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Metabolic Complications Associated with HIV Protease Inhibitor Therapy

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Abstract

HIV protease inhibitors were introduced into clinical practice over 7 years ago as an important component of combination antiretroviral drug regimens which in many ways revolutionised the treatment of HIV infection. The significant improvements in prognosis that have resulted from the use of these regimens, combined with the need for lifelong treatment, have increasingly focused attention on the adverse effects of antiretroviral drugs and on the metabolic complications of HIV protease inhibitors in particular. In this review, the cluster of metabolic abnormalities characterised by triglyceride-rich dyslipidaemia and insulin resistance associated with HIV protease inhibitor therapy are considered, along with implications for cardiovascular risk in patients affected by these complications. Toxicity profiles of individual drugs within the HIV protease inhibitor class are examined, as there is an increased recognition of significant intra-class differences both in terms of absolute risk of metabolic complications as well as the particular metabolic phenotype associated with these drugs. Guidelines for clinical assessment and treatment are emphasised, along with pathophysiological mechanisms that may provide a rational basis for the treatment of metabolic complications. Finally, these drug-specific effects are considered within the context of HIV-specific effects on lipid metabolism as well as lifestyle factors that have contributed to a rapidly increasing incidence of similar metabolic syndromes in the general population. These data highlight the importance of individualising patient management in terms of choice of antiretroviral regimen, assessment of metabolic outcomes and use of therapeutic interventions, based on the assessment of baseline (pre-treatment) metabolic status as well as the presence of potentially modifiable cardiovascular risk factors.

The introduction of HIV protease inhibitor (PI) therapy into clinical practice in 1996 represented a significant step forward in the treatment of HIV infection. The ability of highly active antiretroviral therapy (HAART) regimens incorporating PI drugs to profoundly suppress viral replication has transformed HIV infection into a manageable chronic disease in many patients, and has dramatically improved mortality and morbidity.[1] However, long-term PI treatment has been associated with adverse metabolic effects that were recognised as novel toxicity syndromes in 1997 and 1998,[2-17] and which continue to be studied intensively in 2003. These complications provide significant challenges to clinicians caring for HIV-infected patients, who may be concerned that a mastery of the intricacies of

metabolism has to be added to the virology, immunology and pharmacology knowledge that is already required to practice effectively in this field. However, progress has been made in elucidating the pathogenesis of PI-associated metabolic complications, which in turn provides a foundation for a rational approach to clinical management. Additionally, for those with an interest in human endocrinology and metabolism but who are not HIV clinicians, there are significant opportunities to learn from this 'natural experiment'.

In this review, evidence for causal associations between PI therapy and metabolic abnormalities is presented within the context of the 'lipodystrophy syndrome', with particular emphasis on the pathophysiology of insulin resistance and triglyceride-rich dyslipidaemia. The clinical implications of these metabolic complications are then addressed, focusing specifically on cardiovascular disease risk, and the importance of individualising clinical management to incorporate potentially modifiable host- and disease-related factors. Current approaches to the management of metabolic complications, through interventions such as 'switching' antiretroviral regimens or the use of adjunctive treatments (e.g. lipid-lowering and/or insulin-sensitising drugs), are also explored. This area has also been the subject of a recent review from an International AIDS Society – USA panel,[18] which includes preliminary recommendations for management.

1. HIV Protease Inhibitor (PI) Therapy and the 'Lipodystrophy Syndrome'

Historically, the use of the term 'lipodystrophy syndrome' originates in two reports, published in late 1997[2] and early 1998,[3] describing wasting of subcutaneous fat in the face and limbs of HIV-infected patients treated with the PI indinavir, reminiscent of rare congenital and acquired lipodystrophy syndromes. From late 1997 onwards, others described benign symmetric lipomatoses, localised 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.[2-17] Altered lipoproteins, mimicking the 'atherogenic' profile seen in dyslipidaemic patients with diabetes mellitus were also documented in PI-treated patients and were shown to precede body habitus changes in some patients.[19-30] Insulin resistance and diabetes developed *de novo* or worsened in patients (with and without morphological change), coincident with starting therapy with a PI.[19,24,31-36]

The first systematic study that attempted to provide a unifying definition and description of the syndrome in a large Australian cohort suggested 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.[37] The vast majority of affected patients were receiving PI-containing HAART. The facts that morphological and metabolic changes appeared to aggregate at a population level, their phenotypic similarity to the 'metabolic syndrome' (see table I) and the plausibility of PIs as a unifying cause, all helped drive the view that these changes formed a new single 'lipodystrophy syndrome'[37-39] (figure 1).

Since that time evidence has emerged that subcutaneous fat wasting behaves as an independent or partially independent process, while visceral fat accumulation, dyslipidaemia and insulin resistance appear to be closely linked (figure 2). Clinical trials have demonstrated that the severity of subcutaneous fat wasting is primarily determined by choice (and

Table I. Adult Treatment Panel III criteria for diagnosis of the metabolic syndrome.[a] Presence of three or more clinical features is diagnostic

Abdominal obesity
waist circumference: 40 inches men, 35 inches women
Triglycerides >150 mg/dL (1.7 mmol/L)
Low high-density lipoprotein cholesterol
men <40 mg/dL (1.0 mmol/L)
women <50 mg/dL (1.3 mmol/L)
Blood pressure >130/>85mm Hg
Fasting glucose >110 mg/dL (6.1 mmol/L)

a Note that an alternative definition of the metabolic syndrome has also been proposed by the World Health Organization (see Ford and Giles[40]). The definition provided in this table has been incorporated into National Cholesterol Education Program (NCEP) guidelines.[41]

