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Protease Inhibitor-Induced Diabetic Complications

Incidence, Management and Prevention

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Abstract

Protease inhibitors (PIs) have become a crucial element in the treatment of patients infected with HIV. However, the widespread use of PI therapy has also been associated with a number of metabolic adverse effects, including fat redistribution and hyperglycaemia. The objective of this review is a discussion of the incidence, pathophysiology, management and prevention of PI-associated hyperglycaemia. Initial case reports have been followed by large cross-sectional and cohort studies, which demonstrate that the incidence of PI-induced impaired glucose tolerance, as well as frank diabetes mellitus, is significant and demands attention. Investigations into the pathophysiology behind PI-associated hyperglycaemia have identified an underlying problem of insulin resistance that is presumably caused by both direct PI-induced mechanisms and lipotoxicity. Given this, clinical trials have explored the use of various classes of oral hypoglycaemic agents in the management of PI-induced diabetic complications, and the use of insulin therapy must be considered as well. Newer PI agents are also under

development, with the hope of reducing metabolic adverse effects. In the meantime, prevention, in the form of dietary modification, regular physical activity and periodic screening for impaired glucose tolerance, must receive heightened attention in the care plan of patients receiving long-term PI therapy.

The introduction of protease inhibitors (PIs) in the 1990s revolutionised options for the medical treatment of HIV and AIDS. Indeed, PIs were found to be a potent weapon in the armamentarium of the infectious diseases physician. They became a crucial component of what would eventually be known as highly active antiretroviral therapy (HAART). However, as these agents gained more widespread use reports of metabolic complications associated with PIs began to surface with alarming frequency. The following review discusses PI use and metabolic complications with a focus on the development of glucose intolerance states. Recommendations for management of these complications, as well as methods of prevention, are also addressed.

The literature selection in this review includes articles from the Medline database from 1996 to September 2003, with inclusion criteria limited to English language and human studies. Key search words included 'protease inhibitors', 'anti-HIV agents', 'diabetes mellitus', 'incidence' and 'primary prevention'. Abstracts from the 9th and 10th (2002–2003) Conferences on Retroviruses and Opportunistic Infections are also included in the literature review.

1. Incidence

1.1 Case Reports and General Incidence Data

Among the earliest reports in 1997 were single patient or small group case studies linking the use of PIs to glucose intolerance and, on occasion, frank diabetes mellitus. Visnegarwala et al.[1] published a case report that described a 46-year-old man with advanced-stage AIDS who had already been on antiretroviral therapy (ART). However, the addition of nelfinavir to the patient's regimen led to symptomatic hyperglycaemia within 2 weeks of starting the PI therapy. The patient eventually presented with a glucose level of 657 mg/dL and required neutral protamine hagedorn insulin for management. The authors stated that no sign of occult infection or active pancreatitis was found. Although the patient had been receiving megestrol, which also has the potential to precipitate a state of glucose intolerance, it was noted that the patient had been repeatedly euglycaemic for several months while receiving megestrol therapy prior to the initiation of nelfinavir. Interestingly, at the time of the publication of this case, the authors noted that there had already been 83 reports of new-onset or worsened diabetes associated with several different PIs, which lead the US FDA to issue a Public Health Advisory.[15]

Other early reports (table I) included a case series by Dube et al.,[6] which described seven HIV-infected patients, six of whom were taking indinavir and one who was taking ritonavir. Hyperglycaemia was defined as a random serum glucose level of >10 mmol/L on at least two determinations (fasting serum glucose values were not given). None of the seven patients had any previous history of glucose intolerance prior to initiating PI therapy, although three of the seven did have family histories of diabetes. Non-ketotic hyperglycaemia appeared in all seven patients within 1–7 months after the initiation of PI therapy. The authors further placed this development in the context of their patient population and estimated that 1050 patients in their facility had received PIs between late 1996 and early 1997, when the seven patients developed hyperglycaemia. Therefore, they estimated an incidence rate of <1%.

Further incidence data became available as cross-sectional studies investigating the phenomena of metabolic complications encountered by patients receiving PI therapy were published. A key cross-sectional study was done by Carr et al.,[7] involving 116 patients with the HIV infection who were receiving at least one HIV PI. Additionally, there were two other comparison groups: one group included 32 HIV-infected but PI-naive patients and the other included 47 healthy men with ages and body mass indices (BMIs) that were comparable to the patients

with HIV. Body composition data, in addition to glucose, insulin, c-peptide, free fatty acid, fructosamine, testosterone, sex hormone-binding globulin, prolactin, cortisol and leptin levels were measured after a 12-hour overnight fast. The authors also estimated insulin resistance based on the homeostasis model of Matthews et al.[16] They concluded that "patients receiving HIV PIs frequently develop a syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance, which is common with prolonged therapy, but occurrence of secondary diabetes mellitus is relatively rare".[7] Specifically, they observed one patient who had a previous diagnosis of long-standing type 1 diabetes prior to PI therapy, but this patient's daily insulin requirements reportedly increased by 70% after PI use. Two other patients developed a diagnosis of new-onset diabetes, one of whom required initiation of insulin therapy for management of the condition.

A follow-up study by Carr et al.[8] provided insight into the incidence of not only overt diabetes but also impaired glucose tolerance, as defined by the 1998 American Diabetes Association (ADA) criteria.[17] This report addressed the same cohort of 116 patients with HIV (of whom 113 patients had follow-up) receiving PI therapy as in their 1998 study and introduced a comparison group of 45 HIV-infected but PI-naive patients (28 with follow-up). The authors emphasised that the patients were not on anabolic steroids, corticosteroids or related medications that could have accelerated the development of glucose intolerance. Insulin resistance and serum glucose and insulin levels were assessed as described in the prior study but, additionally, a 75g oral glucose tolerance test (OGTT) was administered and 2-hour post-test glucose levels were recorded.

The authors reported an incidence of 7% of patients receiving PIs and diagnosed with diabetes, as

Table I. Sample of protease inhibitor (PI)-induced hyperglycaemia patient reports and cohorts with incidence data

Study	Study type	Patient characteristics	Incidence of hyperglycaemia in PI-treated patients
Visnegarwala, et al.,[1] 1997	Case report	46-year-old man with HIV receiving a PI	NA
Lee, et al.,[2] 1999	Case report	56-year-old man with HIV receiving a PI	NA
Kan and Nylen,[3] 1999	Case report	45-year-old man with HIV receiving a PI[a]	NA
Hughes and Taylor,[4] 2001	Case report	49-year-old man with HIV receiving a PI[a]	NA
Eastone and Decker,[5] 1997	Case series	5 patients with HIV receiving PIs	NA
Dube, et al.,[6] 1997	Case series	7 patients with HIV receiving PIs	<1% hyperglycaemia
Carr, et al.,[7] 1998	Cross-sectional	116 patients with HIV receiving PIs vs 32 HIV-infected, PI-naive patients vs 47 non-HIV-infected patients with similar body mass indices	1 patient with worsened diabetes 2 patients with new-onset diabetes
Carr, et al.,[8] 1999	Cross-sectional	113 patients with HIV receiving PIs vs 28 HIV-infected, PI-naive patients	16% IGT; 7% diabetes
Behrens, et al.,[9] 1999	Cross-sectional	38 patients with HIV receiving PIs vs 17 HIV-infected, PI-naive patients	46% IGT; 13% diabetes
Paparizos, et al.,[10] 2000	Retrospective analysis	324 patients with HIV receiving PIs	Diabetes: 14.5% (indinavir); 10.7% (ritonavir); 3.6% (saquinavir)
Dever, et al.,[11] 2000	Retrospective analysis	121 patients with HIV receiving PIs in total, 117 patients with no previous diagnosis of diabetes	6% diabetes
Palma-Aguirre, et al.,[12] 2000	Prospective cohort	61 patients with HIV receiving PIs	6.55% hyperglycaemia
Tsiodras, et al.,[13] 2000	5-year historical cohort	221 patients with HIV in total 176 patients receiving PIs vs 45 PI-naive patients	Hyperglycaemia: after PIs: 2.68/100; PI naive: 0.65/100 person-years
Saves, et al.,[14] 2002	Multicentre cohort	1172 patients with HIV in total cohort 493 patients had data available at 12–20 months after initiation of PI therapy	17% IGT or impaired fasting glucose; 6% diabetes

