

Editorial Review

Antiretroviral therapy and the lipodystrophy syndrome

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'Lipodystrophy syndrome' in the setting of HIV infection has come to encompass a collection of morphological and metabolic abnormalities linked with the use of antiretroviral therapy and other risk factors. We review

the clinical literature on this subject as it has evolved historically, taking pertinent methodological issues into account.

History

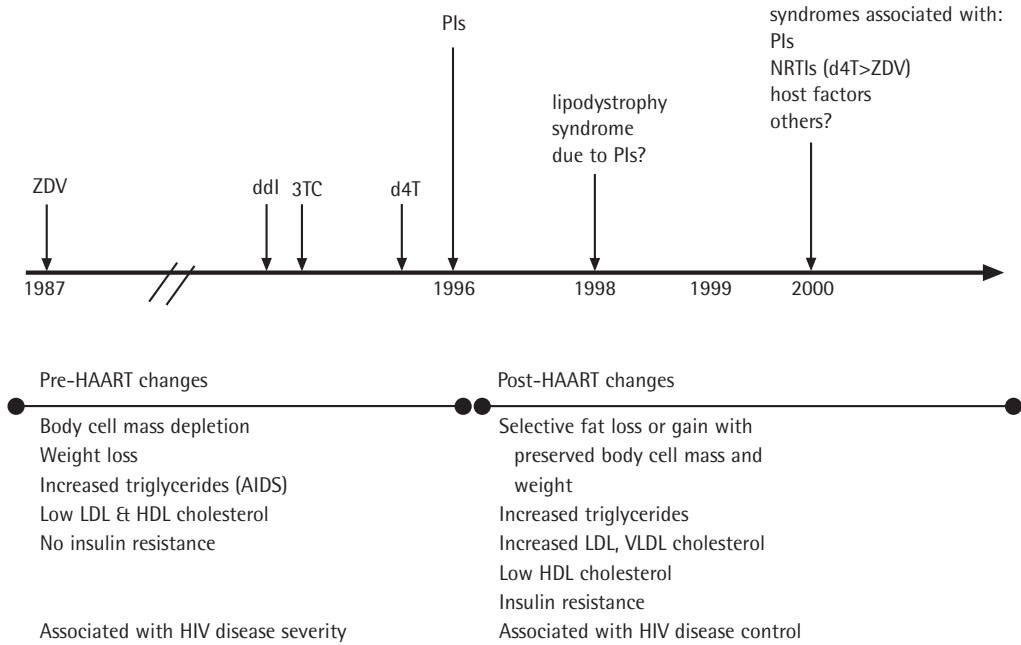
The use of the term 'lipodystrophy' originates in two reports, one published in late 1997 and the other in early 1998, describing wasting of subcutaneous fat in the face and limbs of HIV-infected patients treated with the protease inhibitor (PI) indinavir, reminiscent of rare congenital and acquired lipodystrophy syndromes [1,2]. From late 1997 onwards, others described benign symmetric lipomatoses, localized lipomas, 'buffalo humps', intra-abdominal fat accumulation and breast enlargement in HIV-infected men and women on various antiretroviral combinations, predominantly (but not exclusively) including PIs [3–20]. Altered lipoproteins, mimicking the 'atherogenic' profile seen in dyslipidaemic diabetics; elevated (fasting) serum triglyceride, LDL- and VLDL-cholesterol, apolipoprotein B, E and lipoprotein(a) and reduced HDL-cholesterol were also documented in PI-treated patients and shown to precede body habitus changes in some cases [21–32]. Insulin resistance and diabetes mellitus developed *de novo* or worsened in patients (with and without morphological change), co-incident with starting a PI [2,21,26,32–38].

The fat wasting and the hypertriglyceridaemia were distinguished from that previously described in AIDS by the fact that they typically occurred in those successfully treated with highly active antiretroviral therapy (HAART), even in acute HIV infection and as post-exposure prophylaxis [39–41]. Patients experienced psychological morbidity and increased barriers to good adherence to therapy because of these problems [42,43]. In addition, the spectre of accelerated atherosclerosis was raised by a flurry of case reports of macrovascular (mainly coronary) disease in young dyslipidaemic patients on HAART [44–53].