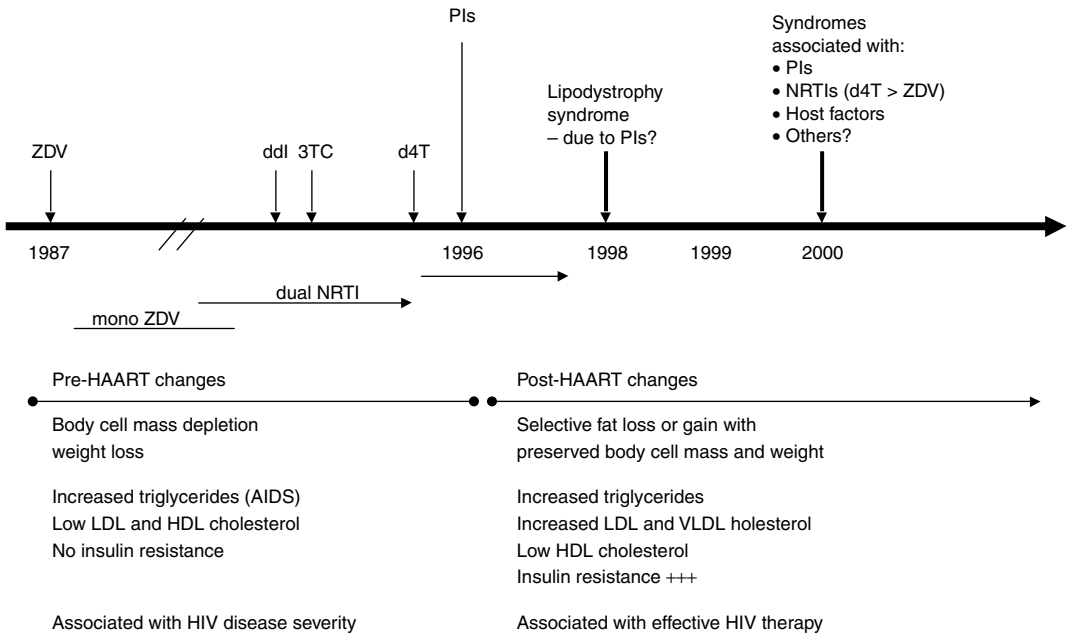

Fig. 1. Timeline of developments in antiretroviral treatment and 'lipodystrophy syndrome(s)'. **3TC** = lamivudine; **d4T** = stavudine; **ddI** = didanosine; **HAART** = highly active antiretroviral therapy; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **NRTI** = nucleoside reverse transcriptase inhibitor; **PI** = protease inhibitor; **VLDL** = very low-density lipoprotein; **ZDV** = zidovudine.

duration) of nucleoside reverse transcriptase inhibitor (NRTI) therapy, particularly stavudine,[42-45] while the use of PI therapy does not have a significant impact on this outcome. Data from switching studies also support this assertion, in that substituting an alternative NRTI for stavudine (in 94% of cases presented to date) has been associated with improvement in fat wasting, while more than 30 clinical trials investigating PI switching have shown no beneficial effects (reviewed by Dreschler and Powderly[46]). However, as will be discussed further, discontinuing PI therapy has been associated with improved metabolic outcomes[46] and there is strong evidence that PIs are causally linked to components of the 'metabolic syndrome', incorporating insulin resistance, triglyceride-rich dyslipoproteinaemia and abdominal/visceral obesity.

2. HIV PI Therapy and the 'Metabolic Syndrome'

It is notable that insulin resistance, triglyceride-rich dyslipoproteinaemia and abdominal obesity cluster at a population level, suggesting that they are related outcomes.[47,48] This is also observed in the setting of HIV PI therapy. Hence, elucidating the molecular pathophysiology of PI-induced metabolic dysregulation may help to unravel the complex biological relationships between fatty acid and glucose metabolism,[49] an area of research of particular current interest as prevalence of the metabolic syndrome and diabetes reach epidemic proportions in the general community.[47-49] While the direct contribution of HIV PI therapy is the focus of this discussion initially, it must be borne in mind that the metabolic effects of HIV infection itself can significantly influence the relationship between these drugs and their metabolic consequences, as will be discussed further.

2.1 PI Therapy and Dyslipidaemia

Dyslipidaemia associated with PI therapy is characterised by increased levels of triglyceride and triglyceride-rich lipoproteins (figure 3). These lipid fractions are normally elevated in the post-prandial

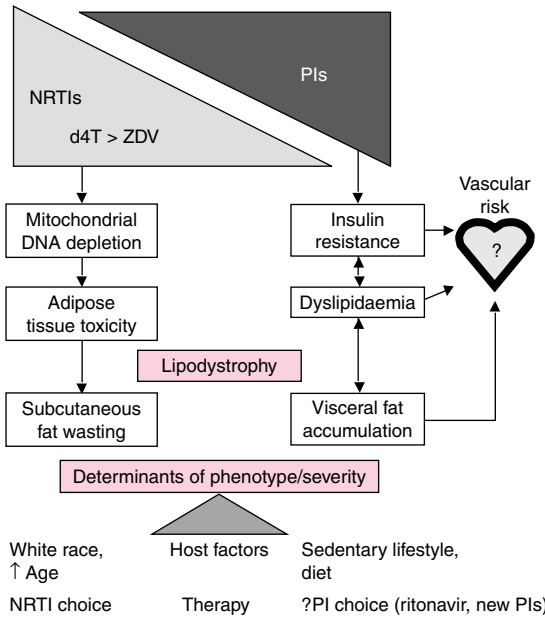

Fig. 2. A multifactorial model of lipodystrophy syndrome(s): a collection of abnormalities with partially overlapping risk factors (PI and NRTI). **d4T** = stavudine; **NRTI** = nucleoside reverse transcriptase inhibitor; **PI** = protease inhibitor; **ZDV** = zidovudine.

phase, and are destined for delipidation in the peripheral circulation by the action of endothelial lipoprotein lipase so that fatty acids may be removed to adipose tissue and stored (after conversion to triglyceride). In PI-associated dyslipidaemia, elevated plasma triglyceride levels are typically accompanied by increased total, very low density lipoprotein (VLDL) and intermediate density lipoprotein (IDL) cholesterol, apolipoproteins B, CIII and E, small-dense low density lipoprotein (LDL) cholesterol, and increased small high density lipoprotein (HDL) cholesterol.[29,50-53] These lipid changes are commonly accompanied by elevated insulin levels and increased levels of free fatty acid have also been observed.[53-55] Dysregulated fatty acid metabolism has been documented in a study by Sekhar and colleagues,[56] who used stable isotope tracer techniques to provide a comprehensive assessment of *in vivo* lipid metabolism dynamics in patients receiving PI-based HAART.[56] Turnover of fatty acids was found to be dramatically increased, with elevated fat oxidation and re-esterification in adipose tissue and liver, increased lipolysis, and markedly decreased clearance of triglyceride-enriched VLDL and chylomicrons.

This metabolic phenotype is typical of defective post-prandial lipid metabolism. Indeed, in a recent study Merwood and colleagues[58] have demonstrated significantly increased post-prandial triglyceride, and IDL, large VLDL, small LDL and small HDL cholesterol in PI-treated patients (n = 23) compared with those receiving non-PI-containing HAART (n = 16). This group has also shown that endothelial dysfunction is associated with this metabolic cluster in PI-treated patients,[59] consistent with population-based studies showing that elevated levels of triglyceride-enriched lipoproteins are independently predictive of cardiovascular disease.[60,61]

Insulin plays a critical role in coordinating the post-prandial metabolic response, in which carbohydrates are utilised as the primary source of fuel for oxidative reactions while fatty acids are directed into adipose stores and converted to triglyceride. This energy store can then be called upon when metabolism must rely more heavily on fatty acids as a fuel source in the postabsorptive or 'fasted' state. Hence, increasing insulin levels after food intake normally increase fatty acid uptake and triglyceride synthesis within adipocytes, and inhibit lipolysis (free fatty acid release from triglyceride) from adipose stores. Dysregulation of this response so that lipolysis is not suppressed in the post-prandial phase leads to inappropriate fatty acid flux and is a proposed mechanism for increased levels of triglyceride-enriched lipoproteins. Dysregulated/increased lipolysis has been demonstrated in the setting of PI therapy by Hadigan et al.,[62] who noted that lipolysis rates independently predicted insulin resistance ($p = 0.03$). Interestingly, this group went on to demonstrate that acute inhibition of lipolysis through the use of acipimox 1000mg in two divided doses in seven insulin-resistant PI-treated patients produced a significant decrease in insulin resistance ($p = 0.01$).[63] These results cannot be generalised from this small and highly selected study, and it must also be recognised that acipimox treatment did not fully restore insulin sensitivity in these patients.

