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Dysregulation of Glucose Metabolism in HIV Patients: Epidemiology, Mechanisms and Management

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Abstract

HIV-infected patients on highly active antiretroviral therapy (HAART) have increased prevalence of a number of chronic metabolic disorders of multifactorial but unclear etiology. These include disorders of lipid metabolism with or without lipodystrophy, insulin resistance, and an increased prevalence of impaired glucose tolerance, diabetes mellitus and cardiometabolic syndrome. While much attention has been focused on the lipid and cardiovascular disorders, few investigations have attempted to characterize the prevalence, incidence, etiology, mechanisms and management of glycemic disorders in HIV patients. In this review, we have focused specifically on a comprehensive assessment of dysglycemia in the context of HIV infection and HAART.

Keywords

HIV; HAART; diabetes mellitus; dysglycemia; lipodystrophy

Introduction

Since the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s, the mortality and morbidity of HIV/AIDS has decreased substantially [1]. In fact, HIV/AIDS has become chronic illness for many patients on HAART. With the increased survival of these patients, there have emerged a number of unexpected consequences of chronic illness, especially in the form of metabolic disease. The chief manifestations of the metabolic defects are related to lipid metabolism, with or without an associated fat “redistribution” or lipodystrophy. Another manifestation – perhaps a consequence of the high prevalence of insulin resistance resulting from the defects in fat metabolism – is an increased frequency of glucose intolerance or frank diabetes mellitus (DM). The mechanisms underlying dysglycemia, and the relationship of the glucose metabolic disorders to those of lipid metabolism and fat redistribution, and to ethnicity, diet and specific HAART agents, are multifaceted, complex and, to some degree, enigmatic. This review will describe the current state of the epidemiology, mechanisms, screening, diagnosis, and treatment of dysglycemia in HIV patients.

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Epidemiology

With the marked increase worldwide in the incidence and prevalence of different forms of diabetes, there has been great interest in determining the frequency and characteristics of diabetes, impaired glucose tolerance (IGT), metabolic syndrome, and cardiac events in HIV-infected patients. In addition to the effects of HAART, other etiologic factors are being investigated. These studies are difficult to perform, and it is especially difficult to separate the effects of HAART from those of HIV infection *per se* or of immune responses to the infection and treatment [1].

The epidemiology of DM has been studied to a limited extent in antiretroviral-naïve HIV patients. In a study which enrolled 419 racially diverse antiretroviral-naïve patients, the baseline prevalence of DM was 2.6% [2]. A similar group of patients had a higher baseline prevalence of diabetes mellitus when coinfecting with hepatitis C virus (HIV/HCV coinfecting group 5.9% vs. 3.3% HIV alone) [3]. In the Women's Interagency HIV Study, HIV-infected women reporting no recent HAART showed a DM incidence rate of 1.53/100 person-years; those reporting HAART containing a protease inhibitor (PI) had a DM incidence of 2.50/100 person-years, and those reporting non-PI-containing HAART had a DM incidence of 2.89/100 person-years. The incidence of DM among HIV-uninfected women was 1.96/100 person-years [4].

Most epidemiological data regarding DM and IGT come from studies of patients on HAART [1]. An early study of HIV patients with lipodystrophy reported a 35% prevalence of IGT and a 7% prevalence of DM, compared to 5% and 0.5% respectively for matched non-HIV controls [5]. The Multicenter AIDS Cohort Study showed a 14% incidence of DM in HIV-infected men exposed to HAART, which was four times higher than among HIV-seronegative controls [6]. Other groups have reported 13.2% incidence of insulin resistance (IR) in HIV-infected children [7], and 13% incidence of IR after 1 year of HAART [8]. The prospective D:A:D study, composed primarily of patients on HAART, showed that the incidence of DM increased with cumulative exposure to HAART (particularly stavudine, a thymidine analogue) with a relative risk of 1.11 after adjustment for other potential risk factors[9].