The first systematic study of these phenomena, in a large Australian cohort, found that subcutaneous fat wasting in the face, limbs, buttocks and upper trunk (termed 'peripheral lipodystrophy') was associated with abdominal visceral obesity, dyslipidaemia and insulin resistance in HIV-infected patients [54]. The vast majority of affected cases were on PI-containing HAART. The facts that morphological and metabolic changes appeared to aggregate at a population level, their phenotypic similarity to 'Syndrome X' and the plausibility of PIs as a unifying cause, all helped drive the view that these changes formed a new single 'lipodystrophy syndrome' [54–56] (Figure 1).

Over the last 2 years, evidence has emerged that body habitus changes, and lipid and glycaemic parameters may behave as independent or partially independent processes [21,57,58]. Not one, but three patterns of body habitus change are discernible within individuals, fat wasting alone (or 'pure lipodystrophy'), fat accumulation alone or a combination of both [58–60]. Furthermore, factors other than PIs – such as nucleoside analogue reverse transcriptase inhibitors (NRTIs), age, gender and race – may independently influence the risk of developing some of these changes [59–72]. Differential effects of antiretroviral agents within the PI and NRTI classes are also possible [54,59,60,62,63,70–72]. Rather than a stereotypic syndrome with a single cause, the 'lipodystrophy syndrome' is increasingly studied as a set of distinct clinical abnormalities – fat loss, fat gain, dyslipidaemia and insulin resistance – that may complicate antiretroviral therapy to variable degrees in different individuals. The extent to which these abnormalities are inter-related is

Figure 1. Time-line of developments in antiretroviral treatment and 'lipodystrophy syndrome(s)'



ZDV, zidovudine; ddI, didanosine; 3TC, lamivudine; d4T, stavudine; PIs, protease inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors.

not clear, and may not ever be so, until their exact aetiopathogenesis is understood. However, attempts to characterize the general phenomenology enough to develop standardized case-definition(s) is important in the meantime.

For researchers, designing lipodystrophy studies (of observational cohort data, randomized clinical trials or pathogenesis studies) and for clinicians that must critically evaluate these studies, several methodological issues have already emerged. Most importantly, the 'lipodystrophy syndrome' cannot be analysed as a single entity at this time. Initially, its components should be analysed individually, though they may have partially overlapping risk factors and intersecting pathogenic pathways. Secondly, study method should be concordant with the dynamic nature of these outcomes.

Methodological issues

Cross-sectional versus longitudinal study design

To date, most studies have used cross-sectional design to analyse cumulative phenomena. Subcutaneous fat wasting, in particular, is a progressive process that increases in severity over time. At some point, this continuous change becomes evident to both patient and physician and 'clinically apparent' fat wasting can then be said to be present. The assignment of this outcome as being 'present' or 'not present' at the arbitrary time of a cross-sectional analysis is entirely subjective, and is

therefore only an approximation of the true division of affected versus non-affected cases in a population. For example, patients who do not have clinically apparent fat wasting may either be truly unaffected or have subtle or less severe change. Fat loss may well be evident on more sensitive, objective measurement of fat mass over time in these patients. On the other hand, patients with clinically apparent fat wasting may have had the problem for a long or a short period of time.

The various forms of fat accumulation, dyslipidaemia and insulin resistance are also acquired changes from a previous baseline. Pre-existing genetically determined risk, as well as HIV infection itself can influence the 'baseline' in any patient before starting antiretroviral therapy. Because of the sequential use of various antiretroviral drugs and drug classes historically, cross-sectional studies are also inherently likely to find associations between cumulative outcomes and drugs in current use, even when drugs in past use are the true culprits. Longitudinal studies in which deviations from baseline are recorded in real-time offers the best way to characterize treatment-associated changes.

Objective body composition measurement

The need for objective measurements has been underscored by the results of the PIILR study, in which serial whole-body dual-energy X-ray absorptiometry (DEXA) scans showed that replacement of PI with one of several non-PI therapies caused worsening of subcu-

taneous fat loss, even though patients subjectively reported fat gain [73].