Nevertheless, these findings raise the possibility that the excessive liberation of fatty acids from adipose tissue may play a significant role in determining both insulin resistance and dyslipidaemia in patients receiving PI therapy.

2.2 PI Therapy and Insulin Resistance

There is now strong evidence from *in vivo* studies in both HIV-infected and seronegative individuals that PI therapy is independently associated with insulin resistance. Probably the most compelling data among a number of recently published studies has shown that a single dose of indinavir 1200mg was sufficient to induce a significant reduction in insulin sensitivity (average decrease 34%, $p < 0.001$) in six healthy controls in a placebo-controlled study in which insulin sensitivity was assessed by euglycaemic hyperinsulinaemic clamp testing.[64] Hence, insulin resistance can be rapidly induced by PI therapy and is not necessarily secondary to changes in fat distribution (i.e. subcutaneous fat wasting or visceral fat accumulation). The use of healthy subjects indicates that neither HIV infection nor concurrent NRTI therapy is required for these effects.

Other studies that have accurately assessed insulin sensitivity *in vivo*, through the use of hyperinsulinaemic euglycaemic clamp[55,65,66] or intravenous glucose tolerance test with frequent sampling of plasma glucose and insulin,[67,68] have consistently demonstrated significant insulin resistance with decreased insulin-stimulated oxidative and non-oxida-

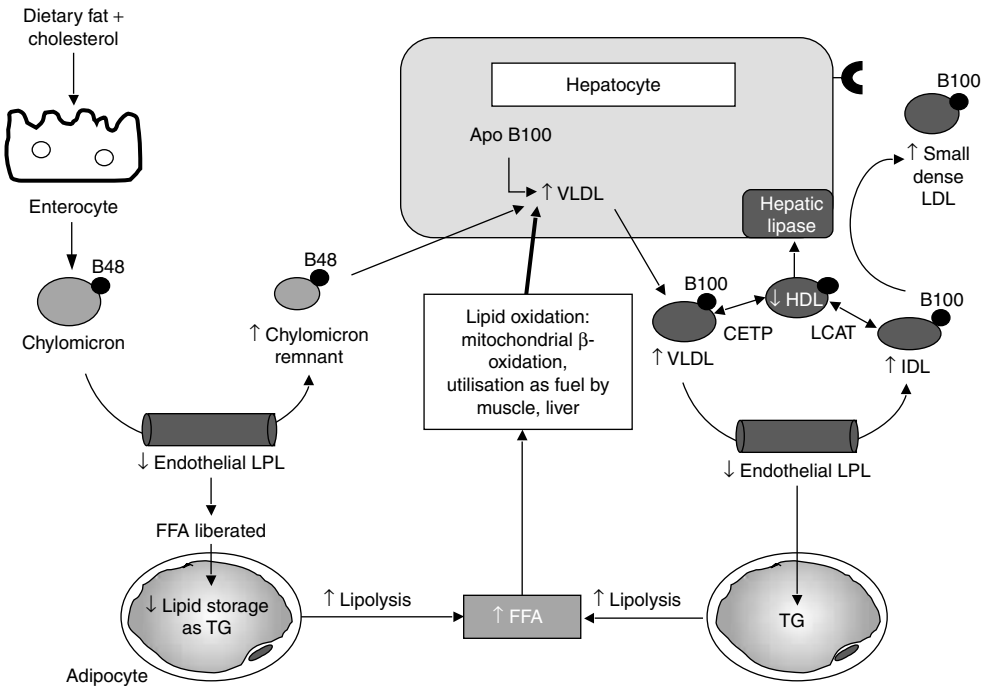

Fig. 3. Insulin resistance and lipid metabolism. Insulin resistance decreases delipidation of chylomicrons (derived from dietary fat) and VLDL-C (from hepatic processing of fatty acids) at the level of lipoprotein lipase, which is produced and secreted by adipocytes in response to insulin. Increased lipolysis from adipocytes, as well as increased chylomicron remnants, increase hepatic processing to produce VLDL-C. VLDL metabolism normally produces LDL that is then readily cleared by LDL receptors. However, 'altered', triglyceride-enriched VLDL is diverted towards the production of IDL from HDL, as well as small, dense LDL that is less effectively cleared via the LDL receptor and is more susceptible to oxidative modification (adapted from Nolan et al.,[57] with permission). **Apo B100** = apolipoprotein B100; **B48** = apolipoprotein B48; **CETP** = cholesterol ester transfer protein; **FFA** = free fatty acid; **HDL** = high-density lipoprotein; **IDL** = intermediate density lipoprotein; **LCAT** = lecithin:cholesterol acyltransferase; **LDL** = low-density lipoprotein; **LPL** = lipoprotein lipase; **TG** = triglyceride; **VLDL** = very low-density lipoprotein; **VLDL-C** = VLDL cholesterol.

tive glucose disposal, and impaired suppression of lipolysis and endogenous glucose production. HIV PIs used in these studies included indinavir, nelfinavir, ritonavir, saquinavir and lopinavir, although it is not possible to differentiate effects of specific drugs. These data suggest that a number of insulin-responsive tissues are involved in this aberrant response. For example, fasting plasma free fatty acids are derived solely from adipose tissue; the liver is the major organ responsible for endogenous glucose production; and skeletal muscle is the most significant site of insulin-stimulated glucose uptake and oxidation.

A recent study has also examined lipid accumulation within skeletal myocytes using magnetic spectroscopy, finding strong correlations between the severity of insulin resistance and the presence of intracellular lipid in soleus muscle (correlation of clamp glucose infusion rate and soleus intramyocellular lipid, $r = -0.71$, $p = 0.0005$).[65] Intrahepatic lipid detected by magnetic resonance imaging has also been observed in insulin resistant PI-treated patients.[69] These results are in agreement with Behrens et al.,[66] who propose that elevated tissue levels of free fatty acids provides a unifying mechanism explaining their observation that skeletal muscle insulin-stimulated glucose transport and phosphorylation is markedly impaired (~50%) among PI-treated patients compared with therapy-naive HIV-infected patients. Grinspoon and colleagues[70] have also demonstrated that elevated fasting free fatty acid levels are strong independent predictors of insulin resistance (measured as insulin response to oral glucose challenge) [$p = 0.03$], controlling for age, gender and body mass index and body composition ($n = 64$).[70] This proposed mechanism of insulin resistance is in accordance with current concepts, which give a prominent pathogenic role to fatty acid dysregulation at the cellular level.[49]

Hence, there is compelling evidence from *in vivo* studies that PI-induced insulin resistance and triglyceride-rich dyslipidaemia have a common association with dysregulated fatty acid metabolism.