Several groups have studied the prevalence of metabolic syndrome (for which one possible criterion is impaired fasting glucose or IGT) in HIV-infected individuals. One group showed that the prevalence of metabolic syndrome was higher among HIV-infected patients on antiretroviral therapy (ART) than among non-HIV-infected healthy controls (15.8% vs. 3.2%) [10]. A Spanish study estimated the prevalence of metabolic syndrome to be 17% in HIV-infected patients receiving HAART [11]. In the Women's Interagency HIV Study, metabolic syndrome was more prevalent in HIV-seropositive than HIV-seronegative women (33% vs. 22%, respectively) [12]. Samaras et al, who also studied HIV-infected individuals on HAART, found the prevalence of metabolic syndrome to be 14% to 18% (using International Diabetes Federation or the National Cholesterol Education Program's Adult Treatment Protocol III criteria, respectively) [13]. However, Mondy et al, who studied a United States population, found that the prevalence of metabolic syndrome was similar between HIV-infected patients (most of them on HAART) and a matched HIV-negative group (25.5% vs. 26.5%, respectively), and that traditional risk factors (anthropomorphic measurements, dyslipidemia, age, and glucose control) played a more significant role in the development of metabolic syndrome than HIV-treatment associated factors [14]. Notably, a case control study suggested that another component of the metabolic syndrome – hypertension – may be directly linked to increased insulin resistance in persons with HIV [15].

Data from relatively small studies and heterogeneous HIV populations suggest that metabolic (including glycemic) abnormalities among HIV patients may be affected by ethnicity [16–19]. HbA1c levels in HIV patients are associated with older age and ethnicity [20]. Among a Hispanic population of HIV patients, the prevalence of metabolic syndrome was 35%, which is high compared to the 24–26% prevalence reported in United States adults living with HIV, but the same as for the general population of Puerto Rico [21]. To date, no studies have systematically addressed the effect of ethnicity and its interaction with glycemic parameters in HIV patients. To address this issue, we analyzed data collected in the Heart Positive study - a large, multiethnic study of hypertriglyceridemic but otherwise healthy patients with HIV infection on stable HAART, all of whom reported no history of diabetes and underwent oral glucose tolerance testing [22–23]. African-Americans had significantly greater impairment of glucose tolerance, as indicated by higher 2-hour glucose and HbA1c levels, than either Hispanics or Non-Hispanic Whites (NHWs). After adjusting for age, sex, HIV duration, HAART duration, smoking, obesity, fasting glucose, fasting insulin and lipid levels, African-Americans and Hispanics had significantly higher HbA1c and 2-hour glucose levels than NHWs [Misra, Balasubramanyam, et al, unpublished data].

These findings are important because there is also an increased risk of myocardial infarction (MI) in HIV infected patients, and both metabolic syndrome and dysglycemia are risk factors for MI. A higher MI incidence rate was seen in HIV-positive men exposed to PIs for 18 months or more [24]. In HIV-infected patients on HAART, the incidence of MI increased with longer exposure to therapy (adjusted relative rate per year of exposure, 1.26) [25]. An extensive search of hospital databases showed that the rate of acute MI was higher in an HIV-infected cohort over non-HIV patients, with a relative risk of 1.75, even after adjusting for age, gender, race, hypertension, DM, and dyslipidemia [26]. The D:A:D group also studied the effects of 13 anti-HIV drugs on the development of MI; of these, only indinavir, lopinavir-ritonavir, didanosine, and abacavir were associated with a significantly increased risk of MI [27].

Mechanisms

The mechanisms of glycemic dysregulation and associated defects in insulin action and secretion in HIV-infected patients are numerous and complex, with new information continually surfacing. The literature to date has focused primarily on defects in lipid metabolism and inflammation, indicating that lipotoxicity and inflammation lead to insulin resistance – one of the consequences of insulin resistance could be dysglycemia [28]. For the purpose of this review, we shall organize the extant data into three classes: studies that exclude the effects of HAART, studies done in the presence of HAART agents while elucidating non-antiretroviral mechanisms, and studies done in the presence of HAART agents that elucidate mechanisms directly related to HAART.

