Prevalence and Pathogenesis of Diabetes Mellitus in HIV-1 Infection Treated With Combined Antiretroviral Therapy

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Abstract: Combined antiretroviral therapy (cART) in the treatment of HIV-1 infection confers significant survival benefit and, by immunoreconstitution, has altered the natural history of this life-threatening disease. Metabolic complications of cART include hyperlipidemia, insulin resistance, and lipodystrophy, with resultant increases in risk for type 2 diabetes and cardiovascular disease. These diseases will present new challenges in the management of HIV infection. This article reviews the prevalence of diabetes mellitus and its antecedents in HIV-infected patients treated with cART. It also reviews the current understanding of mechanisms involved in the pathogenesis of type 2 diabetes in cART considering insulin resistance and insulin secretion, both requisites for the development of type 2 diabetes mellitus.

Key Words: adipokines, diabetes mellitus, fat, glucose, HIV, insulin resistance, insulin secretion, inflammation, lipoatrophy, lipodystrophy, metabolism, obesity

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INTRODUCTION

The most recent report from the Joint United Nations Program on HIV/AIDS reported that HIV infection affected an estimated 39.5 million people worldwide.[1] This epidemic threatens to intersect with another, that of obesity-related type 2 diabetes mellitus. Estimates from the International Diabetes Federation show 246 million adults worldwide have diabetes mellitus,[2] mostly attributable to the concurrent obesity epidemic. Between 8% and 11% of European and North American adults currently have type 2 diabetes[2] with a 50% increase in prevalence extrapolated over the next 2 decades.[3]

The treatment of HIV-1 infection with combined antiretroviral therapy (cART) has significantly altered the natural history of this life-threatening condition. Immunocompetence has come at significant metabolic cost, however, because cART is associated with a range of metabolic complications, including insulin resistance, glucose intolerance, type 2 diabetes mellitus, dyslipidemia, and changes in body fat compartmentalization (lipodystrophy).[4] cART-associated lipodystrophy in HIV infection is now the commonest form of lipodystrophy. These metabolic complications have rapidly translated into increased risk for cardiovascular disease.[4] Currently available drugs that in combination comprise most cART regimens fall into 3 drug classes: protease inhibitors (atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, and tipranavir), nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, emtricitabine, lamivudine, tenofovir, stavudine, and zidovudine), and nonnucleoside reverse transcriptase inhibitors (NNRTIs) (efaviranz, etravirine, and nevirapine) distinguished by class-specific effects on glucose metabolism and distinct drug-specific effects. In addition, 2 newer classes of cART have become available in a number of countries: (1) entry inhibitors for which there are 2 subclasses: fusion inhibitors (enfuvirtide) and CCR5 inhibitors (maraviroc) and (2) integrase inihibtors (raltegravir). At the time of writing, there are no published data of metabolic effects of these 2 newer drug classes.

This review summarizes the current knowledge regarding prevalence and pathogenesis of disorders of glucose metabolism in HIV infection and HIV-associated lipodystrophy, in addition to its treatment.

METHODS

Literature review was performed using the search criteria of type 2 diabetes and HIV, metabolic syndrome and HIV, and insulin resistance and HIV, on the PubMed Database (www.ncbi.nlm.nih.gov/sites/entrez?cmd=search*db=pubmed), examining all journal articles published in English. Studies with control populations or longitudinal data were included for prevalence and incidence data. In vitro and in vivo studies using humans and cell models were considered for the mechanisms in the pathogenesis of disordered glucose metabolism.

Prevalence of Glucose Disorders in HIV Infection and Treated HIV Infection

The currently accepted international criteria for the diagnosis of diabetes mellitus and disorders of glucose metabolism are given in Table 1.[5] Diabetes mellitus and disorders of glucose tolerance were relatively uncommon in patients with

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TABLE 1. Criteria for Diagnosis of Diabetes Mellitus and Disorders of Glucose Metabolism

Method	Diagnostic Category	Fasting Glucose	2-Hour Glucose
Fasting glucose*	Normal	<5.6 mmol/L <100 mg/dL	—
	Impaired fasting glucose	5.6–6.9 mmol/L 100–125 mg/dL	—
	Diabetes	≥7.0 mmol/L ≥126 mg/dL	—
75 g oral glucose tolerance test	Normal	—	<7.8 mmol/L <140 mg/dL
	Impaired glucose tolerance	—	7.8–11.1 mmol/L 140–199 mg/dL
	Diabetes	—	>11.1 mmol/L >200 mg/dL

Adapted from the American Diabetes Association, 2008.[5]
*Fasting refers to no caloric intake for the preceding 8 hours.

