-inhibitor-naïve patients (table 4). Triglyceride and total cholesterol concentrations were stable over time in protease-inhibitor recipients, but there was a significant decline in HDL cholesterol (from 1·13 mmol/L to 1·03 mmol/L; p=0·007, table 2). Glucose metabolism variables did not

<table>
<thead>
<tr>
<th>Lipodystrophy</th>
<th>p</th>
<th>Lipodystrophy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>18 (17%)</td>
<td>Mild</td>
<td>44 (42%)</td>
</tr>
<tr>
<td>Mean (SE) fat percentage</td>
<td>19-4 (1-3)</td>
<td>20-0 (1-1)</td>
<td>15-7 (0-9)</td>
</tr>
<tr>
<td>Mean (SE) fat mass (kg)</td>
<td>13-52 (1-16)</td>
<td>14-93 (0-06)</td>
<td>11-16 (0-76)</td>
</tr>
</tbody>
</table>

### Peripheral

- Total affected 26 (25%) 34 (32%) 27 (26%) 11 (10%) 67 (64%)
- Mean (SE) fat mass* (kg) 1-50 (0-18) 1-24 (0-10) 1-14 (0-16) 1-50 (0-10) 0-03 0-26
- Mean (SE) fat mass (kg) 3-81 (0-32) 3-64 (0-38) 2-36 (0-22) 2-53 (0-22) 2-95 (0-22) 0-003 0-09

### Central

- Total affected 34 (32%) 44 (42%) 31 (30%) 26 (25%) 87 (83%)
- Mean (SE) fat mass (kg) 1-09 (0-11) 1-42 (0-09) 1-31 (0-08) 1-55 (0-18) 1-40 (0-06) 0-09 0-03

### Metabolic variables†

| Glucose (mmol/L) | 5-1 (0-2) | 5-0 (0-1) | 5-3 (0-3) | 5-3 (0-3) | 5-1 (0-1) | 0-64 | 0-86 |
| Glucose at 2 h (mmol/L) | 6-5 (0-7) | 6-1 (0-3) | 6-1 (0-3) | 7-4 (0-8) | 6-3 (0-2) | 0-20 | 0-85 |
| Insulin (miU/L) | 7-5 (1-0) | 9-9 (0-6) | 10-4 (1-2) | 13-13 (2-7) | 10-0 (0-8) | 0-08 | 0-07 |
| C-peptide (miU/mL) | 1-9 (0-2) | 2-6 (0-2) | 2-5 (0-2) | 3-8 (0-4) | 2-7 (0-1) | 0-0007 | 0-001 |
| Insulin resistance (miU miU/L) | 1-73 (0-25) | 2-25 (0-23) | 2-60 (0-34) | 3-86 (1-23) | 2-42 (0-25) | 0-05 | 0-12 |
| Insulin secretion (miU miU/mL) | 1-09 (14) | 1-49 (15) | 1-58 (19) | 1-54 (20) | 1-53 (10) | 0-23 | 0-07 |
| Triglycerides (mmol/L) | 1-8 (0-2) | 3-3 (0-5) | 3-0 (0-3) | 5-0 (1-0) | 3-5 (0-3) | 0-01 | 0-02 |
| Total cholesterol (mmol/L) | 5-6 (0-4) | 5-9 (0-2) | 5-7 (0-2) | 6-2 (0-7) | 5-9 (0-2) | 0-53 | 0-87 |
| HDL cholesterol (mmol/L) | 5-18 (0-09) | 5-06 (0-05) | 5-97 (0-03) | 5-85 (0-08) | 5-99 (0-03) | 0-009 | 0-02 |
| Free fatty acids (mmol/L) | 507 (63) | 469 (43) | 439 (49) | 472 (84) | 459 (30) | 0-82 | 0-51 |

