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Metabolic consequences and therapeutic options in highly active antiretroviral therapy in human immunodeficiency virus-1 infection

Katherine Samaras*

Diabetes Program, Garvan Institute of Medical Research, Department of Endocrinology, St Vincent's Hospital, 384 Victoria St, Darlinghurst, NSW 2010, Australia

The use of highly active antiretroviral therapy (HAART) in HIV-1 infection confers immunological and survival advantages, at the cost of induction of significant metabolic disturbances. These include insulin resistance, disturbances in lipid metabolism, glucose homeostasis, adipocyte physiology and body fat partitioning with peripheral lipoatrophy and visceral obesity. These metabolic disturbances produce clinical manifestations which impact on the future health of the HIV-infected patient, including hyperlipidaemia, lipodystrophy, metabolic syndrome, cardiovascular disease and type 2 diabetes. These conditions are evident in the relative short term as HAART (and possibly HIV infection) appears to accelerate their pathogenesis. The current understanding of the mechanisms and time courses for developing metabolic complications on HAART is reviewed in this paper. The efficacy of therapeutic interventions for insulin resistance, hyperlipidaemia, body fat partitioning disorders and metabolic syndrome is summarized.

Keywords: metabolic syndrome, lipids, glucose, insulin resistance, HIV, diabetes, obesity, lipodystrophy

Introduction

The treatment of HIV infection with highly active antiretroviral therapy (HAART) confers significant morbidity and survival benefits. The advent of effective drugs, which restore immune system function and suppress viral replication, has transformed a once-fatal disease to significantly improved life expectancy. The cost of improved immune function and longevity may include metabolic complications however, which have become apparent with increasingly widespread and longer term use of HAART. These include hyperlipidaemia, insulin resistance, diabetes mellitus and disturbances in body fat partitioning. This leading article will describe the metabolic complications of HAART, specifically disturbances in glucose metabolism, lipids and body fat partitioning, with reference to emerging evidence of adverse long-term sequelae, specifically premature cardiovascular disease and type 2 diabetes, and review the current knowledge of efficacy of therapeutic interventions.

HAART can currently be divided into five drug classes: protease inhibitors (indinavir, ritonavir, nelfinavir, fosamprenavir, saquinavir, atazanavir, tipranavir and darunavir), nucleoside reverse transcriptase inhibitors (NTRIs) (stavudine, zidovudine, lamivudine, abacavir, didanosine, tenofovir and emtricitabine), non-nucleoside reverse transcriptase inhibitors (NNTRIs) (efaviranz and nevirapine) and the newer classes, entry inhibitors (fusion inhibitors: enfuvirtide; and CCR5 inhibitors: maraviroc) and integrase inhibitors (raltegravir). At the time of writing, no metabolic data have been reported from Phase 3 clinical trials: (enfuvirtide, TORO; maraviroc, MOTIVATE 1 and MOTIVATE 2; and raltegravir, BENCHMRK-1 and BENCHMRK-2).

Defining the metabolic complications

Insulin resistance

Insulin resistance refers to the reduced action of circulating insulin to induce uptake of glucose into cells, where glucose then serves as a major substrate for cellular function. Insulin stimulates its cell surface receptor, which sets up a phosphorylation cascade, firstly of insulin receptor substrate-1 which in turn initiates a number of further phosphorylation reactions. These eventually result in translocation of one form of glucose transporters, glucose transporter 4 (GLUT4), from the cytosol to the cell surface where it facilitates glucose entry into the cell. There are many points in this complex pathway where reduced insulin action may be induced. For example, it is known that high circulating fatty acids, through a mechanism termed lipotoxicity, interfere with post-insulin receptor signalling pathways.[1] This is one of the mechanisms postulated to occur in the common form of obesity-induced insulin resistance and type 2 diabetes.

Insulin resistance underlies many metabolic conditions. It is a core feature of type 2 diabetes and accompanies abdominal obesity. It is present in atherothrombotic cardiovascular disease.

