Review

Insulin resistance, glucose intolerance and diabetes mellitus in HIV-infected patients

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An increased prevalence of insulin resistance, glucose intolerance and diabetes has been reported in HIV infection in the highly active antiretroviral therapy (HAART) era. This development might be clinically significant because of its association with cardiovascular morbidity and mortality as well as the therapeutic challenges of managing polypharmacy. The development of insulin resistance, glucose intolerance and diabetes could be related to the underlying HIV infection, the contribution of different antiretroviral agents, treatment-associated weight gain, immune restoration, as well as the non-HIV related factors. Dissecting these factors in clinical practice might be difficult. Clinical studies include short-term treatments in healthy, non-HIV-infected individuals; randomized, controlled trials; comparative studies of different HAART regimens; and randomized studies of switching regimens in patients with viral suppression and stable immune function. This article reviews the latest knowledge regarding the epidemiology, pathogenesis, prevention and treatment of insulin resistance, glucose intolerance and diabetes mellitus in HIV-infected individuals.

Introduction

Advances in antiretroviral therapy (ART) have led to prolonged survival and improved quality of life of HIV-infected patients. While protein–energy malnutrition is common in patients with severe immune deficiencies, patients on combination ART might develop a lipodystrophy syndrome, characterized by peripheral lipoatrophy, central lipohypertrophy and visceral fat redistribution [1–4], accompanied by metabolic abnormalities, including dyslipidaemia and insulin resistance. Recent studies have linked HIV-associated lipodystrophy with an increased risk of symptomatic cardiovascular disease [5].

The pathogenic mechanisms underlying the fat redistribution and metabolic alterations are multifactorial, with distinct but overlapping pathogenic factors for each specific alteration. Factors related to HIV infection and its treatment, as well as hormonal influences, mitochondrial dysfunction, cytokine activation related to immune reconstitution and individual genetic predisposition, have all been hypothesized to be aetiological. This review will describe the pathogenic mechanisms, consequences and management of insulin resistance in HIV-infected patients.

Definitions and prevalence

Insulin resistance is a condition in which a higher-than-normal insulin concentration is needed to achieve a normal metabolic response or, alternatively, a situation in which a normal insulin concentration fails to produce a normal metabolic response [6,7] (Table 1). Impaired fasting glucose is defined as a fasting plasma glucose level ≥110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l) and impaired glucose tolerance as a 2-hour post-prandial (75 g glucose) value 140–199 mg/dl (7.8–11.1 mmol/l). Diabetes mellitus is characterized by hyperglycaemia due to defects in insulin secretion, insulin actions, or both. Diabetes mellitus is defined as either fasting hyperglycaemia (≥126 mg/dl [7.0 mmol/l]) or plasma glucose levels

Table 1. Definitions [8]

	Diagnostic criteria
Impaired fasting glucose	Fasting plasma glucose ≥110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l)
Impaired glucose tolerance	A 2-h post-prandial (75 g glucose) value 140–199 mg/dl (7.8–11.1 mmol/l)
Diabetes mellitus	Fasting hyperglycemia (≥126 mg/dl [7.0 mmol/l])
	Plasma glucose levels ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test
	Random plasma glucose level ≥200 mg/dl (11.1 mmol/l)

Box 1. Pathogenic mechanisms of insulin resistance

Similar in HIV and non-HIV patients
Genetic influences
Elevated circulating free fatty acids
Increased muscle and organ fat
Hormones
Co-morbid diseases
Chronic inflammatory changes (cytokines)
Specific for HIV-infected patients
Lipodystrophy
Highly active antiretroviral therapy (nucleoside reverse transcriptase inhibitors and protease inhibitors)

≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT). Another criterion for the diagnosis of diabetes mellitus is a random plasma glucose level ≥200 mg/dl (11.1 mmol/l) [8].

Insulin resistance is often associated with a cluster of metabolic abnormalities termed the metabolic syndrome that includes hypertension, hypertriglyceridaemia, hypercholesterolaemia, low serum concentrations of high-density lipoprotein (HDL) and truncal adiposity [9].

King *et al*. estimated the prevalence of diabetes in adults worldwide to be 4.0% in 1995, with an expected rise to 5.4% by the year 2025 [10]. The number of non-HIV infected adults with diabetes mellitus is expected to increase from 135 million worldwide in 1995 to 300 million by 2025, with an expected 42% increase in prevalence in developed countries and 170% increase in developing countries [10]. In HIV-infected men exposed to highly active ART (HAART), Brown *et al*. reported a 14% prevalence of diabetes mellitus and a four-times higher incidence of diabetes mellitus than in HIV-seronegative men [11]. Beregszaszi *et al*. reported 13.2% insulin resistance among HIV-infected children [12].

