HIV and HIV treatment: effects on fats, glucose and lipids

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Background: Since the advent of effective antiretroviral therapy, infection with the human immunodeficiency virus has been transformed, in the Western world, to a chronic disease associated with a variety of metabolic complications.

Aims: This review provides a brief summary of our current understanding of the epidemiology, clinical presentation and therapeutic approaches of what is termed ‘the HIV-associated lipodystrophy syndrome’ and of HIV-associated lipid and glucose metabolic abnormalities. Other metabolic associations including lactic acidosis, HIV-associated bone disease and the effect of the virus on other endocrine pathways are outside the scope of this article.

Methods: A bibliographic search was performed using Entrez Pubmed®, edition 2.0, by the National Library of Medicine for articles only in the English language using Boolean operators and the terms ‘HIV, HAART, lipodystrophy, lipoatrophy, lipohypertrophy, hyperlipidemia, diabetes and metabolism, cost of illness’. The Program and Abstract Books of the 8th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV (September 24–26, 2006, San Francisco, USA), the 4th International AIDS Society Conference on HIV Pathogenesis (July 22–25, 2007, Sydney, Australia) and the 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (September 17–20, Chicago, USA) were searched for relative abstracts. Previous publications were used to identify further references. Approximately 1400 articles and abstracts were identified of which 104 were selected for review.

Results: Specific medications and medication classes increase the lipoatrophy and lipodystrophy risk. A change of treatment strategy might be beneficial in improving adipose tissue deposition. The effects of HIV on metabolism offer new insights into cardiovascular disease pathogenesis.

Keywords: HIV/HAART/lipodystrophy/lipoatrophy/lipohypertrophy/hyperlipidemia/diabetes mellitus/insulin resistance/metabolism
Introduction

By March 2007, more than 86,000 people had been diagnosed with HIV in the UK.¹ In 2005, there were around 63,500 people, aged between 15 and 59, living with HIV in the UK, of whom an estimated 20,000 (32%) were unaware of their status.² In 2006, 39.5 million people worldwide were thought to be living with HIV.³ As treatment options become safer and easier to use, the prevalence of people living with chronic HIV infection is expected to rise further. It has also been suggested that HIV-related metabolic abnormalities may increase the risk of cardiovascular disease.⁴ As a consequence, it is likely that the prevalence of HIV-related metabolic complications will increase and knowledge of the emerging bibliography will become ever more pertinent. Research into HIV-associated metabolic disease will also hopefully provide clues for better understanding of the pathogenesis of the metabolic syndrome in patients without HIV infection.

Timeline

In the era before highly active antiretroviral therapy (HAART), the only metabolic abnormality noted in AIDS was the hypertriglyceridaemia associated with the wasting syndrome.⁵ This was attributed to high levels of cytokines accompanying chronic infection.

With the introduction of HAART in the middle of the 1990s, descriptions of patients with body shape abnormalities such as peripheral fat atrophy and central fat accumulation started to emerge. At the same time, it was realized that fat redistribution was also accompanied by insulin resistance (IR) and various lipid abnormalities.⁶ In 1998, Pallela et al.⁷ showed clearly, using national surveillance data, that the introduction of protease inhibitor (PI)-based HAART decreased the HIV-related mortality from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in 1997, with a concurrent decrease of opportunistic infections. Because the initial investigations seemed to suggest that the fat redistribution and the associated metabolic complications were the result of antiretroviral toxicity, some patients started to distrust what was convincingly quite effective antiretroviral therapy. A level of suspicion about HAART arose and spread throughout the Internet subculture and exists to this day. (Unfortunately, many patients also select the Internet as their source of information for ‘alternative’ lipodystrophy treatments: it needs to be clearly emphasized that no evidence supports any of the alternative treatments as such.)

The problem was further compounded as it became apparent that the disease has many different phenotypes and that probably host
characteristics as well as direct viral effects play a role. Indeed, the bibliography of HIV-related metabolic diseases has been hampered by lack of standardization across studies, dissimilarities between populations studied and disparate research methods. Conflicting data exist regarding the epidemiology, the diagnosis and treatment of metabolic and body shape disorders associated with HIV infection. In this review, we will follow the methodological approach recently used in most of the major reviews and guidelines, which is to examine each component of this complex syndrome separately. Increasing evidence suggests that these disorders, although commonly clustering in a syndromal pattern, can occur separately from each other and may potentially have different pathologic pathways.

Definitions that will be used in this review

- HIV-associated lipodystrophy syndrome: a term widely used in the bibliography to describe the HIV-infected patients with some features, or a combination, of peripheral lipoatrophy, central lipohypertrophy, fat redistribution, dyslipidemia and disorders of glucose metabolism. The intensity and the associations of the components of the syndrome can be quite variable. Also it is unclear if hyperlactataemia and loss of bone mineral density are components of the same syndrome and they will be examined separately.