*Corresponding author. Tel: +61-2-9295-8312; Fax: +61-2-9295-8201; E-mail: k.samaras@garvan.org.au

It underlies the dyslipidaemia characterized by hypertriglyceridaemia and low HDL cholesterol. Insulin resistance is also recognized as the core component of the metabolic syndrome (discussed below), having been described by Reaven[2] as the 'common soil' from which all metabolic diseases develop. 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 dyslipidaemia.

Insulin resistance is a pathophysiological state, which can be inferred from historical, clinical and laboratory data. Historically these include family history of type 2 diabetes or cardiovascular disease; clinically, abdominal obesity and hypertension; and biochemically, the presence of disturbed glucose metabolism and dyslipidaemia. Insulin resistance is, however, difficult to quantify and there are no valid measures available for clinical practice.[3,4] The gold standard measure is the hyperinsulinaemic euglycaemic clamp, an invasive technique that is resource and time intensive, and suitable for research alone. Surrogate estimates such as fasting insulin and the homeostasis model assessment[5] are again only suitable for research and epidemiological settings.

Prior to the advent of HAART, studies of insulin resistance in HIV infection showed normal insulin action.[6,7] Protease inhibitors, among HAART drug classes, have been shown specifically to induce insulin resistance in humans and *in vitro*. Early descriptions of insulin resistance in HIV-infected HAART recipients were in the context of drug-induced lipodystrophy,[8–10] a known insulin resistant state. In studies using hyperinsulinaemic euglycaemic clamp, HIV-infected subjects with lipodystrophy using protease inhibitors had insulin action half that of age-, BMI- and waist-matched HIV-infected controls who had never used protease inhibitors.[10] Insulin resistance develops rapidly after a single dose of the protease inhibitor indinavir, in healthy, HIV-negative subjects, with a reduction in insulin sensitivity (by hyperinsulinaemic euglycaemic clamp) of ~30%.[11] *In vitro* studies have shown indinavir acutely reduced insulin-stimulated glucose uptake in an adipocyte cell line.[12] At a cellular level, mechanisms of protease inhibitor-induced insulin resistance have been found to be independent of early steps in post-insulin receptor signalling and with intact insulin-induced GLUT4 translocation.[11] Importantly, numerous protease inhibitors reduced glucose uptake, with indinavir being most potent.[11] In a different cell line in culture, protease inhibitors reduced GLUT4 translocation by some 50%, independently of insulin signalling pathways.[11] More recently, non-competitive, reversible binding of protease inhibitors to GLUT4 has been demonstrated.[13] In addition to these selective effects on glucose transporter molecules, indinavir in cell culture has also been shown to reduce phosphorylation of a key step in post-receptor insulin signalling and that of mitogen-activated protein kinase activation.[14]

Although *in vitro* studies have suggested that most protease inhibitors will reduce insulin action in studies of drug incubation in cell lines,[11] prospective human studies indicate that there may be differences between protease inhibitors. For example, a study of the protease inhibitor amprenavir (in triple therapy HAART) found no change in surrogate measures of insulin resistance at 24 weeks.[15] By 48 weeks there was a trend towards insulin resistance; however, increased truncal fat and hyperlipidaemia had also developed and may have explained alterations in insulin resistance.[15] Further, *in vivo* studies of non-infected volunteers showed that atazanavir (with boosting doses of ritonavir) did not alter glucose excursions following an oral glucose tolerance test.[16] Thus, human *in vivo* studies indicate drug-specific differential effects on glucose metabolism within the protease inhibitor class.

Protease inhibitors may exert specific effects on insulin resistance through pathways independent of those defined for insulin-mediated glucose uptake. The protease inhibitor indinavir has been shown to reduce adipocyte differentiation, by reducing levels of the potent adipogenic proteins sterol regulatory element-binding protein-1 (SREBP-1) and peroxisome proliferator-activated receptor-γ (PPAR-γ).[14] The process of adipogenesis appears to be critical to normal insulin sensitivity, since it is increasingly understood that normal adipocyte function and adipocyte-derived cytokines (such as adiponectin) contribute to insulin sensitivity, though mechanisms are yet to be fully elucidated.