a Patient developed diabetic ketoacidosis.

IGT = impaired glucose tolerance; **NA** = not applicable.

well as 16% who received a diagnosis of impaired glucose tolerance. In total, this amounted to an impressive incidence rate of 23% of PI recipients who developed some degree of glucose intolerance during therapy (for a mean duration of 13.6 months). This rate is even more striking when compared with the incidence of glucose intolerance in the healthy population at large from whom the study patients were drawn. The authors report that "less than 1% of healthy Australian men of similar age and BMI have diabetes, and less than 3% have impaired glucose tolerance".[8,18] However, there were a number of limitations to this study, including the lack of a controlled comparison for OGTT data, since OGTT testing was administered predominantly to the patients receiving PI therapy but to few of the PI-naive patients. The authors also admitted that "patients were not randomised to PI therapy, so we cannot exclude confounding by unmeasured variables that differed between groups".[8]

Nonetheless, the impressive incidence rate of glucose intolerance noted by Carr et al.,[8] was also seen in a cross-sectional study by Behrens et al.[9] Thirty-eight patients infected with HIV-1 who were receiving at least one PI were compared with 17 PI-naive patients with HIV. In this study, all patients in both groups underwent the OGTT. Among the findings was an incidence rate of 46% of PI treated patients with impaired glucose tolerance; 13% of these patients fitted the criteria for frank diabetes. In contrast, only 24% of the PI-naive patients were glucose intolerant and none had diabetes. Interestingly, the only criteria used were the 1985 WHO guidelines[19] for diagnosis post OGTT loading, which, in fact, could have led to an underestimation of the incidence. The authors noted that when the 1997 ADA fasting criteria[20] were used, three more patients receiving PIs were found to have impaired glucose tolerance and two more had frank diabetes, whereas all PI-naive patients had normal fasting glucose levels.

An important component of this study was the additional measurement of fasting glucose, insulin, proinsulin and c-peptide levels at baseline, 30, 60, 120 and 180 minutes following a 75g oral glucose load, which allowed calculation of the area under the concentration-time curve (AUC) for these parameters. The results showed statistically significant increases in AUC for glucose, c-peptide and proinsulin levels in the PI treated group compared with the PI-naive patients. This was a highly significant finding, in that the PI-naive patients were receiving forms of ARTs that did not include PIs, leading to the conclusion that it was neither the HIV infection itself, nor the ART, but rather the use of PIs that appeared to cause an increase in insulin resistance. This is significant in light of the possible association between HIV infection itself and insulin resistance; although an older clinical study of HIV-infected patients showed an increase in insulin sensitivity, recent cross-sectional studies suggest that the presence of HIV infection even in the absence of PI therapy could lead to insulin resistance.[21]

Larger studies rapidly followed. Paparizos et al.[10] performed a retrospective analysis of 324 HIV-infected patients receiving PI therapy that excluded any patients with pre-existing diabetes. A strength of this study was its description of the incidence rates associated with individual PIs: 14.5% of patients receiving indinavir developed diabetes and the corresponding figures for ritonavir and saquinavir were 10.7% and 3.6%, respectively. Tsiodras et al.[13] published results of a 5-year historical cohort study involving 221 HIV-infected patients, of which 45 patients were PI naive and 176 received PI therapy. A strength of this study was the longitudinal nature of the follow-up: patients were enrolled from 1993 to 1998 and were followed-up for at least 6 months. However, a limitation of the study was the lack of fasting glucose data; assessment required the use of only random glucose levels in defining hyperglycaemia (defined as 2 or more serum glucose values of >7.8 mmol/L) and frank diabetes (single random glucose level of >11.1 mmol/L). A unique feature was the study's presentation of incidence data in terms of person-years of follow-up: the incidence rate of hyperglycaemia in patients who were PI naive was 0.65 per 100 person-years, whereas the corresponding rate of hyperglycaemia for patients after PI therapy was initiated was 2.68 per 100 person-years. Overall, the authors found a 5-fold increase in the incidence rate of hyperglycaemia associated with PI therapy.

1.2 Newer Incidence and Prevalence Data

A major article published in May 2002, documented the results of the APROCO (Antiproteases Cohorte) study, which enrolled 1172 patients with HIV-1 from 47 healthcare centres distributed throughout France.[14] Additionally, a substudy termed APROCO-MC (APROCO-Metabolic Complications) used a cross-sectional design to assess metabolic changes in 614 of the original APROCO study patients (494 men and 120 women). Fasting glucose as well as 2-hour OGTT glucose levels were measured and the 1998 WHO diagnostic criteria[19] were used to define impaired glucose tolerance and diabetes. 493 of the enrolled patients had glucose data available for review at either 12 or 20 months after initiation of PI therapy for prevalence assessment. Seventeen percent of these patients developed impaired glucose tolerance by either fasting or 2-hour OGTT criteria and 6% developed frank diabetes, which is intriguingly similar to the results found by Carr et al.[8] in 1999. Of interest, APROCO-MC included patients receiving most of the major current PIs (saquinavir, ritonavir, indinavir and nelfinavir). The prevalence of diabetes was higher in month 20 than at month 12 of follow-up, but more patients were receiving nelfinavir at month 12 and more patients were receiving indinavir at month 20. Thus, the authors could not rule out whether the duration of therapy or drug-specific effects were responsible for the difference in prevalence at 12 and 20 months.

The subsequent publication of an abstract from the APROCO group extends the follow-up period further: 184 patients were followed up for 36 months after the initiation of PI therapy. In this group, the prevalence of glucose tolerance abnormalities (impaired glucose tolerance and frank diabetes) was 28% and the prevalence of frank diabetes was 10% at 36 months.[22]

As is evident from the previous two sections, although the early case reports have given way to more extensive multicentre cohort studies, much of the available incidence and prevalence data have been derived from sources that lack the strength of design of a randomised controlled trial. However, this void is being addressed: for example, the AIDS Clinical Trials Group 384 is a randomised, partially double-blinded, controlled multicentre trial to evaluate antiretroviral treatment strategies, including addressing questions such as whether PI therapy should be given prior to, or following, non-nucleoside reverse-transcriptase inhibitor (NNRTI) use.[23] As results from studies with a rigorous design appear, further information on the incidence and prevalence of PI-induced metabolic effects will become available.

