

Clinical issues in **HIV/AIDS**

This is the fifth in a series of bulletins focusing on advances in therapy for HIV/AIDS, particularly developments in triple therapy employing protease inhibitors.

This bulletin looks at the problem of fat redistribution and metabolic

abnormalities in HIV/AIDS patients, and to what extent it is related to drug therapy. There is also a website review looking at sites providing the latest research information.

Watch out for further update bulletins in the coming months.

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Commentary

Lipodystrophy is physically and socially disfiguring for patients, it is a therapeutic dilemma for clinicians and a spur to research for investigators and pharmaceutical companies.

It is not really a dystrophy at all but a complex redistribution of body lipid tissue. This typically results in loss of fat from the face, buttocks and arms, and increased deposition of fat around the breasts, back of the neck and abdomen. Elevation of serum cholesterol, insulin resistance and increased glucose levels may also be seen.

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Commentary continued

Such changes are seen in some HIV-positive patients on combination therapy containing protease inhibitors (PIs), but the syndrome is also observed in those taking combinations using reverse transcriptase treatment without PIs and in patients who take no anti-retrovirals at all, as well as non-HIV-infected patients such as long-term survivors of chronic illness (for example, leukaemia).

These changes may indicate long-term cardiovascular risk, but we can only wait, anticipate and observe to know if this is the case. At the moment the clinical picture can be described, however, no case definition has yet been agreed and this must be urgently addressed to facilitate further understanding. The difficulty in obtaining quantitative measurements of fat loss or fat accumulation also needs to be overcome.

For the clinician, lipodystrophy represents a dilemma. Should one change therapy because of lipodystrophy if all the other parameters are favourable? What do we tell patients about dietary management, lipid-lowering drugs and long-term cardiovascular risk? Is it a drug effect (on adipocyte differentiation, on steroid regulatory element binding protein

or on tumour necrosis factor alpha), an HIV effect (on proteins involved in the regulation of lipid metabolism) or the magnification of a genetic predisposition ('permitted' by prolonged survival)? It may of course be multifactorial. How do we investigate, diagnose and clarify the phenomenon?

For researchers (including our sponsors) it is a stimulus to look into aspects of causation, pharmacology (is it a class effect or not?) and how best to advise both prescriber and patient.

For the patient it has replaced Kaposi's sarcoma as the 'Mark of Cain', visually displaying to others the stigmata of HIV seropositivity, and for their sake we must quickly improve the knowledge base. As the pop song suggests, 'There are more questions than answers', but in the best traditions of this journal we have invited an article from Dr Graeme Moyle and Christine Baldwin, who are well qualified to lead us through this conundrum.

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Fat redistribution and metabolic abnormalities in HIV infection

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Several new clinical and metabolic phenomena have been observed in individuals receiving combination antiretroviral therapy. The metabolic abnormalities include altered lipid handling leading to hyperlipidaemia, and insulin resistance sometimes leading to impaired glucose tolerance or diabetes mellitus. Clinical abnormalities include altered body fat distribution, both lipoatrophy (loss of subcutaneous fat, mostly in the face and peripheries) and lipohypertrophy (localised fat gain – most often central adiposity, but also localised fatty masses and breast enlargement). Most initial reports focused on individuals receiving highly active antiretroviral therapy, including protease inhibitors (PIs); however, subsequent reports have indicated that both metabolic and clinical abnormalities may be observed in people naive to PI therapy.

Antiretroviral therapy

The introduction of PIs as part of potent antiretroviral regimens (highly active antiretroviral therapy, HAART) has dramatically modified the outcome of HIV-1 infection.¹ However, standard HAART regimens including PIs are not able to eradicate HIV-1 infection,^{2,3} and treatment deintensification to more convenient maintenance regimens following induction of virological control with HAART regimens has not been able to maintain the suppression of HIV replication.⁴⁻⁶ Thus, the current HIV therapeutic paradigm involves prolonged, intensive (≥ 3 drug) antiretroviral regimens for an indefinite period.