Disturbances of glucose metabolism and risk for type 2 diabetes

Prior to the availability of HAART, type 2 diabetes was relatively uncommon in HIV infection. Early reports indicating an increased prevalence of disorders of glucose metabolism were derived in cohorts of patients with lipodystrophy. In the first of these studies, the prevalence of diabetes was 2% among protease inhibitor recipients with lipodystrophy,[8] rising to 7% over 14 months of observation.[9] The overall prevalence of disorders of glucose metabolism (diabetes mellitus, impaired fasting glucose and impaired glucose tolerance) was 25%.[9] Other early studies also report higher rates of type 2 diabetes in HIV-associated lipodystrophy: 7% compared with 0.5% of otherwise healthy controls; impaired glucose tolerance was present in more than 35% of HIV-infected patients as compared with 5% of controls.[17] These and other early studies[18] require consideration within the historical context of drugs commonly used in HAART. Specifically, in the early HAART era, certain protease inhibitors, such as indinavir and ritonavir, were commonly used in drug regimens. These particular drugs have potent effects on insulin resistance described above and are used less frequently currently as major components of HAART regimens.

More recently, prospective studies report 10% of HIV patients treated with HAART developed diabetes during 4 years of follow-up, compared with 3% in HIV-seronegative men.[19] After adjusting for age and BMI, this difference represented a >4-fold increase in relative risk of developing diabetes.[19] Human studies have shown a 25% to 50% reduction in measures of insulin secretion and β-cell function after 12 weeks of protease inhibitor added to pre-existing NRTI or commenced in addition to NRTI.[20]

Apart from direct protease inhibitor-induced effects on insulin resistance described above, discrete and independent insults to glucose metabolism may arise from HAART-induced dyslipidaemia and lipotoxicity, and effects on adipokine metabolism and lipodystrophy. These are discussed in turn below. Further insults to glucoregulation are the effects of HAART subtypes on pancreatic β-cell insulin production. Protease inhibitors have been shown to reduce insulin secretion *in vivo*.[20] *In vitro* work in the insulin-secreting cell line INS-1 have shown a gradation of impairment of insulin with different protease

inhibitors.[21] Cell culture studies of rodent islets and the MIN6 β-cell line have also shown protease inhibitors impair glucose sensing and inhibit insulin release.[22] Although mechanisms for these effects are not clear, GLUT-2 is a candidate since it is considered to be involved in glucose sensing which is necessary for initiation of the insulin secretion cascade.

NRTIs may have distinct effects on diabetogenesis: NRTIs induce mitochondrial dysfunction, with well-documented effects on adipose tissue and hepatic and neurological toxicities. NRTIs inhibit mitochondrial DNA polymerase-γ, impairing synthesis of mitochondrial enzymes generating ATP. Recent studies have highlighted that NRTI-induced mitochondrial toxicity may extend to diabetogenesis: in HIV-infected women, NRTI exposure increased the relative risk of development of diabetes by 80% for NRTI exposure <3 years and more than doubled risk for exposure exceeding 3 years.[23] The potential role of NRTI-induced mitochondrial toxicity in the development of diabetes is relatively unexplored, but may be critical.