HIV infection before the advent of cART. In a study of 419 treatment-naive HIV-infected subjects, 2.6% had diabetes.[6] A further study of 1400 HIV-infected patients attending a hospital clinic found that the prevalence of hyperglycemia (defined as random glucose >11.0 mmol/L) was 2%.[7] Dissecting out whether HIV infection per se increases risk for diabetes is challenging due to difficulties in matching for potential confounders to derive normal population data. A study that examined HIV-negative (n = 710) and untreated HIV-infected patients (n = 157) found that fasting glucose was similar between treatment-naive HIV-infected patients and HIV-negative patients.[8] Fasting glucose was significantly lower in untreated HIV-infected patients compared with HIV-infected cART recipients.[8] Of note, study subjects were overweight [by body mass index (BMI)] and in this regard, the study cohort is representative of the parallel community problem of obesity and its diabetes-promoting effects. A further important aspect of this study was matching for abdominal obesity (by waist to hip ratio).[8] A 7% prevalence of diabetes mellitus was found in HIV-infected treatment-naive subjects compared with 5% in HIV-negative subjects.[8] Using the prevalence rates from the HIV-negative population, HIV infection was associated with a 2.2-fold increase in the relative risk of diabetes.[8]

The earliest reported cases of treatment-related diabetes mellitus in HIV infection were associated with pentamidine use in the setting of treating Pneumocystis carinii infection, in the mid-1990s.[9–11] Pentamidine is a pancreatic beta cell toxin therefore, not unexpectedly, these cases were characterized by insulin deficiency, ketoacidosis, and the requirement for insulin therapy.[9]

Since cART has been the treatment standard, the restoration of immune function has markedly diminished progression to AIDS and its consequences. Within the current treatment paradigm, early cases of diabetes mellitus were linked to protease inhibitor use, with cases of hyperglycemia appearing within 7 months of drug commencement.[12–14] Contemporaneous with these reports was the rapid identification of numerous other metabolic complications associated with cART, including hyperlipidaemia and lipodystrophy, which will remain confounders when attempting to dissect the unique contributors to changes in glucose metabolism. Additional confounders include the following: societal changes, such as the obesity epidemic and increasing sedentariness; increases in HIV infection rates in ethnic groups with genetic susceptibility to type 2 diabetes (such as the US Hispanic and South East Asian population); and cART composition, as evidence of class-specific and drug-specific adverse effects alters drug regimens over time. cART is not usually static for any patient; across the patient population, there are wide variations in drugs used within cART. All these factors become confounders that must temper the interpretation of data viewed on the prevalence of diabetes mellitus in HIV-infected patients.

Evidence for increased prevalence of disorders of glucose metabolism was initially derived from patient cohorts with cART-associated lipodystrophy. One such study reported the prevalence of diabetes mellitus at 2% in protease inhibitor recipients with lipodystrophy,[15] with the rate rising to 7% after 14 months of further observation.[16] This study reported the overall prevalence of all disorders of glucose metabolism (diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance) at 25%.[16] Other early studies also report higher rates of disorders of glucose metabolism in cART-associated lipodystrophy: diabetes mellitus in 7% compared with 0.5% of otherwise healthy controls; and impaired glucose tolerance in 35% of HIV-infected patients as compared with 5% of controls.[17] These figures require consideration of specific drugs used in cART at that time, such as the protease inhibitors, indinavir and ritonavir, which potently increase insulin resistance. Recognition of these drug-specific effects has led to less frequent inclusion of these drugs as the major components in current cART regimens.