2.3 Metabolic Complications and Body Composition Abnormalities

There are a number of potential confounding factors that need to be considered when examining relationships between HIV PI therapy, metabolic complications and body composition abnormalities. These factors, along with a paucity of longitudinal data, have combined to ensure that the role of visceral/abdominal fat accumulation within the 'lipodystrophy syndrome' remains relatively poorly understood. First, it remains unclear if PI therapy contributes to visceral adipose tissue accumulation independent of its effects on lipid/glucose metabolism. Current evidence suggests that insulin resistance is the dominant risk factor for visceral adiposity, as a number of studies have demonstrated that patients with the 'mixed lipodystrophy syndrome' (i.e. those with lipoatrophy as well as visceral adiposity) have more prominent insulin resistance compared with patients with lipoatrophy alone.[51,54,71] The rapidity of onset of PI-associated metabolic complications in the absence of body composition changes[64,72,73] also argues that increased visceral fat is a consequence of dysregulated insulin metabolism and post-prandial lipid metabolism, rather than its cause.

Secondly, the prevalence of abdominal obesity in the developed world is rapidly increasing (with age-adjusted estimates of 38.6% among US adults, ranging from 23% and 30.5% for African-American and White males, respectively, to 62% and 43.5% for African-American and White females, respectively).[47] In this context, so-called 'lifestyle factors' such as dietary fat intake and amount of exercise, along with increasing age, are likely to be important risk factors in the general population as well as among PI-treated patients. The high rate of abdominal obesity among developed societies,[47] and the high degree of variability in objectively measured visceral fat area in these populations,[74] may also make it difficult to use this endpoint as a means of discriminating 'cases' and 'controls' in cross-sectional analyses.

It has been argued in a study by Mynarcik and colleagues[75] that lipoatrophy itself may contribute

to risk of insulin resistance. However, no correlation between insulin resistance and limb fat was documented among the lipodystrophic patients in this study, although diminished ability of insulin to suppress free fatty acid levels (i.e. to inhibit lipolysis from adipose tissue) was highly correlated with insulin resistance in this group ($r = 0.56$, $p < 0.001$).[75] Other studies have shown powerful associations between visceral fat area and insulin resistance independent of lipoatrophy,[65,67] in keeping with clinical data that patients with 'pure lipoatrophy' have relatively preserved insulin sensitivity.

Once established, does visceral adiposity represent an independent risk factor for sustained metabolic abnormalities? Data presented recently by Dr Peter Reiss[76] in a plenary presentation at the 10th Conference on Retroviruses and Opportunistic Infections, Boston, USA, suggest that this is the case. For example, in the Spanish Nevirapine, Efavirenz, Abacavir (NEFA) study (involving switching PI therapy to non-NRTI [NNRTI]), the metabolic benefits of PI switching therapy were greatly reduced in patients with pre-existing body composition changes.[77]

To conclude, visceral fat accumulation is certainly associated with the use of HIV PI therapy. However, current evidence suggests that this component of the 'lipodystrophy syndrome' may best be considered as a downstream effect of the metabolic effects of PI drugs.

2.4 Potential Mechanisms of PI-Associated Metabolic Complications

Three mechanisms by which PI therapy may initiate insulin resistance and dyslipidaemia are supported by *in vitro* studies, and are indirectly supported by clinical data. It should be noted that these pathophysiological mechanisms may well be overlapping, and are not mutually exclusive (figure 4).

2.4.1 Defective Activation and Nuclear Translocation of the Transcription Factor Sterol Regulatory Element-Binding Protein 1

Sterol regulatory element-binding protein (SREBP) is an endoplasmic reticulum-derived transcription factor common to adipose tissue and the liver that plays a critical role in inducing the signature adipocyte response to post-prandial insulin release.[78-80] In adipocytes it is involved (either directly or via downstream stimulation of peroxisome proliferator activated receptor gamma [PPAR-γ]) in increasing fatty acid uptake (via lipoprotein lipase) and fatty acid synthesis from carbohydrate precursors (via fatty acid synthase), inhibiting lipolysis (via hormone sensitive lipase), increasing adipocyte differentiation, and increasing uptake and utilisation of glucose as an energy substrate (via insulin-sensitive glucose transporter 4 [GLUT4], glucokinase) [figure 4].[78-80] Caron et al.[81] and Bastard and colleagues[82] have provided elegant studies indicating that PI therapy inhibits the translocation of active SREBP-1c from endoplasmic reticulum and nuclear membranes to the nucleus. They also detected altered electrophoretic mobility of activated SREBP-1, suggesting abnormal processing or phosphorylation of active SREBP-1 after proteolytic activation from its 125 kDa precursor form. Other studies corroborate these results *in vitro*,[83-85] indicating that pharmacological doses of PI drugs may directly induce insulin resistance in adipocytes, as well as a defect in the late stages of adipocyte maturation characterised by decreased expression of nuclear transcription factors CCAAT-enhancer binding protein (C/EBP)-α and PPAR-γ.[83-85] Interestingly, defective SREBP processing may also be central to the pathogenesis of Dunnigan-type familial partial lipodystrophy, a severe monogenic form of insulin resistant lipodystrophy that resembles HAART-associated lipodystrophy phenotypically.[86] The underlying genetic defect in this condition involves mutations in the *LMNA* gene that encodes nuclear lamin A, a protein involved in the organisation of the nuclear membrane and the regulation of trafficking of transcription factors into the nucleus. It has been proposed that mutated *LMNA* products may interact abnormally with SREBP, so that activation of nuclear transcription factors is impaired[86] (see figure 4). *In vitro* (using 3T3-F442A mouse adipocyte cell lines), a hierarchy of PI effects has been suggested, with half-maximal effective concentrations (EC_{50}) on insulin signalling pathways of