DEXA has dominated as the test of choice in studies of fat wasting, as it is quick to perform and is precise and accurate for small changes in total body and appendicular fat mass. The infrastructure for its use is usually established in centres that routinely offer bone density monitoring. The abdominal subcutaneous and visceral fat compartments may change in opposing directions in some patients, so single-cut CT scans at L4 are preferable to DEXA for analysing abdominal fat [14,68]. ‘Fat redistribution’ is a term favoured by some, but simultaneous fat loss/fat gain is not present in all patients, so it may be unwise to use appendicular to central fat ratios derived from DEXA scans as a global measure of any possible morphological change. For example, patients with subcutaneous fat wasting but no visceral fat accumulation may have a low appendicular to central fat ratio, comparable to those with well preserved subcutaneous fat. Whole-body magnetic resonance imaging (MRI) is highly precise and accurate [74], but is not widely available and may be prohibitively expensive.

Cheaper techniques such as anthropometry, bioelectric impedance testing (BIA) and ultrasonography are attractive for clinical practice, but all may lack both precision and accuracy unless conducted under highly standardized conditions. Ultrasonography has only been evaluated against clinically assigned ‘lipodystrophy’ cases, not against validated techniques such as DEXA or MRI [75]. Both DEXA and MRI are less operator-dependent than ultrasound and BIA, but still require standardization of calibration when compared between machines and centres. Whatever the technology of choice, tests carried out serially in treatment-naïve patients acting as their own controls, reduce the difficulties of inter-machine variability.

Statistical methods

Most studies have needed to use logistic regression models to do multivariate analysis because of their cross-sectional design, although this method is inherently not suited to time-dependent outcomes. Longitudinal studies, ideally starting in treatment-naïve patients prior to therapy, naturally lend themselves to time-to-event statistical analyses such as Cox proportional hazards models or Kaplan–Meier estimates. These methods give a more accurate relative risk associated with antiretroviral drug exposure in particular, because the outcome is recorded in the context of the specific drug taken at the time the outcome first develops, as opposed to the drug most recently taken.

Stavudine was introduced to clinical practice some years after zidovudine, and not long before the first PI. Individual PIs followed in comparatively quick succession. Hence, the whole PI class and stavudine were the

predominant ‘current’ therapies in many early study populations and may have been partial surrogate markers for each other, as well as for prior prolonged NRTI therapy (Figure 1). However, studies that simply compared current PI-treated with PI-naïve patients (without matching concurrent/past therapies), were designed *a priori* to implicate PIs. Any independent contribution of current or past NRTIs to any outcome of interest could never have been determined. There is now evidence that duration of NRTI therapy is independently associated with subcutaneous fat wasting in PI-treated and PI-naïve patients, and hence this may confound analysis of PI effects and comparisons within the NRTI class in cross-sectional studies [59,60,62,63,70–72].

Case definition

If the ideal methodological approach to a cumulative process could always be followed (objective body composition measurement with known precision limits, repeated at sufficient frequency from a known baseline, before any antiretroviral therapy, adjusted for diet and exercise) an ‘ideal’ case definition could also be based on such approaches. For example, case definition criteria for fat wasting might be of the form ‘a >x% loss in percentage leg fat on DEXA scan from pre-treatment baseline without significant loss in lean body mass or change to diet or exercise over 6 months’. In real clinical practice however, the data to develop such a ‘longitudinal’ case definition are rarely available. Patients with unknown pre-treatment baselines for body composition, lipid and glycaemic parameters may present at any stage of their treatment history. Hence, a practical case definition, which can be applied at a single assessment will be helpful to researchers and clinicians that only have cross-sectional data. A multi-centre case definition study aiming to generate a cross-sectional case definition for morphological changes with discriminative specificity against disease controls such as ‘HIV wasting syndrome’ and obesity (and similarly for metabolic changes) is now underway.

Risk factors

The variability in case ascertainment, end-points, statistical methods and adjustment for bias may explain the variability in prevalence figures and variability in the magnitude of risk associated with some factors in many cross-sectional, observational cohort studies. However, certain risk factors have been consistently identified across studies, and their associations with lipodystrophy-related outcomes has not been abrogated where adjustment to minimize confounding factors has been attempted [63]. More recent retrospectively designed lipodystrophy substudies within prospective randomized clinical trials