The prevalence of alterations in glucose metabolism differed in the pre-HAART era compared with the HAART era. Hommes *et al*. used the euglycaemic insulin clamp technique to demonstrate that asymptomatic, HIV-infected men in the pre-HAART era had increased rates of insulin clearance and increased sensitivity of peripheral tissues to insulin [13]. Gan *et al*. used the hyperinsulinaemic–euglycaemic clamp to show that lipodystrophy is associated with increased lipid content in muscle and insulin resistance in protease inhibitor (PI)-treated HIV-infected men [14].

The prevalence of insulin resistance, glucose intolerance and diabetes in HIV-infected subjects increased significantly following the introduction of HAART. Diabetes mellitus is relatively uncommon (2–5% in most series), while insulin resistance is more common and is found in about 50% of PI-treated patients, compared with about 25% of patients on nucleoside therapy, in one study [5].

Multiple reports in the literature documented the development of non-ketotic hyperglycaemia 1–7 months after starting treatment with certain PIs [15–18]. In 1997, after receiving 83 reports of cases of new or exacerbated diabetes mellitus and hyperglycaemia in HIV-infected patients taking PIs, the US Food and Drug Administration (FDA) published an alert in the FDA Medical Bulletin concerning possible increased blood glucose in HIV patients on this class of drugs. Twenty-seven of the 83 cases required hospitalization and five cases resulted in ketoacidosis. In these cases there were no data demonstrating that the drugs directly caused the condition [18]. Hadigan *et al*. demonstrated that HIV-infected patients with lipodystrophy had higher fasting insulin levels and more frequent impaired glucose tolerance compared with case-matched, healthy control subjects from the Framingham Offspring Study [1].

Pathogenesis of insulin resistance

The development of insulin resistance, glucose intolerance and diabetes mellitus in the HIV-infected population is multifactorial (Box 1). Some of the pathogenic processes are the same as in non-HIV-infected individuals, such as genetic influences, increased free fatty acid concentrations, visceral fat accumulation, increased muscle and organ fat, hormonal alterations, chronic inflammation and co-morbid diseases. Other pathogenic factors might be related to HIV infection itself, its treatment, treatment-associated weight gain or immune restoration, or to a return to a previous state of health that included the susceptibility to alterations in glucose metabolism. Relatively few studies of metabolic abnormalities have been done in antiretroviral-naive patients [13]. Alterations in body composition and hyperinsuli-

naemia were described in HIV-infected patients in the early-HAART era, irrespective of PI use. These subjects were on nucleoside reverse transcriptase inhibitor (NRTI) therapy, which might affect insulin sensitivity [19,20]. Hyperinsulinaemia was also noted both in patients with truncal adiposity and in patients with <90% ideal body weight, in whom reduced insulin levels would be expected [19].

Antiretroviral effects

NRTI-associated mitochondrial toxicity

Lipodystrophy, insulin resistance and diabetes were described soon after the initial application of PIs in early 1996, whereas NRTIs had been in use since 1986. For this reason, PIs were initially considered the most likely cause of these conditions. The possibility that NRTIs could be related to lipodystrophy was first raised by Brinkman *et al*. [21]. The mitochondrial hypothesis states that these toxicities represent organ-specific effects of specific NRTIs. These agents, which are nucleoside analogues and designed to inhibit HIV reverse transcriptase, also inhibit DNA polymerase-γ, the DNA polymerase active in mitochondrial replication [22]. In contrast, non-nucleoside reverse transcriptase inhibitors (NNRTIs) do not inhibit DNA polymerase-γ.

This hypothesis and the results of experimental studies suggest that differences within the NRTI class variably affect different organs. Clinical signs and symptoms are related to the specific organ and function involved; for example, mitochondrial dysfunction in adipose tissue leads to lipoatrophy, mitochondrial dysfunction in the liver leads to lactic acidosis and hepatic steatosis, and mitochondrial dysfunction in nerves leads to neuropathy. Many factors, including inflammation and oxidative stress, affect mitochondrial function in addition to NRTIs. Depending on the level of mitochondrial dysfunction, energy metabolism is affected at multiple points, with cell death by apoptosis an ultimate outcome [23]. While mild deficiency might be undetectable, there is a threshold beyond which mitochondrial dysfunction becomes clinically manifest. Multiple studies have shown that HIV infection itself and also ART induce alterations of mitochondrial membrane potential leading to mitochondrial-dependent cell apoptosis [24–28]. Mallon *et al*. demonstrated in adipose tissue biopsies from non-HIV-infected, healthy volunteers that dual-NRTI therapy (zidovudine/lamivudine, stavudine/lamivudine) could cause mitochondrial dysfunction, even in the absence of mitochondrial DNA depletion [29]. These effects are related to the specific NRTI used. Tenofovir and abacavir are poor inhibitors of DNA polymerase in adipose tissue and so are less toxic to the mitochondria [23,30,31]. Several *in vitro* studies showed that stavudine and zidovudine reduce the lipid content of adipocytes and induce apoptosis via mitochondrial toxicity [32–35]. In addition, the activities of lipoprotein lipase, acetyl coenzyme A synthase and glucose transport proteins in subcutaneous adipose tissue are decreased in HIV-infected lipoatrophic subjects on HAART [23]. Up to 15–20% of the treated population develops mitochondrial toxicity from NRTI therapy, suggesting a possible genetic predisposition to NRTI toxicity. However, no genes have been identified yet [22]. A recent pharmacogenetic study showed that a single nucleotide polymorphism in the resistin gene is associated with an increased risk of developing metabolic changes (increased total cholesterol, low-density lipoprotein [LDL], triglyceride and insulin resistance) on HAART [36].