Disturbances of lipid metabolism and risk for cardiovascular disease

Numerous studies have reported increased risk for CVD in HIV-infected HAART-recipients.[24–30] Most recently the DAD: study reported a 32% increase in the relative risk of CVD over the 5 years following initiation of HAART; this risk appeared greater with protease inhibitor exposure.[27] This study found increases in traditional cardiovascular risk factors occurred in parallel to the increased incidence of CVD events reported.[27] Importantly, in non-infected patients, lipid abnormalities are observed perhaps for decades prior to the clinical manifestation of CVD; in contradistinction, CVD appears to develop early after the onset of relatively mild LDL changes. A retrospective cohort study recently reported higher rates of acute myocardial infarction in HIV-infected patients compared with non-infected patients; rates of hypertension and diabetes were higher in HIV-infected patients.[28] The relative risk of acute myocardial infarction was almost doubled after adjustment for age, gender, race, diabetes, dyslipidaemia and hypertension; however, gender stratification analyses indicated a greater susceptibility for women than men.[28] Not all studies have shown increased cardiovascular risk.[29] Many of the published studies in this area are limited by factors such as retrospective study design, incomplete case ascertainment, event definitions, relatively low event rates and incomplete HAART exposure data. The observation of possibly increased cardiovascular risk is not explained by the current state of knowledge of mechanisms for accelerated atherogenesis in this patient group.

HIV infection *per se* is associated with disturbances in lipids including low total-, HDL- and LDL-cholesterol and hypertriglyceridaemia.[31] The virus (or fluctuations in its activity) itself may increase cardiovascular risk. The SMART study found a 60% increase in the relative risk of fatal or non-fatal cardiovascular disease in patients who had interrupted HAART (drug conservation) compared with continuous viral suppression.[30] Whether these findings are explained by discrete effects of the virus on atherogenesis or effects of the host-response to the virus in promoting atherogenesis is unclear.

Several cross-sectional studies of HAART recipients have shown increased carotid intima-medial thickness (IMT).[32–35] The largest prospective study to date has shown no differences in rate of progression of IMT over 3 years between HIV-infected subjects receiving protease inhibitors, on non-protease inhibitor HAART and uninfected controls, matched for age, gender, ethnicity, smoking status and blood pressure.[32] Cross-sectional studies have also shown no difference in IMT in non-smoking HIV-infected HAART recipients, irrespective of total-cholesterol levels.[33] In contrast, a large case–control study found site-specific differences in IMT: IMT values were 24% greater at the carotid bifurcation in HIV-infected HAART recipients compared with age- and gender-matched controls and nearly 6% greater in the common carotid artery.[34] Vascular risk was increased by 4% to 14%.[34] Lipodystrophy appears to have an additional impact on IMT: the risk of carotid IMT is increased 3-fold in HIV-infected HAART recipients with lipodystrophy. Interestingly, IMT was related to circulating levels of monocyte chemoattractant protein-1, which were higher in those subjects with lipodystrophy.[35] Studies in HIV-infected subjects at low cardiovascular risk (non-smokers and normal lipids) have demonstrated endothelial dysfunction using brachial artery ultrasound.[36] Other studies have also demonstrated worse endothelial dysfunction in HIV infection in subjects with higher HIV viral load,[37,38] suggesting HIV itself and/or host responses are involved in the pathogenesis of atherosclerotic arterial disease.

Protease inhibitor therapy increases fasting total- and HDL-cholesterol and triglycerides with variations within the drug class; ritonavir induces greater dyslipidaemia, and atazanavir exerts the mildest effects.[39] Lipid effects occur early; studies in HIV-negative subjects show increases after 2 weeks of ritonavir.[40] The NRTI and NNRTI HAART classes also induce lipid disturbances[41] and, in combination, the lipid disturbances are more pronounced.[42] Combined therapy induces more severe lipid disturbances than single therapy and those patients with higher triglycerides at HAART initiation show the greatest deterioration in LDL-cholesterol and triglycerides.[43]

Body fat partitioning disorders: lipodystrophy

Lipodystrophy refers to changes in body fat partitioning. Lipoatrophy refers to diminution of fat tissue which, in HIV-infected HAART recipients, occurs specifically in the subcutaneous tissues of the limbs. There can be body fat redistribution, with increased fat deposition in the central region, predominantly in the visceral fat depot, but also in the upper chest, breasts and dorsocervical hump. Lipodystrophy has not been observed in patients with long-term, non-progressive HIV infection and thus is not considered to be due to HIV *per se*. This form of wasting is to be distinguished from the wasting syndromes that characterized untreated HIV infection early in the history of the disease, which was due to loss of lean muscle mass.