1.3 Timing of Onset of Hyperglycaemia

The duration of PI therapy preceding the onset of hyperglycaemia, whether symptomatic or biochemical, is a matter of debate. Review of the literature shows that the timing of onset has been seen as early as 2 weeks after initiation of PI therapy,[1] and Noor et al.[24] have even shown inhibition of insulin-stimulated glucose disposal after just a single dose of indinavir. However, the majority of the literature describes the development of hyperglycaemia several months after PI initiation.[3,5,6,8,10,11] A number of studies record the diagnosis of new-onset hyperglycaemia or frank diabetes as occurring following >12 months of PI therapy and in some instances, as late as ≥2 years after initiation of the PI therapy.[4,14]

1.4 Relationship to Fat Redistribution

Early reports speculated that the abnormalities in glucose metabolism seen with PI therapy were either a direct result of, or at least in part related to, the occurrences of fat redistribution that were noted in patients receiving PI therapy.[7] However, data published since 2000 have cast serious doubt on that relationship and have implied that impaired glucose tolerance may, in fact, pre-date fat redistribution or even occur in the absence of any changes in body composition.[14,25] For example, Mulligan et al.[25] studied 20 HIV-positive, PI-naive patients with paired data that were analysed before and after PI therapy. Paired data were also collected for a comparison group of nine patients who tested positive for HIV but were treated with lamivudine and no PI. Mean follow-up was 3–5 months. A final comparison group of 12 patients with HIV infection, but not treated with either lamivudine or a PI, was also followed for 8 months. All patients denied the use of megestrol, growth hormone or anabolic steroids

(other than testosterone or dehydroepiandrosterone). Fasting glucose levels, serum insulin levels and body composition parameters were measured.

The authors noted that fasting glucose levels statistically significantly increased after the initiation of PI therapy and insulin levels doubled, so the insulin/glucose ratio significantly increased, as did insulin resistance calculated by the homeostasis model of Matthews et al.[16] Further, "these metabolic changes occurred in the absence of evidence of accrual or redistribution of body fat, in that we saw no significant changes in either total or regional fat content. Our results argue strongly against the notion that the changes in lipid and glucose metabolism after initiation of PI therapy are the result of central fat accumulation *per se*".[25]

The APROCO-MC study[14] provided further confirmatory evidence by describing 464 patients with both glucose level and fat redistribution data. Fourteen percent of patients developed neither metabolic complications nor fat redistribution, 48% had both complications and 17% had only fat redistribution, but a full 21% had only metabolic changes in the complete absence of fat redistribution. Thus, although there is some evidence that fat redistribution may directly or indirectly contribute to insulin resistance, it appears that fat redistribution is not always a necessary pre-requisite to diabetic complications.

1.5 Circumstances of Clinical Presentation

1.5.1 Diabetic Ketoacidosis versus Non-Ketotic Hyperglycaemia

The majority of published reports describe the disturbance in glucose metabolism that is associated with PI therapy to be similar to that of type 2 diabetes, which is associated with insulin resistance. Thus, many of the described presentations of hyperglycaemia have been with asymptomatic patients and, in general, patients have been found to be non-ketotic.

However, there have been several published reports of diabetic ketoacidosis, which is presumably induced by PI therapy.[3,4,26] Kan and Nylen[3] reported a 45-year-old HIV-infected man who presented with a glucose level of 929 mg/dL, an anion gap of 17 and positive serum ketones (1 : 4 dilution ratio). The patient had been diagnosed with AIDS in 1996 and received aerosolised pentamidine from August 1996 to April 1997. However, his presentation with diabetic ketoacidosis occurred 11 months after the pentamidine therapy was stopped and the patient had been euglycaemic while on that medication. The patient had been started on ART including indinavir in February 1997, which was continued for 13 months up until the onset of diabetic ketoacidosis. Also, Hughes and Taylor[4] described a patient who received indinavir, stavudine and lamivudine for >2 years before presenting with diabetic ketoacidosis. This patient's presenting glucose level was 420 mg/dL, but he was severely acidotic with a pH of 7.11, bicarbonate levels of 5 mEq/L and an anion gap of 32. Thus, severe metabolic acidosis as a result of PI therapy-induced hyperglycaemia is a potential presentation that clinicians should be aware of.

1.5.2 Acanthosis Nigricans

As noted previously, much of the incidence data describes patients whose presentations of frank diabetes or impaired glucose tolerance may be slow-onset in development or even mostly asymptomatic. However, an unusual presentation outlined in a case report by Mellor-Pita et al.,[27] is the development of marked acanthosis nigricans in a patient receiving PI therapy. The 36-year-old man had had HIV for 5 years and received HAART including ritonivir for 19 months, with a change in regimen to include nelfinavir and saquinavir later. He was diagnosed with diabetes approximately 9 months after starting ritonavir therapy. On physical examination, the patient was noted to have a BMI of 26 kg/m^2, an increase in abdominal fat and "a velvet … hyperpigmentation in the axillas and elbows".[27] Cutaneous biopsy of the axilla was consistent with acanthosis nigricans and the patient was treated with oral hypoglycaemic agents. Although this is a single case report, the appearance of acanthosis nigricans as a marker of insulin resistance could be consistent with the incidence study data showing increased insulin levels following PI therapy.

1.6 Population Characteristics

An interesting epidemiological question is whether any variability exists in the incidence rates

of PI-induced hyperglycaemia depending on demographic characteristics. Dever et al.[11] directly addressed this question in their article on PI-induced hyperglycaemia in a predominantly ethnic minority, urban patient population that was 80% African-American and 98% men. The primary care facility was the Veterans Affairs New Jersey Health Care System. They conducted a retrospective study reviewing 121 HIV-infected patients who had received a PI over a 1-year enrolment period. Four of the 121 were known to have diabetes at baseline. Of the remaining 117 patients studied, seven patients (6%) developed new-onset symptomatic diabetes, which was defined as a random blood glucose level of 200 mg/dL on more than one occasion and was associated with symptoms (predominantly polyuria and polydipsia). The mean onset of symptoms was 11 weeks after PI-therapy was initiated. Only one of the seven patients was obese (BMI 34.0 kg/m^2). In assessing this study's incidence data, several points can be made: there may have been an overestimation of incidence because of the presence of confounding variables, given that two of the seven patients who developed new-onset diabetes had also received megestrol (although no patients received other common agents of drug-induced hyperglycaemia such as corticosteroids, anabolic steroids or pentamidine). Alternatively, there may have been an underestimation of the incidence rate since the authors' criteria for diagnosing new-onset diabetes was somewhat limiting, in that no fasting glucose data were obtained.

Another notable study of PI-induced hyperglycaemia in an Hispanic population is that by Palma-Aguirre et al.[12] Sixty-one patients who were non-diabetic at baseline had glucose levels obtained monthly during a 6-month monitoring period following PI initiation. The hyperglycaemia incidence rate was found to be 6.55%. In both the Dever et al.[11] and Palma-Aguirre et al.[12] studies, it was considered that these predominately minority populations could have a hereditary pre-disposition to the development of diabetes. Yet, it is worth noting that the 6% incidence rate in the Dever study and 6.55% rate in the Palma-Aguirre study have surprisingly little variability from the 7% incidence rate noted by Carr et al. [8] in their study on a population from Sydney, Australia, and the 6% incidence rate noted in the APROCO-MC[14] study based in France, which included mostly homogeneous, Caucasian populations.