Table 1. Summary of switching studies

Study author [ref]	Switch	Randomized	<i>n</i>	Follow-up weeks	Body habitus	TGs	Cholesterol	Insulin resistance
Martinez <i>et al.</i> [79]	PI to NVP	No	23	32	▼ WHR	▼ 57%	▼ 22%	▼ 45%
Riuz <i>et al.</i> [80]	PI to NVP	Yes	60	36	NS (DEXA)	▼ 23%	▼ 11%	NS
Tebas <i>et al.</i> [81]	PI to NVP	No	40	30	NS (DEXA)	▼ 44%	No change in LDL Rise in HDL cholesterol	ITT normalized in three patients with high BSL
Goebal <i>et al.</i> [82]	PI to ABC	Yes	211	40	-	▼	▼	▼
CNA30017 Rozenbaum <i>et al.</i> [83]	PI to ABC	Yes	32	12	NS (skin folds WHR)	NS	NS	NS
CNA30017 Carr <i>et al.</i> PIILR study [73]	PI to ABC NVP HU ADV	Yes	80	24	Worsening of s.c. fat loss (DEXA)	▼	▼	NS
Moyle <i>et al.</i> [85]	PI to EFV	No	11	12	-	▲	▲	-
Gharakhanian <i>et al.</i> [86]	PI to EFV	No	33	48	NS (skin-fold)	NS	NS	NS
Bonnet <i>et al.</i> [87]	PI to EFV	No	43	24	NS (DEXA)	NS	NS	NS
Martinez <i>et al.</i> [88]	PI to EFV	No	20	24	▼ WHR	▼ 31%	NS	▼ 28%
Viciano <i>et al.</i> [89]	PI to EFV	No	39	24	NS (WHR)	▲	▲	-
Saint Marc <i>et al.</i> [94]	d4T to ZDV or ABC	No	59	52	▲ Leg s.c. fat 36% (CT)	▼ 29%	NS	NS
Polo <i>et al.</i> [95]	d4T/ddl to ZDV/3TC	No	10	24	-	▼	-	-

NS, no statistically significant change reported; WHR, waist hip ratio; PI, protease inhibitor; ABC, abacavir; ADV, adefovir; d4T, stavudine; ddl, didanosine; EFV, efavirenz; NVP, nevirapine; ZDV, zidovudine; 3TC, lamivudine; HU, hydroxyurea; ITT, insulin tolerance test; BSL, blood sugar level; s.c., subcutaneous.

and randomized reversibility studies have added evidence of a contributory role for these factors discussed below.

Protease inhibitors

The odds of having fat wasting increases with the duration of PI treatment [56,62,63]. Time to onset of clinically apparent fat wasting is markedly accelerated when PIs and NRTIs are combined compared with NRTIs alone [63]. PI use also increases the probability of intra-abdominal fat accumulation, dyslipidaemia and insulin resistance in HIV-infected patients [21,54,56]. Short-term ritonavir use leads to dyslipidaemia in the absence of body composition changes in healthy volunteers [76], and elevated triglyceride levels have also been observed in HIV-seronegative individuals receiving short-term PIs (predominantly indinavir) for post-exposure prophylaxis [77]. All PIs licensed in 1996/1997 have been implicated, though ritonavir is more likely to cause malignant hypertriglyceridaemia compared with

other PIs [21,32]. Amprenavir may be relatively benign [78].

Table 1 summarizes the results of reversibility studies that may give indirect evidence of the contribution of PIs to lipodystrophy syndrome(s). Replacement of PI with abacavir or the NNRTI nevirapine leads to decreased serum triglyceride levels and LDL cholesterol levels after 6–12 months [73,79–84]. Insulin resistance measured by rigorous intravenous insulin tolerance testing (ITT) also improves after PI to abacavir switch [82,84]. A PI to efavirenz switch appears to have less impact on metabolic abnormalities and can cause a rise in cholesterol levels, though this may be predominantly HDL-cholesterol [85–89]. Improved insulin sensitivity has not been shown with efavirenz introduction after 1 year of follow-up [90]. Objective improvement in fat wasting up to 12 months has not been demonstrated in any PI switch study to date where concurrent NRTI treatment has continued or been intensified [73,79–89].