In the era of HAART, body fat partitioning changes appear early after HAART initiation and is progressive.[8,9,44] Factors associated with lipoatrophy include HAART duration and CD4 count at HAART initiation.[45] Numerous studies have now established that NRTI use is the major contributor to peripheral lipoatrophy,[44,46–48] particularly stavudine. NRTIs affect DNA polymerase-γ and deplete mitochondrial DNA, shown in the adipocytes of HIV-negative volunteers following 6 weeks of either zidovudine/lamivudine or stavudine/lamivudine[49] and more recently in adipocytes of HIV-infected stavudine recipients,

where mitochondrial DNA depletion was predicted by duration of stavudine therapy.[50] Lactic acidosis, a biochemical index of mitochondrial dysfunction, is associated with worse lipoatrophy.[51]

The diagnosis of lipodystrophy is made clinically, often aided by the patient's own perception of fat attrition. Apart from loss of subcutaneous fat, prominence of musculature of the limbs and veins is other sign. Anthropometry can document redistribution of fat to the abdominal region, with a simple waist measure useful in detection and metabolic risk evaluation. Dual energy X-ray absorptiometry can also document limb and abdominal fat, though is resource intensive. Measures such as CT and MRI visceral fat are useful tools in research, though costly; the clinical utility of CT is limited by potential risks from cumulative radiation exposure.

Initial hypotheses regarding the pathogenesis of lipodystrophy suggested a major role for protease inhibitors: the homology of protease inhibitors to retinoic acid binding protein resulted in interference with key steps in adipocyte differentiation, thereby inducing apoptosis.[52] Numerous studies have now tested this hypothesis by using thiazolidinediones in HAART-associated lipodystrophy with the aim of increasing signalling down this pathway of adipocyte differentiation; however, no longer term increase in adipose mass has been found.[53–55] Subsequent studies indicate complex protease inhibitor effects on adipocytes. Effects upstream of PPAR-γ have been suggested to play a causative role in lipoatrophy, with evidence of inhibition of the SREBP-1 activation of the RXR-PPAR-γ heterodimer[14] in adipocytes derived from HIV-infected subjects; however, multiple other effects have been shown *in vitro*. Studies of both protease inhibitors and NRTIs suggest diverse effects in differentiating and differentiated adipocyte cell lines, with marked alteration in the expression and secretion of the adipokines IL-6, TNFα, IL-1β and adiponectin in differentiating adipocyte cell lines and little or less marked effect in differentiated cell lines.[56] Peripheral adipocytes derived from lipoatrophic subjects show lower concentrations of adipogenic factors critical to adipocyte differentiation pathways, compared with uninfected controls.[57] *In vivo* studies of the NRTIs in seronegative humans show effects on the functionality of adipocyte mitochondria, with decreased transcription of mitochondrial RNA.[49] This study also reported down-regulation of PPAR-γ and, concomitantly, peroxisome proliferator-activated receptor-γ coactivator-1, which is perhaps central to adipocyte nuclear responses to mitochondrial dysfunction.[49]

Metabolic syndrome

Metabolic syndrome describes the clustering of abdominal obesity, disorders of lipid and glucose metabolism and hypertension, phenotypes closely associated with visceral obesity, metabolic dysregulation, and risk for type 2 diabetes and cardiovascular disease. Although controversy and debate exist around its relative importance compared with individual risk factors and its definition, two definitions have been promulgated internationally by pre-eminent scientific bodies, notably the American Heart Association[58] and the International Diabetes Federation.[59]