Recent studies suggested that genetically acquired mitochondrial dysfunction is the underlying cause of insulin resistance and diabetes mellitus in the general population [37]. It is uncertain whether this is related to a single mutation or polymorphism, or if several genetic alterations lead to type 2 diabetes. However, insulin resistance is an expected result of mitochondrial dysfunction in skeletal muscle and adipose tissue, irrespective of whether the underlying cause is genetic or acquired. Mitochondrial dysfunction decreases energy production and clearance of reducing equivalents, which slows the Krebs cycle and decreases pyruvate fatty acid metabolism. As a result, glucose disposal decreases irrespective of insulin content, which is the definition of insulin resistance. Some of the reducing equivalents are consumed in the production of lactate from pyruvate, and free fatty acids are also released from the adipocytes into the serum. Both excess lactate production and increased levels of circulating free fatty acids have been documented in HIV-infected individuals [38–40].

Antiretrovirals and free fatty acid metabolism

Fatty acid concentrations modulate insulin resistance *in vivo*. Increased fatty acid levels can induce hyperinsulinaemia and insulin resistance through several mechanisms: by increasing hepatic gluconeogenesis, by decreasing hepatic insulin extraction, by impairing insulin secretory response of β-cells to glucose and by competing with glucose as substrate to be oxidized by the muscle [41–43]. In the pre-HAART era hypertriglyceridaemia, decreased triglyceride clearance and increased free fatty acid concentrations were identified in patients with AIDS [44]. The increased concentrations of free fatty acids are related in part to fat redistribution and to inflammation [45,46], but mitochondrial dysfunction could also contribute to the alterations. In multiple studies stavudine has been

associated with abnormally increased lipolysis, increased free fatty acid concentrations and abnormal fat distribution (mainly lipoatrophy), contributing to insulin resistance in HIV-infected patients [39,47]. Free fatty acid concentrations are higher in women than in men [46]. Brown *et al*., in the Multicenter AIDS Cohort Study, showed that cumulative exposure to NRTIs, especially stavudine, was associated with hyperinsulinaemia and insulin resistance [48]. In contradiction to previous studies, this study did not associate cumulative PI exposure with insulin resistance. Lo *et al*. found a similar relationship between cumulative NRTI exposure and insulin resistance, and also a direct association between insulin resistance and serum lactate level, and postulated that chronic increased lactate level (muscle-derived or adipose-derived) might directly alter insulin sensitivity [49,50].

PI-associated insulin resistance

Early studies associated the use of PIs with the development of lipodystrophy, dyslipidaemia and insulin resistance [5,51,52]. At physiological concentrations there are intra-class differences in the metabolic effects of PIs, including insulin resistance. Carr *et al*. demonstrated that patients receiving PI-based HAART who developed changes in body fat redistribution had significantly higher triglyceride, cholesterol, insulin and C-peptide levels than PI recipients without morphological changes [51]. Insulin resistance is compensated for in most patients by increased insulin secretion, but could lead to clinically significant hyperglycaemia in patients with an underlying predisposition to diabetes mellitus. Murata *et al*. demonstrated that indinavir causes insulin resistance by inhibiting insulin-stimulated glucose uptake in adipocytes, selectively inhibiting the function of the Glut4 glucose transporter [53]. The inhibitory effect of PIs on Glut4 activity, the rate-limiting step in glucose uptake into muscle and adipose tissue, might be a major cause of insulin resistance in HIV patients receiving this class of drugs.

The inhibitory effect of indinavir on tissue glucose uptake was demonstrated using the technique of hyperinsulinaemic, euglycaemic clamp testing by Noor *et al*. [54,55]. These studies, as well as the *in vitro* studies, indicate that the effect is completely reversible. The precise mechanism of inhibition is unknown. Other studies have examined the role of other PIs on glucose metabolism and have documented intra-class differences in the inhibition [56–58,84]. Atazanavir, given alone or in combination with low-dose ritonavir, did not significantly affect insulin sensitivity by the hyperinsulinaemic, euglycaemic clamp method, while the results of studies with lopinavir/ritonavir are discordant [56,58,59]. Noor *et al*. induced insulin resistance by clamp and OGTT after administration of lopinavir/ritonavir after 10 days and 5 days of treatment, respectively, in healthy HIV-negative subjects [56,58]. In contrast, Lee *et al*. did not find an increase in insulin resistance after 4 weeks of therapy with lopinavir/ritonavir [59]. These results suggest that some adaptation might have occurred between weeks one and four after starting therapy. Dube *et al*. showed that amprenavir-based therapy in PI-naive patients was not associated with short-term insulin resistance, but a trend toward insulin resistance appeared late in the study, following weight gain [60]. Lee *et al*. showed that a single dose of amprenavir in HIV-negative men did not decrease insulin-mediated glucose disposal, had no effect on fasting glucose and did not suppress free fatty acid levels during the clamp, the last being another function of insulin that is impaired in patients with insulin resistance [57].