Prospective reports show that diabetes mellitus developed in 10% of HIV-infected cART recipients during a 4-year follow-up period compared with 3% in HIV-seronegative men.[8] After adjusting for age and BMI, this difference represented a greater than 4-fold increase in relative risk of developing diabetes mellitus.[8] The effect of initiation of cART on diabetes mellitus incidence in treatment-naive patients has been reported recently by the Data Collection on Adverse Events of Anti-HIV Drugs.[18] Incident cases of diabetes mellitus were identified by fasting glucose with an incidence of 5.7 per 1000 person-years follow-up.[18] The strongest predictor was exposure to stavudine (relative risk of 1.19).[18] These reports may however under represent all cases of diabetes mellitus because fasting glucose alone was used for diagnosis. Studies have shown fasting glucose may be relatively insensitive for detecting all cases of diabetes mellitus: 72% of HIV-infected men meeting criteria for diabetes mellitus (by the 75 g oral glucose tolerance test) had nondiabetic fasting glucose levels.[15,16] These data indicate the utility of the 75 g oral glucose tolerance test in early detection of diabetes mellitus for early treatment instigation and diabetes complication prevention, at least in men. The oral glucose tolerance test is a necessary (perhaps integral) tool in studies aiming to capture all cases of diabetes mellitus in this patient population.

The impact of cART-associated lipodystrophy on diabetes prevalence also requires consideration. The presence of

lipodystrophy is associated with progression to insulin secretory failure: more than 14 months, the prevalence of diabetes mellitus increased from 2% to 14% in a cohort with a high prevalence of lipodystrophy.[16] In the large cohort study, the Lipodystrophy Case Definition Study [n = 1081, HIV-infected cART recipients (half with lipodystrophy)], the prevalence of diabetes was 7% in those with lipodystrophy and 3% in those without.[19] With early regimens, body fat partitioning changes appeared soon after cART initiation and were progressive.[15,16,20] Factors associated with lipodystrophy include the CD4 count at cART initiation and cART duration.[16] Use of the NRTI, stavudine, is implicated as the major contributor to peripheral lipoatrophy[20–23]; recognition of this has again altered drug composition within cART with the overall aim of avoiding this sequelae. Consequently, the changing prevalence of lipodystrophy may alter subsequent rates of hyperglycemia development.

The prevalence of diabetes in HIV infection can also be expected to vary from one population to another, modified by factors such as genetic susceptibility, obesity prevalence rates, and sedentariness. One study found family history of diabetes was a risk for developing diabetes on protease inhibitors.[24] This case–control study of 49 HIV-infected subjects with diabetes found an odds ratio (OR) of 3.3 for family history, in age, gender, and ethnicity-matched controls.[24] However, several other studies have found no effect of family history.[16,25] There may be ethnicity-associated genetic susceptibility to the development of diabetes. A prospective study of HIV-infected patients in the Los Angeles area found a prevalence of diabetes mellitus of 12% amongst all protease inhibitor recipients at baseline.[26] After 3 years, the incidence of new cases of diabetes was 7% and all were African Americans.[26]

A further consideration is the impact of obesity on diabetes prevalence in HIV infection. A large US study (n = 1669) reported prevalence rates of overweight and obesity similar to that of the general population: 31% and 14% in their HIV-infected patients.[27] As obesity has a promoting effect on insulin resistance and progression of the beta cell secretory defect to frank hyperglycemia and diabetes mellitus, it can be expected that HIV-infected patients with coexisting obesity may have a higher prevalence of diabetes than that reported before the obesity epidemic.

Only a few studies have specifically examined prevalence of glucose disorders specifically in HIV-infected women. One study found a 12% prevalence of diabetes mellitus in HIV-infected female cART recipients, compared with 13% in HIV-negative women, using the 75 g oral glucose tolerance test.[28] Important confounders in this study were differences in BMI and waist to hip ratios between the 2 groups: 86% of HIV-negative women were overweight or obese compared with only 67% in HIV-infected subjects, and abdominal obesity (by waist to hip ratio) was significantly less in the HIV-infected groups.[28]

A cohort from the Women's Interagency HIV Study (n = 1785) reported diabetes mellitus incidence at 2.8% in protease inhibitor recipients vs 1.2% in those who had never received cART and 1.4% in the HIV-negative controls.[29] In this study, the HIV-negative women had higher rates of overweight/obesity (33% vs 23% in the HIV-infected women) but only half the incidence of diabetes,[29] indicative that diabetes mellitus develops in female cART recipients at lower adiposity levels. However, a later study from the Women's Interagency HIV Study found no difference between HIV-infected women and controls.[30] Significant differences were evident between HIV infected and controls for age, BMI, and hip circumference; nevertheless, exposure to NRTI over 3 years increased the relative risk of incident diabetes mellitus 2.6-fold.[30]