Nucleoside analogue reverse transcriptase inhibitors (NRTIs) as a class also increases the risk of fat wasting [59,60,62–64,70–72], and NRTI therapy alone, in the absence of PI use, is a sufficient condition for these changes to arise [59,61–63,71]. As with PI use, risk is duration-dependent [63]. Within the class of NRTIs, stavudine use provides a greater risk than zidovudine use in non-randomized studies [59,60,62,63,71,72]. The excess risk of stavudine has been estimated at 1.9 for the first 18 months of therapy, after adjustment for the potential biases against stavudine in observational data, including older age and longer prior NRTI therapy in some stavudine users [63]. A randomized clinical trial in treatment-naïve patients, comparing zidovudine/lamivudine with stavudine/didanosine, found that fat loss and fat gain occurred in both groups, but the stavudine/didanosine arm showed consistently higher prevalence up to 30 months of follow-up [91]. This concurs with pooled cross-sectional analysis of patients enrolled in a lipodystrophy substudy of two randomized clinical trials comparing stavudine/didanosine, stavudine/lamivudine or zidovudine/lamivudine with either indinavir (Ozcombo I) or nevirapine (Ozcombo II) as a first antiretroviral regimen. Fat wasting by physician assessment and DEXA scan was associated with a stavudine-containing regimen, with greatest prevalence in the stavudine/didanosine groups [92]. A more recent randomized trial comparing stavudine/lamivudine/indinavir to zidovudine/lamivudine/indinavir regimens in 96 stavudine/PI-naïve patients has also found a higher prevalence of peripheral fat wasting in the stavudine group at 30 months [93]. Two non-randomized reversibility trials show a (slow) increase in fat mass and reductions in triglyceride 12 months after switch from stavudine to zidovudine or abacavir [94,95] (Table 1). Comparisons between competing antiretroviral agents such as stavudine and zidovudine or, to a lesser extent lamivudine and didanosine, can be made within the NRTI class. However, it is inherently problematic to assess the risk of zidovudine (or stavudine) relative to lamivudine (or didanosine), as they are so often used together. Lamivudine has been associated with abdominal obesity and buffalo humps in one study [62] but others have detected no associations. As abacavir has tended to be used in place of PIs or NNRTIs in triple NRTI HAART regimens, its own effects relative to other NRTIs are yet to be determined.

It has not been clear from observational data whether NRTIs are both sufficient and necessary for development of lipodystrophy, as PI treatment without past or current NRTIs is rare in clinical practice. However, two randomized studies of dual PI therapy (ritonavir/saquinavir) in the absence of NRTI use have shown a low risk of subjective body composition changes (~6–8%) over 2–4 years of follow-up [96,97].

Intensification of therapy with stavudine was associated with an increased incidence of lipodystrophy (predominantly fat wasting [97]), to ~25% in both studies. This would suggest that risk of fat wasting is dominated by inclusion of stavudine into a PI (ritonavir/saquinavir)-alone regimen.

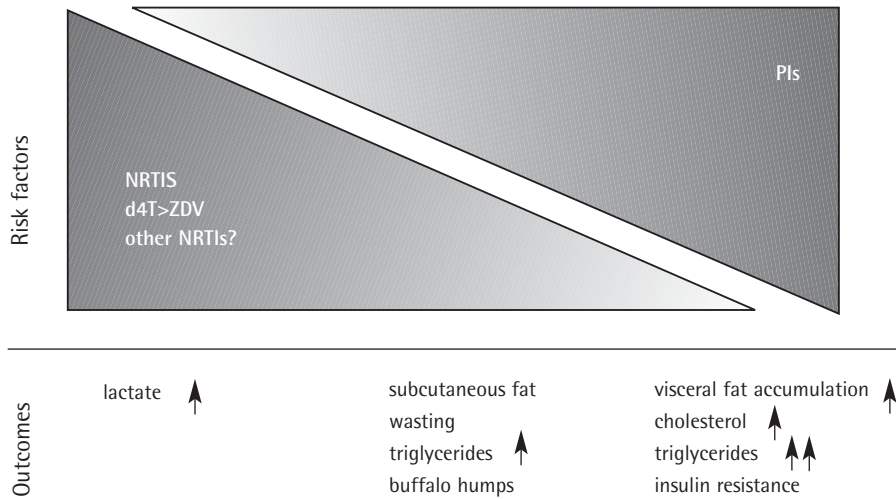
Visceral obesity has been anecdotally noted in PI-naïve individuals [74], but overall the link between NRTIs and intra-abdominal fat accumulation is weak [60,71,93]. With respect to metabolic abnormalities, mild-to-moderate hypertriglyceridaemia (and hyperlactataemia) has been demonstrated in PI-naïve patients, where it has been associated with duration of stavudine [99] and shown to regress after replacement of stavudine [94]. However, stavudine did not have a significant effect on triglyceride and total cholesterol levels compared with ritonavir/saquinavir in the Prometheus study [99]. In general, dyslipidaemia and insulin resistance appears predominantly PI-, not NRTI-related.