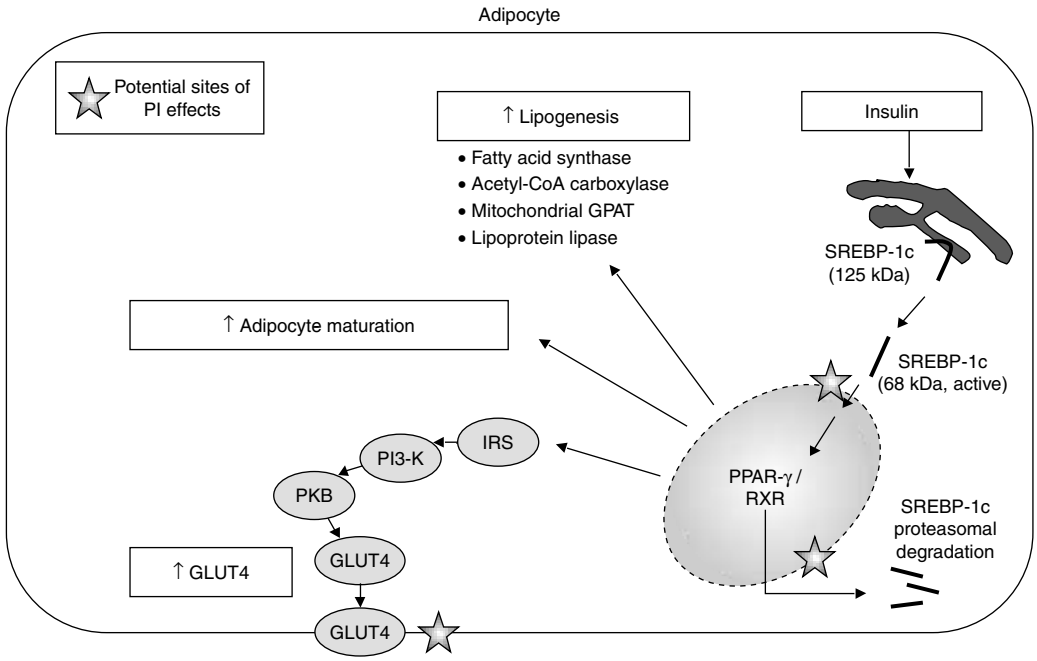

Fig. 4. SREBP-1, PPAR-γ and insulin signalling pathways. SREBP is activated by insulin and acts to promote lipogenesis and adipocyte differentiation via multiple pathways, acting both directly and via intranuclear activation of PPAR-γ/RXR nuclear transcription factors. Potential sites of protease inhibitor (PI) effects on metabolism are indicated. **Acetyl-CoA** = acetyl-coenzyme A; **GLUT4** = insulin-sensitive glucose transporter 4; **GPAT** = glycerol phosphate acyltransferase; **IRS** = insulin receptor substrate; **PI3-K** = phosphatidylinositol 3-kinase; **PKB** = protein kinase B; **PPAR-γ** = peroxisome proliferator activated receptor-γ; **RXR** = retinoid-X receptor; **SREBP** = sterol regulatory element-binding protein.

16 μmol/L (indinavir), 25 μmol/L (nelfinavir) and >100 μmol/L (amprenavir).[87]

2.4.2 Direct, Reversible Inhibition of Insulin-Sensitive Glucose Transporter-4

Murata et al.[88-90] have demonstrated reversible inhibition of GLUT4 induced by a number of PI drugs, most notably by indinavir. In primary rat adipocytes, indinavir rapidly inhibited glucose uptake at pharmacologically relevant concentrations (inhibition constant [K_i] ~10 μmol/L), while decreased insulin sensitivity was also seen in rats acutely exposed to indinavir 15 mg/kg that reversed within 4 hours of ceasing indinavir infusion. These data suggest that PI drugs interact directly with the insulin-responsive glucose transporter at the cell surface of adipocytes and skeletal muscle cells. This observation has also been confirmed by Ben-Romano and colleagues,[91] who have elegantly demonstrated that translocation of GLUT4 is unaffected.

2.4.3 Proteasomal Inhibition

Unlike other HIV-1 PIs, ritonavir appears to have activity as a proteasome inhibitor at pharmacological doses[92] and shows specificity for a proteasomal pathway involved in the degradation of SREBP-1.[93] Accordingly, ritonavir appears to increase hepatic triglyceride production via increased stabilisation of nuclear SREBP-1c.[94] Research by Distler and colleagues[95] is also in keeping with this mechanism, in which there is increased hepatic sensitivity to fatty acid stimulus, leading to increased VLDL and apolipoprotein B production and secretion.

2.5 Differentiating the Effects of Specific PI Drugs on Metabolic Outcomes

Taken together, these mechanisms provide a possible explanation for clinically observed differences in metabolic outcomes associated with specif-

ic PI drugs. For example, ritonavir is notable within the PI class for its ability to induce hypertriglyceridaemia,[30] and its use was associated with marked elevations of triglyceride and apolipoprotein B levels in HIV-negative individuals over a 2-week period.[72] This effect may be attributed to its specific ability to increase hepatic triglyceride production secondary to its activating effects on SREBP-dependent lipid metabolism in the liver. Similar results have been obtained in ten healthy volunteers treated with lopinavir 400mg/ritonavir 100mg twice daily for 4 weeks, in whom fasting triglyceride levels rose significantly while insulin sensitivity remained stable, as measured by euglycaemic, hyperinsulinaemic clamp.[73] On the other hand, indinavir therapy in HIV-negative individuals is associated with acute induction of insulin resistance,[64,96] although triglyceride-rich dyslipidaemia was not observed in the initial 4 weeks of therapy.[96] This suggests that the acute inhibition of insulin-stimulated glucose transport (via GLUT4), which is most potently induced by indinavir,[88] may be the primary mechanism in the early stages of therapy.

Following from these observations, preliminary studies involving the more recently introduced PI drugs, atazanavir and amprenavir, suggest that they are relatively benign. In one study (BMS AI424-044),[97] 'intraclass' PI switching from nelfinavir to atazanavir therapy was associated with decreased total and LDL cholesterol (−16% and −21%, respectively), and decreased triglycerides (−28%) [$p < 0.001$] to levels comparable with baseline values obtained prior to nelfinavir introduction. This is in keeping with *in vitro* studies in which atazanavir performed well in comparison with other HIV PIs[98] (although amprenavir was not included in these analyses). Regarding amprenavir, prospective evaluation of metabolic outcomes in patients commencing therapy has shown no evidence of insulin resistance associated with this drug to 48 weeks.[99] Another study comparing the effects of ritonavir-boosted amprenavir (600 or 900mg) with either efavirenz or tenofovir over 24 weeks[100] indicate that the tenofovir plus amprenavir regimen (n = 60) is associated with only a modest increase in triglyceride levels (~40 mg/dL) and no significant effects on total, LDL or HDL cholesterol. Similarly, among 31 heavily pretreated patients commencing salvage therapy with ritonavir-boosted amprenavir (600mg), no significant increases in total cholesterol ($p = 0.8$) or triglyceride ($p = 0.4$) were observed over 16 weeks. In 13 patients with elevated cholesterol levels at baseline (>200 mg/dL [>5.2 mmol/L]), total cholesterol decreased significantly (median difference 33 mg/dL [0.85 mmol/L], $p = 0.029$); with a similar effect observed in eight patients with baseline triglyceride levels >200 mg/mL (median difference in triglyceride 82 mg/mL [2.1 mmol/L], $p = 0.001$).[101]

Further research is required to establish the metabolic profile of these drugs in large numbers of HIV-infected patients, as current data are generally limited to 48 weeks. As these HIV PIs enter routine clinical practice, these long-term results are awaited with interest.

3. Clinical Relevance of PI-Associated Metabolic Complications

While the pathophysiology of metabolic abnormalities associated with PI therapy has so far been the dominant focus of this review, the clinical relevance of these adverse effects and the pertinent factors that require consideration in managing these complications in clinical practice need to be considered. The clinical implications of PI-induced metabolic syndromes may be distilled as a number of questions.

- What is the most appropriate method of testing for these complications and when should these tests be performed?
- Are these metabolic complications associated with increased morbidity or mortality within a timeframe that is relevant to HIV-infected patients? In particular, will the benefits of effective HIV therapy be offset by increased risk of cardiovascular disease and/or diabetes?
- What are the most appropriate treatment strategies in cases where metabolic complications are established?

These issues are the focus of the following sections.