The long-term risks of intensive antiretroviral therapy have not been established. The longest clinical trials with HIV therapies have been around three years, with most studies using PI or non-nucleoside reverse transcriptase

inhibitor (NNRTI) triple therapy being closed after 12–18 months of follow-up. The long-term effects of untreated HIV infection have, however, been established through a number of cohort studies, which provide actuarial assessments of risk of disease progression based on CD4 and viral load measurements. Thus, while the risks of not treating HIV are clearly established, the point at which the risk versus benefit of therapy favours intervention is not clearly established.⁷

Metabolic effects of HIV infection and antiretroviral drugs

Hypertriglyceridaemia (but not diabetes mellitus or fat redistribution) was recognised as a complication of HIV infection before the availability of antiretroviral therapy. This phenomenon was typically associated with disease progression, immune dysregulation and wasting disease. Chemokine mediators for this phenomenon included interferon-alpha and tumour necrosis factor-alpha. Additionally, levels of high density lipoprotein (HDL, so-called 'good' cholesterol) and total cholesterol are commonly diminished in untreated HIV infection.⁸

Therapy with PIs, both in uninfected volunteers and in patients with HIV infection, results in rises in low and very low density lipoproteins (LDL and VLDL, so-called 'bad' cholesterols), total cholesterol and triglycerides.⁹⁻¹⁶ The extent of changes appears to vary with drug dose or exposure, and between different PIs and across individuals in a population. Increased plasma levels of triglycerides in patients treated with ritonavir⁹ was the only metabolic abnormality reported before the approval and marketing of PIs. This elevation shows a dose dependency, an issue that requires consideration when choosing

doses of ritonavir in combination PI regimens. However, hypertriglyceridaemia has been described in association with all marketed PIs, albeit at a lower prevalence.^{10-13,15,16} The prevalence of hyperlipidaemia (raised triglycerides and cholesterol) in HIV-1 infected patients treated with PIs at one year is high (>50%).¹⁰⁻¹⁶

The virological control achieved with PI-based triple therapy regimens does not appear to correct HIV-associated falls in HDL. However, therapy has been associated with an increase in body weight and an improvement in the nutritional status of HIV-1 infected patients, possibly as a result of improved gut function.^{17,18} Use of the NNRTI efavirenz is also associated with rises in total cholesterol; however, this increase is partially accounted for by a rise in HDL.¹⁹ The mechanism through which this rise occurs has not yet been established.

Increases in LDL and total cholesterol may place susceptible individuals at increased risk of ischaemic heart disease (IHD) and other vascular disease. Those at greatest risk include individuals with a family history of IHD or familial hyperlipidaemia, those with sedentary habits, smokers and older individuals. Additionally, body shape changes may add further to risk by altering the waist:hip ratio, an independent risk factor for IHD.²⁰ Reports of episodes of myocardial infarction or angina shortly after initiation of antiretroviral therapy are complicated by the presence of additional cardiac risk factors in many of these individuals. Additionally, lipid elevations were neither striking nor prolonged in these individuals before infarction.^{15,21-24} As there may be an infectious component to IHD (both *Chlamydia pneumoniae* and cytomegalovirus have been implicated²⁵), these early events may have represented immune restoration phenomena rather than lipid-associated IHD. Elevation of triglycerides may place individuals at risk of pancreatitis, with fatal cases having now been reported.²⁶ Concomitant use of the nucleoside analogue didanosine (ddI), which has been associated with a low (<1%) but important incidence of pancreatitis, may also add to this risk.²⁷

Diabetes mellitus

Insulin resistance has been reported in patients treated with PIs.^{10,11} Diabetes mellitus was first reported as a consequence of HIV therapy among a small proportion of recipients of ddI monotherapy during high-dose developmental

studies and the US expanded access programme for this drug.^{28,29} The US Food and Drug Administration first reported on PI-associated diabetes mellitus in June 1997,³⁰ when 83 cases of new-onset hyperglycaemia or worsening of pre-existing diabetes were described. Type 2 (non-insulin-dependent) diabetes has been the type of diabetes mellitus associated with PI therapy,^{12,31-37} although treatment requirements in pre-existing Type 1 (insulin-dependent) diabetes may increase after starting therapy.¹² The prevalence of diabetes in HIV-infected patients treated with PIs is low at one year (<1%), although asymptomatic hyperglycaemia has been reported in 10-50% of patients on long-term PI therapy.^{12,31,32,34-37}