Other PI-associated effects include alterations in gene expression, altered adipocyte differentiation and decreased lipid metabolism [32,33,61–67]. Studies have also shown that PIs might promote loss of mitochondrial membrane potential and apoptosis [68,69], though nelfinavir has an anti-apoptotic effect [70,71]. Apoptosis in HIV-lipodystrophic patients on or off HAART is also promoted by increased levels of cytokines (tumour necrosis factor [TNF]-α, interleukin (IL)-1, IL-6, interferon-α) [72–76]. Domingo *et al*. demonstrated that TNF-α might have a role in subcutaneous adipocyte apoptosis in the setting of fat redistribution in HIV-infected patients on HAART [77–79].

NNRTIs and insulin resistance

There are no consistent data showing insulin resistance in patients started on NNRTI regimens. Shahmanesh *et al*. showed that nevirapine-containing regimens have a more favourable glucose–insulin profile than antiviral regimens containing efavirenz or PIs [80].

Non-antiretroviral effects

Role of adipokines and cytokines in insulin resistance

Adipose tissue not only secretes fatty acids that contribute to insulin resistance, but also directly modulates the effects of insulin through the secretion of cytokines and adipokines. Pro-inflammatory cytokines stimulate lipolysis and inhibit adipose tissue lipogenesis, thus exacerbating the increases in free fatty acid concentrations. Studies by Johnson *et al*. [38] and Mynarcik *et al*. [76] demonstrated associations between lipoatrophy, insulin resistance and increased circulating concentrations of pro-inflammatory cytokines and soluble TNF receptors. TNF-α, IL-1 and IL-6 affect adipocyte differentiation and apoptosis in addition to having direct effects on insulin resistance [38,73,74,81]. Amprenavir and ritonavir have been shown to increase

leptin expression [82]. Leptin regulates food intake via its action in the central nervous system. Adiponectin concentrations are altered in patients on PI-based regimens with lipodystrophy, insulin resistance and other metabolic alterations [83,84]. In one study, the adiponectin:leptin ratio predicted insulin sensitivity and potential cardiovascular risk [76]. The role of PIs and NRTIs, as opposed to immune reconstitution, immune activation and other factors, is uncertain. There is no evidence that NNRTIs affect adipokine and cytokine release or activity.

Hepatitis C virus (HCV) infection

HCV infection is an additional risk factor for insulin resistance and diabetes mellitus in HIV/HCV-coinfected patients. Larranga *et al.* showed that HIV/HCV-coinfected subjects on HAART have higher insulin resistance, higher levels of activated platelets and higher endothelial dysfunction than subjects without HIV/HCV coinfection [85]. Two other recent studies showed a higher risk of new-onset hyperglycaemia in subjects with HCV infection treated with PI-based regimens [86,87].

Hormonal factors influencing insulin resistance

Hormonal factors might contribute to the lipodystrophy syndrome and insulin resistance, though the cause–effect relationships have not been satisfactorily defined. Hyperinsulinaemia was observed more in amenorrhoeic HIV-infected women than eumenorrhoeic HIV-infected women [19]. In HIV-infected non-diabetic men insulin concentrations correlate inversely with serum free testosterone concentrations. Increased insulin resistance in hypogonadal HIV-positive subjects is not a function of increased sex hormone-binding globulin. If hyperinsulinaemic, hypogonadal HIV-positive men are treated with physiological, replacement doses of testosterone, there is an improvement in insulin sensitivity without significant change in lipid parameters [20]. The decrease in insulin resistance might be associated with an increase in lean body mass [20]. Supraphysiological doses of testosterone and its analogues might promote insulin resistance [88,89].

Consequences of insulin resistance

HAART has improved survival and quality of life of patients with advanced HIV infection. Concerns have arisen that the deleterious effects of HAART on glucose metabolism, lipid metabolism and body fat distribution might have serious consequences for the affected individual. Currently, the benefits of ART outweigh the risk of side effects of the therapy. Morphological changes found in patients with lipodystrophy syndrome can have negative impacts on individuals' psychological outlooks [90], which could lead to non-adherence to HAART and its consequences.

Insulin resistance occurs as part of the metabolic syndrome that might lead to the development of type 2 diabetes, atherosclerosis, hypertension or polycystic ovarian syndrome, depending on the genetic background of the individual. Dyslipidaemia, insulin resistance and fat redistribution are all associated with accelerated cardiovascular disease. Early observations noted the development of myocardial infarction or sudden cardiac death in young HIV-infected patients on HAART [91]. Epidemiological studies in large numbers of patients produced conflicting results regarding the possible increased risk of cardiovascular disease due to PI therapy, but most studies have concluded that there is an increased risk in HIV-infected patients receiving HAART therapy.

