Metabolic complications of antiretroviral therapy
van der Valk, M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)
Increased risk of lipodystrophy when including nucleoside analogue reverse transcriptase inhibitors in the treatment of HIV-1 infection with protease inhibitors

M. van der Valk, E.H. Gisolf, P. Reiss, F.W.N.M. Wit, A. Japour, G.J. Weverling and S.A. Danner on behalf of the Prometheus study group*

*AIDS 2001, 15:847-855*
Author's affiliations

E.H. Gisolf, F.W.N.M. Wit
International Antiviral Therapy Evaluation Center (IATEC), Academic Medical Center, Amsterdam, the Netherlands;

P. Reiss, S.A.Danner
Division of Infectious Diseases, Tropical Medicine and AIDS, Department of Internal Medicine, Academic Medical Center, Amsterdam, the Netherlands

A.Japour
ABBOTT Laboratories, Abbott Park, IL, USA

G.J.Weeverling
Department of Clinical Epidemiology and Biostatistics, University of Amsterdam, the Netherlands.

* Prometheus study team listed at the end of this chapter
Introduction

The use of protease inhibitor (PI)-containing combination antiretroviral therapy has recently become associated with increasing reports of a lipodystrophy syndrome, which involves central fat accumulation and peripheral fat wasting. [1-3] These changes in body fat distribution and the frequently accompanying metabolic disturbances such as hyperlipidemia have generally been attributed to the use of a PI, given the temporal relationship between the widespread introduction of PIs and initial reports of the syndrome. It is important to realise however that patients who develop lipodystrophy syndrome while taking PIs, almost always are concomitantly receiving treatment with nucleoside analogue reverse transcriptase inhibitors (NRTIs), and frequently will also have had extensive prior NRTI-exposure. Several observations suggest that NRTIs may independently contribute to the development of this syndrome. First, several observational cohort studies have shown duration of exposure to NRTIs to be an independent risk factor in the development of the syndrome during the use of PI-containing therapy.[4-6] Second, the lipodystrophy syndrome is increasingly being reported in patients who have never been exposed to PIs.[7-9]

Results from randomised clinical trials which may clarify the relative contribution of PIs and NRTIs in the development of the lipodystrophy syndrome are not yet available. The long-term follow-up of patients enrolled in the Prometheus study provided a unique opportunity to address this issue as patients in this trial, half of whom had never received prior antiretroviral treatment, were randomly assigned to treatment with either the PIs ritonavir (RTV) plus saquinavir hard gel capsules (SQV) alone, or RTV/SQV plus the NRTI stavudine (d4T).
Methods

Study design

The Prometheus study was a multicenter, open-label, randomised controlled trial, the main results of which have recently been reported.[10] In short, patients were eligible if they had documented HIV-1 infection, were 18 years of age or older and had not used PIs and/or d4T prior to study entry. Participants were randomly assigned to either RTV 400 mg twice daily (BID) plus SQV 400 mg BID or RTV 400 mg BID plus SQV 400 mg BID plus d4T 40 mg BID (30 mg BID if body weight <60 kg). Before randomisation, patients were stratified according to their antiretroviral treatment history, baseline serum HIV-1 RNA, and baseline CD4+ T-cell count. Patients could intensify treatment after 12 weeks of follow-up by adding wherever possible two new NRTIs or non-nucleoside reverse transcriptase inhibitors to their regimen. During each scheduled visit, blood total cholesterol and triglyceride levels were obtained. Fasting was not mandated for blood draws. Standardised follow-up and data collection was continued in all instances, including in patients who prematurely discontinued study medication. After the original 48-week follow-up, the protocol was extended to continue standardised data collection every 12 weeks up to week 96. Enrolment began in January 1997 and the last patient completed 96 weeks of follow up in December 1999. During the study, lipodystrophy was reported prospectively by the treating physician. Lipodystrophy was considered to be present when the physician judged the patient’s body appearance to be compatible with that diagnosis.