Host factors

Older age increases risk of subcutaneous fat wasting [60,63,100]. Gender may have an influence on the lipodystrophy phenotype. Increased truncal adiposity, rather than subcutaneous fat wasting, appears to be a dominant manifestation in women [68,100–104], an observation confirmed in a MRI study of body composition [103]. In general, the visceral fat depot makes only a small contribution to total adipose stores in women (~6%) compared with men (~20%) [105], a factor which is thought to decrease the risk of vascular disease in women [106]. In contrast, women with lipodystrophy may develop a more ‘android’ body habitus with waist:hip ratios closely approximating those of affected men [101]. This is associated with hyperinsulinaemia, hyperandrogenaemia (increased free testosterone and increased LH:FSH ratio) and hyperlipidaemia [107], which appears to be determined predominantly by visceral fat mass rather than with PI therapy *per se* [101,102,107]. The striking lack of difference in insulin, glucose and lipid levels between age-matched men and women on antiretroviral therapy in a recent study highlights the ‘android’ nature of both metabolic and body composition changes in women [101].

Independent studies in diverse populations have found that race influences the risk of body habitus changes. White Caucasian race increased relative risk of subcutaneous fat wasting by 3.9 times in an Australian cohort [63]. White race was also associated with increased prevalence of fat wasting in a multicentre US cohort study [104] and, conversely, African-American origin decreased risk of fat wasting in another US cohort [69]. Study of a Nigerian cohort suggests that the prevalence of truncal obesity (~60%) is greater than that of fat wasting (~30%) in this group [108]. Among Oriental

Figure 2. A 'multifactorial model' of 'lipodystrophy syndrome(s)' – a collection of abnormalities with partially overlapping risk factors (PIs and NRTIs)



Additional effects of age, sex and race are not shown.

populations, one study from Korea found no evidence of body composition changes on DEXA scan among 45 individuals receiving PI-containing HAART, despite significant increases in triglyceride and insulin levels, and lower HDL-cholesterol, compared to controls [109]. A study of a mainly Chinese Singaporean cohort found that PIs were significantly associated with fat accumulation and mixed accumulation and atrophy, while prevalence of isolated fat wasting was not increased in treated HIV-infected patients [110]. In contrast, a prevalence study in Japan has indicated a profile very similar to that seen in Caucasian populations [111].

These data suggest that body composition changes occur in most racial populations and in females as well as males, but that the phenotype may vary considerably. Subcutaneous fat wasting is prominent in Caucasian males, while women and non-Caucasian races may be more prone to develop truncal adiposity. Aside from methodological reasons already mentioned, racial differences may also account for the widely varying prevalence rates of 'lipodystrophy syndrome(s)' in different study populations.

Risk factors and aetiopathogenesis

Though the aetiopathogenesis of lipodystrophy syndrome(s) in HIV-infected patients is unknown, several hypotheses, relating to retinoic acid-dependent cell signalling, mitochondrial genomic or biochemical toxicity, cytokine effects, immune restoration and others, have been put forward to explain the clinical and epidemiological observations made to date. Some of these ideas are being tested *in vitro* and *in vivo*. There are several key observations to be explained. NRTI

therapy alone provides sufficient conditions for development of fat wasting and contributes independently to risk of fat wasting in those on NRTIs plus PIs. NRTIs have a lesser association with abdominal fat accumulation and mild hypertriglyceridaemia. Conversely, PIs alone are sufficient to induce moderate and severe dyslipidaemia in the short term, are associated with abdominal fat accumulation and insulin resistance, and may have a lesser (independent) association with fat wasting. Risk associated with agents within the NRTI and PI classes differ. The highest prevalence, and shortest time to onset of fat wasting is reported when PIs and NRTIs are combined compared with the use of either class alone. In general, different antiretroviral drugs are associated with greater differences in risk of lipodystrophy-related outcome measures than any known differences in virological or immunological effects. Thus, the emerging model of lipodystrophy syndrome(s) is that of a collection of partially overlapping PI-, NRTI-, and PI plus NRTI-associated phenomena (Figure 2). The final expression of these phenomena additionally depends on the age, gender, race and other unknown genetic traits of the individual.