Studies that exclude the effects of HAART

As the pathophysiology of insulin resistance (IR) in HIV involves many factors operating simultaneously, some laboratories have performed *in vitro* studies to isolate the effects of the HIV virus in T-cells from the other variables. In a recent study of the proteomic composition of HIV-1 infected CD4 cells, Chan et al found an increase in the concentration of fatty acid synthase (FASN) after HIV-1 infection [29]. Rasheed et al also performed proteomic analysis of a human T-cell line and reported upregulation of 18 HIV-modulated proteins and their interacting pathways, which would be expected to promote fatty acid synthesis and dysregulate multiple pathways of lipid metabolism. They concluded that HIV replication in human T-cells *per se*, independently of the effects of antiviral drugs or other factors, can affect lipid metabolism [30]. In support of this hypothesis, recent human studies have shown that untreated HIV-infected individuals have higher levels of circulating FASN

than those on antiretroviral therapy, and that HCV co-infection can also elevate FASN levels. Serum levels of insulin and inflammatory cytokines were correlated positively with FASN levels [31], indicating that the disruption of lipid metabolism within HIV-infected immune cells could contribute to both systemic lipid metabolic defects and an inflammatory form of whole body IR, and thereby to dysglycemia.

Furthermore, evidence of HIV-mediated inflammatory IR was noted in a number of insulin-regulated pathways prior to the HAART era. The Grunfeld laboratory found that interferon- α levels were higher in patients with AIDS compared to those with uncomplicated HIV infection and matched healthy controls [32]. Concomitantly, AIDS patients had increased triglyceride levels, but not increased TNF levels when compared to HIV patients without AIDS [33]. A more recent cross-sectional study found that TNF- α levels were higher in HAART-naïve HIV patients than their HAART-treated counterparts. Levels of the insulin-sensitizing hormone adiponectin were decreased in both groups compared to healthy controls, and were correlated inversely with IR as measured by the homeostatic model assessment of insulin resistance (HOMA-IR) [34].

Studies in presence of HAART while elucidating non-antiretroviral mechanisms

Insulin sensitivity is affected through multiple other mechanisms including lipodystrophy [35], viral effects [36–38], HCV co-infection [19], growth hormone deficiency [39], low CD4 count [40], and hepatic steatosis [41]. Most studies investigating these mechanisms have been performed on antiretroviral-treated patients. Multiple studies suggest that traditional risk factors such as increased age, positive family history, increased BMI, and smoking are more important than HAART in the development of IR [42–43].

Lipodystrophy, reflecting profound defects in lipid turnover kinetics [35, 44] clearly induces severe insulin resistance and the tendency to hyperglycemia. Hyperinsulinemic-euglycemic clamp studies have demonstrated that compared to non-lipodystrophic patients, HIV patients with lipodystrophy have decreased insulin-stimulated glucose disposal [45–46], increased intramyocellular lipid [45], and impaired skeletal muscle glucose uptake [46]. Lipodystrophic patients also have increased fasting plasma levels of free fatty acids and insulin [16], and a higher percentage of hepatic fat (associated with increased serum insulin levels) [47]. Clamp studies also suggest that insulin-resistant (but nondiabetic) HIV lipodystrophic individuals may have an increased insulin secretion rate due to both endogenous nonglucose secretagogues (including free fatty acids) and absent negative feedback of insulin on β -cells [48].

During any infectious process, the release of cytokines may affect glucose metabolism. In HIV infection, there is an increased release of TNF- α , IL-6 and IL-8 by both infected T cells and adipose tissues – these cytokines can induce inflammatory insulin resistance and are associated with increased levels of HOMA-IR [36]. Activities of the HIV-1 accessory proteins Vpr and Tat have potential roles in initiating or aggravating insulin resistance. Vpr has been shown to inhibit PPAR- γ -mediated transcriptional co-activation *in vitro* (which might induce an inflammatory or lipotoxic form of insulin resistance in adipose tissues and liver) [37] and to decrease specific transcriptional effects of insulin such as inhibition of phosphoenolpyruvate carboxykinase (PEPCK) expression [38], which would promote gluconeogenesis and fasting hyperglycemia. Tat is known to activate NF κ B, which would induce TNF- α production, block FFA uptake by adipocytes and suppress insulin receptor signaling – all of which could potentially decrease glucose disposal by blunting Glut4 translocation, and promote insulin resistance by increasing serine phosphorylation of insulin receptor substrate-1 (IRS-1) [38, 49]. In HIV patients initiating HAART, levels of TNF- α after 48 weeks of treatment were associated with incident DM [49].