Lipodystrophy

Long-term antiretroviral therapy has been associated with abnormal body fat distribution, also called lipodystrophy.¹²

Initially, a link was made between the development of lipodystrophy and PI therapy.¹² However, patients receiving nucleoside analogue or NNRTI-based triple therapy may also develop this syndrome.³⁸ Additionally, it may be that chronic HIV-1 infection itself is associated with fat redistribution or that effective therapy may amplify pre-existing clinical and metabolic disorders.³⁹⁻⁴¹

Lipodystrophy has been recognised later than hyperlipidaemia and hyperglycaemia as an adverse effect of PI therapy. This may have been partly because of the heterogeneity of the clinical manifestations of lipodystrophy.

A consensus case definition for lipodystrophy to enable comparison of studies does not currently exist, and the reported clinical manifestations of lipodystrophy have not been homogeneous. Their manifestations can be broadly divided in two groups:

- Those with a predominance of localised fat deposition (lipohypertrophy).
- Those with peripheral fat wasting (lipoatrophy).

Lipohypertrophy is generally central and may manifest as visceral fat accumulation,^{42,43} enlargement of breasts,^{44,45} or development of localised fat deposits, most commonly cervical fat pads (also called 'buffalo humps').^{41,46-49} Patients on PI therapy with central adiposity^{42,49} have less subcutaneous abdominal fat than HIV-1 controls not using PIs. Thus, fat redistribution syndrome may be distinguished from weight gain secondary to improved nutritional status (where fat accumulates evenly in subcutaneous areas).

Additionally, depending on the presence of peripheral fat loss, these individuals may also have stable rather than increased weight. The lipohypertrophy observed during antiretroviral therapy may be in part influenced by sex hormones; in males intra-abdominal fat accumulation is most common, while in females breast enlargement is most common.⁴⁵ Breast enlargement (not truly gynaecomastia as the enlargement is in fat not breast tissue) in males has also been observed.

With peripheral fat wasting,^{45,50} patients may have a relative weight loss. Subcutaneous fat is lost from areas including the legs (Figure 1), buttocks, arms, chest and facial fat pads (most commonly buccal, naso-labial and temporalis, but occasionally also periorbital). Peripheral fat loss leads to vein prominence and increased muscle definition. Loss of subcutaneous fat also leads to increased folding of the skin, most readily observed around the knees, buttocks and face. The characteristic presentation of lipodystrophy is well known in HIV-affected communities, this has led to the stigmatisation of individuals with the syndrome.

Associations with the syndrome

Variability in clinical manifestations of fat redistribution and metabolic derangements may reflect different pathogenetic mechanisms, as well as genetic and environmental influences. However, the cross-sectional design of most available studies reporting lipodystrophy do not allow us to determine whether the observed clinical differences were simply reflecting different evolutionary periods in the natural history of lipodystrophy. Recent data from a prospective study in Australia have suggested that elevation of triglycerides on therapy was associated with an increased risk of future fat redistribution.⁵¹

Associations in cross-sectional studies do not necessarily reflect causation and must be interpreted with caution. Time on therapy, and specifically time on PI therapy, has been associated with fat redistribution.¹² Abnormal body fat distribution has been generally described in patients after at least six months of antiretroviral therapy.¹² A predominance of central adiposity seems to develop sooner after the introduction of therapy^{41,47,49} than does peripheral fat wasting.^{12,50} Other reported associations include age (>40 years), abnormal pre-therapy lipids, family history of diabetes mellitus (for development of diabetes), high body



Figure 1. Peripheral fat wasting from the legs of an HIV-infected patient

mass index (BMI, for risk of central adiposity), low BMI (for peripheral lipoatrophy), and use of ritonavir-based therapy.^{12,32,51}

More recently, associations in several studies have been made with specific nucleoside analogues (NAs), most commonly stavudine (d4T) or lamivudine (3TC).^{38,52} However, many studies that have failed to find a specific nucleoside analogue association have also been reported. These reports have generally not corrected for time on NA therapy; d4T and 3TC are the most widely prescribed NAs and their good tolerability potentially means that these agents may be taken for more prolonged periods than less convenient or tolerable nucleoside agents.