Coexistent hepatitis C virus (HCV) infection with HIV infection seems to increase diabetes risk in some but not in all studies. HCV infection is associated with increased insulin resistance.[31] A retrospective study of 1230 HIV-infected cART recipients (50% coinfected with HCV) offers valuable insights. Diabetes mellitus prevalence was doubled in those coinfected with HCV, 5.9% compared with 3.3% in subjects with HIV infection alone.[32] Incident cases of diabetes mellitus were more common in those with HCV coinfection: 5.8% vs 2.8%; the incidence of hyperglycemia per 100 person-years was 4.9 in those with HCV coinfection (95% confidence interval: 3.4 to 7.1) vs 2.3 in those with treated HIV infection alone (95% confidence interval: 1.4 to 3.7).[32] In contrast, the Swiss HIV Cohort Study of 6513 subjects did not find HCV coinfection a risk factor incident diabetes mellitus.[33]

The majority of published studies on diabetes mellitus in HIV infection arise from westernized nations where cART is generally available. The Swiss HIV Cohort Study found black or Asian ethnicity increased risk for diabetes mellitus 2.2-fold and 4.9-fold, respectively.[33] Sparse data exist in Africa or Asia where HIV infection is a major problem, but cART may not be readily available or may be based around older, less expensive drugs that appear less frequently in western cART regimens.

Further, the triple impact of ethnic susceptibility to diabetes (such as South East or Southern Asians) increasing obesity prevalence and cART (particularly older regimens) is unknown. This is a significant issue in resource-poor settings with high rates of HIV infection, where diabetes independently causes substantial morbidity, disability, and premature loss of life.

In contrast, in settings where access to effective HIV infection treatment is limited or late (for example South Africa), the prevalence of diabetes mellitus may decrease due to the devastating effect on number of adults surviving to middle age.[34] Statistical modelling of increased cART availability within South Africa has predicted diabetes incidence to increase from 1% to 11%.[35]

Metabolic Syndrome

Metabolic Syndrome refers to the constellation of the phenotypes of abdominal obesity, hyperlipidemia, elevated fasting glucose, and hypertension which are closely associated with risk for diabetes mellitus and cardiovascular disease. The debate surrounding the predictive value of metabolic syndrome pivots around whether, as a composite, it predicts a multiplicative or additive increase in risk for these conditions. Diagnostic criteria have been promulgated by preeminent scientific bodies (American Heart Association[36] and the International Diabetes Federation[37] (Table 2) and scientific scrutiny and evaluation continues.

The impact of metabolic syndrome on accelerating the risk of diabetes mellitus in treated HIV infection requires

discussion. From the outset, it was recognized that HIV-associated lipodystrophy was characterized by metabolic syndrome phenotypes[15] before international dissemination of diagnostic criteria for metabolic syndrome. Several studies have now examined criteria-defined metabolic syndrome in treated HIV-infected patients. The first study reported a prevalence rate of 17% using National Cholesterol Education Program–ATP-III criteria in 710 patients in Spain, with risk factors including BMI and past or present exposure to protease inhibitors.[38] The strongest risk was current protease inhibitor use, with OR of 4.2; after adjustment for age and BMI, the presence of metabolic syndrome was related to use of the NRTI, stavudine (OR: 1.74), and the protease inhibitor combination of lopinavir/ritonavir (OR: 2.46).[38] Lipodystrophy rates were similar in those with and without metabolic syndrome (60%–66%); overall, 12% had fasting glucose >6.1 mmol/L, but no data for diabetes were presented.[38] A further study from the US Nutrition in Healthy Living Study (n = 477) reported metabolic syndrome prevalence at 24%, associated with higher viral load, higher BMI, higher trunk to limb fat ratio, the use of lopinavir/ritonavir, and the NRTI didanosine.[39] This study also reported an incidence rate of metabolic syndrome of 1.2 per 100 person-months, based on 88 new cases of metabolic syndrome developing over 7026 person-months of follow-up and was predicted by increasing viral load, increasing weight, and use of lopinavir–ritonavir or didanosine.[39] Important considerations within this study cohort were the high rates of poverty and obesity (over 50%).[39] Data on diabetes incidence within this cohort are not yet available but will eventually yield important data on the intersection between treated HIV infection and the adverse sociodemographic factors of obesity and poverty.