HIV co-infection with HCV is associated with a higher prevalence of hyperglycemia. This correlates with the fact that HIV/HCV co-infected patients on HAART demonstrate greater insulin resistance, higher levels of activated platelets, and more endothelial dysfunction than HIV patients without co-infection [50]. When patients with HIV/HCV co-infection are placed on PI-based HAART, they have significantly increased risk of new-onset hyperglycemia [19, 51].

Lipodystrophic HIV patients also have accelerated fatty acid flux to the liver with blunted fat oxidation, factors that predispose them to accelerated reesterification in the liver and the development of hepatic steatosis [28, 35, 44, 52]. Sutinen et al suggest that insulin resistance in HIV patients is related more closely to fat accumulation in the liver than to intra-abdominal fat [47]. Consistent with this sequence of events leading to insulin resistance, Hadigan et al have shown that blocking lipolysis acutely with acipimox improved insulin sensitivity in this group of patients [53].

The prevalence of hepatic steatosis in HIV-infected patients is high, especially in patients with chronic HCV or on nucleoside reverse transcriptase inhibitors (NRTIs) [41]. Rates of steatosis in HIV/HCV coinfecting persons range from 40%–69% [54–55], while in HIV-infected patients without viral hepatitis coinfection, the rate is about 30% (although most were diagnosed with ultrasound rather than the gold standard of liver biopsy) [56]. The latter is at the upper end of the prevalence range for the general US population [57]. NRTIs may also induce hepatic steatosis via inhibition of mitochondrial DNA replication; hence use of these agents may exacerbate the tendency towards triglyceride accumulation in the liver [58]. Recent data suggest that fatty liver may cause insulin resistance via multiple mechanisms, many involving hepatic adipokines which are involved in the pathogenesis of type 2 diabetes [59].

Partial or complete growth hormone (GH) deficiency is common among HIV patients, and is associated with both HIV lipodystrophy and insulin resistance [39]. Schwarz et al treated HIV lipodystrophic men with low-dose (3 mg/day) growth hormone for six months, and found that insulin sensitivity, measured by hyperinsulinemic-euglycemic clamp, was initially reduced, but returned to baseline after six months of therapy; this was associated with a significant decrease in hepatic lipogenesis and serum triglyceride levels [60]. D'Amico et al demonstrated that the mechanism underlying this effect is related to the ability of *physiologic GH replacement* to decrease whole body lipolytic rates [61]. It is critical to understand that the dose of GH must be physiologic, in the setting of some degree of GH deficiency, to obtain a therapeutically beneficial effect. Most studies, generally using supraphysiologic doses of GH, have shown that GH treatment improves visceral adiposity but worsens glycemic control [62–63]. To illustrate this principle, tesamorelin (growth hormone releasing hormone, or GHRH) administration – which normalizes but does not elevate circulating GH and IGF-I levels – is associated with reduction in truncal and visceral adiposity without change in lipids or glucose tolerance [64]. Recently, another study using hyperinsulinemic-euglycemic clamps reported that 3-month treatment with IGF-1/IGFBP3 improved whole body glucose uptake and glucose tolerance (while increasing hepatic gluconeogenesis) and improved fasting triglycerides, though visceral adiposity remained the same [65].