3.1 Assessing and Monitoring Metabolic Complications of PI Therapy

The ideal time to first assess the metabolic status of a patient is before the introduction of HIV PI therapy. There are a number of reasons for this. First, in any patient a 'baseline' measure of metabolic status provides a reference point that allows a more informed interpretation of any subsequent effects of therapy. Secondly, this approach allows the identification of underlying metabolic abnormalities that may independently increase cardiovascular risk and which may alter decisions about choice of antiretroviral therapy (ART) regimen. It must be remembered that the prevalence of the metabolic syndrome (defined in table I) is high in the general community (~30% according to a large population-based US study[47]) and is also age-dependent, rising steeply in both males and females aged >40 years. There is also an appreciable prevalence of genetically determined dyslipidaemia (~1% with familial combined hyperlipidaemia, 0.2% with familial hypercholesterolaemia)[102] and of diabetes (4–5%).[103] It would be predicted that these diseases may be exacerbated by PI therapy; therefore, early recognition is important. It is also critical that modifiable factors (e.g. smoking, hypertension, sedentary lifestyle and obesity) are identified and incorporated into an overall assessment of cardiovascular risk. This is especially true of smoking, which remains a highly prevalent cardiovascular risk factor among HIV-infected individuals. Global cardiovascular risk, and the contribution of modifiable risk factors, may be calculated using available algorithms (e.g. Framingham risk equations and US National Cholesterol Education Program [NCEP] III risk calculator;[104] a New Zealand-based calculator is also highly recommended[105]).

This approach of obtaining a baseline assessment also allows for the identification of metabolic effects of HIV infection itself, which may be significant. In a plenary talk at the recent 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV (September 22–25, 2002, San Diego, CA), James Neaton of the University of Minnesota, Minneapolis, MN, USA provided an illuminating review of the influence of HIV infection on metabolic outcomes. Utilising data from two large HIV studies (SMART, involving ART-experienced patients; and FIRST, in which patients are ART naive at baseline), and comparing these with US population-based data (the Multiple Risk Factor Intervention Trial [MRFIT] and the National Health and Nutrition Examination Survey [NHANES]), he noted that levels of total cholesterol in heavily ART-treated men involved in the SMART study were comparable with age-matched men from the general population, while levels were significantly lower in ART-naive patients from the FIRST study. This is in keeping with research showing that advancing HIV infection is associated with decreased levels of total, HDL and LDL cholesterol, while triglyceride levels are associated with progression to AIDS.[106] Therefore, the effects of PI therapy on metabolic parameters need to be placed into the context of the baseline value, determined by the patient's HIV status as well as other factors (e.g. genetic predisposition to hypercholesterolaemia). A 'change in total cholesterol' associated with PI therapy that restores cholesterol levels to normal, is unlikely to have the same impact on cardiovascular risk as an elevation of cholesterol from normal to pathological levels.

Otherwise, recent guidelines recommend that fasting glucose and lipid assessment should be performed prior to commencing or switching of a new ART regimen, and should then be repeated 3–6 months later and at least annually in patients who remain on stable therapy.[18]

3.1.1 What Tests Should be Performed?

The choice of tests needs to be predicated on providing information that can be used to determine cardiovascular risk, and which may guide interventions. The minimum lipid evaluation should include a fasting measurement of triglyceride, and total, HDL and LDL cholesterol. From these parameters, the 'non-HDL' cholesterol fraction provides an estimate of triglyceride-rich lipoproteins. This measure has been incorporated into recent NCEP guidelines

that stress the importance of recognising and diagnosing the metabolic syndrome.[41] This may be particularly valuable in PI-treated patients as an assessment tool and therapeutic guide. Where it is available, measurement of apolipoprotein B can also provide a useful marker of the number of atherogenic lipoparticles present, which can help to differentiate atherogenic hypertriglyceridaemic states from those that are more benign.[61] Diabetes should also be excluded with fasting glucose assessment; ideally, with incorporation of an oral glucose tolerance test to identify those with impaired glucose tolerance. While insulin resistance appears to be a common problem among PI-treated patients, this is difficult to assess accurately in clinical practice and at this time does not warrant specific therapeutic intervention if diabetes is not present. Again, recent guidelines offer a very practical and reasonable approach to assessment and monitoring in this setting.[18]

3.2 HIV PI Therapy and Cardiovascular Risk

There is justified concern that the cluster of lipid and glucose abnormalities associated with 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 whether the dyslipidaemia (and immune restoration) induced by HAART increases this baseline risk independent of improved survival or improved surveillance. It is also worth considering, when attempting to interpret the available data, that the progression from the earliest events in the atherogenic process to atherosclerotic plaque formation, and finally to the development of overt vascular disease, is one that occurs over years or even decades. Consequently, it should not be expected that studies of 'hard' cardiovascular endpoints, such as incidence of myocardial infarction and/or death attributable to cardiac disease, are likely to discern the influence of PI therapy on cardiovascular risk with any precision at this time (i.e. 6 years after the introduction of PI drugs into clinical practice).

Initial case reports of premature vascular disease in those with dyslipidaemia and/or insulin resistance while receiving HAART[107-116] have now given way to larger cohort and population-based studies of cardiovascular disease among HAART recipients.[117-121] Results have been conflicting, with evidence both for[117-119] and against[120,121] increased incidence of cardiovascular disease among PI recipients. However, some discernible patterns are emerging. The first is that traditional cardiovascular risk factors (i.e. smoking, hypertension) remain important predictors of overt vascular disease, suggesting that the metabolic complications of PI therapy may hasten the progression of vascular disease in those who are already predisposed. The second is that cardiovascular risk may be decreased in patients who have not commenced ART and who have uncontrolled HIV infection.[120] As mentioned in section 3.1, advancing HIV disease and immune deficiency is accompanied by changes in lipoprotein metabolism characterised by decreased levels of total, LDL and HDL cholesterol, as well as decreased apolipoprotein B.[106] Progression to AIDS is associated with elevated triglyceride levels,[122] while the other metabolic parameters fall in parallel with CD4+ cell counts.[123] It is also possible that HIV-associated loss of cell-mediated immune function may limit the progression of atherosclerosis, in keeping with current concepts of atherogenesis as an inflammatory process[124,125] involving specific T-cell and macrophage populations.[126-128] Hence, the 'baseline' level of cardiovascular risk prior to the introduction of PI therapy, which is determined in part by immunological status, may have a significant modulating effect.

Probably the most direct evidence for an association between PI therapy, triglyceride-rich dyslipidaemia and cardiovascular disease has come from a study of endothelial function in PI-treated patients with dyslipidaemia.[59] Endothelial dysfunction is considered to be an early event in atherogenesis,[124] involving loss of the endothelial response to ischaemic or mechanical stimuli with an appropriate (nitric oxide-mediated) vasodilatory response. It can be assessed non-invasively by measuring brachial artery flow-mediated dilatation (FMD). In this study, involving 22 PI-treated and 15 PI-

naive HIV-infected adults, PI therapy was associated with elevated triglycerides and triglyceride-rich lipoproteins, and these metabolic parameters (chylomicrons, IDL and VLDL cholesterol) were in turn predictive of impaired endothelial function (linear regression model $R^2 = 67\%$, $p < 0.01$). Overall, FMD in the PI-treated group was significantly reduced compared with the PI-naive group (2.8± 4.6% vs 6.1± 6.7% [mean ± SD], $p = 0.005$). These data provide evidence for the atherogenic potential of the PI-associated metabolic phenotype, and identify associations between endothelial dysfunction and specific lipoprotein fractions that have previously been shown to determine cardiovascular risk in HIV-negative populations with triglyceride-rich dyslipidaemia.[60,129-131]

Two studies have assessed coronary artery morphology directly using electron beam computed tomography (CT) in 85 patients, of whom ~40% had significant dyslipidaemia for approximately 24 months.[132,133] No structural changes were noted in either study, although concurrent positron emission tomography scanning suggested the presence of endothelial dysfunction in the coronary vasculature.