Management issues

Two major areas of concern to patients and clinicians are: (i) assessment and management of dyslipidaemia and insulin resistance, particularly in relation to its impact on vascular risk; and (ii) halting and/or reversing the body habitus changes. The strategies already being used in current clinical practice are lipid-lowering therapy, and switching antiretroviral drugs.

Dyslipidaemia and vascular risk

There is justified concern that the cluster of lipid and glucose abnormalities that may accompany PI therapy constitutes an atherogenic metabolic profile. How the baseline risk of vascular disease in HIV-infected patients compares with the general population is not clear, nor is whether the dyslipidaemia (and immune restoration) induced by HAART increases this baseline risk, independent of improved survival or improved surveillance. There have been several case reports of premature vascular disease in those with dyslipidaemia and/or insulin resistance on HAART [44–53]. While early short-term retrospective analyses in PI-treated populations did not identify an increased rate of vascular events [112,113], a recent French study suggests that the rate of myocardial infarction is higher among men receiving PIs for longer than 18 months, compared with the age-matched general population, and that there is a dose–effect relationship [114].

An association between PI therapy and atherosclerosis is suggested by studies of endothelial function and of arterial wall morphology. Endothelial dysfunction is considered to be an early event in atherogenesis [115], and involves loss of the capacity of the endothelium to respond to an ischaemic or mechanical stimulus with an appropriate vasodilatory response. It can be assessed non-invasively by measuring brachial artery flow-mediated dilatation. A more direct indicator of atherosclerosis may be arterial wall thickness and presence of atherosclerotic plaque in the carotid arteries. Three recent studies of carotid wall intima media thickness (IMT) [116–118] and one study of endothelial function [119] ascribes increased risk of atherosclerotic changes to PI use. In one study of carotid IMT, PI use exerted the strongest influence on risk of carotid lesions in a logistic regression analysis (OR 12.5), while cigarette smoking and CD4 T cell counts of >200 cells/ μ l were also predictive [118]. This dominant effect of PI therapy *per se* rather than the associated dyslipidaemia was also found in a study of endothelial function in which a multiple linear regression model incorporating PI therapy, systolic blood pressure and heart rate explained 67% of the variance in endothelial function [119]. Another study of carotid IMT in 29 dyslipidaemic PI-treated patients found that abnormal IMT was significantly associated with age and LDL-cholesterol [117]. Notably, none of these studies demonstrated a correlation between atherosclerotic changes and the typical dyslipidaemic profile associated with PIs (increased total cholesterol and triglycerides, and decreased HDL-cholesterol). The association between abnormal IMT and elevated LDL-cholesterol is also interesting, given that this cholesterol fraction is often not significantly affected by HAART [101].

One caveat to these findings is that changes in carotid

vessels may not necessarily correlate with increased risk of coronary artery lesions. Two studies have assessed coronary artery morphology directly using electron beam-computed tomography in 85 patients, of whom ~40% had significant dyslipidaemia for approximately 24 months [120,121]. No structural changes were noted in either study, although concurrent positron emission tomography scanning suggested the presence of endothelial dysfunction in the coronary vasculature.

In the absence of incidence data regarding HAART-associated vascular disease, many physicians are extrapolating from risk predictions in other settings and applying (US) National Cholesterol Education Program (NCEP) or similar consensus guidelines for lipid lowering therapy [122–126]. Small clinical studies indicate that gemfibrozil for hypertriglyceridaemia, atorvastatin and pravastatin for hypercholesterolaemia or mixed LDL-cholesterol and triglyceride elevations are safe despite pharmacokinetic interaction and show modest lipid-lowering effect [122–127]. However, it is not yet known if lipid-lowering in the context of HAART-treated HIV infection will result in the same reductions in vascular events as has been documented in the general population. The studies of endothelial function and structure in HIV-infected, PI-treated patients, suggest that lipid levels alone may be an imperfect surrogate marker for true vascular risk. Indeed, even in the general population it is not yet resolved that fasting blood levels of cholesterol and triglyceride levels alone are the best surrogates of atherogenesis.