During the initial 48 weeks of follow up (i.e. before general awareness of the syndrome in the HIV physician and patient community), lipodystrophy would only have been prospectively reported as a study-associated adverse event. When follow up was extended for a second year, the lipodystrophy syndrome had meanwhile become widely recognised and lipodystrophy was now pre-printed on the study data
collection forms, requesting the physicians to purposely to indicate its presence or absence at every follow-up visit. All study physicians were made actively aware of this change in data collection for lipodystrophy during study site visits. In addition, following the first analysis of prospectively collected information, in May/June of 2000, physicians were asked to review retrospectively the clinical records of every patient that they had reported to have developed lipodystrophy. They were requested to complete a questionnaire that queried whether the lipodystrophy reported had been composed of solely lipoatrophy of the face, arms, legs, or buttoc, or solely fat accumulation in the abdomen, breasts or elsewhere, or both.

The protocol and all amendments were approved by the institutional review boards of all participating institutions. All patients gave written informed consent.

Statistical analysis

For the primary analysis, patients were analysed according to their randomly assigned treatment regimen. In addition, analyses of subgroups were performed according to whether patients had been antiretroviral naive or RTI-experienced at study entry. Furthermore, to study the relative risk of concurrent exposure to NRTIs and PIs versus sequential exposure to NRTIs and PIs, the occurrence of lipodystrophy in antiretroviral naïve patients randomised to RTV/SQV/d4T was compared with that in NRTI-experienced patients randomised to RTV/SQV alone. Time to onset of lipodystrophy was reported as median and interquartile ranges (IQR). Kaplan-Meier curves, which were based on the prospectively reported presence of lipodystrophy, were generated to indicate the time to onset of lipodystrophy, stratified by treatment regimen. Patients who were not reported to have developed lipodystrophy were censored at their last follow-up visit. P-values were calculated using the log rank test.
For the analysis of blood lipid concentrations, determinations of triglycerides and cholesterol were only considered for the period in which patients were taking randomised treatment which could include treatment intensification as described above. In order to correct for intraindividual variation in lipid concentrations (given the uncertainty as to whether bloods had been drawn fasting or not), the median of the triglyceride and cholesterol levels obtained between weeks 3 and 48 were calculated for each patient. The difference was then calculated between the value obtained at baseline and this median, as a measure of the absolute change in triglycerides and cholesterol following the initiation of treatment.

Baseline serum HIV-1 RNA levels and CD4 cell counts, as well as the changes in these markers during treatment, are reported as median and IQR and compared between the treatment groups as randomised, using the Wilcoxon's two-sample test. This analysis was limited to the initial 48 weeks of treatment as HIV-1 RNA determinations were performed in a single central laboratory using a single assay (Roche Amplicor) only during this period, but not thereafter.

Potential risk factors for development of lipodystrophy were explored by univariate Cox proportional hazard analysis. Patients who were not reported to have developed lipodystrophy were censored at their last follow-up visit. Parameters considered as potential predictors of lipodystrophy were treatment arm, age, gender, prior treatment with NRTIs, total duration of NRTI-exposure, baseline cholesterol and triglyceride levels and increases in cholesterol and triglyceride concentrations during treatment. Variables with a \( P \) value less than 0.15 in the univariate analysis were entered in a multivariate model. All calculated \( P \)-values were two-tailed and considered statistically significant if \( P < 0.05 \).

Data were analysed using the SAS software package (version 6.12, SAS Institute, Cary, North Carolina, USA).
Lipodystrophy in treated HIV-infected patients

Results

Patient disposition, baseline characteristics and treatment intensification regimen

Of the total 208 patients randomised into the Prometheus study, six patients who never started randomised treatment (one in the RTV/SQV arm, five in the RTV/SQV/d4T arm) were excluded (Figure 1). Another 27 patients with incomplete data through 96 weeks of follow-up were likewise excluded from the current analysis, in the majority of cases because they had become lost to follow-up, or had withdrawn consent for further data collection during the initial 48 week study period or the subsequent long-term follow-up. These latter patients were comparable at baseline to the remaining 175/202 (87%) patients included in the current analysis, with respect to treatment randomisation, stage of HIV infection, and prior treatment with NRTIs. At baseline, patients in the two treatment arms were comparable with respect to demographic characteristics, serum HIV-1 RNA level and CD4 cell count (Table 1).