Numerous studies have now estimated the prevalence of metabolic syndrome in HIV-positive HAART recipients. The prevalence of metabolic syndrome has been reported as 14% to 25%.[60–63] Metabolic syndrome prevalence was either similar to[62,63] or greater[61] than that of control groups. Metabolic syndrome in HIV-infected HAART recipients was associated with greater insulin resistance and lipid disturbances, and a pro-inflammatory milieu with higher C-reactive protein levels and lower adiponectin levels.[60] Metabolic syndrome presence was associated with higher BMI, higher viral load, and use of ritonavir-boosted lopinavir and didanosine.[62] Interestingly, two studies suggest specific anthropometric limitations to the metabolic syndrome definitions promulgated when applied to HIV-infected HAART recipients. Waist circumferences were lower in HIV-infected HAART recipients compared with the uninfected population despite similar prevalence rates for metabolic syndrome,[62] and 50% of HIV-infected HAART recipients met non-anthropometric criteria for metabolic syndrome, but this reduced to 17% when waist-based anthropometric cutoffs were applied.[60] As such, metabolic syndrome definitions may not be sufficiently sensitive for HIV-infected HAART recipients.

Two studies have reported the incidence of metabolic syndrome after HAART initiation. One study found the prevalence of metabolic syndrome increased from 16% to 25% over 48 weeks, with an incidence rate of 14/100 patient years.[64] A recent 3 year study following HAART initiation in treatment-naive patients reported a baseline prevalence of metabolic syndrome of 9% and an incidence of 12/100 patient years.[65] The relative risk of developing diabetes was increased 4-fold in those with metabolic syndrome prior to HAART commencement.[65] In those developing metabolic syndrome on HAART, the risk of diabetes was increased 4- to 5-fold and cardiovascular disease 3-fold.[65]

In HIV-infected HAART recipients, intermediary measures of atherosclerosis, such as carotid artery IMT were greater in those with metabolic syndrome than without.[66] Carotid IMT was similar between HIV-infected BMI- and age-matched HIV-negative women.[67] Carotid IMT was greater, however, in a subgroup receiving protease inhibitor compared with other HIV-infected subjects and HIV-negative controls.[67] In a 3 year prospective controlled study, carotid IMT progression was not linked to HIV-HAART or subtype, but to LDL-cholesterol and homocysteine levels.[68] Carotid IMT has been found to relate to epicardial fat thickness and visceral adipose tissue measures in HIV-infected HAART recipients; those with metabolic syndrome had significantly higher IMT and epicardial fat thickness.[69]

Metabolic syndrome in HIV-infected HAART recipients represents the sum of drug toxicities on glucose and lipids, impaired adipose tissue function, underlying genetic predisposition to metabolic disease, and environmental pressures of poor diet, sedentariness and socioeconomic status. Further studies on whether there is unique susceptibility of HIV-infected HAART recipients are awaited.

Therapeutic approaches in managing the metabolic complications of HAART

The primary aim of treatment in HIV infection is to suppress viral replication and reduce viral load. Longer term management of HAART recipients requires screening for the physical and metabolic complications described above. Readers are also referred to a recent review of this topic.[45]

Disorders of glucose metabolism: insulin resistance, impaired glucose tolerance and type 2 diabetes mellitus

Disorders of glucose metabolism such as impaired glucose tolerance and type 2 diabetes will respond to lifestyle modification, including regular physical activity, caloric restriction and modest weight (waist) reduction. Some of the most convincing data arise from the Diabetes Prevention Programme, which found modest weight reduction and increased physical activity reduced the conversion of impaired glucose tolerance to frank diabetes by nearly 60%.[70] Thus, all patients should be engaged in lifestyle strategies promoting weight maintenance in those of healthy weight (and waist). Patients who are overweight or obese may be considered at high risk for disorders of glucose metabolism, since the added lipotoxic burden of obesity may accelerate the metabolic complications of HAART. Where resources are available, these patients should be targeted for active lifestyle improvement and weight reduction.