Another risk factor for developing lipodystrophy and dysglycemia may be a low CD4 count (<200 cells/ μ L) [40]. Data from the longitudinal HIV Outpatient Study suggest that increased duration of HIV infection, high viral load and low CD4 nadir prior to initiation of HAART, as well as prolonged survival and duration, may be the most significant risks to developing lipodystrophy [66]. Studies exploring the associations of CD4 cell count with abnormal glucose levels in HIV patients show inconsistent results. Low CD4 cell count was

associated with IGT and DM in patients co-infected with HIV, hepatitis C and hepatitis B virus [67]. El-Sadr et al reported an inverse relationship between CD4 counts and insulin resistance in HIV patients, but no relationship between CD4 counts and fasting glucose concentrations [2]. Our group recently showed that among multiethnic, hypertriglyceridemic HIV patients on HAART without a history of diabetes, an interaction was observed between CD4 counts and ethnicity that affected glycemic levels. Specifically, African Americans with CD4 <300/cc and Hispanics with CD4 ≥ 300/cc had the most impaired glucose response following oral challenge, when compared to non-Hispanic Whites [Misra, Balasubramanyam, et al, unpublished data].

Studies in the presence of HAART elucidating mechanisms that are directly related to HAART

Clinically measurable alterations in body fat depots are seen in association with the use of both protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) [68]. In vitro cellular studies suggest that various PIs may induce lipolysis or block adipogenesis via decreased expression of the transcription factor SREB1c [69]⁶⁹, ultimately leading to consequences such as decreased expression of critical regulators of lipid metabolism such as lipoprotein lipase and fatty acid synthase [70]. NRTIs may also promote fat cell apoptosis [71]. However, the clinical relevance of these *in vitro* data is limited because they employed high concentrations of these drugs, generally exceeding those used in clinical practice [68].

Significant hormonal and cytokine alterations that could affect glucose metabolism occur in HIV patients on HAART. Most studies have focused on the adipokines leptin and adiponectin, though recent studies are uncovering potential roles for many other endocrine and paracrine factors [72].

Hypoleptinemia, along with hypertriglyceridemia and hyperinsulinemia, is observed in HIV patients with lipoatrophy and six or more months of HAART treatment [73]. Leptin's physiologic effects primarily involve coordinating the body's physiologic response to starvation. During prolonged fasting its levels decline disproportionately to the fat loss and result in apparently adaptive changes in a variety of diverse hormonal axes, including the thyroid, reproductive and endocrine-immune axes. Administration of leptin in this state partially or wholly reverses these hormonal changes associated with starvation [74]. Leptin also participates in the regulation of insulin sensitivity. A small randomized, controlled trial by Lee et al showed that two months of physiologic leptin replacement (with r-met-HuLeptin) in hypoleptinemic HIV patients on HAART improved fasting insulin levels and HOMA-IR, along with reductions in body weight and fat mass, with no adverse effects on treatment [75]. A small, non-randomized study by Mulligan et al in a similar group of patients showed that 6 months of escalating doses of physiologic leptin replacement improved the ability of insulin to suppress endogenous glucose production while decreasing both glycogenolysis and gluconeogenesis [76].

Adiponectin, in addition to its significant anti-inflammatory and anti-atherosclerotic effects, also enhances insulin-mediated suppression of gluconeogenesis and glucose release, and increases liver FFA oxidation and muscle glucose uptake [77–78]. Its transcription is mediated by the SREBP1/PPAR γ pathway [79]. Adiponectin levels are low in HIV-infected individuals with lipodystrophy and hypertriglyceridemia [80–81]. Hypoadiponectinemia is seen in HIV infected patients even prior to the initiation of HAART, though it worsens after initiation [34, 82]. Addy et al demonstrated that serum adiponectin levels correlated negatively with insulin resistance as measured by HOMA-IR among HIV patients on HAART, though this relationship became nonsignificant after adjusting for NRTI use [83]. A study of HIV-infected children with fat redistribution showed that decreased levels of

adiponectin were associated with insulin resistance (as assessed by the insulin/glucose ratio), even after controlling for HIV treatment [84].

The pathogenesis of insulin resistance in HIV can also be classified with regard to the class of antiretroviral treatment. Most effects are related to the use of NRTIs and PIs [1, 85].

NRTIs include thymidine analogues (e.g., stavudine, zidovudine) which, in addition to inhibiting HIV reverse transcriptase, also inhibit DNA polymerase- γ , active in mitochondrial replication [86]. This leads to mitochondrial dysfunction; in the muscle and liver, this is linked to lipotoxic insulin resistance from the inability of these tissues to oxidize fat [87]. NRTIs also promote lipotrophy in adipose tissue [88].