Baseline HIV-1 RNA was significantly higher in patients who were antiretroviral naïve compared with those with prior antiretroviral experience (median HIV-1 RNA 4.6 log\textsubscript{10} copies/ml (IQR 4.2-5.1) vs. 4.2 log\textsubscript{10} copies/ml (IQR 3.5-4.7) (p=0.0001, Wilcoxon two-sample test)). Baseline CD4\textsuperscript{+} cell counts were 255 x 10\textsuperscript{6} cells/l (IQR 90-445) and 243 x 10\textsuperscript{6} cells/l (IQR 133-328) in the naïve and experienced patients, respectively (p=0.29).

Of the antiretroviral experienced patients, all had been exposed to zidovudine (median exposure 94 weeks), 56% to zalcitabine (57 weeks), 41% to lamivudine (30 weeks), 26% to didanosine (23 weeks), 9% to nevirapine (34 weeks), and 7% to loviride (104 weeks).
### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>RTV/SQV (n=87)</th>
<th>RTV/SQV/d4T (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (IQR) age (years)</strong></td>
<td>37 (33-46)</td>
<td>36 (31-45)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75 (86%)</td>
<td>73 (83%)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (14%)</td>
<td>15 (17%)</td>
</tr>
<tr>
<td><strong>Risk for HIV-1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual contacts</td>
<td>60 (69%)</td>
<td>58 (66%)</td>
</tr>
<tr>
<td>Heterosexual contacts/ endemic area</td>
<td>23 (26%)</td>
<td>23 (26%)</td>
</tr>
<tr>
<td>IV drugs</td>
<td>3 (3%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td><strong>CDC stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>38 (44%)</td>
<td>38 (43%)</td>
</tr>
<tr>
<td>B</td>
<td>27 (31%)</td>
<td>29 (33%)</td>
</tr>
<tr>
<td>C</td>
<td>29 (25%)</td>
<td>21 (24%)</td>
</tr>
<tr>
<td><strong>Antiretroviral experience</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naive</td>
<td>44 (51%)</td>
<td>50 (57%)</td>
</tr>
<tr>
<td>Experienced</td>
<td>43 (49%)</td>
<td>38 (43%)</td>
</tr>
<tr>
<td><strong>Median (IQR) serum HIV-1 RNA (copies/ml)</strong></td>
<td>4.3 (3.9-5.0)</td>
<td>4.5 (4.0-4.8)</td>
</tr>
<tr>
<td><strong>Median (IQR) CD4+ cells (cells/mm³)</strong></td>
<td>255 (130-410)</td>
<td>235 (115-370)</td>
</tr>
</tbody>
</table>

RTV = ritonavir; SQV = saquinavir (hard gel capsules); d4T = stavudine; IQR = interquartile range

In the RTV/SQV arm (n=87) 24% of patients remained on randomised treatment throughout 96 weeks; 46% intensified treatment after a median of 25 weeks (IQR 22–49), and 30% prematurely discontinued study medication at some point during the 96 weeks of follow-up. In the RTV/SQV/d4T arm (n=88) 60% remained on randomised treatment, 7% intensified treatment after a median of 41 weeks (IQR 22–49), and 33% prematurely discontinued study medication (Figure 1). Intensification for all patients in the RTV/SQV/d4T arm was with lamivudine. In patients randomised to RTV/SQV alone, intensification included d4T in 36/40 patients (90%). Of the 4 remaining patients, 3 intensified treatment with zidovudine and lamivudine, and one with lamivudine alone.
Figure 1 Patient disposition