Metformin has been found to improve insulin sensitivity and reduce abdominal fat in HIV-infected HAART recipients with lipodystrophy and may be beneficial in the management of abdominal obesity.[71,72] It is generally well tolerated but care should be exercised in patients at risk of lactic acidosis; heart failure and renal impairment are also relative contraindications. The thiazolidinediones class of insulin sensitizers has been shown in numerous studies to reduce insulin resistance in HIV-associated lipodystrophy[9,71,72] and may be considered in those patients with type 2 diabetes and impaired glucose tolerance. Limitations of this drug class include fluid retention and possible exacerbation of risk for cardiac morbidity. Adequate glucose control may require standard antidiabetic approaches such as sulfonylurea and insulin therapy.

Lipid disorders

Interventions for treating HAART-associated dyslipidaemia include lifestyle modification such as reduction in dietary fat intake from saturated sources, increased physical activity and weight reduction where obesity is present. Where these strategies are unsuccessful in reducing lipids to the normal range, drug therapy is indicated. Drug therapy needs to consider the relative increases in each of LDL-cholesterol and triglycerides. Standard LDL-lowering therapy with HMGCoA reductase inhibitors is more complex than usual, since protease inhibitors alter hepatic cytochrome P450 metabolism of most statins, either potentiating or attenuating statin levels. Pravastatin appears the least affected. Few data exist on the efficacy of ezetimibe (which reduces cholesterol absorption) in HIV-infected HARRT recipients.

Where hypertriglyceridaemia predominates, fibrate therapy with either gemfibrozil or fenofibrate is appropriate; modest benefits using fish oil supplementation[73] and acipimox[74] have also been reported.

Lipodystrophy

Lipodystrophy remains the most difficult HAART complication to reverse. Switching NRTIs from the thymidine analogues stavudine or zidovudine to abacavir has shown modest improvement; an 11% increase in limb fat at 6 months.[75] At 2 years, the increase in limb fat was 35%.[76] Benefits of a change in HAART composition need to be weighed up against the toxicities of other agents and the risk of hypersensitivity reactions to abacavir. Thymidine-analogue sparing NRTI regimens in treatment-naive HIV-infected subjects have shown sparing of limb fat with significantly higher arm fat at 3 years.[48]

Numerous studies have evaluated the effects of thiazolidinediones, insulin-sensitizing agents used in type 2 diabetes, which promote peripheral fat deposition. Numerous placebo-controlled studies have evaluated the potential effects of these drugs in lipoatrophy associated with HAART, with variable or no measurable effect on body fat, summarized elsewhere.[77] The largest and longest randomized trial to date did not find any effect on fat mass, despite improvements in insulin resistance and adiponectin levels.[9] Co-existent NRTI use may mitigate against the potential effects of thiazolidinediones. Lipid-lowering therapy with pravastatin produces a small increase in limb fat;[78] the mechanism of this effect is unclear.

Strategies to reduce abdominal obesity have shown more benefit. Metformin has been found to reduce visceral and subcutaneous abdominal fat, in addition to insulin resistance.[79] These benefits are augmented by concomitant increases in physical activity.[80] Combination rosiglitazone and metformin therapy did not reduce visceral obesity in HAART recipients, though insulin resistance was reduced.[81] Growth hormone therapy has been reported to reduce abdominal fat, in association with improved lipids.[82] Studies with the growth hormone secretagogue, growth hormone releasing hormone, also reduced abdominal visceral fat without altering parameters of lipid and glucose metabolism.[83] A trial of recombinant methionyl human leptin in lipodystrophy reduced truncal fat and improved insulin resistance, but did not increase measures of peripheral fat.[84]

Metabolic syndrome

Few studies have been published examining interventions to benefit metabolic syndrome in HAART. An intensive lifestyle modification programme of HIV-infected subjects with metabolic syndrome reduced waist and blood pressure but not lipids.[85] Further studies are required.

Summary

Metabolic complications associated with HAART in HIV infection increase the risk for cardiovascular disease and diabetes. Drug-induced disturbances in lipids, insulin resistance and adipocyte physiology are implicated. Careful evaluation to detect and active strategies to ameliorate these metabolic complications are now part of the clinical expertise of physicians involved in the management of HIV infection.

Transparency declarations

None to declare.

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