Incidence of morphological and lipid abnormalities: gender and treatment differentials after initiation of first antiretroviral therapy

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Objective To provide population-based incidence estimates for constituent symptoms of human immundeficiency virus (HIV)-related lipodystrophy syndrome and to identify possible independent predictors of accrued cases.

Design Prospective population-based cohort.

Methods Study subjects were antiretroviral-naive individuals who initiated treatment between October 1998 and May 2001 and provided completed self-reported data regarding the occurrence of lipoatrophy, lipohypertrophy and increased triglyceride and cholesterol levels. Possible predictors of incident lipoatrophy, lipohypertrophy, dyslipidaemia and mixed lipodystrophy (symptoms of both lipoatrophy and lipohypertrophy) were identified using logistic regression modelling. A sub-analysis restricted to subjects retaining original treatment at study completion was conducted using similar methods.

Results Among the 366 study subjects, cumulative incidence was 29% for lipoatrophy, 23% for lipohypertrophy, 9% for dyslipidaemia, and 13% for mixed lipodystrophy after a median duration of 12 months of antiretroviral therapy. In an intent-to-treat analysis incident lipoatrophy and lipohypertrophy were independently associated with initiation of protease inhibitor (PI)-containing regimens, (adjusted odds ratio [AOR] = 1.94; 95% CI: 1.25–3.03 and AOR = 1.76; 95% CI: 1.09–2.85, respectively) and female gender (AOR = 2.06; 95% CI: 1.03–4.12 and AOR = 2.36; 95% CI: 1.17–4.74, respectively). Both mixed lipodystrophy and reported dyslipidaemia were associated only with PI inclusion in the initial regimen (AOR = 2.27; 95% CI: 1.14–4.53 and AOR = 2.14; 95% CI: 1.26–3.65, respectively). Similar results were obtained in analysis of individuals retained in initial treatment groups throughout follow-up.

Conclusion Incident morphological and lipid abnormalities are common among individuals initiating first-time antiretroviral therapy. Use of PI was consistently associated with all lipodystrophy-related abnormalities after adjustment for a broad range of patient personal, clinical and treatment characteristics.

Keywords Lipodystrophy, dyslipidaemia, antiretrovirals, protease inhibitors

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Standard care with highly active triple combination antiretroviral therapy for human immunodeficiency virus (HIV) infection has been linked to the emergence of morphological and lipid abnormalities often appearing in constellation as a syndrome of HIV-associated lipodystrophy.1 Morphological changes include
localized lipohypertrophy of the abdomen, breasts and dorso-
cervical region, and peripheral lipatrophy of the face, buttocks,
arms and legs. 1–3 Metabolic changes include increased cholesterol
and triglyceride levels. 1–3

Cross-sectional and retrospective analyses indicate prevalence
rates ranging from <10% to >80% for these abnormalities (for
a review see ref. 4). While the aetiology of these abnormalities
remains obscure, reports have identified increased risk associated
with exposure to protease inhibitors (PI),1,2,5–8 and nucleoside
analogue reverse transcriptase inhibitors (NRTI)7,9–11 among
other factors.

Inconsistencies in study findings may be due to variations
in diagnostic criteria or outcomes assessment. While objective
methods such as dual energy X-ray absorptiometry (DEXA),
computed tomography (CT), and magnetic resonance imaging
(MRI) have been used, the resulting data is not well standard-
ized in the context of HIV-associated lipodystrophy. These tech-
niques can also be prohibitively costly and difficult to access.
Therefore, many larger studies have relied on patient self-report
and subjective/semi-qualitative clinical examination.6,11–18 Patient
self-report, while subject to misclassification, has been shown to
be highly concordant with clinical findings of morphological
abnormalities.5 Variability may also be due to differences in study
design. Many aetiological investigations have relied on cross-
sectional,10,13,16,19 and/or retrospective17,18,20 analyses or
have included highly selected study subjects.15,18,20

Neither the incidence of lipodystrophy-associated abnormalities
nor the possible predictors of emerging symptoms subse-
quent to first initiation of standard therapy have been well
described. Here we report the cumulative incidence and possible
predictors of lipodystrophy-associated symptoms and lipid
abnormalities based on prospective self-report data from an
observational cohort of people initiating a variety of antiretro-
viral regimens.