Klein *et al.* found a significantly higher risk of myocardial infarction in the HIV-infected group compared with an HIV-negative group, but no differences in coronary artery disease or myocardial infarction rates in patients taking PI-based or non-PI-based HAART [92]. Bozzette *et al.* found no increase in hospitalizations or deaths from cardiovascular or cerebrovascular causes in treated, HIV-infected patients [93]. Currier *et al.* found a significantly increased risk of cardiovascular disease in young women but not in older women or in men [94]. One explanation for these divergent results is that the risk of symptomatic atherosclerosis related to HAART therapy is relatively low given the current mean duration of therapy, compared with the classical risk factors, so that it can be detected only in patient groups with very low absolute underlying risk.

The results of other studies suggest than an increased risk of cardiovascular disease occurs mainly in HIV-infected patients on PI-based regimens. A French group, who studied HIV-seropositive men, noted an approximately threefold increase in the relative risk of myocardial infarction in patients treated with PIs for more than 30 months, while shorter treatment periods showed no increased risk [95]. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group prospectively collected data on the incidence of myocardial infarction on HIV-infected patients on combination ART. In this study cohort 81% of the population had been exposed to ≥1 antiretroviral drug, 75% to combination ART, 67% to different PIs and 30% to NNRTIs. The study showed that combination ART was associated with a 26% relative increase in the rate of myocardial infarction per year of exposure during the first 4–6 years of treatment [5]. A follow-up study in this cohort showed that the risk of myocardial infarction, although relatively low, continues to increase with longer exposure to

HAART over the first 7 years of use [96]. More recent data from the D:A:D study confirmed increased risk of myocardial infarction in association with PI exposure but not with NNRTI exposure [97].

Several studies have evaluated the use of surrogate markers for cardiovascular disease, such as ultrasensitive C-reactive protein (CRP) level, flow-mediated dilation (FMD) of the brachial artery following an ischemic stimulus, serum plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA) concentrations, as well as carotid intima media thickness, as determined by ultrasound examination. Several studies in the general population have demonstrated a direct correlation between the results of ultrasensitive CRP determinations in serum and the risk and severity of cardiovascular disease [98–101]. There are no published studies looking at the ultrasensitive CRP level in HIV patients, though preliminary data, published in abstract form, appear to link CRP results to classical risk factors. Vasodilatory properties of the endothelium are affected during atherogenesis, even before the development of the atherosclerotic plaque [102] and can be demonstrated by assessing the degree of FMD of the brachial artery following an ischemic stimulus [103]. Stein reported that subjects receiving PI-based regimens had markedly impaired endothelial function demonstrated by FMD [104]. Nolan found conflicting results: an unexpected preservation of endothelial function and preserved FMD in dyslipidaemic PI-treated individuals [105]. Solanges showed that endothelial dysfunction in HIV-infected patients correlated with the level of HIV replication and with the use of intravenous drugs [106]. FMD correlates with insulin resistance. Ardigo demonstrated that insulin resistance with compensatory hyperinsulinaemia, in the absence of other risk factors for atherosclerosis in apparently healthy individuals, is an independent predictor of decreases in flow-mediated vasodilation [107]. Repaglinide, in patients with impaired glucose intolerance, besides controlling hyperglycaemia, increased flow-mediated dilatation in a glucose-dependent manner [108].

Increased risk of coronary artery disease and cerebrovascular events has been associated with high levels of PAI-1 and tPA, markers of impaired fibrinolysis. Hadigan *et al*. demonstrated increased concentrations of tPA and PAI-1 in association with lipodystrophy and hyperinsulinaemia in HIV-infected patients [109]. Treatment with metformin significantly reduced insulin resistance as well as PAI-1 and tPA concentrations in HIV-infected patients with lipodystrophy [110]. Currier *et al*. measured the impact of HIV infection and ART on the development of subclinical atherosclerosis by measuring carotid intima media thickness. They found that greater age, lower HDL cholesterol and higher body mass index, factors known to increase the risk of atherosclerosis, increased the carotid intima media thickness. They did not find an association between carotid intima media thickness and either HIV infection or PI exposure [110]. Instead, this and other similar studies showed that the classic risk factors for atherosclerosis predicted carotid intima media thickness. Recent data from the Conference on Retroviruses and Opportunistic Infections suggested that long-term HIV infection might be an independent risk factor for early atherosclerosis. Increased intima media thickness was found to be significantly more common in HIV-positive individuals than in the control group [111].

In summary, proposed explanations for atherosclerosis in HIV-infected patients include both the underlying genetic and behavioural (for example, cigarette smoking) effects as well as the effects of HIV infection and its treatment. Importantly, insulin resistance is a known risk factor for the development of atherosclerosis, so any factor that promotes insulin resistance could increase risk. At present, both the specific role of PIs in the development of atherosclerosis and the magnitude of the increase in cardiovascular risk in HIV-infected patients are uncertain.