Taken together, these data suggest that PI therapy contributes to an atherogenic metabolic profile, and that increased cardiovascular risk is likely to manifest through triglyceride-rich dyslipidaemia and the 'metabolic syndrome' phenotype, as recognised in recent NCEP guidelines. It is important to recognise, however, that other factors may significantly modulate the atherogenic process. These include well established cardiovascular risk factors, such as smoking and hypertension, and in the specific case of the HIV-infected patient, immunological as well as metabolic consequences of HIV infection itself.

4. Approaches to Treatment of PI-Associated Metabolic Complications

The fundamental concept in managing the complications of PI therapy is that treatment should be based on the global assessment of cardiovascular risk, rather than on the interpretation of individual parameters. The obvious exception to this rule is in patients with concomitant diabetes who, fortunately, remain uncommon at present (~2–5%).[30]

4.1 Adjunctive Lipid-Lowering Therapy

The NCEP guidelines mentioned earlier (see section 3.1),[41] which are also summarised in the published guidelines for management of PI complications,[18] provide a rational basis for decisions regarding use of lipid-lowering therapy. A particularly important aspect of this approach is the assessment of '10-year risk' of cardiovascular disease. Of note, for patients with a predicted high level of risk (>20%, representing those with existing vascular disease or diabetes), the recent Heart Protection Study[134] ($n \approx 20\,000$) has demonstrated that the use of HMG-CoA reductase inhibitor (statin) therapy is associated with significant reduction of major vascular events (~25%) and mortality (~13%) irrespective of the severity of hyperlipidaemia when statin therapy was initiated. In these patients, simvastatin therapy over 5 years was associated with reduction of LDL cholesterol in the order of 1.0 mmol/L (38 mg/dL).[134]

This view of the success of lipid-lowering therapy being measured by effects on vascular outcomes rather than magnitude of cholesterol reduction may be particularly relevant in the context of PI-associated dyslipidaemia, as trials involving both statins and fibric acid derivatives have had limited impact on cholesterol and triglyceride levels.

The efficacy of statins in treating PI-associated dyslipidaemia has been recently investigated by Stein et al.[135] ($n = 16$) and by Doser et al.[136] ($n = 16$). In both studies, statin therapy produced statistically significant improvements in cholesterol and triglyceride fractions, but the magnitude of the effect observed prompted both investigators to conclude that benefit was limited. In the first placebo-controlled study, using pravastatin 40 mg/day, the atherogenic lipoprotein subfractions specifically affected by PI therapy were identified (increased small LDL and large VLDL cholesterol particle levels, and decreased large HDL cholesterol). Compared with these 'baseline' values, pravastatin therapy was associated with significant reductions in LDL cho-

lesterol and small VLDL cholesterol particle levels. However, the level of large VLDL particles did not change ($p = 0.44$), nor did average LDL particle size ($p = 0.23$). In the second study, the use of fluvastatin 40 mg/day for 4 weeks resulted in levels of total cholesterol <7.0 mmol/L (270 mg/dL) in only 8 of 16 participants, compared with 6 of 16 at baseline. However, total cholesterol decreased from a mean value of 8.0 mmol/L (SD 0.5) to 6.5 mmol/L (SD 0.4) in the study ($p < 0.01$), consistent with results seen in the Heart Protection Study. Similar results were presented in 2001,[137] in which no significant benefit from lipid-lowering therapy was found (n = 103, 92% men, 82% receiving PI therapy) over a median of 70 weeks of follow up, with the use of statins and fibric acid derivatives according to NCEP guidelines using a stepwise approach (33 received second regimens and 15 received third regimens). In this study, only 16% of those continuing PI therapy reached target levels of LDL and total cholesterol after >52 weeks. Finally, a randomised trial (ACTG 5087[138]) comparing pravastatin and fenofibrate therapy for lipid lowering in PI-treated patients with elevated triglyceride and LDL cholesterol levels has been halted by its data and safety monitoring board after 12 weeks, as <5% of patients responded to either drug alone, with response measured as a composite of LDL cholesterol and triglyceride reduction. In 136 patients who then progressed to combination therapy (pravastatin plus fenofibrate), response rates remained at ~10%.[138]

Despite the evidence for limited efficacy of statins and/or fibric acid derivatives, recent data point to an increasing use of lipid-lowering drugs among patients receiving PI therapy. In an analysis of a US managed care database[139] (1998–2001, n ≈ 3500 per year), lipid-lowering therapy was prescribed for 18.4% of PI recipients in 2001, compared with 12.2% of non-PI-treated patients and 5.5% of ART-naive patients in the same period. This prevalence was higher than in 1998, when 8.7% of PI-treated patients were treated for dyslipidaemia.[139] A similar analysis, utilising the Californian Medi-Cal database (1996–2000) also revealed a bias towards treating younger patients, particularly males.[140]

4.2 Switching HIV PI Therapy

A recent review has summarised the results of reversibility studies presented or published to date (2002).[46] If patients and their physicians want to revise therapy to improve metabolic profiles, then there is evidence that this may occur within a 6- to 12-month period if PIs are replaced with an NNRTI (nevirapine or efavirenz) or with abacavir in triple NRTI regimens.[46] Interestingly, the NNRTIs nevirapine and efavirenz have been associated with a specific metabolic profile that appears to be anti-atherogenic. This was most clearly observed in the Atlantic trial,[141] in which the use of nevirapine was associated with increased levels of 'large' HDL cholesterol. A recent small study (n = 32) comparing efavirenz (NNRTI) and nelfinavir (PI) therapy has also revealed that 16 weeks of PI use preferentially increased atherogenic small HDL cholesterol 44.8% from baseline, while efavirenz therapy increased large (anti-atherogenic) HDL cholesterol by 41% on average.[142] Importantly, replacing effective PI therapy with an NNRTI or NRTI has not been associated with loss of antiretroviral efficacy.[46]

There may also be a role for intra-class PI switching, in which atazanavir or amprenavir are introduced in place of another PI drug. As previously mentioned in section 2.5, switching from nelfinavir to atazanavir in the BMS AI424-044 study decreased total and LDL cholesterol as well as triglyceride to levels comparable with those obtained before the introduction of nelfinavir.[97] Further studies in this area are awaited.

Although the benefit that can be expected from switching PI therapy is difficult to quantify because of the varying methodology used in switching studies, it appears to be at least comparable with the effects seen with statin therapy, particularly in studies involving switching to nevirapine and abacavir.[46]

4.3 Recommendations for Preventing and Treating Dyslipidaemia

The fact that prevalence rates of the metabolic syndrome (and of diabetes) are rapidly increasing in developed countries suggests that factors involved

in pathogenesis are likely to be modifiable. In particular, attention to dietary modification and increasing energy expenditure through exercise would be predicted to reduce the risk of metabolic complications in the setting of PI therapy, as well as to reduce cardiovascular risk.[143] Hence, in all patients commencing HIV PI therapy, interventions that may promote these 'lifestyle' changes are likely to have substantial benefits.[144,145] Similarly, modification of traditional cardiovascular risk factors should also be attempted, with a recognition that these interventions may have a greater impact on cardiovascular risk than dyslipidaemia itself.