Methods

In British Columbia, Canada, the distribution of antiretrovirals
free of charge to all eligible province residents is centralized in a
provincial HIV/AIDS drug treatment programme. All patients
are registered in the programme when first prescribed any anti-
retroviral agent. A complete prospective record of all therapies
prescribed is maintained in addition to demographic and clinical
data. Consenting patients provide additional information,
including the occurrence of known or suspected adverse drug
effects, through annual voluntary self-administered question-
naires. Since October of 1998, these have included symptoms and
laboratory abnormalities associated with lipodystrophy
syndrome including lipoatrophy of the face, arms or legs,
lipohypertrophy (weight gain in the abdomen or breasts and/or
buffalo hump) and increased cholesterol and triglycerides.
All data is, therefore, based on patient self-report which may be
particularly problematic for accuracy of reported lipid abnor-
malities. To assess the accuracy of self-reported dyslipidaemia
survey responses were compared to actual laboratory values for
134 individuals with laboratory data available within 3 months
prior to survey. Of those reporting high cholesterol or high
triglycerides 94% and 84% had laboratory values indicating
high cholesterol (defined as >5.2 mm/dl) or triglycerides
(defined as >2.3 mm/dl), respectively. These findings indicate a
low rate of false positives for self-reported dyslipidaemia in this
study.

The study population for the present analysis included antiretroviral-naïve individuals who initiated treatment
between October 1998 and May 2001 and provided completed
data regarding the occurrence of adverse drug effects at least
3 months and no more than 24 months after therapy initiation.

A broad range of socio-demographic and clinical charac-
teristics were investigated in preliminary bivariate analyses. These
included patient age, ethnicity, gender, employment status, edu-
cation level, transmission risk group, plasma viral load (pVL)
and CD4 cell count at baseline, and change in pVL and CD4
over follow-up. Treatment variables assessed included initial
prescription of therapy by regimen makeup, therapy class in-
clusion (PI, NRTI and non-nucleoside analogue reverse
transcriptase inhibitors [NNRTI]) and total duration by class and
by agent for each of four PI, five NRTI and three NNRTI.
Variables significant at the P < 0.05 level were offered for in-
clusion in logistic modelling to assess independent contributions
to each of four incidence outcomes: lipatrophy; lipohyper-
trrophy; dyslipidaemia; and mixed lipodystrophy (defined as
having both peripheral lipoatrophy and one or more areas of
lipohypertrophy).

Initial models followed the intent-to-treat principal, retaining
all subjects grouped for analysis by initial treatment regimen.
This approach has been used to gain information on lipodystrophy-
associated abnormalities in clinical trials and is useful in com-
paring the results of these trials to those obtained by other
methods. A sub-analysis was restricted to those people who
remained on the initial treatment regimen throughout follow-
up. This approach ensures that confounding or other complex
treatment-related phenomena that may arise as a result of
multiple therapy switches or temporary therapy cessation are
minimized.

Results

Table 1 summarizes initial prescribed regimens, the proportion
of subjects remaining on initially prescribed therapy and
duration of follow-up for the 366 subjects eligible for analysis.
Thirty per cent of individuals initiated antiretroviral treatment
with regimens including two or three NRTI and one NNRTI,
49% with two or three NRTI plus a PI, 10% used two PI includ-
ing Ritonavir as a boosting agent, and 11% were restricted to
dual PI therapy. Overall, 59% of subjects initiated therapy
with PI-containing regimens, 30% with NNRTI, and 100%
utilized NRTI inclusive regimens. In terms of non-treatment
characteristics median age was 38 years, 68% were Caucasian,
89% male, 52% had greater than a high school education and
47% were employed. Median CD4 count at entry was 320
cells/mm3 (interquartile range: 100–430), median pVL was
66 500 copies/ml and 16% had been diagnosed as having
AIDS. Over the course of follow-up the median decline in
pVL was 66 298 copies/ml and CD4 cell counts increased by
120 cells/mm3.

In total 216 (59%) of those initiating treatment remained on
their first prescribed regimen at follow-up. These subjects did
not differ substantially from the study group overall in terms of
baseline characteristics or changes in laboratory markers (data
not shown).
After a median duration of therapy of 12 months (range: 3–23 months) the cumulative incidence was 29% for lipohypertrophy, 23% for lipoatrophy, 9% for increased cholesterol or triglycerides and 13% for mixed syndrome. The occurrence of lipid abnormalities and of morphological changes appear to be independent, with those having morphological abnormalities at no greater risk of concomitant lipid disturbances ($\chi^2 P = 0.299$).