Diagnosis and management of insulin resistance in HIV-infected patients

There is significant biological and analytic variability in the measurement of blood glucose concentrations. In fact, glucose measurements might be underestimated in clinical practice because of the use of red- or speckled-top collection tubes without additives instead of grey-top tubes or other tubes that inhibit glucose metabolism after collection. Variability in the measurement of insulin might be related to the precise method of blood collection and handling, as well as variations in the different assays.

Various organizations (World Health Organization, National Cholesterol Education Program Adult Treatment Panel III, The American Association of Clinical Endocrinologists, International Diabetes Federation) elaborated different diagnostic criteria in an effort to detect and treat subjects with insulin resistance earlier, with the hope of reducing the long-term risk of cardiovascular disease. However, there are no generally accepted criteria for diagnosing insulin resistance syndrome in routine clinical practice. The hyperinsulinaemic, euglycaemic clamp method is the most accurate means of determining insulin resistance, but is time-consuming, expensive and used mainly for research purposes. Moreover, the results can be misleading. For example, insulin resistance is detected by the clamp as a

Box 2. Summary of diagnosis and management of insulin resistance in HIV-infected patients

Fasting serum glucose measurement
- Before starting treatment
- 3–6 months after starting HAART
- Yearly thereafter

Oral glucose tolerance test

In patients with family history of diabetes, obesity or metabolic syndrome, on HAART
- At the first visit
- Repeat when there is clinical suspicion of impaired glucose tolerance

Avoidance

In patients with impaired glucose tolerance or diabetes mellitus avoid starting stavudine

Lifestyle modification
- Diabetic education
- Self-monitoring of blood glucose
- Aerobic and resistance training

Metformin
- Monitor for lactic acidosis after initiation of therapy, during the first months
- Contraindicated in patients with renal failure (serum creatinine >1.5)

Thiazolidinediones
- Monitor liver function tests every 2 months for the first 12 months of treatment
- If AST and ALT are more than 2.5× the upper limit of the normal, thiazolidinediones should not be started

Switching therapy
- Switch from PI-based HAART to include NNRTI or NRTI
- Switch from thymidine NRTI in the presence of diabetes or glucose intolerance (controversial)

ALT, alanine transaminase; AST, aspartate transaminase; HAART, highly active antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

lower infusion rate/flux rate at maximal insulin concentration and a constant blood glucose concentration. However, in reality, glucose flux is normal in patients with insulin resistance, while insulin and/or glucose concentrations are higher.

Clinically, management has been based more on glucose than on insulin measurements (Box 2). The International AIDS Society guidelines [112] are similar to the recommendations for the HIV-negative population established by the American Diabetes Association [113]. All HIV-infected patients should undergo routine testing of the fasting serum glucose before starting treatment, 3–6 months after starting potent antiretrovirals and yearly thereafter. Patients with family history of diabetes, obesity or metabolic syndrome, or who are taking HAART, especially a PI-based regimen, should have a standard OGTT carried out during the first visits to test for impaired glucose intolerance. Then, OGTT should be repeated when there is clinical suspicion of impaired glucose tolerance.

There are three general approaches to treatment-associated toxicities; avoidance through the strategic choice of antiretrovirals, switching antiretroviral regimens in the event that toxicities become apparent, and pharmacological therapy to minimize the toxicity.

Avoidance

Some NRTIs have been implicated in the pathogenesis of lipodystrophy and many of the metabolic abnormalities are observed in treated HIV-infected patients, including insulin resistance. Several studies found that cumulative exposure to NRTI [1,48], particularly lamivudine [68] and stavudine [48,114], were associated with insulin resistance. Lamivudine has been widely used in practice and clinical trials and this drug does not seem to induce significant insulin resistance. Shlay *et al*. showed that a thymidine analogue-containing regimen (didanosine and stavudine) was associated with increased insulin concentrations and insulin resistance compared with a thymidine analogue-sparing regimen (abacavir and lamivudine) [115].

Switching therapy

Insulin resistance, glucose intolerance and diabetes mellitus, once diagnosed, should lead to re-evaluation of the antiretroviral regimen in an attempt to mitigate the metabolic alterations. The alternatives include switching, interrupting or stopping the patient's antiretroviral regimen and/or starting new medication to treat diabetes or dyslipidaemias. Changes in antiretroviral regimens have been associated with short-term improvements in insulin resistance [116]. Clinical evidence of diabetes mellitus might disappear after switching the patient from PI-based HAART. Most of the first 'switch studies' investigated a switch from a PI-based regimen to a nevirapine-, efavirenz- or abacavir-based regimen, and more recently there has been an increasing interest in nucleoside-switch trials (from stavudine or zidovudine) [116–133] (Table 2). In general, there are significant improvements in insulin resistance and serum lipid concentrations when therapy is switched from a PI to include an NNRTI or NRTI, though some studies of NNRTIs failed to show improvements in lipid concentrations. In these studies, there was no clear evidence of clinically apparent reversion to normal fat distribution. In one of the studies 91% of patients subjectively reported a partial improvement in their body shape, particularly in peripheral fat wasting, but no objective evidence of improvement was found [117]. In the MITOX Extension Study, switching from thymidine analogues to abacavir had no impact on glycaemic parameters [134].