Though the use of NCEP or similar guidelines is certainly prudent for dyslipidaemic patients, other risk factors in all PI-treated patients need to be addressed, including in women who may acquire the ‘android’ lipodystrophy phenotype and lose their gender-related vascular protection [101]. Lifestyle measures to reduce vascular risk should be actively encouraged. Resistance exercise training in HIV-infected adults has led to reduction in trunk fat and hypertriglyceridaemia, as well as improved strength and lean body mass [127,129]. Minimizing smoking, hypertension and diabetes is paramount, particularly in those with a family history of premature vascular disease. In patients with pre-existing cardiovascular disease, dyslipidaemia and/or diabetes mellitus who are commencing antiretroviral therapy, PI-sparing HAART regimens may merit consideration. In centres where the expertise and technology is available, serial assessments of vascular function and structure performed longitudinally in PI-treated patients should be an important research priority.

Switching antiretroviral therapy

Table 1 summarizes the results of reversibility studies that have been presented or published to date. At the present time, data regarding long-term risk/benefit of

revising therapy are scant. If patients and their physicians want to revise therapy to improve metabolic profiles, then there is evidence that this may ensue within a 6–12-month period if PIs are replaced with nevirapine or abacavir [73,79–84], or if stavudine is replaced with zidovudine or abacavir [94,95]. If the goal of revision is to reverse established fat wasting, then there is little evidence at the current time that a PI switch alone will achieve this in less than 12 months. To date, reversibility of fat wasting has only been documented after non-randomized replacement of stavudine with zidovudine or abacavir [95,96]. Trials in which there are randomized changes to PIs as well as NRTIs within the same study are currently underway. At this time of uncertainty, enrolling patients in a reversibility trial with objective measures of body composition change may be the best way for physicians to switch therapy in their patients with lipodystrophy syndrome(s).

While these studies are predicated on a potential for reversal of body composition changes, it must be borne in mind that the biological mechanisms of adipose loss and gain are poorly understood at present. ‘Reversibility’ is dependent, not only on removal of the offending drug(s), but also on the capacity for regeneration of adipose tissue. This is, in turn, critically dependent on whether the pathological processes involved affect mature adipocytes but allow normal potential for adipocyte growth and differentiation; or whether the reservoir of adipocyte precursors and stem cells are also targeted, leading to diminished adipose acquisition as well as increased loss. Longitudinal data also suggests that the process of subcutaneous fat wasting is non-linear, following a decelerating trajectory over time [63]. If reversibility of these changes follows a similar pattern, with small gains in fat mass first and larger incremental gains later, revision of therapy in patients with established severe fat wasting may require longer than 6 or 12 months for demonstrable reversibility.

Other therapies for visceral obesity and insulin resistance such as metformin, PPAR- γ agonists, anabolic steroids and recombinant human growth hormone are being studied in small clinical trials and may have a role for selected patients in the future. These have been reviewed elsewhere [131].

Conclusions

The initial observations from cohort studies are being confirmed and extended by (retrospectively designed) cross-sectional analyses of randomized clinical trials and reversibility studies. It is to be hoped that objective measures of body composition (for example, whole-body DEXA with L4 single slice CT) and metabolic parameters (for example, fasting blood lipid profiles, insulin resistance indices and lactate) will now be

prospectively incorporated into routine toxicity monitoring within randomized clinical trials. This will additionally ensure that quality assurance issues for such monitoring are addressed.

Perhaps the immediate priority for clinical care is to determine which of our current HAART combinations are least likely to lead to metabolic or morphological change in those who are unaffected (ie ‘fat-sparing’ regimens) or will allow reversal of established changes, while maintaining good virological control. To that end, greater investment in randomized switching studies is required. By necessity, assignment of ‘cases’ at a single time-point amongst antiretroviral-experienced patients requires a consensus case definition. This will be inevitably imperfect for time-dependent outcomes and will need regular revision as new information comes to light. Ultimately, it is likely to be replaced by an aetiopathological definition(s). As data obtained from clinical observational studies and clinical trials continues to inform and direct *in vivo* and *in vitro* pathogenesis studies, the mechanisms common to apparently disparate elements of the lipodystrophy syndrome and other complications of antiretroviral therapy should be revealed.

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