Table 2 summarizes the findings of multivariate analysis for each of lipohypertrophy, lipoatrophy, dyslipidaemia and mixed lipodystrophy in the cohort overall. Both incident lipoatrophy and lipohypertrophy were independently associated with use of PI containing regimens (adjusted odds ratio [AOR] = 1.94; 95% CI: 1.25–3.03 and AOR = 1.76; 95% CI: 1.09–2.85, respectively). Risk of lipoatrophy and lipohypertrophy were also significantly greater for women (AOR = 2.06; 95% CI: 1.03–4.12 and AOR = 2.36; 95% CI: 1.17–4.74, respectively). Mixed lipodystrophy was associated only with PI inclusion in the treatment regimen (AOR = 2.27; 95% CI: 1.14–4.53) as was the occurrence of dyslipidaemia (AOR = 2.14; 95% CI: 1.26–3.65).

In the sub-sample of individuals remaining on initial treatment throughout follow-up univariate analysis revealed PI use, female gender and use of triple therapy to be significantly associated

Table 1 | Initial treatment regimens and duration of follow-up

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n (%)</th>
<th>On initial therapy at follow-up n (%)</th>
<th>Person-months follow-up on initial therapy</th>
<th>Total person-months follow-up$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or 3 NRTI$^b$/1 NNRTI$^c$</td>
<td>109 (30)</td>
<td>78 (72)</td>
<td>968</td>
<td>1375</td>
</tr>
<tr>
<td>2 or 3 NRTI/1 PI$^d$</td>
<td>176 (49)</td>
<td>106 (60)</td>
<td>1948</td>
<td>2330</td>
</tr>
<tr>
<td>2 or 3 NRTI/PI/Ritonavir</td>
<td>39 (11)</td>
<td>18 (46)</td>
<td>323</td>
<td>491</td>
</tr>
<tr>
<td>2 NRTI only</td>
<td>39 (11)</td>
<td>14 (36)</td>
<td>333</td>
<td>406</td>
</tr>
</tbody>
</table>

Pl (n = 217)

| Indinavir | 141 (39) | 94 (67) | 1639 | 1900 |
| Nelfinavir | 35 (10) | 23 (66) | 247 | 377 |
| Saquinavir | 31 (9) | 22 (67) | 333 | 406 |
| Ritonavir | 49 (13) | 29 (59) | 415 | 636 |

NNRTI (n = 111)

| Nevirapine | 104 (28) | 91 (88) | 905 | 1231 |
| Delavirdine | 1 (0) | 1 (100) | 10 | 25 |
| Elavirenz | 7 (2) | 6 (86) | 65 | 148 |

NRTI (n = 366)

| Stavudine | 328 (70) | 225 (88) | 2493 | |
| Didanosine | 50 (14) | 36 (72) | 456 | 642 |
| ddC | 29 (1) | 15 (50) | 25 | 25 |
| AZT | 104 (28) | 75 (72) | 1040 | 1289 |
| 3TC | 308 (84) | 280 (91) | 2998 | 3894 |

$^a$ For individuals initiating therapy with specified regimen format.

$^b$ Nucleoside analogue reverse transcriptase inhibitor.

$^c$ Non-nucleoside analogue reverse transcriptase inhibitor.

$^d$ Protease inhibitor.

Table 2 | Possible predictors of incident symptoms among 366 participants in intent to treat and 216 participants remaining on initial treatment regimen

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intent to treat</th>
<th>Remaining on initial regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AOR$^a$</td>
<td>95% CI</td>
</tr>
<tr>
<td>Lipoatrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI$^b$ class</td>
<td>1.94</td>
<td>1.25–3.03</td>
</tr>
<tr>
<td>Female</td>
<td>2.06</td>
<td>1.03–4.12</td>
</tr>
<tr>
<td>Lipohypertrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI class</td>
<td>1.76</td>
<td>1.09–2.85</td>
</tr>
<tr>
<td>Female</td>
<td>2.36</td>
<td>1.17–4.74</td>
</tr>
<tr>
<td>Lipid abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI class</td>
<td>2.14</td>
<td>1.26–3.65</td>
</tr>
<tr>
<td>Mixed lipodystrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI class</td>
<td>2.27</td>
<td>1.14–4.53</td>
</tr>
</tbody>
</table>

$^a$ Adjusted odds ratio.

$^b$ Protease inhibitor.
with various outcomes of interest. For purposes of direct comparison, in final model building runs PI use was forced into all models and gender was included in those for lipohypertrophy and lipoatrophy. No other variables retained significance after adjustment for these variables. As shown in Table 2, trends were consistent with those noted in the comprehensive analysis. However, PI use and gender displayed marginal significance except for the relationship between PI use and lipoatrophy (AOR = 2.08; 95% CI: 1.11–3.56).