Table 2. Switch studies

Description of the study (switch)	Study design	Patients, *n*	Median follow up, months	Method used to evaluate insulin resistance	Change in insulin resistance	References
PIs to NVP	Cohort	23	8	Glucose	Decreased	[117]
PIs to NVP	Cohort	23	14	Glucose, insulin	Decreased	[118]
PIs to EFV	Cohort	34	10	Glucose measurements (OGTT), insulin dosage	None	[119]
PIs to EFV	RCT	93	12	Fasting glucose, insulin	Decreased	[120]
PIs to EFV	Cohort	26	12	Glucose and insulin levels fasting and after OGTT	3/5 OGTT normalized	[121]
PIs to EFV	Cohort	41	12	Glucose, insulin and pro-insulin level fasting and after OGTT	None	[122]
PIs to NVP or EFV	Cohort	30	12	Glucose, insulin, proinsulin	No significant decrease in fasting glucose	[123]
PIs to NVP or EFV		40	12	Glucose, insulin, pro-insulin	Decreased	[124]
PIs to ABC	Substudy RCT	34	12	Fasting glucose, insulin	Not significantly decreased	[125]
PIs to ABC	Substudy RCT	31	12	Intravenous insulin tolerance test	Decreased	[126]
PIs to ABC or EFV	Cohort	16	12	OGTT, fasting insulin	2/4 cases of diabetes resolved	[127]
PI to ABC/ NVP/ADV/HU	RCT	81	12	Fasting insulin and glucose, OGTT	None. Three patients ceased/diminished treatment for DM	[128]
PIs to ABC or EFV or NVP	Substudy RCT	81	6	Fasting glucose and insulin	Decreased	[129]
d4T discontinuation	Cohort	36	9	OGTT, fasting glucose, insulin	Decreased C-peptide in PI group	[130]
d4T or AZT or ABC vs continued PI use	RCT	111	6	Fasting glucose	None	[131]
PIs to NVP or EFV or ABC	RCT	460	12	Fasting glucose	Fasting plasma glucose higher in EFV group than NVP, ABC groups	[132]
PIs to ABC or EFV or NVP	RCT	90	24	Fasting glucose, insulin	Decreased	[133]

ABC, abacavir; ADV, adefovir; AZT, zidovudine; d4T, stavudine; DM, diabetes mellitus; EFV, efavirenz; HU, hydroxyurea; NVP, nevirapine; OGTT, oral glucose tolerance test; PI, protease inhibitor; RCT, randomized controlled study.

Replacing PI therapy with abacavir, nevirapine or efavirenz raised the question of virological safety of these 'switch studies'. In one study, Martinez *et al*. showed that, when therapy was switched from a PI to nevirapine, efavirenz or abacavir in patients with virological suppression, there was a trend toward a higher rate of virological failure among the abacavir group [132].

Lifestyle modification

For patients with persistent fasting hyperglycaemia, established guidelines for treating diabetes mellitus in the general population should be applied [112]. Diabetic patients should be educated to prevent acute complications, to increase the compliance with treatment and to reduce the risk of long-term complications. Self-monitoring of blood glucose is an important component of therapy, allowing patients to evaluate their response to therapy and to adjust their diet and physical activity. Regular exercise improves blood glucose control, reduces cardiovascular risk factors and improves well-being, contributing at the same time to weight loss in HIV-negative patients [113]. However, it is uncertain whether exercise affects insulin resistance similarly in HIV-infected patients as it does in HIV-negative subjects, especially in the face of continuing HAART. However, despite this uncertainty, aerobic and resistance training should be encouraged in HIV-infected individuals with any impairment of glucose metabolism or lipodystrophic changes. Driscoll *et al*. reported that metformin in combination with exercise training in HIV-infected subjects with fat redistribution and hyperinsulinaemia was more effective in reducing waist-to-hip ratio, blood pressure and insulin levels than metformin alone [135]. Gavrila *et al*. found a negative association between insulin resistance, fasting triglyceride levels

Table 3. American Diabetes Association glycaemic treatment goals [149]

Biochemical index	Normal	Goal	Action suggested
Fasting/pre-prandial plasma glucose, mg/dl (mmol/l)	<110 (6.1)	90–130 (5–7.2)	<90 (5) or >150 (7.2)
Postprandial plasma glucose, mg/dl (mmol/l)	<140 (7.8)	<180 (10)	Not applicable
Bedtime plasma glucose, mg/dl (mmol/l)	<120(6.6)	110–150 (6.1–7.6)	<110 (6.1)or >180 (10)
HbA1c, %	<6	<7	>8

and habitual aerobic and combined aerobic and resistance training in HIV-positive subjects [136]. Yarasheski *et al*. found a similar inverse relationship between total or aerobic exercise and fasting triglyceride levels, but no significant differences in insulin levels in HIV-infected patients [137].