The HIV Lipodystrophy Case Definition Study, an international collaboration from 32 centers has provided data on 788 treated HIV-infected patients. Metabolic syndrome prevalence rates were 14%–17%.[25] Lipodystrophy rates in this cohort were high, 57% overall.[37] Diabetes mellitus prevalence was 14% by International Diabetes Federation (IDF) criteria (vs 3% in those without) and 18% in those with metabolic syndrome by ATP-III criteria (vs 2% in those without).[25] Higher levels of the inflammatory marker C-reactive protein (CRP) and lower levels of the antiinflammatory molecule adiponectin were found in those with metabolic syndrome[25]; both molecules are implicated in diabetes pathogenesis.

The incidence of metabolic syndrome after the initiation of cART in treatment-naive HIV-infected subjects has now been reported in 2 studies. The prevalence of metabolic syndrome increased from a pretreatment rate of 16%, to 25% after 48 weeks of cART, with a metabolic syndrome incidence rate of 14 of 100 patient-years.[40] More recently an incidence of 12 of 100 patient-years has been reported after cART initiation with a 3-year 3 follow-ups.[41] The relative risk of developing diabetes mellitus was increased 4-fold in those with metabolic syndrome at baseline and 4-fold to 5-fold in incident cases of metabolic syndrome.[41] Further prospective studies of the progression from metabolic syndrome and cART-associated lipodystrophy to diabetes and its atherothrombotic complications are awaited.

It is important to consider other factors that dynamically influence the prevalence of metabolic syndrome, including national trends in obesity, nutrition, and sedentariness, and genetic/ethnic susceptibility to metabolic syndrome. Specifically for cART recipients, changes in the pattern of use of older drugs such as stavudine may also influence the prevalence into the future. Metabolic syndrome in treated HIV is reviewed in detail elsewhere.[42]

TABLE 2. Criteria for Diagnosis of Metabolic Syndrome

International Diabetes Federation[37]	NCEP–ATP III[36]
Waist >94 cm in men/>80 cm in women	Any 3 of the following:
Plus 2 of the following:	Waist >102 cm in men/>88 cm in women
Glucose >5.6 mmol/L	Glucose >6.1 mmol/L
HDL <1.20 mmol/L	HDL <1.0 mmol/L in men and <1.2 mmol/L in women
Triglycerides >1.7 mmol/L	Triglycerides >1.7 mmol/L
sBP >130 mmHg	Blood pressure >130/85 mmHg
dBP >85 mmHg	

dBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; sBP, systolic blood pressure.

Pathogenesis of Type 2 Diabetes in Treated HIV Infection

Hyperglycemia is the end point of a series of processes that result in the failure of the pancreatic beta cells to secrete sufficient insulin to maintain glucose levels within the narrow normal range. Insulin secretory demand is determined by the ambient sensitivity of tissues to insulin to promote glucose uptake (insulin sensitivity). When there is resistance to the action of insulin, a compensatory increase in insulin secretion is required to permit normal glucose uptake. The failure of beta cells to secrete sufficient insulin may be a consequence of multiple factors including genetic or programmed factors (suggested by family history of type 2 diabetes) or the toxic effects of elevated circulating lipids (beta cell lipotoxicity).[43] In treated HIV infection, lipotoxicity may represent drug-induced effects, the consequences of lipodystrophy or both,[15,44,45] however, it is possible that multiple other factors impact.

cART Effects on Insulin Resistance

In the regulation of glucose metabolism, insulin induces glucose uptake by stimulating insulin receptors on cell surfaces. This sets up a cascade of phosphorylation steps of key cellular substrates that result in translocation of glucose transporter 4 (GLUT4) from the cell cytosol to the cell surface, where it facilitates glucose entry into the cell. Insulin action may be interfered with at numerous points within this complex network, resulting in insulin resistance. High circulating fatty acids can interfere with postinsulin receptor signalling pathways in muscle, for example, inducing lipotoxicity, and this is one of several mechanisms involved in insulin resistance in obesity-induced type 2 diabetes.