The issue of gender-related effects on the incidence of PI- and HIV-induced metabolic derangements has also received much attention. In 1999, Hadigan et al.[28] studied a group of HIV-infected women and found that the patients had evidence of hyperinsulinaemia and truncal adiposity. However, these occurred at baseline, independent of PI use, although the authors could not rule out the possibility that direct or indirect effects of PIs could worsen these issues. Galli et al.[29] studied 655 patients (most of whom were started on a combination of three or more drugs, including a PI), looking for independent risk factors for morphological alterations and found that female gender was a risk factor for the development of type 2 and type 3 adipose tissue alterations.

The issue of male gender and androgen effect has also been evaluated. Hadigan et al.[30] studied HIV-infected men and found that, as in women, fasting hyperinsulinaemia could be present even in those receiving HAART therapy containing nucleoside analogue reverse-transcriptase inhibitor (NRTI) agents but no PIs. However, they also noted that, in these individuals, the addition of PIs could worsen the metabolic derangements. A further intriguing finding was an inverse relationship between endogenous androgen levels in HIV-infected men and insulin resistance; the authors further found that testosterone administration improved insulin sensitivity in association with higher levels of lean body mass. However, the authors cautioned that this was the case in hypogonadal men and that the effects of androgen administration in eugonadal individuals was not a focus of this study. This caution was further emphasised in a subsequent trial by Hadigan et al.[31] that showed that HIV-infected women with evidence of fat redistribution had hyperandrogenaemia and an increased luteinising hormone/follicle-stimulating hormone ratio that was reminiscent of the findings in women with polycystic ovarian syndrome. Overall, the authors concluded that the "use of androgens to increase weight and lean body mass [and potentially improve insulin sensitivity] may be beneficial in HIV-infected patients … in whom androgen levels are deficient … [but] andro-

gen administration may not be necessary or prudent among women with clinical lipodystrophy and [already] increased androgen levels".

1.7 Pathophysiology

Prior speculation about the mechanism through which PIs cause metabolic derangement initially focused on β-cell related mechanisms. It was suggested that protease inhibition itself could interfere with β-cell insulin processing and secretion. Visnegarwala et al.,[1] in the 1997 early case report regarding PI-induced diabetes, mentioned that "human processing of proinsulin to cleave c-peptide requires serine endopeptidases[;] these endopeptidases may … play a more critical role in processing proinsulin and other prohormones". However, this concept was directly countered by Yarasheski et al.,[32] who conducted *in vitro* rat studies on an insulinoma cell line and studied the ability of indinavir to inhibit proinsulin-to-insulin conversion. They concluded that the levels of insulin and c-peptide secretion observed in indinavir-treated islets were not statistically significantly different from secretion observed in control islets and concluded that there was an "absence of an inhibitory effect of indinavir on proinsulin-to-insulin conversion … and … on glucose-induced insulin and c-peptide secretion. *in vitro*".

Furthermore, the article of Yarasheski et al.[32] also detailed an *in vivo* human cross-sectional study using indinavir. Patients were divided into five groups: (i) healthy HIV negative controls; (ii) HIV infected subjects who were nondiabetic and not taking PI therapy; (iii) HIV infected subjects who were nondiabetic but were receiving indinavir; (vi) HIV infected subjects with newly diagnosed diabetes taking indinavir; and (v) HIV infected subjects who were nondiabetic but had BMIs matched to the group with newly diagnosed diabetes. In all of these groups, plasma proinsulin, insulin, c-peptide and glucagon levels and glutamic acid decarboxylase antibody titres were measured. The HIV-infected subjects with newly diagnosed diabetes who were taking indinavir did have statistically significant increases in c-peptide, insulin, proinsulin and glucagons levels and the proinsulin/insulin ratio, when compared with all of the four other groups, including the BMI-matched nondiabetic group. This led the authors to comment that "insulin secretion was increased in the study subjects with diabetes. Absolute insulin deficiency was not the cause of HIV PI-associated diabetes. This conclusion is consistent with the absence of an inhibitory effect of indinavir on proinsulin-to-insulin conversion by rat INS-1 cells".[32] The authors concluded from this that insulin resistance, i.e. a defect at the level of insulin action, rather than defective insulin processing, might be the fundamental mechanism behind PI-induced hyperglycaemia.

More recent data have attempted to further quantify PI agent effects on insulin action. A key report by Murata et al.[33] addressed insulin action from the viewpoint of glucose disposal and noted that "glucose transport into muscle is a rate-limiting step in whole body glucose disposal … [and] insulin acutely stimulates glucose uptake". Specifically, insulin-stimulated glucose uptake relies upon Glut4 translocation. Glut4 and Glut1 are glucose transporter isoforms that are expressed in muscle and fat. To study the effects of PI agents on Glut1 and Glut4 activity, xenopus laevis oocytes were injected with Glut1 or Glut4 messenger RNA and 2-deoxyglucose uptake was measured. The results showed that, although Glut1 transport activity was unaffected, the intrinsic transport activity of Glut4 was significantly inhibited, up to 45%, by indinavir. As ritonavir and amprenavir also inhibited Glut4 activity significantly (54% and 42%, respectively), the authors concluded that PIs as a class may inhibit the transport function of Glut4 and that this could be the direct cause of insulin resistance induced by PI agents.

This observation has since been given further credence by *in vivo* whole animal and human studies. Hruz et al.[34] performed glucose tolerance tests on PI-naive rats. Glucose and insulin levels were measured in rats treated with indinavir versus controls. Levels during the first 30 minutes of the glucose tolerance tests were significantly elevated in the indinavir group versus the control group ($p < 0.05$). Euglycaemic-hyperinsulinaemic clamp studies were also performed and showed that indinavir significantly reduced the glucose infusion rate needed to maintain euglycaemia. The authors concluded that "the acute *in vivo* effect of indinavir on glucose tolerance in rats is entirely consistent with direct inhibition of Glut4 being the mechanism of insulin resistance".[34] Further, Noor et al.[24] per-

formed a randomised, double-blinded, placebo-controlled, cross-over study of the effects of indinavir on glucose disposal in six healthy HIV-negative men. They found that total and non-oxidative insulin-stimulated glucose disposal was statistically significantly decreased in all subjects by a single oral dose of indinavir. Since a rate limiting step in insulin-stimulated glucose disposal is Glut4-mediated intracellular transport of glucose, these results can be considered to be further support for PI inhibition of Glut4 transport function as a mechanism of PI-induced hyperglycaemia. Interestingly, both Schambelan et al.[35] and Leow et al.[36] have hypothesised that the use of a PI (or, at least, indinavir) may also lead to insulin resistance through adverse effects on peroxisome proliferator-activated receptor (PPAR)-γ (i.e. inhibited expression).