### Other†

- Duration of protease-inhibitor therapy (months) 18-2 (2-0) 21-8 (2-0) 25-0 (1-4) 23-3 (1-5) 23-2 (0-8) 0-02 | 0-01 |
- Duration of HIV-1 infection (years) 1-1 (0-1) 9-1 (0-6) 9-4 (0-6) 11-7 (1-0) 9-5 (0-4) 0-0009 | 0-0006 |
- CD4 count (cells/µL) | 400 (55) | 505 (44) | 470 (62) | 578 (76) | 403 (33) | 0-42 | 0-19 |
- HIV-1 RNA (log10 copies/mL) | 3-13 (0-23) | 3-54 (0-19) | 3-21 (0-18) | 3-01 (0-21) | 3-35 (0-19) | 0-47 | 0-37 |
- Weight (kg) | 72-7 (2-4) | 75-6 (1-7) | 74-0 (1-5) | 72-5 (2-2) | 74-6 (1-0) | 0-81 | 0-56 |

*Comparisons between protease-inhibitor recipients and protease-inhibitor-naïve patients at each timepoint. There was no significant difference within either group over time.

**Table 3: Body composition and metabolic variables in 105 protease-inhibitor recipients followed up for a mean 21 months according to lipodystrophy self-report scale**

**Table 4: Prevalence of clinically significant dyslipidaemia at both assessments**

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride &gt;2·0 mmol/L</td>
<td>58 (50%)</td>
<td>52 (50%)</td>
<td>0-003</td>
</tr>
<tr>
<td>Cholesterol &gt;5·5 mmol/L</td>
<td>67 (58%)</td>
<td>63 (61%)</td>
<td>5-11%</td>
</tr>
<tr>
<td>HDL cholesterol &lt;0·9 mmol/L</td>
<td>24 (23%)</td>
<td>26 (25%)</td>
<td>8-17%</td>
</tr>
<tr>
<td>Increased triglyceride and cholesterol</td>
<td>44 (38%)</td>
<td>51 (49%)</td>
<td>2-5%</td>
</tr>
<tr>
<td>Increased triglyceride or cholesterol</td>
<td>78 (67%)</td>
<td>77 (74%)</td>
<td>12 (26%)</td>
</tr>
</tbody>
</table>

*Comparisons between protease-inhibitor recipients and protease-inhibitor-naïve patients at each timepoint. There was no significant difference within either group over time.
alter significantly in protease-inhibitor recipients over time. Demographic variables were well matched between the subgroups of patients receiving the various protease-inhibitor regimens. There was no significant difference between any two groups in body-fat measures or lipodystrophy score at follow-up (data not shown). The only metabolic variable that differed was triglyceride concentration, which was significantly greater in those receiving ritonavir and saquinavir than in those receiving indinavir, nelfinavir, or nelfinavir-saquinavir combination (5·6 mmol/L, 2·8 mmol/L, 2·7 mmol/L, and 3·4 mmol/L, respectively; all p<0·05).

**Prediction of lipodystrophy severity**

The durations of protease-inhibitor therapy and of HIV-1 infection were significantly associated with a greater severity of lipodystrophy (table 3). There was no association between lipodystrophy severity and baseline or current CD4-cell count or viral load. In the multiple regression model of age, duration of HIV-1 infection, weight, CD4-cell count, and viral load before protease-inhibitor therapy, duration of protease-inhibitor therapy, and AIDS status, the significant independent predictors of current total fat mass were duration of protease-inhibitor therapy (β=−0·25, p=0·03), and weight and CD4-cell count before protease-inhibitor therapy (β=−0·29, p=0·005 and β=−0·01, p=0·02, respectively). This model explained only 34% of the variance in current total fat mass.

Current triglyceride and HDL-cholesterol concentrations were significantly associated with both the presence and severity of lipodystrophy (table 3). Triglycerides and C-peptide at the 1997 assessment were both significantly associated with current lipodystrophy severity (table 5).