Discussion

Our results indicate a high incidence of morphological and lipid abnormalities among those initiating first-time antiretroviral therapy. Few comparable estimates of incidence are available, although reported figures are in agreement with the data presented here. A similar study of therapy-naïve patients initiating triple drug regimens reported a prevalence of morphological changes identified subjectively by both physician and patient of 17% after a median of 18 months of therapy. Similarly, a study of 121 people treated with triple therapy for primary HIV infection reported a cumulative incidence of morphological changes of 18% at 24 months based on clinical exam. Studies conducted among non-naïve subjects utilizing PI inclusive therapy report comparable rates of incidence.

Multivariate analyses indicate PI class exposure in each of the symptom groups examined here. While some studies have not implicated treatment-related factors in the occurrence of morphological abnormalities, the majority have identified specific PI or PI use in general as possible predictors of prevalent symptoms. Studies utilizing symptom-specific analyses have also noted associations between duration of PI exposure in both lipoatrophy and abdominal obesity, and PI-containing highly active antiretroviral therapy (HAART) duration and any lipodystrophy and lipoatrophy. One study of HAART-exposed individuals has reported significantly increased risk of lipohypertrophy with PI class therapy. Reported dyslipidaemia in our cohort was also independently associated only with use of PI-inclusive regimens. These findings are consistent with the known effects of PI on lipid profiles and prior reports describing lipid abnormalities among those with treatment-related lipodystrophy.

The occurrence and differential rates of presentation of lipodystrophy symptoms among women have been well described. Unfortunately, many aetiological studies have not included substantial numbers of female subjects or have not assessed gender as an independent variable. Despite restricted power in our study (n = 40), we noted a greater than twofold increased risk of both lipoatrophy and lipohypertrophy among women. Martinez et al. have similarly reported a relative hazard of 1.87 among women for lipodystrophy overall among naïve subjects exposed to PI inclusive triple therapy. Three other studies that have included analysis by gender noted no increased risk among women, however, these studies were also limited by power constraints. While reporting bias is a possible explanation for our findings, no increased risk of mixed lipodystrophy among women was noted suggesting that simple over-reporting is not likely to have occurred.

The data presented here do not indicate a role of immune reconstitution as indicated by improvements in pVL and/or CD4 cell count in the development of symptoms as has been suggested in some reports. It is important to note that such previously published results were not adjusted for treatment adherence and that our findings are consistent with those of further studies.

The data reported here is based on patient self-report, and therefore subject to the limitations of this methodology. However, identification of morphological abnormalities in clinical practice and large cohort studies is likely to remain reliant on relatively subjective measures. Moreover, patient assessment of morphological abnormalities has been shown to correspond well to the findings of physical exam. It should be noted, however, that under-reporting of abnormal lipids may be problematic if physicians do not communicate these findings to patients or if recall among patients is poor.

The data presented here indicate a high incidence of lipodystrophy-associated abnormalities among those initiating antiretroviral therapy. Increased risk associated with initiation of PI-inclusive regimens and among women is cause for concern. The long-term clinical consequences of these disorders are not clear at this time. However, morphologically defined lipodystrophy has been associated with cardiovascular risk factors such as increased fasting insulin levels and diastolic blood pressure, impaired glucose tolerance, diabetes and hypertriglyceridaemia among HIV positive subjects. Moreover, there is some evidence that women may be more susceptible to the adverse metabolic effects of PI-containing regimens. Clearly, large prospective studies of women need to be undertaken to determine whether the traditional consideration of female gender as a protective factor in terms of cardiovascular risk applies equally to those receiving PI-inclusive antiretroviral therapy for HIV infection.

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KEY MESSAGES

- A population-based estimate indicates that symptoms or abnormalities consistent with human immunodeficiency virus (HIV)-associated lipodystrophy syndrome may occur in up to 29% of antiretroviral-naïve patients 12 months after initiation of triple antiretroviral therapy for HIV disease.
- Both morphological and metabolic abnormalities are strongly associated with the inclusion of a protease inhibitor in the therapeutic regimen whereas neither nucleoside nor non-nucleoside use were associated with increased risk of these adverse effects.
- Women may be at increased risk of morphological symptom development or early symptom development. However, this finding requires validation in cohorts with larger numbers of women.

References