The debate as to whether the inducement of insulin resistance or the impairment of β-cell function is the primary mechanism of PI-induced glucose intolerance has now come full circle with a recent study by Woerle et al.[37] The authors describe 13 HIV-infected patients before and after 12 weeks of PI-based treatment. They concluded that "protease inhibitor-containing regimens impair glucose tolerance in HIV-infected patients by *two* mechanisms: 1) inducement of peripheral insulin resistance … and 2) reduction in pancreatic β-cell function". However, this dual conclusion is not in contradiction with the aforementioned studies disproving endopeptidase inhibition as a cause of PI-induced impairment of β-cell function, as the authors propose that "insulin itself may be important for maintaining normal β-cell function … the same mechanism by which protease inhibitor-containing regimens cause insulin resistance in the peripheral tissues might be operative in the pancreatic β-cell".[37]

In addition to the direct PI-induced mechanisms, recent literature has suggested a role for lipotoxicity in insulin resistance. Gan et al.[38] studied ten HIV-infected patients with lipodystrophy who had received PI therapy and ten HIV-infected controls who had never received PIs and had no clinical evidence of lipodystrophy. A hyperinsulinaemic-euglycaemic clamp was performed to assess insulin resistance, dual energy x-ray absorptiometry (DEXA) scanning provided body composition data, magnetic resonance imaging evaluated visceral and subcutaneous adipose tissue and magnetic resonance spectroscopy assessed intramyocellular lipid levels. The patients with lipodystrophy were found to have lower insulin-stimulated glucose disposal than controls as well as less limb fat but had an increased visceral fat/total abdominal fat ratio and increased intramyocellular lipid levels.

Similarly, Luzi et al.[39] performed a study of 12 HIV-1-infected patients who were on concurrent PI and NRTI treatment and compared them to 12 healthy controls. Intramyocellular triglyceride content was measured in the soleus muscle by means of proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy and found to be significantly increased in the HIV-infected patients versus the controls. Insulin sensitivity (assessed by the quantitative insulin sensitivity check index [QUICKI]) was also significantly lower in the HIV-infected patients and was inversely correlated with intramyocellular triglyceride levels.

Another recent article by Yarasheski et al.[40] presented data from a cross-sectional study of 22 non-obese, HIV-infected patients in whom insulin sensitivity was assessed with a hyperinsulinaemic-euglycaemic clamp. Hepatic and soleus muscle lipid contents, visceral adipose tissue and subcutaneous abdominal adipose tissue distribution were also assessed. Their finding of an inverse correlation between insulin sensitivity and hepatic and soleus muscle lipid content and visceral adipose tissue was consistent with the findings of the groups in the studies discussed previously. Finally, these findings fit with a mechanistic link between PI and insulin resistance that has been theorised by Leow et al.,[36] who state that "PIs may … contribute to IR [insulin resistance] by inhibiting the LPR [lipid binding domain of the low density lipoprotein (LDL) receptor], an important receptor responsible for clearance of triglycerides … the increased levels of free fatty acid … in turn contribute to IR via competitive metabolism of substrates (Randle's cycle)".

2. Management

2.1 Pharmacological Treatment

2.1.1 Metformin

Much of the evidence regarding pharmacological treatment options for PI-induced diabetes has centred around metformin because of the incidence studies that have pinpointed insulin resistance as a primary pathophysiological problem.[7,8,32] The case report by Hughes and Taylor[4] (described in section 1.5.1) of a 49-year-old man with indinavir-induced diabetic ketoacidosis is an anecdotal example. This patient initially required continuous insulin infusion until his acidosis was corrected and was eventually discharged and prescribed subcutaneous insulin. However, even after the indinavir had been discontinued for 1 month, he still required as much as 70–80 units of insulin daily. He was subsequently administered metformin and showed improvement in glucose control. Six months after discharge, the patient continued on metformin 500mg twice daily and a much reduced insulin regimen (36 units daily).

One of the first multi-patient studies to specifically address the effects of metformin on insulin resistance induced by PI therapy was published by Saint-Marc and Touraine[41] in 1999. This was an open label, non-placebo controlled study consisting of 29 patients (7 women and 22 men) with HIV who had noted central adiposity after initiating PI treatment. Patients were included if they had insulin resistance, defined by a fasting insulin level of >20 μIU/mL and at least one of the following: (i) 60-minute, post-glucose insulin concentration of >200 μIU/mL (normal 45–80); and/or (ii) 120-minute insulin concentration higher than the 60-minute concentration or >150 μIU/mL (normal 35–65). Twenty-seven patients completed the study, 14 of whom were randomised to receive metformin 850mg three times daily. The other 13 patients were given no pharmacological treatment (non-placebo controls). Two patients were withdrawn from the study because they experienced abdominal cramping and diarrhoea while taking metformin. Basal plasma glucose, insulin and c-peptide levels measured after 2 months were statistically significantly decreased in the metformin group versus the control group. Additionally, the authors calculated the sum total of insulin concentrations after OGTT (measured at 0, 60 and 120 minutes) and also found that this value was considerably decreased in the metformin group versus the control group after 2 months (316.2 ± 59 vs 512.4 ± 121, respectively; $p < 0.01$). Overall, the conclusion was that metformin therapy considerably decreased insulin resistance, as shown by the decreased plasma insulin response to oral glucose administration.

The first randomised, double-blinded, placebo-controlled trial involving metformin for the treatment of insulin resistance in patients receiving HAART was presented by Hadigan et al.[42] in 2000. Eighty-three patients with known HIV and clinical evidence of fat redistribution were enrolled, of which a larger percentage were receiving PI therapy. Thirty-three patients were found to have impaired glucose tolerance (defined as 2-hour OGTT glucose level of 140–200 mg/dL or a fasting insulin level of >15 μIU/mL). Patients who met the criteria for frank diabetes were excluded. In all, 25 patients completed the randomised trial, of whom 22 were receiving PI therapy. Fourteen patients were randomised to receive metformin 500mg twice daily for 3 months and 11 patients received placebo. OGTT serum levels were used to calculate the AUC for insulin and glucose. Interestingly, the insulin AUC was reduced in both the placebo and the metformin groups at 3 months, but there was a significantly greater decrease in the metformin group ($p = 0.01$). Overall, the authors noted a 20% reduction in insulin AUC and considered this indicative of increased insulin sensitivity because of metformin, although a euglycaemic-hyperinsulinaemic clamp was not done to confirm this. Hadigan et al.[43] published a subsequent report on this same patient group, in which tissue type plasminogen activator (tPA) antigen and plasminogen activator inhibitor-1 (PAI-1) levels were measured. Increased PAI-1 and tPA antigen levels reflect impairments in the fibrinolytic system and thus may be associated with increased coronary artery disease risk. The authors found these levels to be significantly reduced in the metformin versus placebo groups at 3 months. Thus, metformin was thought to improve the patients' cardiovascular risk profile via both improved insulin sensitivity and improved fibrinolytic potential. Additionally, no lactic acidosis or increase in lactate level was seen,

although patients did experience gastrointestinal adverse effects (diarrhoea-related symptoms).

The potential risk of lactic acidosis must be considered when prescribing metformin therapy for PI-associated hyperglycaemia. This issue is particularly relevant to patients receiving HAART because the multi-agent regimens may include not only PI agents but also NRTIs. There is a known association between NRTIs, lactic acidosis and hepatic steatosis. A hypothesised mechanism of NRTI-induced lactic acidosis involves mitochondrial toxicity and cellular injury, although the actual clinical development of severe decompensated lactic acidosis with steatosis is rare.[44] The US Department of Health and Human Services (DHHS) 'Guidelines for the Use of Antiretroviral Agents'[44] do note that some experts have suggested routine measurement of serum chemistries and anion gap levels every 3 months for patients receiving NRTI therapy.