**Discussion**

We found that self-assessment by patients, physical examination, fasting triglycerides and C-peptide, and central abdominal fat mass measured by DEXA were useful in the diagnosis of lipodystrophy syndrome. Predictors of subsequent lipodystrophy severity included weight before protease therapy, the duration of therapy, and fasting triglyceride and C-peptide concentrations on therapy. After almost 2 years of potent HIV-1 protease-inhibitor-containing therapy, lipodystrophy was very common, was progressive in most cases, did not resolve spontaneously, and was rated as severe by 11% of patients. There were many cases of hyperlipidaemia and disturbances in glucose homeostasis likely to place a substantial proportion of patients at risk of cardiovascular disease and diabetic complications.

Patients and clinicians were in agreement (98%) on the diagnosis of lipodystrophy. Our data may be biased, however, because only two experienced clinicians examined patients for lipodystrophy, and our patients, particularly the protease-inhibitor recipients with abnormal physical features, might have been better informed about the syndrome than others. The comparability between patients’ and clinicians’ diagnoses when large numbers of physicians are involved is being studied.

Total body fat mass could not be used to distinguish between mild and absent lipodystrophy owing to its wide normal variability; however, estimation of fat mass before and some time after the start of therapy may be informative. The greater fasting triglyceride and C-peptide concentrations and central abdominal fat mass in patients with mild lipodystrophy than in those with no lipodystrophy suggest that patients’ perceptions were correct and more sensitive than most DEXA measures. Because of the lack of a validated diagnostic standard, the sensitivity, specificity, and predictive powers of these measures could not be calculated. On the basis of these data, we propose a working case definition of the lipodystrophy syndrome, which requires further study (panel).

Patients’ ratings agreed better with peripheral than with central fat measurements. Central fat on DEXA shows both declining subcutaneous and accumulating intra-abdominal fat. A better association with central fat might be seen on computed tomography, which can reliably define both fat stores.1 Also, changes in the dorsocervical fat pad or the face will not be recorded by DEXA. The scoring system may also be imperfect because of differing patients’ perceptions of severity, although we believe that it is a patient’s assessment of a visible problem that is more likely to affect therapy decisions. The scoring system did not assess breast-fat accumulation because few women were available to be studied.

**Proposed case definition for protease-inhibitor-related lipodystrophy syndrome**

**Physical features**

Clinical evidence (physical examination or patient’s report) of one or more of the following since the start of HIV-1 protease-inhibitor therapy

- Fat wasting of the face, arms, legs, or buttocks (possibly with prominence of leg and arm veins)
- Fat accumulation in the abdomen or over the dorsocervical spine

**Metabolic features**

One or more of the following since start of HIV-1 protease-inhibitor therapy

- Fasting hyperlipidaemia (cholesterol >5·5 mmol/L or triglyceride >2·0 mmol/L)
- Fasting C-peptide >2·5 mmol/L
- Impaired fasting glucose (6·1–7·0 mmol/L) or diabetes mellitus (>7·0 mmol/L) on fasting blood glucose
- Impaired glucose tolerance (7·8–11·1 mmol/L) or diabetes mellitus (>11·1 mmol/L) on 2 h blood glucose by oral glucose tolerance test

Patients should not have any of the following within 3 months of assessment

- AIDS-defining event or other severe clinical illness
- Anabolic steroids, glucocorticosteroids, immune modulators
Fasting triglyceride and C-peptide concentrations at a mean 13-6 months of therapy predicted lipodystrophy severity at 21 months. This finding should allow patients at high risk of developing severe lipodystrophy to be identified early in therapy. However, we still need to find out when these markers become predictive. The association of lower weight before protease-inhibitor therapy with subsequent severity suggests that patients’ characteristics play a part in expression of the syndrome.