In an animal model, Murata et al showed that the protease inhibitor indinavir induced insulin resistance by selectively inhibiting the function of the Glut4 transporter, which is responsible for insulin-stimulated glucose uptake into muscle and adipose tissue [89–90]. The effect was then demonstrated in human subjects, via use of hyperinsulinemic-euglycemic clamp [91–92]. It has also been suggested, based on a 60% homology of the HIV-1 protease with the cytoplasmic retinoic-binding protein type-1 (CRABP-1) and the low-density lipoprotein receptor-like protein (LRP), that PIs could interfere with normal triglyceride metabolism, thus inducing lipotoxic insulin resistance in tissues [93]. There is currently no experimental evidence to support this mechanism *in vivo*. There is better evidence for specific effects of PIs on glucose transporters. By binding and inhibiting Glut4, the first-generation PIs indinavir and zalcitabine acutely impair insulin-regulated glucose uptake in muscle [94] and also inhibit glucose-stimulated insulin secretion in cultured pancreatic beta cells and in mice [95]. However, newer PIs such as atazanavir and tipranavir show little to no acute effect on insulin sensitivity [96–97]. Chronically, longer exposure to PIs may disturb insulin signaling and indirectly lead to impaired glucose uptake via mechanisms dependent on IRS-1, Akt, and/or SOCS-1 [85].

There are no consistent data showing the development of IR following treatment with NNRTIs, fusion inhibitors, CCR5 antagonists or integrase inhibitors [1].

Screening and Diagnosis

The Infectious Diseases Society of America (IDSA) recommends the assessment of fasting glucose and fasting lipids prior to and within 4–6 weeks after starting HAART [98]. Additionally, the International Association of AIDS-USA recommends repeating these measurements at the time of switching therapy, 3 to 6 months after switching therapy, and at least annually thereafter while on stable therapy [99]. Patients with pre-existing DM should have hemoglobin A1C (HbA1C) monitored at least every 6 months with a goal of <7%, following American Diabetes Association (ADA) Guidelines [98, 100].

The diagnosis of DM should be made in accordance with ADA Guidelines [100–101]. HbA1c should not be used for diagnostic purposes in HIV patients as it may underestimate glycemia, especially among patients on NRTIs; this may be a result of NRTI-induced macrocytosis [102]. Additionally, the oral glucose tolerance test may be used to detect IGT or DM in selected HIV patients who have a normal fasting glucose [67].

While it is still important to screen for DM as a risk factor for coronary heart disease (CHD), DM might not be a CHD “risk equivalent” among HIV patients as it is in the general population. The D:A:D study showed a 7.6% incidence of MI in HIV patients with preexisting DM and no preexisting CHD, and a 31.1% incidence of MI in patients with preexisting CHD but no preexisting DM [103].

Management

DM and IGT should be managed according to current ADA guidelines [100], which also apply to non-HIV populations. To date, there are no large clinical trials that deal specifically with glucose management in a HIV population. However, several studies on metabolic abnormalities in HIV do shed some light in the area of HIV-specific glycemic management.

The substitution of thymidine analogues (e.g., stavudine and zidovudine) with other antiretroviral treatments (ARTs) has been successful as a therapeutic approach to decreasing the severity and clinically observed frequency of lipodystrophy [104–106]. As this class of drugs as well as PIs has been associated with increased insulin resistance, it is suggested that similar substitutions could be instituted to improve insulin sensitivity and dysglycemia. While this is plausible, there are currently no data suggesting that switching ARTs is beneficial to HIV patients with hyperglycemia [98].

The IDSA recommends lifestyle modifications (exercise, diet, and weight loss) as the first step in managing hyperglycemia [98]. Earlier studies on lifestyle modifications showed equivocal results, with only some showing improvements in insulin sensitivity [107–110]; in these studies most patients were receiving thymidine analogue NRTI therapy. One of these studies was repeated from 2003–2007, with fewer subjects taking thymidine analogues. In that study, diet and exercise-induced weight loss led to decrease in visceral and subcutaneous fat and improved insulin sensitivity [111]. The Heart Positive study recently showed a small but significant decrease in HbA1c in the arm randomized to receive only intensive diet and supervised exercise among hypertriglyceridemic but euglycemic HIV patients on HAART [23].