Though metformin itself can be associated with lactic acidosis, it is worth noting that this usually occurs in the presence of predisposing risk factors such as renal, cardiac or hepatic dysfunction or respiratory disease.[45] Additionally, the incidence of lactic acidosis from metformin therapy (0.03 cases per 1000 patient-years[46]) is at least 10-fold less than the incidence rates cited for lactic acidosis from NRTI therapy (1.3–3.9 cases per 1000 person-years of NRTI exposure).[44,47] Nonetheless, since life-threatening lactic acidosis is a rare adverse effect of metformin or NRTI therapy, the possibility of concurrent use of metformin and NRTI leading to an increased risk of severe hyperlactatemia, though not established, cannot be overlooked.[48]

2.1.2 Thiazolidinediones

Walli et al.[49] published a pilot study consisting of a small case series of six patients with new-onset diabetes who were receiving PI therapy. The patients were treated with troglitazone 400 mg/day and an intravenous (IV) insulin tolerance test was performed to assess peripheral insulin sensitivity. Four of the six patients had marked increases in insulin sensitivity after 3 months of therapy with troglitazone, two of whom actually had a complete return of insulin sensitivity to normal levels. The patients demonstrated improved fasting and postprandial glucose, fructosamine and glycosylated haemoglobin levels as well. Although no patients had an increase in liver enzymes, which were monitored monthly during therapy, the study had to be discontinued because troglitazone was withdrawn from the market for safety concerns regarding life-threatening hepatotoxicity.

Following the withdrawal of troglitazone, newer thiazolidinediones have been introduced, including rosiglitazone and pioglitazone. In order to assess these newer agents, a number of clinical trials have been conducted.[50-55] For example, regarding diabetic complications, Sutinen et al.[51,52] have performed a randomised, double-blind, placebo-controlled study of 30 patients with HAART-associated lipodystrophy who were assigned to rosiglitazone 8mg or placebo for 24 weeks. They found that, although insulin resistance was improved with rosiglitazone, there was actually an increase in serum triglyceride levels and no increase in subcutaneous fat, which indicated that there was no reversal of lipodystrophy with rosiglitazone.

Gelato et al.[53] also performed a pilot study of the effects of rosiglitazone on HIV patients with insulin resistance. Nine HIV-infected patients, who were presently or previously receiving PI therapy, had insulin resistance documented by a hyperinsulinaemic-euglycaemic clamp and eight of the nine patients received rosiglitazone 4mg twice daily for at least 6 weeks. The authors also calculated visceral and subcutaneous adipose tissue. Insulin sensitivity was improved, although not completely normalised and the subcutaneous adipose tissue to visceral adipose tissue ratio increased after rosiglitazone therapy. However, it is also of note that one patient had to stop taking the medication because of an elevation in liver function tests, three patients actually had an increase in triglyceride levels after taking rosiglitazone and half the patients had weight gain.

In 2004, more randomised-controlled trials specifically addressing the use of rosiglitazone in patients with HIV lipodystrophy were published. Carr et al.[55] performed a trial involving 108 HIV-1-infected lipoatrophic adults who were randomised to rosiglitazone 4mg twice daily or placebo for 48 weeks. They found that adiponectin levels and insulin sensitivity increased, but were not able to establish any benefit on lipodystrophy with rosiglitazone. Hadigan et al.[54] published a study

that included 28 HIV-infected men and women with previously documented hyperinsulinaemia and evidence of fat redistribution. Patients were randomised to 3 months of therapy with rosiglitazone 4 mg/day or placebo. Results showed statistically significant improvements in insulin sensitivity as measured by hyperinsulinaemic-euglycaemic clamp testing, increased adiponectin levels and improved peripheral fat deposition in patients receiving rosiglitazone compared with those receiving placebo. However, mean total cholesterol and LDL cholesterol levels also increased in patients receiving rosiglitazone compared with those receiving placebo. Further clinical trial data are needed to evaluate the efficacy and safety of the use of these agents in the management of the metabolic complications associated with PI use.

2.1.3 Insulin Therapy

Although oral hypoglycaemic agents are attractive options, they do pose difficulties in terms of a lack of flexibility with titration of dosing and possible adverse effects. Thus, patients with PI-induced diabetic complications may benefit from insulin as a major therapeutic modality, either alone or in combination with oral agents. It should also be noted that, as insulin is an anabolic hormone, it may be of particular benefit in this population.

2.1.4 Exercise and Nutrition

Moderate physical activity and proper nutrition are important in any patient population with impaired glucose tolerance or diabetes, regardless of the primary aetiology. Exercise and nutrition are key components of both the treatment and prevention of diabetic complications (for more information, see section 3).

2.1.5 Substitution of Non-Protease Inhibitor Antiretroviral Agents in Place of Protease Inhibitors

The Adult AIDS Clinical Trials Group (AACTG) 2003 guide[56] includes information on insulin resistance and diabetes. One of the suggestions mentioned is the possibility of substitution therapies, specifically "when an HIV patient is at significant risk for cardiovascular disease, a clinician might consider substituting a non-PI-containing regimen and/or using a lipid-lowering drug" (AIDS Alert).

An encouraging example of this substitution was described in a case report by Botella et al.[57] in 2000. A 47-year-old man had been treated with indinavir for 10 months, after which he was noted to have fat wasting of the extremities and a markedly elevated fasting glucose level of 43.6 mmol/L, with a non-acidotic pH and trace ketonuria. The patient was begun on insulin therapy and indinavir was discontinued, with a non-nucleoside antiretroviral agent (nevirapine) started in its place. Only 1 month after PI discontinuation, the patient was able to be taken off insulin and both basal and postprandial glucose levels had normalised. The authors point out that in spite of the severity of the initial metabolic derangement, the patient had an impressively rapid reversal of hyperglycaemia after cessation of the PI.

A similar substitution therapy was performed in a group of patients in a 1999 report by Martinez et al.,[58] in which 23 consecutive patients with HIV underwent longitudinal analyses after having PI replaced, in all cases, by nevirapine. Of note, all patients were NNRTI naive and nevirapine was the form available in Spain at the time of the study. The group consisted of 11 women and 12 men with a median age of 38 years at baseline. Fasting plasma glucose and insulin levels were measured at baseline and every 3 months. The 1998 ADA criteria[17] for the diagnosis of impaired fasting glucose levels and diabetes were used. A fasting insulin resistance index (FIRI) was calculated based on the method by Duncan et al.[59] At month 6 after the replacement of PI therapy with nevirapine, the glucose level had decreased by 15% ($p = 0.008$) and the FIRI had decreased by 45% ($p = 0.0001$). Yet, the authors admit that the limitations of their study include the small number of patients enrolled and the relatively short period of follow-up. Of note, Martinez et al.[60] have recently followed this study with a larger, multicentre, randomised clinical trial, also in Spain, in which patients were switched from PI therapy to nevirapine, efavirenz or abacavir. However, the authors comment that this study was designed to address the question of maintenance of viral suppression in the face of a more simplified HAART regimen, which suggests that conclusions regarding improvements in metabolic abnormalities or lipodystrophy could not be definitively stated from this study.