Treatment of diabetes mellitus

Insulin resistance is associated with increased cardiovascular disease risk. At present there is no FDA approved treatment for insulin resistance. Drugs that reduce insulin resistance might delay onset of type 2 diabetes and might reduce cardiovascular disease risk. If drug therapy is required, insulin-sensitizing agents, such as metformin or a thiazolidinedione should be considered [112], as these drugs have been shown to prevent or delay the development of diabetes in HIV-negative patients with pre-diabetes. The glycaemic treatment goals are shown in Table 3. It is important to reiterate that these drugs have not been approved for use in non-diabetic patients in either HIV-infected or non-infected individuals.

Metformin

Biguanides have been in use for over 40 years in diabetic patients without HIV infection. Hadigan *et al*. showed that metformin administered in HIV-infected patients with fat redistribution and abnormal oral glucose tolerance and hyperinsulinaemia, resulted in a 20% reduction in insulin area under the curve on oral glucose tolerance testing, as well as significant reductions in weight and diastolic blood pressure [138]. Metformin therapy was associated with a reduction in visceral and subcutaneous abdominal fat content. Metformin administration is associated with a low risk of lactic acidosis, and no cases of lactic acidosis were observed in this study. Hadigan *et al*. also demonstrated that metformin therapy in HIV-infected patients with lipodystrophy and insulin resistance resulted in decreased PAI-1 and tPA. Decreasing hyperinsulinaemia and the level of PAI-1–tPA complex will theoretically minimize the endothelial injury and thrombus formation [109]. Similar data were obtained by Saint-Marc *et al*. who studied the effect of metformin in HIV-infected patients with insulin resistance but no overt diabetes, who had central adiposity after starting PI therapy. They noticed a significant decrease in basal plasma glucose, insulin and C-peptide concentrations and also a marked decrease in both total and visceral adipose tissue [139].

Clinical monitoring for lactic acidosis is recommended in the first months after initiation of therapy with metformin. Plasma lactate levels should be measured if new symptoms suggesting lactic acidaemia develop during metformin treatment. Patients with impaired renal function or with a venous lactate level more than twice the upper normal limit should not be started or continued on metformin [112]. While there might be a concern for lactic acidosis in patients on HAART treated with metformin due to altered mitochondrial functions, only one case of fatal lactic acidosis has been reported to date, in a man with advanced HIV infection treated with didanosine, stavidine, tenofovir and metformin [140].

Thiazolidinediones

The thiazolidinediones increase insulin sensitivity, increase glucose metabolism in muscle and promote adipogenesis [141–143]. Two thiazolidinediones, rosiglitazone and pioglitazone, are approved for the management of diabetes mellitus and these two drugs do not pose a significant hepatotoxicity risk. Arioglu *et al*. observed that troglitazone therapy decreased haemoglobin A_{1c} levels, decreased triglyceride levels and also caused a small but statistically significant increase in body fat without a significant change in weight in non-HIV infected patients with congenital lipodystrophies [144]. There are relatively few studies looking at the effects of thiazolidinediones in HIV-infected patients with insulin resistance. Hadigan *et al*. showed that rosiglitazone improved insulin resistance, adiponectin level, lipoatrophy and decreased hyperinsulinaemia and free fatty acid levels, despite the ongoing use of ART, including a PI, in many of the patients [145]. In contrast, Carr *et al*. found that rosiglitazone did not improve lipoatrophy in HIV-infected adults on HAART. They found that rosiglitazone improved fasting insulin levels, plasma adiponectin but not plasma leptin, with a paradoxical increase in triglycerides, total cholesterol and LDL cholesterol levels [146]. To explain the discrepancies between these studies, we have to consider that the

patients included in Hadigan's study were insulin resistant, while in Carr's study this condition was not an inclusion criterion. Sutinen *et al*. also showed that rosiglitazone improves insulin resistance, decreases serum insulin concentrations and decreases fatty infiltration of the liver [147]. In HIV-infected patients, rosiglitazone not only decreases serum insulin but also decreases plasma PAI-1 and liver fat content suggesting that the fatty liver might contribute to plasma PAI-1 levels by affecting the synthesis or the clearance of PAI-1 [148]. In patients receiving thiazolidinediones, the FDA recommends monitoring liver function tests every 2 months for the first 12 months of treatment. Patients with aspartate transaminase and alanine transaminase more than 2.5× the upper limit of normal should not be started on thiazolidinediones [112].

There are few data on using oral sulfonylureas, meglitinides and related hypoglycaemic agents in HIV-1-infected patients with insulin resistance. Neither metformin nor any of the thiazolidinediones available on the market have been shown to reduce the risk of cardiovascular disease in non-HIV-infected patients with the metabolic syndrome, pre-diabetes, or diabetes. Thus, there is not sufficient evidence to recommend these drugs for anything other than their glucose-lowering action [149].

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