Insulin resistance is considered central to cardiometabolic disease; as mentioned above, it underlies type 2 diabetes

but is also present in atherothrombotic cardiovascular disease.[46–48] Insulin resistance is considered to be the link between the clustering of metabolic disturbances within metabolic syndrome, including abdominal obesity, diabetes, heart disease, hypertension, and dyslipidemia. Insulin resistance is difficult to measure in vivo. The most accurate and gold standard measure of insulin sensitivity is the resource-intensive and staff-intensive hyperinsulinemic euglycemic clamp. Other surrogate measures of insulin resistance include the homeostasis model assessment and, for epidemiological and larger population-based studies, fasting insulin levels.

Clamp studies of HIV-infected subjects before the cART era showed normal insulin action.[49] In the era of cART, 1 drug class in particular, protease inhibitors, have been shown to induce insulin resistance in vivo and in vitro. The most informative studies demonstrating drug effects are those administering single drugs to HIV-negative healthy controls; prospective studies of cART initiation in HIV-infected treatment-naive patients are less informative because there is confounding by the multiple drugs used in treatment. A single dose of the protease inhibitor, indinavir, induced a 30% reduction in insulin sensitivity (by hyperinsulinemic euglycemic clamp) in healthy HIV-negative subjects.[50] Intraclass differences with protease inhibitors are also evident: ritonavir reduced insulin action by 15%, but amprenavir had no effect, again in single-dose studies of HIV-negative volunteers.[51] More recently, a study of 2 different regimens in treatment-naive HIV-infected subjects found reduced insulin action by clamp after 3 months with a protease inhibitor–NRTI regimen (ritonavir-boosted lopinavir plus zidovudine/lamivudine), but no effect on insulin action with a protease inhibitor–NRTI-sparing regimen (ritonavir-boosted lopinavir plus nevirapine).[52] Thus newer protease inhibitor–based regimens may be less detrimental to insulin action than older regimens, particularly when used without a NRTI. A summary of clamp studies of insulin action with cART and/or single drugs is shown in Table 3.

In vitro studies using cell models have helped clarify mechanisms of protease inhibitor–induced insulin resistance. In an adipocyte cell line, all protease inhibitors acutely reduced insulin-stimulated glucose uptake.[53] Separate cell culture work has found that protease inhibitors halved GLUT4 translocation independently of insulin signalling pathways with noncompetitive reversible binding of protease inhibitors to GLUT4 as the mechanism of action.[54] Reduced phosphorylation of mitogen-activated protein kinase activation has also been demonstrated, a key step in postreceptor insulin signalling.[55]

Prospective human studies confirm the differences between protease inhibitors in their ability to induce insulin resistance: amprenavir, for example, does not alter surrogate measures of insulin resistance by 24 weeks.[56]

The mechanisms by which protease inhibitors induce insulin resistance probably extend beyond those currently defined. Protease inhibitors reduce adipocyte differentiation by altering potent adipogenic proteins, such as sterol regulatory element-binding protein-1, peroxisome proliferator-activated receptor-γ.[55] Adipocyte differentiation, normal adipocyte function, and secretion of adipokines (such as adiponectin) are now understood to feed into the regulation of insulin sensitivity. As such, these protease inhibitor effects on adipocyte function may also impact on whole body insulin resistance and glucose regulation. The contribution is well defined, however, beyond associative relationships between low adiponectin levels and insulin resistance and lipodystrophy.[25,57]

Insulin sensitivity in treated HIV infection with lipodystrophy is also reduced,[15,16,58] as expected as lipodystrophy is a known insulin-resistant state. Clamp studies of protease inhibitor–treated HIV-infected subjects with lipodystrophy, insulin sensitivity as half that found in HIV-infected protease inhibitor-naive controls who were age-matched, BMI-matched, and waist-matched.[58]

As discussed above, NRTIs also contribute to insulin resistance.[52] Novel work in healthy HIV-negative controls demonstrated that 4 weeks of stavudine reduced insulin sensitivity (measured by clamp) associated with reduced mitochondrial DNA in muscle tissue and reduced mitochondrial function assessed by ^{31}P magnetic resonance spectroscopy.[59] Reduced expression of mitochondrial genes involved in metabolism have also been shown in the adipoocytes of stavudine-treated HIV-negative controls[60]; in concert, these studies suggest that mitochondrial effects may account for at least some of the metabolic complications associated with cART, in addition to the well-known mitochondrial-related neurological adverse effects.

cART Effects on Insulin Secretion

In addition to cART effects on the action of insulin on peripheral glucose uptake, there is also evidence of cART effects on the secretion of insulin. Again, interpreting studies requires consideration of the multiple drugs comprising cART