When oral medications are necessary to treat diabetes, metformin and thiazolidinediones (TZDs) have insulin-sensitizing properties that are beneficial in patients with insulin resistance and dysglycemia. The use of these medications must be balanced with the potential for adverse reactions.

Among HIV patients on HAART, metformin treatment reduced serum fasting insulin levels [112] and insulin area under the curve on oral glucose tolerance testing [113]. There is a very small risk of lactic acidosis associated with the use of metformin in the general population; however, since the incidence of lactic acidosis is higher in HIV patients due to the use of NRTIs (especially stavudine and didanosine) [114–115], plasma lactate levels should be measured if the patient develops symptoms of acidemia while on metformin. If the patient has a serum creatinine or venous lactate concentration more than twice the upper normal limit, metformin should not be prescribed [99].

Rosiglitazone, a TZD, improved insulin sensitivity as measured by hyperinsulinemic-euglycemic clamp [116], decreased serum insulin levels [117–118], increased adiponectin levels [116, 118] and reduced free fatty acid levels [116] in HIV patients. However, rosiglitazone was also associated with detrimental effects on serum total cholesterol, triglycerides, HDL-C, and LDL-C [119]. Since a meta-analysis by Nissen et al raised concern about increased risk of MI and cardiovascular death in diabetic patients treated with rosiglitazone [120], the US FDA has restricted its use [121]. Pioglitazone may be a useful alternative, as it generally elevates serum HDL-C levels with a neutral impact on other lipid markers [119], and may decrease the risk of MI in diabetic patients [122]. However, there are only two large published studies of the effects of pioglitazone in HIV patients [123]. In one study pioglitazone treatment demonstrated no benefits on fasting glucose or insulin levels [124]. In another study, pioglitazone reduced insulin resistance and increased serum adiponectin levels [125]. It appears that pioglitazone should be used with some caution in

hyperglycemic HIV patients, given the well known TZD adverse effect of fluid retention. TZDs should be avoided in HIV patients with NYHA Class III and IV heart failure [126].

There are currently no large trials exploring the use of sulfonylureas, meglitinides, GLP-1 agonists, DPP-IV inhibitors, or α -glucosidase inhibitors on HIV patients taking HAART [1]. A single case report shows that treatment with a combination of exenatide, metformin, and repaglinide improved insulin sensitivity and led to significant weight loss in a diabetic HIV patient on HAART [127]. GLP-1 agonists (like exenatide) control diabetes through several mechanisms, including glucose-dependent stimulation of insulin secretion, suppression of inappropriate glucagon secretion, slowing of gastric emptying, appetite suppression, and resulting weight loss [128]. A large trial would be useful in the assessment of diabetes management via GLP-1 agonists in this population. Nevertheless, if glycemic management cannot be optimized with oral agents or GLP-1 agonists, insulin therapy should be initiated [129].

Conclusions

HIV infection and HAART presents challenges to the diagnosis and management of dysglycemia. Most epidemiological data suggest that dysglycemia is associated with HAART use. However, the mechanisms of dysglycemia appear to be both HAART-dependent and HAART-independent. Much of the literature focuses on the role of underlying lipid metabolic defects and inflammation, showing that lipotoxicity and inflammatory disorders lead to insulin resistance and eventually dysglycemia [28]. However, there is a paucity of information regarding the glucose metabolic defects in this population, and more studies would be helpful. At this point, DM or IGT management is best guided by ADA recommendations [100], with a few modifications as described above. Switching antiretrovirals may help in theory, but we do not as yet have sufficient evidence to support this approach. Physiologic leptin replacement may be useful to treat dysglycemia, but this agent is still investigational. A comparison of current diabetic therapies via randomized controlled trials would be helpful in designing more specific treatment strategies for dysglycemia in the HIV population.

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