The top part of the figure shows the disposition of all 208 patients randomised into the study, and the reasons for only 175 patients remaining for analysis with data available for 96 weeks of follow up. The bottom part of the figure then illustrates the treatment characteristics of these remaining 175 patients at the completion of 96 weeks of follow up, in each of the two treatment arms. pt. = patients; RTV = ritonavir; SQV = saquinavir (hard gel capsules); d4T = stavudine; ART = antiretroviral therapy.
Chapter 2

HIV-1 RNA and CD4 cell responses during treatment

Following treatment no significant differences were observed in the degree of virus suppression and immune recovery that was achieved. HIV-1 RNA levels declined 1.9 log_{10} copies/ml (IQR 1.4-2.4) between week 0 and week 48 in the RTV/SQV arm (with 85% reaching serum HIV-1 RNA <400 copies/ml at week 48) and 2.1 log_{10} copies/ml (IQR 1.6-2.4) in the RTV/SQV/d4T arm (91% <400 copies/ml)(p=0.21). Median increases in CD4 cell counts between week 0 and week 48 were 160 x 10^6 cell/l (IQR 80-280) and 180 x 10^6 cell/l (IQR 120-290) for the RTV/SQV- and RTV/SQV/d4T arm, respectively (p=0.60).

Occurrence of lipodystrophy

Lipodystrophy was reported in a total of 29/175 (17%) patients during the 96 weeks of follow-up. It was more frequent in patients who were randomly assigned to treatment with RTV/SQV/d4T (22/88, 25%), than in patients assigned to treatment with RTV/SQV alone (7/87, 8%) (p=0.003, \( \chi^2 \) test). Likewise, when limiting the analysis to patients who were antiretroviral naive at enrolment, patients randomised to RTV/SQV/d4T (12/50, 24%) were significantly more likely to develop lipodystrophy than patients randomised to RTV/SQV alone (2/44, 5%)(p=0.008, \( \chi^2 \) test). Lipodystrophy was reported in 1/14 (7%) antiretroviral naïve patients, who continued treatment with nothing but RTV/SQV for the entire period of follow-up.

In the antiretroviral-experienced patients randomised to RTV/SQV alone, the duration of NRTI-exposure before study entry (median 98 weeks, IQR 53-214 weeks) was very similar to that of antiretroviral naïve patients randomised to RTV/SQV/d4T and thus exposed to NRTIs for the first time during the study (follow-up 96 weeks). The first group can be considered to have had sequential exposure to NRTIs and PIs, whereas the second group had concurrent exposure to NRTIs and PIs. Lipodystrophy was reported in 5/43 (12%) and 12/50 (24%) of these two
Lipodystrophy in treated HIV-infected patients

particular groups of patients, respectively (relative risk 2.06, 95% confidence interval (CI) 0.79-5.39).

Time to lipodystrophy

Lipodystrophy was reported after a median of 68 weeks (range, 49-96 weeks). There was a significant difference in the occurrence of lipodystrophy over time between patients randomised to RTV/SQV alone and those randomised to RTV/SQV/d4T (p=0.003, log rank test)(Figure 2a). The same difference was observed when the analysis was restricted to antiretroviral naïve patients reported significantly (p=0.009, log rank test)(Figure 2b).

Patients who intensified RTV/SQV therapy with d4T were followed for a median of 63 weeks (range 11-86 weeks) after the addition of d4T. Lipodystrophy occurred in 4/36 (11%) patients from this group a median of 42 weeks after the addition of d4T (range 28-81 weeks).