TABLE 3. Human In Vivo Studies of Insulin Action Measured by Hyperinsulinemic Euglycemic Clamp in HIV Infection

Study	Study Type	Status	Controls	Drug Class	Duration	Specific Drugs	Effect
Hommes et al[49]	Observational	HIV+	Healthy HIV−	Nil	—	Untreated	No difference
Gan et al[58]	Observational	HIV+, with LA	HIV+, no LA	All	—	All	50% less in treated HIV
Blumer et al[52]	Intervention (HAART initiation)	HIV+	HIV+	PI + NRTI vs PI + NNRTI	12 wks	LPV/r + ZDV/3TC, LPV/r + NNRTI	25% reduction with NRTI, no effect of NNRTI with PI
Noor et al[50]	Intervention	HIV−	HIV−, placebo	PI	Single dose	Indinavir	30% reduction
Lee et al[51]	Intervention	HIV−	Randomized cross over	PI	Single dose	Amprenavir, ritonavir	No effect, 15% reduction
Fleischman et al[59]	Intervention	HIV−	Placebo	NRTI	4 wks	Stavudine	Decreased

3TC, lamivudine; LA, lipoatrophy; LPV/r, ritonavir boosted lopinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ZDV, zidovudine.

and methodologies used. In HIV-infected patients, who commenced a protease inhibitor (at the same time as commencing, or already receiving, a NRTI), measures of insulin secretion and beta cell function reduced by 25%–50%.[61] Beta cell dysfunction (estimated by insulin, proinsulin, and C-peptide responses to an ingested glucose load) is reported in cART recipients compared with untreated HIV-infected subjects.[62]

In vitro work in the insulin-secreting cell line INS-1 have shown impairment of insulin secretion with the protease inhibitors ritonavir, nelfinavir, and saquinavir but not amprenavir or indinavir.[63] Cell culture studies of rodent islets and the MIN6 β-cell line have also shown protease inhibitors impair glucose sensing and inhibit insulin release.[64] Although mechanisms for these effects are not clear, GLUT-2 is a candidate because it is considered to be involved in glucose sensing which is necessary for initiation of the insulin secretion cascade.

CART AND INFLAMMATION

Inflammation is a recognized contributor in diabetogenesis. Elevated proinflammatory markers such as CRP, tumor necrosis factor-α (TNF-α), and interleukin-6 and low levels of the antiinflammatory molecule adiponectin characterize insulin resistance and type 2 diabetes. Increased levels of CRP, TNF-α, interleukin-6 and low levels adiponectin are found in treated HIV- infection.[65–70] The proinflammatory profile is worsened in the presence of clinical lipoatrophy, worse than that found in insulin resistant obesity.[70] Insulin resistance measured by hyperinsulinemic clamp was predicted by TNF-α and low adiponectin levels, independent of body fat partitioning.[70] Studies examining the predictive value of inflammatory molecules in treated HIV infection are awaited to determine whether these associations promote progression to diabetes independently of body fat changes and for specific drug class effects.

SUMMARY

Interpretation of available data indicates that patients with treated HIV infection are at increased risk of diabetes mellitus, in part contributed to by class-specific and drug-specific adverse metabolic effects, the effects of lipodystrophy, and the impact of the modern epidemic of obesity. Changes in the demographics of HIV infection will also impact, with higher infection rates now occurring in populations who have genetic susceptibility to diabetes mellitus. The drugs that form cART have now been in use for over a decade and their effects on (at least) body fat partitioning, metabolic syndrome, and disorders of glucose metabolism seem progressive. Numerous areas are uncharted: what is the natural history of diabetic complications in HIV infection? Will the lipid disorders found in treated HIV infection and lipodystrophy accelerate the progression to, and severity of, diabetes mellitus and its associated atherothrombotic cardiac disease? Are there interactions between hyperglycemia and other drug-induced effects such as neuropathy and renal dysfunction? Long-term and prospective studies will assist in clarifying the numerous questions pertaining to the natural history of diabetes mellitus in treated HIV infection. Further, HIV-associated lipodystrophy and HIV-associated metabolic syndrome are human models of accelerated lipotoxicity that may provide important mechanistic insights into the most common form of diabetes mellitus.

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