Hyperlipidaemia or diabetes associated with protease-inhibitor therapy has been reported to occur within weeks.10-13,15 We found a high rate of abnormal glucose homeostasis, most after glucose loading, and that no readily measurable variable, such as lipodystrophy severity or hyperlipidaemia, was associated with diabetes or impaired glucose tolerance. Patients on stable HIV-1 protease-inhibitor therapy should therefore have fasting lipids and glucose tolerance assessed (perhaps by an oral glucose tolerance test). Increasing peripheral fat wasting, central adiposity, and insulin resistance may incur additional risks for diabetes over time, which suggests that metabolic assessments should be repeated regularly.

The 83% prevalence of lipodystrophy after only 21 months of therapy is worrying if antiretroviral therapy needs to be life-long. The increased prevalence was not due to inclusion of buffalo hump as a criterion, because no patient had this feature in isolation. Although overall lipodystrophy was reported as severe in only 11% of patients, it was regionally severe in 25%. The fact that lipodystrophy was severe in only a tenth of patients may explain its lower prevalence in other studies that did not use questionnaires.1,7

The mean rate of fat loss in the second year of protease-inhibitor therapy was 0·13 kg per month. This rate is less than the 0·40 kg per month estimated over the first 13·6 months of therapy.1 Fat wasting must have finite limits, however, so the rate of fat loss should decline with increasing duration of therapy. Switching or cessation of protease-inhibitor therapy was not the reason (data not shown). The difference could, of course, reflect the use of prospective data. This decline in fat loss, and apparent fat gain in some patients, suggests the presence of compensatory mechanisms for fat loss induced by protease inhibitors.

Hyperlipidaemia at degrees associated with cardiovascular morbidity occurred in 74% of protease-inhibitor recipients. Our cut-offs may be conservative because cholesterol concentrations above 5·0 mmol/L and triglyceride concentrations above 1·6 mmol/L have been identified as clinically significant.16-23

Abnormalities in glucose homeostasis were found in 23% of protease-inhibitor recipients. Few protease-inhibitor-naive patients had oral glucose tolerance assessed and therefore no controlled comparison was possible. However, less than 1% of healthy Australian men of similar age and body-mass index have diabetes, and less than 3% have impaired glucose tolerance.24 Development of glucose intolerance seemed to be due to increasing insulin resistance, as is often the case in people without HIV-1 infection.11 The question of why insulin secretion should be unable to compensate for insulin resistance deserves investigation. Possibilities include therapies toxic to pancreatic islet cells, such as pentamidine8 and didanosine, and increased circulating lipids that not only interfere with glucose uptake in myocytes but may also impair islet-cell insulin secretion.11

Nelfinavir, with or without saquinavir, caused all components of the syndrome with severity similar to indinavir, and ritonavir plus saquinavir, after 21 months of therapy. Earlier in therapy, however, all outcome measures were significantly worse in patients receiving ritonavir and saquinavir than those on indinavir.1 This finding suggests that the final outcome with any regimen is similar, but that onset is more rapid with ritonavir and saquinavir than with either indinavir or nelfinavir. Switching of therapies between assessments in many patients may have confounded this finding.

Our study had other limitations. Patients were not randomised to protease-inhibitor therapy, so we cannot exclude confounding by unmeasured variables that differed between groups. We were unable to compare formally the effects of various protease inhibitors, and could only estimate the rates of fat loss over time. When metabolic values plateau after starting therapy is unclear, particularly for glucose tolerance, which was only studied once.

Longer-term follow-up is required to assess whether macrovascular and microvascular complications of impaired glucose tolerance and hyperlipidaemia will develop. The combination of insulin resistance and hyperlipidaemia may synergistically accelerate any risk of vascular disease. Attention to other factors that can accelerate vascular disease, such as smoking, physical inactivity, and hypertension is advisable. We recommend that all patients receiving HIV-1 protease inhibitors have glucose homeostasis and fasting lipids assessed early in therapy and regularly (perhaps annually) thereafter.

References
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incidence, risks and endocrinologic evaluation. 5th Conference on Retroviruses and Opportunistic Infections, Chicago, February, 1998 (abstr 408).