Risk factors for the development of lipodystrophy

In the multivariate Cox proportional hazard analysis, randomisation to RTV/SQV/d4T was found to be the strongest independent risk factor for the development of lipodystrophy (hazard ratio (HR) 3.83, 95% CI 1.61-9.14) (Table 2). Both baseline median cholesterol levels and median increases in these levels during treatment were higher in patients with lipodystrophy than in patients without lipodystrophy (baseline 4.9 mmol/l (IQR 4.2-5.3) versus 4.3 mmol/l (IQR 3.9-5.0) and increase 2.2 mmol/l (IQR 1.3-2.9) versus 1.3 mmol/l (IQR 0.8-2.0), respectively). Higher baseline cholesterol and higher increases in cholesterol levels during treatment were both independently associated with the development of lipodystrophy (HR 1.57, 95% CI 1.03-2.40 and HR 1.64, 95% CI 1.12-2.40, respectively). Having received antiretroviral therapy before enrolment, duration of prior treatment, use of a particular NRTI before study entry, gender, age, baseline CD4+ cell count, serum HIV-1
RNA, triglyceride level, and increase in triglyceride level during treatment, were not significantly associated with the development of lipodystrophy in the multivariate analysis.

**Figure 2 Kaplan-Meier analysis for lipodystrophy free-survival**

(a) analysis for all patients by treatment arm; (b) Analysis limited to antiretroviral therapy naive patients; RTV = ritonavir; SQV = saquinavir (hard gel capsules); d4T = stavudine; p = p-value log rank test; n = number of patients
In the antiretroviral naïve patients, randomisation to RTV/SQV/d4T (HR 6.65, 95%CI 1.47-30.1) and the increase in cholesterol during treatment (HR 2.47, 95%CI 1.25-4.88) were independently associated with the occurrence of lipodystrophy. When limiting the analysis to antiretroviral-experienced patients, no significant risk factors were identified.

In those with lipodystrophy, fat accumulation as the sole characteristic was reported retrospectively by physicians to have been present more frequently in patients randomised to the PI-only arm, while isolated peripheral lipoatrophy was more commonly reported in those randomised to d4T/RTV/SQV (fat accumulation only in 2/7 (29%) versus 2/22 (9%) patients, and isolated lipoatrophy in 1/7 (14%) versus 7/22 (32%) patients, in the RTV/SQV, and d4T/RTV/SQV arms, respectively. Neither of these differences reached statistical significance (p=0.24 and p= 0.63 by Fisher's exact two sided t-test, respectively). The concomitant presence of fat accumulation and peripheral lipoatrophy was reported at a very similar frequency in both arms (57% in the PI-only arm and 59% in the d4T arm respectively) (Table 3).
Table 2 Cox proportional hazard model for potential risk factors for the development of lipodystrophy

<table>
<thead>
<tr>
<th></th>
<th>all patients (n = 175) hazard ratio (95%CI)</th>
<th>therapy naive patients (n=94) hazard ratio (95%CI)</th>
<th>pretreated patients (n=81) hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>univariate p</td>
<td>multivariate p</td>
<td>univariate p</td>
</tr>
<tr>
<td>treatment arm RTV/SQV/d4T</td>
<td>3.41 (1.45-7.97) 0.005</td>
<td>3.83 (1.61-9.14) 0.002</td>
<td>5.78 (1.29-25.8) 0.02</td>
</tr>
<tr>
<td>baseline cholesterol (pemmoll)</td>
<td>1.38 (0.96-1.98) 0.08</td>
<td>1.57 (1.03-2.40) 0.03</td>
<td>1.33 (0.81-2.18) 0.26</td>
</tr>
<tr>
<td>increase in cholesterol (pemmoll)</td>
<td>1.56 (1.21-2.01) 0.001</td>
<td>1.64 (1.12-2.40) 0.01</td>
<td>2.25 (1.45-3.50) 0.001</td>
</tr>
<tr>
<td>baseline triglycerides (pemmoll)</td>
<td>1.31 (1.09-1.57) 0.004</td>
<td>1.11 (0.89-1.38) 0.37</td>
<td>1.27 (1.01-1.60) 0.04</td>
</tr>
<tr>
<td>increase in triglycerides (pemmoll)</td>
<td>1.16 (1.03-1.31) 0.02</td>
<td>0.93 (0.79-1.10) 0.4</td>
<td>1.18 (0.95-1.47) 0.12</td>
</tr>
<tr>
<td>baseline HIV-RNA (log10 copies/ml)</td>
<td>1.58 (0.92-2.71) 0.1</td>
<td>1.67 (0.90-3.10) 0.1</td>
<td>1.80 (0.69-4.67) 0.23</td>
</tr>
<tr>
<td>gender (male)</td>
<td>1.14 (0.43-2.98) 0.79</td>
<td>1.01 (0.23-4.50) 0.99</td>
<td>1.23 (0.35-4.36) 0.75</td>
</tr>
<tr>
<td>age (per year)</td>
<td>1.02 (0.98-1.05) 0.37</td>
<td>1.03 (0.98-1.08) 0.29</td>
<td>1.00 (0.95-1.06) 0.93</td>
</tr>
<tr>
<td>baseline CD4+ cell count (cell/mm3)</td>
<td>0.37 (0.05-2.96) 0.35</td>
<td>0.21 (0.01-3.15) 0.26</td>
<td>1.45 (0.04-52.6) 0.84</td>
</tr>
<tr>
<td>pre-treatment (naive)</td>
<td>0.83 (0.40-1.71) 0.61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Characteristics of lipodystrophy in each of the two treatment arms