Attempts to determine the incidence of lipodystrophy are problematic because diagnosis has relied on subjective clinical definitions. Estimates of the prevalence vary widely depending on the definition of lipodystrophy, the design of the study, the geographical area and the time since the onset of antiretroviral therapy. Thus, reported prevalence of lipodystrophy ranges from 2% to 74% after 3–18 months of therapy.^{12,47,49,50}

Pathogenesis of metabolic and fat distribution abnormalities

The pathogenesis of these metabolic and clinical phenomena remains speculative. Before the advent of PIs, metabolic parameters described in clinically stable HIV-1-infected patients (normal or increased plasma triglycerides, decreased plasma cholesterol – specifically HDL⁸ – and

increased insulin sensitivity) were different from those seen in association with PI therapy (hypertriglyceridaemia, hypercholesterolaemia, and decreased insulin sensitivity).

Several hypotheses regarding the pathogenetic mechanisms for the lipodystrophy syndrome exist. The hypotheses regarding the contribution of protease inhibitors generally focus on the homology between HIV protease and human enzymes involved in fat and/or insulin handling, suggesting that a PI may inhibit some key human protein(s).

Carr *et al*⁵³ have shown that the catalytic region of the HIV-1 protease shares considerable homology with regions within two proteins that regulate lipid metabolism: LDL-receptor-related protein and cytoplasmic retinoic-acid-binding protein type 1 (CRABP-1). In this hypothesis, PIs inhibit the CRABP-1-modified and cytochrome P₄₅₀ 3A (CYP3A)-mediated synthesis of 9-cis-retinoic acid, an activator of the retinoid X receptor and peroxisome proliferator-activated receptor type gamma (PPAR-gamma), which regulate adipocyte differentiation and apoptosis.⁵⁴ PI binding to the LDL-receptor-related protein would impair hepatic chylomicron uptake and triglyceride clearance by the endothelial LDL-receptor-related protein-lipoprotein lipase complex. The resulting hyperlipidaemia would explain the anomalous fat distribution and the insulin resistance.

One drawback of this hypothesis is that homology in the primary structure of proteins does not necessarily imply homology in their tertiary structure. A recent *in vitro* study has partially supported this hypothesis: indinavir was specifically noted to block retinoid signalling, whereas other approved PIs were found to inhibit adipogenesis.⁵⁵ These differences in *in vitro* effects may help to explain some differences in clinical manifestations. Blocking retinoid signalling may also affect CRABP-2, a receptor located in the skin, which may explain the dry skin, body hair loss and nail dystrophies observed in many indinavir recipients.^{56,57}

An alternative, or additional, hypothesis, raised by Martinez and Gatell, involves the possibility that insulin may be a substrate of the HIV-1 protease.⁵⁸ They suggested that if a substrate (insulin) is shared by several enzymes (insulin-degrading enzymes and the HIV-1 protease), it is possible that inhibitors of one of the enzymes (the HIV protease) could also inhibit the other insulin-degrading enzymes. The

resulting hyperinsulinaemia would, initially, enhance insulin's physiological effects with a net increase in fat and accumulation of intra-abdominal fat resulting from a high density of glucocorticoid receptors stimulating lipoprotein-lipase activity in this region. Later, insulin resistance would predominate, resulting in an increase in subcutaneous lipolysis,⁵⁹ and a compensatory insulin hypersecretion that could lead to Type 2 diabetes in predisposed individuals. Insulin resistance is known to develop early in many patients treated with PIs.^{10,11}

Stricker and Goldberg⁶⁰ also hypothesised that HIV-1 PIs interact with a group of human aspartic proteases called cathepsins, which are responsible for the degradation of glucagon, insulin, insulin-like growth factors and binding proteins. In this theory, increased concentrations of these hormones would produce fat accumulation and hyperglycaemia.