In patients with an estimated 10-year risk of cardiovascular disease >20%, consideration should be given to switching PI therapy if this option is available and is predicted to be virologically safe. Current evidence also supports the use of lipid-lowering therapy in these patients, irrespective of the severity of dyslipidaemia or the magnitude of response to lipid-lowering therapy, based on data from HIV-uninfected populations.

In those patients whose risk is estimated at <20%, the situation is less clear-cut. In these cases, a review of the baseline metabolic profile of the patient can be informative.

1. *Normal lipid/lipoprotein parameters before PI therapy*. In these patients, the benefits of lipid-lowering therapy are likely to be marginal, while non-pharmacological approaches may have significant impact in reducing metabolic complications. Reducing cardiovascular risk through attention to other factors (e.g. smoking, hypertension) is certainly warranted.

2. *Abnormal lipid/lipoprotein parameters before PI therapy*. Patients with untreated HIV infection who have elevated LDL cholesterol levels may have genetically determined hypercholesterolaemia and may require lipid-lowering therapy in addition to lifestyle modification, particularly if there is a positive family history of cardiovascular disease.

Otherwise, management should be guided by currently available guidelines. However, an important caveat is that lipid-lowering drugs are unlikely to decrease cholesterol to 'goal' levels in patients receiving PI therapy. Within this context: (i) lipid-lowering drugs should ideally be prescribed for their therapeutic benefits on cardiovascular disease, as determined by global risk assessment; and (ii) failure to meet therapeutic goal levels should not automatically lead to the use of combined or intensified therapy. Choice of lipid-lowering therapy should be guided by the dyslipidaemic phenotype, with the use of fibric acid derivatives when hypertriglyceridaemia is the dominant manifestation and statins for hyperlipoproteinaemia. Within the statin class (reviewed in Schambelan et al.[18]), concomitant use of simvastatin or lovastatin with PI therapy should be avoided, as there is increased risk of drug toxicity as a result of PI-associated inhibition of the cytochrome P450 3A4 metabolic pathway. Atorvastatin may also be potentiated (~70%) by PI therapy and should be commenced at a low dosage initially (i.e. 10 mg/day). Pravastatin therapy does not appear to be affected by concomitant PI use.

4.4 Management of Insulin Resistance and Diabetes Mellitus

Experience with the management of diabetes in patients receiving HIV PI therapy is limited at this time and no specific recommendations can be made in terms of treatment. The presence of diabetes confers an independent high risk of cardiovascular disease and is likely to warrant statin therapy for this reason.[134] This is also a situation in which PI therapy should be avoided where possible. Otherwise, the disease should be managed according to established guidelines.[146]

Studies of the pathophysiology of PI-associated metabolic complications suggest a rational basis for the use of thiazolidinediones (rosiglitazone, pioglitazone) as insulin-sensitising drugs in this setting. The target of action of these drugs, PPAR-γ, lies in the transcriptional pathway that is normally stimulated by SREBP-1 and which appears to be defective in the presence of PIs. *In vitro*, rosiglitazone has been shown to 'rescue' the adverse effects of PI therapy on insulin signalling,[87] and these drugs have also shown promise as therapeutic agents in cases of inherited lipodystrophy, which may also

involve defects in the SREBP-1/PPAR-γ pathway.[147] Limited data from small studies also suggest benefit in HIV-infected patients receiving PI therapy.[148,149] For example, in a study involving eight subjects with significant insulin resistance at baseline (insulin sensitivity assessed using hyperinsulinaemic-euglycaemic clamp [34% of age and BMI-matched controls]), insulin sensitivity improved by 59% after 6–12 weeks of rosiglitazone 8 mg/day. The results of further large studies are awaited before this therapeutic approach can be recommended.

Metformin has also been studied as an insulin sensitising agent in two cohorts, both selected for the presence of insulin resistance and visceral/abdominal obesity. The first study, performed by Saint-Marc and Touraine[150] in France, involved 27 patients with central obesity (average visceral adipose tissue area on CT scanning ~200 cm^2) and hyperinsulinaemia in either the fasting or post-glucose state. Randomised therapy with metformin for 2 months at relatively high dose (n = 14, 850mg three times daily) was associated with significant improvements in visceral adiposity compared with controls (decrease of 37.5% vs gain of 10.4%, $p < 0.01$), as well as in fasting and post-glucose insulin levels ($p < 0.01$ for both parameters). Metformin was generally well tolerated, with no reports of lactic acidosis, although two patients withdrew because of gastrointestinal adverse effects (diarrhoea and abdominal cramps). The second study, by Grinspoon and colleagues[151] in Boston also selected patients with impaired glucose tolerance and/or fasting hyperinsulinaemia associated with central obesity, based on a waist-hip ratio of >0.9 for men and >0.8 for women. Metformin therapy (n = 14, 500mg twice daily) was compared with placebo over 3 months. Visceral fat mass also decreased, although non-significantly, in this study (decrease of 6.3% vs gain of 7.7% in controls, $p = 0.08$), while post-glucose insulin levels decreased by 20% among those on metformin ($p = 0.01$). Diarrhoea was common in this study, affecting 69% of participants on metformin, although there were no withdrawals.

The only caveat for metformin use is that weight loss associated with this drug may involve both subcutaneous and visceral fat depots, so that lipoatrophy may worsen in patients with this complication. For example, in the Boston study,[151] loss of subcutaneous fat mass (~4.3% from baseline) was comparable with loss of visceral fat on CT scanning, so that the ratio of visceral fat to subcutaneous fat remained unchanged ($p = 0.71$). Hence, this therapy appears to be ideal for patients who have insulin resistance and visceral adiposity associated with HIV PI therapy, but who have been spared the problem of lipoatrophy (which is predominantly NRTI associated).

5. Conclusions

The use of PI therapy is independently associated with dyslipidaemia and insulin resistance, and by implication to an increased risk of cardiovascular disease. However, there are a number of factors that may modulate the severity of metabolic complications associated with this drug class. These include treatment-related factors (choice of PI therapy), host factors (e.g. diet and exercise status, presence of pre-existing metabolic syndromes) and disease-related factors (metabolic consequences of HIV infection *per se*). Similarly, the global assessment of cardiovascular risk, which provides a guide to the use of therapeutic interventions, such as lipid-lowering therapy, incorporates a number of potentially modifiable risk factors that require consideration along with the direct effects of PI therapy. Therefore, assessing, monitoring and managing the metabolic complications of PI therapy requires an approach that is both individualised and holistic.

Further elucidation of the pathophysiological mechanisms underlying PI-associated metabolic complications, as a means of designing therapeutic interventions that are biologically rational, is awaited with interest. It is also hoped that this 'natural experiment', involving the use of therapy in patients who are monitored by their physicians over prolonged periods, can provide insights into the pathogenesis of other highly prevalent syndromes such as the metabolic syndrome and diabetes.

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