<table>
<thead>
<tr>
<th></th>
<th>Lipoatrophy only</th>
<th>Fat accumulation only</th>
<th>Fat accumulation and lipoatrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ritonavir/ saquinavir (n=7)</td>
<td>1/7 (14%)</td>
<td>2/7 (29%)</td>
<td>4/7 (57%)</td>
</tr>
<tr>
<td>stavudine / ritonavir / saquinavir (n=22)</td>
<td>7/22 (32%)</td>
<td>2/22 (9%)</td>
<td>13/22 (59%)</td>
</tr>
</tbody>
</table>

n: number of patients; RTV: ritonavir; SQV: saquinavir; d4T: stavudine; CI: confidence interval; p: p-value
Lipodystrophy in treated HIV-infected patients

Discussion

The widespread prolonged use of potent combination antiretroviral therapy in patients with HIV-1 infection has become associated with an increasing number of reports concerning body fat redistribution and metabolic abnormalities, commonly referred to as lipodystrophy syndrome. It has been suggested from several observational studies that both PIs and NRTIs may contribute to the development of this syndrome.[4-6] Definitive evidence for the contribution by each of these drug classes however has been difficult to obtain, as PIs are rarely prescribed alone without concomitant prescription of NRTIs. To our knowledge, ours is the first report concerning the occurrence of lipodystrophy in patients who were randomly allocated to treatment with just PIs, or PI plus one NRTI.

Patients randomised to RTV/SQV/d4T were significantly more likely to develop lipodystrophy than those randomised to RTV/SQV alone. This difference was also observed in the subgroup of patients who were antiretroviral naive prior to the study, as well as in the subset of these who remained on their randomised treatment throughout the complete 96 weeks of follow-up. Reporting of lipodystrophy during the first year, i.e. before general awareness of the syndrome in the HIV physician and patient community, was solely on the basis of its recognition as a potential study-associated adverse event, and this may have resulted in an underestimation of the syndrome's prevalence. In view of the randomised nature of the study however, this should have effected both arms to a similar extent, and should not have significantly biased either treatment arm for the difference in prevalence that we observed. Only a single patient who had never been exposed to NRTIs developed lipodystrophy, which was limited to fat accumulation, while using RTV/SQV alone. These results strongly support the suggestion that NRTIs contribute to the development of antiretroviral therapy-associated lipodystrophy, as has recently been hypothesised.[11,12] The first reports concerning a possible association between lipodystrophy
and NRTI-use were publicly presented in June 99. All of the patients in our analysis were reported as having lipodystrophy before this date. Therefore, even though our study was not blinded, it is highly unlikely that the findings would have been biased by physicians being more likely to report lipodystrophy in the d4T-containing arm of the study.