Speculation regarding the role of nucleoside analogues has focused on the known inhibition of human mitochondrial DNA polymerase gamma by these agents.⁶¹ Human fat cells vary from white (mostly peripheral 'storage' cells) to brown (in adults, mostly central cells involved in thermogenesis). The colour differences relate to the difference in mitochondrial load, the more metabolically active brown fat cells having a higher load of mitochondria. Therefore, inhibition of adipose cell mitochondria could result in different effects:

- Toxicity would be greater in the white, peripheral cells with a lower mitochondrial reserve, leading to apoptosis of these cells and hence to loss of peripheral fat mass and release of fat (particularly triglyceride-rich fats) into the systemic circulation.
- Brown cells would have slowed metabolism but would continue to accumulate fat, leading to an increase in central fat mass.⁶²

Mitochondrial inhibition with nucleoside analogues may be also associated with additional metabolic and laboratory abnormalities, including lactic acidosis, transaminitis and hepatic steatosis.⁶¹

Thus, the differences in the clinical presentation of metabolic manifestations of this syndrome may relate to two or more contributory mechanisms, the relative contributions varying between individuals. This further complicates the potential for 'simple' management of the syndrome.

Assessment of an individual on antiretroviral therapy

Evaluation of patients receiving therapy routinely includes measurement of viral load, immune profile, renal and hepatic function and full blood count, as well as weight and clinical examination, on a three-monthly basis. The high frequency of metabolic abnormalities on antiretroviral therapy demands that additional evaluations are now routinely included. These should preferably be performed in a fasted state. Laboratory tests should include cholesterol with HDL:LDL ratio, triglycerides (with lipase if triglyceride levels are raised), glucose and glycosylated haemoglobin and lactate (+ pyruvate and anion gap).

In an individual presenting with clinical changes, testosterone, thyroid function and Apo-E, as well as blood pressure and dietary assessment, should be considered. Serum cortisol is normal in this syndrome.⁶³

Objective assessment of lipodystrophy in clinical trials has generally involved anthropometrics (specifically waist:hip ratio), dual X-ray absorptiometry (DEXA) scanning and single slice CT or MRI scanning. However, normal values for the results of such examinations are not established and will vary with machine calibration and observer variation, so they cannot be routinely recommended.

Management of metabolic and clinical abnormalities

The decision to initiate therapy is a balance between the risks and potential benefits of therapy versus the risks of leaving HIV infection untreated.⁷ In most infected individuals, the balance is likely to favour intervention at some point. In this case, the positive effects of antiretroviral therapy compensate for the negative effects. This should be the case for all individuals established on therapy. Therefore, the prolonged withdrawal of therapy to manage these problems does not represent a reasonable option. Management of these problems is therefore about judging the risks of individual therapies in individual patients. If a patient on a successful (that is, fully suppressive) antiretroviral therapy develops metabolic abnormalities, continuation or not of the regimen and of each component would depend on the severity of metabolic effects, the past therapy history and the availability of options that may have a lower risk of causing these abnormalities while maintaining viral control. This is inevitably, therefore, a balancing act.

Evidence that diet and aerobic exercise are useful in improving abnormal body fat distribution is lacking. However, they clearly represent ways to maintain general health and reduce elevated blood lipids and cardiovascular risk factors, and so should be routinely recommended. Aerobic exercise specifically improves peripheral insulin use and thus may be therapeutic. In animal models, fat intake as a proportion of dietary intake may influence the site of fat deposition.⁵⁵ A 'normal' fat diet is therefore recommended. Changes in diet should only be undertaken with advice from a dietitian to avoid a change in total calorie intake, which may worsen the syndrome. Additionally, encouraging reduction in smoking is useful for reducing IHD risk. Adequate psychological support should be offered when the development of clinically apparent lipodystrophy is accompanied by psychological repercussions.

Statins and fibrates have demonstrated efficacy in lowering lipids. Fibrates predominately reduce triglycerides, while statins predominately affect cholesterol. While no drug interactions are anticipated with fibrates, some statins are metabolised by CYP3A and may therefore have important interactions with PIs. Pravastatin is the agent from this class with the least likelihood of interaction and is thus the preferred choice.⁶⁴ The effect of these lipid-lowering drugs on the natural history of lipodystrophy is not yet known.