Although the reports discussed in this section provide some evidence in support of substitution

therapy, the evidence for using this method to resolve other metabolic derangements besides insulin resistance (such as hyperlipidaemia and fat redistribution) caused by PI use has also been challenged in several reports. Moyle et al.[61] performed a single-arm observational cohort of 26 patients who were switched from PI therapy to the NNRTI efavirenz. The authors found that, although "improvements in glucose tolerance and falls in insulin resistance were observed", nonetheless, "resolution of lipid abnormalities was incomplete and worsened after switching in some cases".[61] Domingo et al.[62] also studied seven men and seven women who were initially receiving PI therapy. Unlike the prior studies, this was a randomised trial in which eight patients were randomised to be switched from PI to nevirapine, whereas six patients were randomised to remain on a regimen of indinavir-based HAART. The patients underwent subcutaneous biopsies for evidence of adipocyte apoptosis, conducted at baseline and then at follow-up (range 6 to 16 months). The findings showed that "insulinaemia decreased significantly in patients switched to nevirapine … ($p = 0.01$), and the glucose insulin ratio increased significantly… ($p = 0.01$)", but subcutaneous adipocyte apoptosis was still present "in lipotrophic areas of patients with HAART-associated lipodystrophy despite switching from indinavir to nevirapine, suggesting that such a strategy will be useless for reversal of lipoatrophy".[62]

Overall, multiple authors discourage discontinuation of PI therapy as a first-line management strategy,[48,63] and the DHHS Guidelines state that "most experts would recommend continuation of HAART in the absence of severe diabetes". [44]

2.1.6 New Treatment Options

If the discontinuation of PI therapy is not an ideal method of managing metabolic complications, then perhaps the replacement of the offending PI with a newer agent of the same class could be of benefit. This novel approach is highlighted by recent articles.[64,65]

A review by Moyle[64] offers an in-depth introduction to some of the newer PIs currently under development. These include atazanavir, which is listed as being in phase III development at the time of publication of the cited article. Of note, atazanavir subsequently received approval by the FDA in June 2003.[66] Its advantages include once-daily administration, trial-proven antiretroviral effects similar to nelfinavir and data demonstrating no statistically significant elevations in total cholesterol, fasting LDL, or fasting triglyceride levels compared with baseline values. Although this absence of dyslipidaemia development is encouraging, the article makes no mention of specific data regarding fasting glucose levels or insulin resistance. Still, atazanavir is not thought to inhibit the Glut4 transporter, which could be a distinct advantage of this agent given the suspected involvement of Glut4 in the mechanism of PI-induced insulin resistance (see section 1.7). Yet, a potential disadvantage has been the observation of atazanavir-induced hyperbilirubinaemia (although this has not been associated with hepatotoxicity and appears to be reversible).[64]

Moyle also describes two other new PI agents, tipranavir and mozenavir. Mozenavir is particularly intriguing because of its metabolism by glucuronidation, instead of cytochrome P450 3A4 hepatic metabolism, which may lessen drug interactions. However, there are no data from these phase II studies regarding the effects of these agents on glycaemic variables, so whether these agents provide any distinct advantage metabolically over the older PIs remains to be established.

Unlike the other newer PIs mentioned, the agent amprenavir has been the subject of a specific study regarding its metabolic effects, as described by Dube et al.[65] Fourteen PI-naive patients were initiated on amprenavir-based ART for a 48-week course. The patients were evaluated at baseline and at 2, 8, 16, 24, 32, 40 and 48 weeks, with fasting glucose and insulin levels, an OGTT (75g load) and also an IV-glucose tolerance test (IVGTT). Insulin resistance was assessed by analysis of the IVGTT data and calculations were also done using the homeostasis model of Matthews et al.[16] The AUCs for glucose and insulin from the OGTT were calculated. Results showed that, after 48 weeks, there were no statistically significant changes in mean fasting plasma glucose levels versus baseline. Also encouraging was the absence of a significant decrease in insulin sensitivity during the first 24 weeks; however, insulin sensitivity was decreased at 48 weeks. The 30-minute plasma insulin and glucose levels

and AUCs were unchanged, but the 120-minute plasma glucose level was significantly increased at 24 weeks compared with baseline (146 ± 13 mg/dL vs 114 ± 7 mg/dL, respectively; p = 0.02). Furthermore, four of the patients who had normal baseline glucose tolerance testing were found, on re-evaluation at week 24, to have then progressed to fit criteria for impaired glucose tolerance.

The authors point out that these results can be considered to be an improvement when compared with a prior study they had done on indinavir that had shown significant decreases in insulin sensitivity after only ≤8 weeks of administration of that agent. However, it is clear that although most of the effects of amprenavir on glucose metabolism might perhaps be delayed when compared with indinavir, they nonetheless can appear eventually. It is therefore questionable as to how much of a long-term advantage amprenavir would provide, if any, over older PIs in long-term HAART.

Besides the introduction of newer agents within the PI class, research has also looked into new alternative therapies. Nystrom et al.[67] published an intriguing case report on the efficacy of a fibric acid derivative bezafibrate in reducing hypertriglyceridaemia as well as improving glucose uptake and endothelial function. A patient who had received PI therapy and developed diabetes was given bezafibrate therapy daily for 3 months. Whole body glucose uptake was calculated by administration of a hyperinsulinaemic clamp and increased by 51% after therapy; insulin and triglyceride levels decreased and endothelial-dependent, flow-mediated dilation increased. The authors hypothesised that the improvement in glucose uptake could reflect an improvement in Glut4 activity because of the decreased serum triglyceride levels or because of a direct effect of bezafibrate on Glut4 activity.

Even more novel approaches have been outlined by Leow et al.,[36] including administration of leptin and adiponectin. Leptin is an adipocyte-secreted protein that has been used to treat severe obesity in leptin-deficient mice and it is also associated with improvements in insulin resistance in mice with lipodystrophy. Adiponectin is an adipocytokine whose secretion has been shown to be increased after administration of PPAR-γ agonist medications (i.e. thiazolidinediones) for improved insulin sensitivity. Studies of the co-administration of leptin and adiponectin for the improvement of insulin resistance are being investigated.[36] However, it is clear that further evaluations, in both animal and human models, will be necessary before the safety and efficacy of such novel factors can be established.

3. Prevention

There is general agreement that the prevention of diabetic complications in the population of patients receiving PI therapy encompasses many of the same measures that the general population must use to prevent onset or progression of type 2 diabetes. In particular, the items cited in the synopsis of recommendations to prevent or delay diabetes from the ADA Position Statement (2002) are applicable.[68] They recommend:

- regular physical activity;
- screening via fasting plasma glucose level or 2-hour OGTT (75g glucose load);
- follow-up counselling;
- close attention to modifying other cardiovascular disease risk factors such as tobacco use, hypertension and dyslipidaemia.

That a proper assessment of cardiovascular risks is essential in this population has been further highlighted by the recent publication of the DAD (Data collection on Adverse events of anti-HIV Drugs) study, an observational study of eleven established HIV cohorts.[69] The results showed that patients receiving an antiretroviral regimen using agents from all three of the major antiretroviral classes had a particularly high prevalence of multiple risk factors for cardiovascular disease and that regimens combining PIs with NNRTIs were associated with the highest prevalence of dyslipidaemia in the study.