One could expect that patients who are simultaneously exposed to both drug classes may be at highest risk. Our observation that antiretroviral-naïve patients who were allocated to RTV/SQV plus d4T were more likely to develop lipodystrophy than NRTI-experienced patients who were allocated to PIs alone and thus discontinued prior use of NRTIs, supports such a view, although the difference did not reach statistical significance, possibly as a result of limited numbers of participants in each of these two subgroups. Although the pathogenesis of the lipodystrophy syndrome remains unclear, it seems plausible that the concurrent presence of both PI- and NRTI-mediated biological mechanisms offers a greater likelihood for the syndrome to develop. With respect to PIs, it has been suggested that they may adversely interact with different host cell proteins involved in lipid metabolism, by virtue of a partial amino-acid sequence homology between such proteins and the HIV-1 protease.[13] For NRTIs, drug-induced mitochondrial dysfunction in adipocytes has been suggested as a potential mechanism involved in the induction of lipodystrophy. [11,12] NRTIs may differ in the degree to which they inhibit mitochondrial function and their effect may be cell type-dependent, as has been observed in vitro. [14,15] In a number of observational studies, the current use of d4T as opposed to that of zidovudine was found to be associated with a greater risk of developing lipodystrophy, and peripheral lipoatrophy in particular.[5,16] Our group recently reported that the concurrent use of RTV or indinavir results in significantly higher plasma exposure to d4T.[17] If this likewise would result in higher intracellular d4T-triphosphate levels in target adipose tissue, and mitochondrial toxicity is indeed involved in the pathogenesis of the
lipodystrophy syndrome, the concurrent exposure of our patients to both RTV and d4T may have been particularly harmful.

In contrast to what was reported from a number of observational studies, we did not find the duration of prior NRTI-exposure, age, or gender to be additional independent risk factors for the development of lipodystrophy. [5,6,18,19] This may possibly be explained by a much shorter median time of two years prior NRTI-exposure in our study population, as compared to the much longer NRTI-exposure reported in the observational studies.[4,5] Only 27 patients included in our study were women, which may have been insufficient for demonstrating a gender difference.

Higher baseline total cholesterol levels as well as higher increases in total cholesterol levels during treatment were associated with a somewhat higher likelihood of developing lipodystrophy, particularly in the subset of patients without prior antiretroviral experience. Such weak associations between metabolic and body appearance changes are consistent with findings in other studies.[1,20] Others have speculated that the changes in body composition and metabolic parameters may not be directly drug-induced, but may be secondary to suppression of HIV infection and the return of host immunity towards normal.[21] In our study, no major differences were observed regarding either the degree of HIV suppression achieved or the level of immune recovery as measured by changes in CD4+ lymphocyte numbers, between patients assigned to either treatment arm. Although this does not necessarily refute the importance of indirect therapy-related mechanisms, it does suggest that NRTIs directly contribute to the pathogenesis of the lipodystrophy syndrome.

An important limitation of our study is the subjective method by which lipodystrophy was diagnosed and prospectively reported by the treating physicians. In addition, specification as to whether lipoatrophy, fat accumulation or both were present was sought retrospectively. In the
absence of a consensus case definition of antiretroviral therapy-associated lipodystrophy, it is reassuring however that other studies have found good agreement between lipodystrophy as assessed by physicians on the one hand, and by the use of objective measurements such as dual energy X-ray absorptiometry (DEXA) and abdominal computed tomography on the other hand.[22]

In conclusion, the results from this randomised study strongly support that nucleoside analogue reverse transcriptase inhibitors contribute to the development of antiretroviral therapy-associated lipodystrophy syndrome. The low incidence of lipodystrophy in patients with no or limited NRTI-exposure, at least over a period of two years, warrants the further evaluation of NRTI-sparing regimens as potentially less toxic alternatives to current standard potent combination antiretroviral regimens.
Lipodystrophy in treated HIV-infected patients

References


Lipodystrophy in treated HIV-infected patients


*The Prometheus Study Group:*