PPAR-gamma agonists such as troglitazone and retinoid X receptor agonists may be useful, however, the clinical use of troglitazone may be limited because of the risk of severe hepatic insufficiency. Other drugs from these families are still under investigation. Drugs from the glitazone class are not currently available in the UK. Metformin, which improves peripheral insulin use, has been reported to provide reductions in insulin resistance and lead to reductions in intra-abdominal fat.⁶⁵ This drug, however, carries some risk of lactic acidosis. Recombinant human growth hormone at a dose of 6 mg/day subcutaneously may improve localised fat masses;⁶⁶ however, as with anabolic steroids, this drug leads to loss of peripheral fat.

Surgical removal of fat accumulations has been tried in individual cases with no subsequent short-term recurrence,⁴¹ but the long-term benefit of this procedure is unknown.

Discontinuation of a component of therapy involves consideration of two outcomes:

- Maintaining virological control.

- Improving clinical/metabolic effects.

Switching from a PI to an NNRTI has shown benefit in some cases,⁶⁷⁻⁶⁹ although prolonged (up to one year) follow-up may be necessary for this benefit to be clearly established. However, in some cases, loss of virological control or persistence of metabolic changes has been noted.⁶⁷⁻⁶⁹ Switching between PIs has also produced mixed results.^{70,71} Insufficient data are available on switching from a PI to a third nucleoside analogue.

Switching between nucleoside analogues may be a possible approach. Formal studies are now evaluating these approaches.

Conclusion

Though not yet proven, much observational data link prolonged antiretroviral therapy with a significant risk of developing fat redistribution syndrome. Although PIs were initially linked

with this syndrome, other factors may also play a role as not every patient receiving PIs develops the same metabolic abnormalities and the same body changes have been observed in PI-spared patients. Hyperlipidaemia and insulin resistance commonly precede the development of clinically apparent lipodystrophy. PIs are suspected of causing this syndrome by inhibiting some human protein(s) involved in lipid and carbohydrate metabolism. Nucleoside analogues may contribute through mitochondrial toxicity in adipocytes. Routine management of HIV-1-infected patients treated with highly active antiretroviral therapies requires that metabolic evaluations be included in clinical care. Both passive (switching from one drug regimen to another) and active (diet, lipid-lowering agents, antidiabetic drugs or others) approaches are under investigation for the management of this syndrome.

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Website review

Using the internet is a good way of keeping up-to-date with the latest HIV/AIDS research, and the websites described below are some of the best.

● **www.medscape.com** is a good site to subscribe to. Registration is straightforward, and after you have stated your preferences of speciality the service is excellent. Reports are sent to you regularly (approximately weekly) and usually contain at least a summary report of the major international conferences and workshops. At present, the First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV (San Diego, 26–28 June 1999) is expertly summarised by Donald Kotler (12 pages and 38 references). The article can be viewed with tables, figures and other web enhancements. The weekly summary usually comes with offers of reduced price medical equipment and books, and occasionally advice on financial investments (from a US perspective of course).

Do not forget to clean up your hard disc occasionally to deal with the temporary files sent down from such services.

● **www.nih.gov.od.oar** is an excellent website from the US National Institutes of Health Office of AIDS Research. OAR is responsible for the development of an annual comprehensive plan and budget for all NIH AIDS research, and the programme is particularly strong in the fields of therapeutics, vaccines, natural history and epidemiology, behavioural and

social sciences, aetiology and pathogenesis, training and infrastructure, and information dissemination.

The information aspect is certainly well covered and you can attend 'virtual conferences', although you will need a RealAudio player and plug-in installed. A free real player can be downloaded from www.real.com to facilitate this.

Particularly useful features of this site are the links to other NIH sites (great statistics and graphs here) and a long list of acronyms used in HIV.

● **www.hivinsite.ucfs.edu**, the website of the University of California, San Francisco, describes itself as 'A visionary institute for AIDS science'. It is comprehensive, accurate and very up-to-date, which is what one would expect from one of America's leading health science institutions. The 'About' section is particularly useful.

● **www.amnh.org/exhibitions/epidemic**, the American Museum of Natural History's website, is the place to visit to see a brilliant online exhibition called 'Epidemic: The World of Infectious Disease'. The visuals are excellent and the information revealing. The section on transmission includes visuals of a man sneezing, which is a highlight. This site leaves you literally itching for more.

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