Similarly, the AACTG guide (Aids Alert) states the following points:[56]

- "All HIV patients should be educated about following a healthy, balanced diet with regular exercise as a way to prevent diabetes, and clinicians should recommend weight loss to patients who are obese and at a higher risk of developing diabetes."
- "It's also advisable to perform a complete cardiovascular risk assessment and to encourage patients to make lifestyle changes, including stop-

ping smoking, adhering to a lipid-lowering diet, and engaging in aerobic exercise."

Further emphasising the importance of dietary modification, Hadigan et al.[70] performed a study evaluating dietary intake in 85 HIV-infected men and women with fat redistribution in at least one or more areas, of whom 69% were receiving a PI. The results showed that 53% of all patients consumed <20 g/day of dietary fibre; women had a significantly lower fibre intake level than men and a 5g increase in daily dietary fibre intake led to a 14% reduction in the insulin AUC measurement following a 75g OGTT. The duration of PI use and the dietary polyunsaturated-to-saturated fat ratio were positively associated with insulin AUC as well. Hence, the authors suggest that dietary modification, with a focus on altering polyunsaturated fat intake and increasing dietary fibre, may be of assistance in treating insulin resistance in this patient population. However, Leow et al.[36] have noted that the specifics of dietary modification are still under debate, as these associations have not yet been confirmed in other studies.

With regard to the recommendations regarding physical activity, one important caveat is raised by Dube,[21] who notes that aerobic exercise could exacerbate fat wasting by causing a reduction in subcutaneous fat, so less intensive routines are likely to be preferable. However, overall, the impact of moderate exercise on HIV infection is thought to be relatively benign.[63]

Other authors have made specific suggestions regarding the frequency of screening. The AACTG guide suggests that HIV-infected patients receiving PI treatment should have their fasting glucose level checked at the onset of therapy and at intervals of 3–6 weeks afterward. Hughes and Taylor[4] suggest monitoring of baseline fasting serum glucose levels with follow-up every 3 months. The DHHS Guidelines[44] suggest doing so for at least the first year of PI treatment in patients with no prior history of diabetes. They also emphasise the importance of patient education, particularly regarding potential presentations of symptomatic hyperglycaemia, such as polydipsia, polyphagia and polyuria. An interesting suggestion by Wanke et al.[63] is the development of a clinical assessment tool or routine questionnaire to be distributed to patients at risk. Questions could assess cardiovascular disease risk factors as well as issues regarding changes in body shape. In addition, concomitant medications that may further increase the risk of glucose intolerance should be noted, such as megestrol, pentamidine, corticosteroids or anabolic steroids. A patient group of particular concern is the subset of HIV infected patients receiving PI therapy who are pregnant; the DHHS Guidelines state that "because pregnancy is an independent risk factor for impaired glucose tolerance, closer monitoring of blood glucose levels should be done".[44]

Another controversy that has arisen occasionally is the question of which laboratory tool is most appropriate for screening: fasting plasma glucose level versus the 2-hour OGTT. The DHHS Guidelines recommend fasting blood glucose measurements rather than routine glucose tolerance testing, although they note that this recommendation is based only on level III evidence, i.e. expert opinion. However, Carr et al.[8] found that their study's overall incidence rates for diabetes and impaired glucose tolerance were 7% and 16%, but only 2% and 7%, respectively, were diagnosed using fasting glucose values. Similarly, Saves et al.[14] noted that nearly one-third of the diagnoses of diabetes in their study were made solely by 2-hour OGTT criteria. Indeed, even the ADA-National Institute of Diabetes and Digestive and Kidney Diseases (NIDDKD) position statement mentions that the 2-hour OGTT "appears to identify more people who have impaired glucose homeostasis and, thus, more people who will progress to diabetes", but also notes that this may be because of the choice of the cut-off point for impaired fasting glucose level rather than actual sensitivity or specificity differences between the two methods.[68] However, the ease of administration of the fasting plasma glucose measurement compared with 2-hour OGTT must be taken into account as well. We conclude that, at a minimum, fasting plasma glucose levels should be checked routinely, but we also suggest that the 2-hour OGTT should be done when practical, in order to identify more high-risk patients.

Finally, the most definitive method of prevention of PI-induced metabolic complications involves the avoidance of PI agents as first-line therapy. Although it is a conservative strategy, this approach

has been suggested by the International AIDS Society-USA Panel. The Panel specifically states that "consideration should be given to avoiding use of a protease inhibitor-based regimen as initial therapy… in patients with preexisting abnormalities of glucose metabolism or with first-degree relatives with diabetes mellitus".[35] This concept has been subjected to clinical trials analysis in a randomised study by van Leeuwen et al.[71] HIV-1-infected patients who were antiretroviral drug-naive and had a plasma HIV-1 RNA concentration of at least 500 copies/mL were randomised to a PI-based regimen (stavudine, didanosine and indinavir) or a non-PI-based regimen (stavudine, didanosine and nevirapine or stavudine, didanosine and lamivudine). When virological efficacy was defined as viral suppression to <500 copies/mL, there were no statistically significant differences between the study groups at week 48. However, the authors did note the following caveat: if virological efficacy was defined as viral suppression to <50 copies/mL, then the lamivudine-based regimen showed significantly less efficacy than the other regimens.

4. Conclusion

In spite of the impressive antiretroviral efficacy achieved by PIs and their central role in HAART, the incidence of impaired glucose tolerance and frank diabetes has been significant and demonstrated repeatedly in multiple studies since 1997. Early case reports have given way to large, multicentre cohort studies with a specific focus on the metabolic complications caused by PI use. Several studies across vastly different demographic populations have documented an incidence rate of approximately 6% for the development of frank diabetes with PI use, although rates as high as 14% or more have been reported. Additionally, the incidence rate of impaired glucose tolerance is even more substantial and ranges from 16% to 46% in some studies. The duration of PI use before the onset of aberrations in glucose metabolism has varied widely, with case reports documenting onset only 2 weeks after PI initiation or as late as several years afterward.

An important point is that, although patients who develop metabolic complications while receiving PI therapy often have concomitant glucose intolerance and fat redistribution, these processes can occur separately from each other. Thus, the absence of fat redistribution does not necessarily indicate a reduced risk of progression to diabetes for patients receiving PI therapy.

The management of hyperglycaemia is important, particularly for proper leukocyte functioning to prevent infection and for the proper formation of granulation tissue to facilitate wound healing.[48] Thus, the options include much of the usual pharmacological armamentarium, including metformin and thiazolidinediones, which are employed against type 2 diabetes in the non HIV-infected population. The risk of lactic acidosis related to metformin use must be remembered, especially as patients receiving HAART are often treated with NRTI agents that have also been associated with lactic acidosis and hepatic steatosis. Insulin therapy may be necessary in substantial numbers of the population of patients with HIV receiving PI therapy who develop hyperglycaemia. Active research is on-going into the development of new PI agents, such as those that may avoid inhibition of the Glut4 transporter, with the goal of reducing the incidence of PI-induced insulin resistance. Meanwhile, preventative measures include regular physical activity and routine screening for glucose intolerance in the patients who continue to be maintained on long-term PI therapy.

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