- Lipoatrophy: The loss of subcutaneous fat in the face, arms, legs, abdomen and/or buttocks.

- Lipohypertrophy/fat accumulation/lipomatosis: Increase of adipose tissue within the abdomen where it represents a true excess of visceral fat tissue, accumulation of fat in the dorsocervical area (‘buffalo hump’), the breasts of both men and women, the suprapubic area, under the axillae and over the anterior aspect of the neck.

The HIV-associated lipodystrophy syndrome

Prevalence of the lipodystrophy syndrome

Most studies so far have summated data regarding lipoatrophy and lipohypertrophy under the term lipodystrophy, so no large study has measured the prevalence of each of the components separately. Also, because of differences in definitions, age, race, lifestyle factors, antiretroviral medications and duration of treatment as well as methodological differences, there is no agreement about how frequently the syndrome occurs, with reports ranging from 10 to 80%. A large study that recruited 1035 participants calculated that 50% appeared to have
probable lipodystrophy, with 36% reporting peripheral wasting, 33% abdominal weight gain, 6% buffalo hump and 10 and 12% increased triglyceride or cholesterol levels, respectively.\textsuperscript{11} This study was also based on self-reporting. Several other studies attempting to describe lipodystrophy were performed\textsuperscript{12–14} but assessments were mostly based on self-reporting and without validation of the data.

A more rigorous case–control study recruited 1081 consecutive, HIV-infected, adult outpatients (261 women) without active AIDS, from 32 sites worldwide.\textsuperscript{15} Cases had to have clinically evident signs of lipodystrophy, concordant between the patient and doctor. Scores for lipodystrophy were assigned based on a model including age, sex, duration of HIV infection, HIV disease stage, waist-to-hip ratio, anion gap, serum high-density lipoprotein (HDL) cholesterol concentration, trunk-to-peripheral fat ratio, percentage leg fat and intra-abdominal-to-extra-abdominal fat ratio. Their model had a sensitivity of 79% and a specificity of 80% for the diagnosis of lipodystrophy. However, models for pure lipoatrophy or lipomatosis could not be developed due to low prevalence. If this definition is accepted and used consistently in future studies, a more precise estimate of the body composition changes in several HIV subgroups might be achieved. Unfortunately, the requirement to use dual-energy X-ray absorptiometry (DEXA) and computer tomography (CT) scanning for the measurements makes this model cumbersome and expensive in daily clinical practice, and a widely acceptable model that uses mostly clinical parameters is needed.

To make matters even more complicated, not all studies agree that lipohypertrophy is a true component of HIV-related fat distribution changes, emphasizing the need to study each component of the metabolic syndrome separately, preferably in a prospective manner. Attention needs to be paid to possible confounding by factors not specific to HIV disease as well. A large ongoing cohort study, the Fat Redistribution and Metabolic Changes in HIV infection study\textsuperscript{16,17} (FRAM and FRAM 2) will hopefully clarify our understanding of fat and metabolic changes in HIV infection and the impact of these changes on cardiovascular disease in this population.

It is of note that a retrospective cross-sectional analysis\textsuperscript{18} from the multicentre AIDS cohort study failed to identify increased subclinical atherosclerosis in HIV-infected patients on HAART compared with non-infected patients and found a similar prevalence of coronary artery calcium between HIV-negative and HAART-treated patients.

**Prevalence of the metabolic syndrome in HIV**

Maybe of more direct clinical applicability since it has been shown to be directly related to cardiovascular risk,\textsuperscript{19} the prevalence of the
metabolic syndrome, that encompasses disturbances in glucose, insulin and lipid metabolism and is associated with abdominal obesity, was recently calculated\textsuperscript{20} in a part of the cross-sectional lipodystrophy case definition cohort.\textsuperscript{15} The prevalence of metabolic syndrome was 14% (n = 114, 83 men) by International Diabetes Federation criteria and 18% (n = 139, 118 men) by U.S. National Cholesterol Education Program Adult Treatment Panel III (ATPIII) criteria. Metabolic syndrome was more common in those currently receiving PIs (P = 0.04). In this cohort, the prevalence of metabolic syndrome was lower than that reported for the general population but it was associated with a substantially increased prevalence of type 2 diabetes.

\section*{Lipoatrophy}

\subsection*{Characteristics}
Lipoatrophy is the loss of subcutaneous fat in the face, arms, legs, abdomen and/or buttocks. Veins and muscles become more prominent with the loss of supporting subcutaneous fat. It should not be confused with the wasting syndrome of AIDS since it occurs more frequently among patients responding to HIV therapy and is not accompanied by substantial loss of lean tissue mass.

Although there is fat loss in the abdomen as well, truncal subcutaneous fat atrophy is often less noticeable than fat atrophy elsewhere, especially if there is concomitant visceral fat deposition, keeping the waist circumference stable. Visceral fat accumulation can only be recognized by serial magnetic resonance imaging (MRIs) or CT scans of the abdomen, making truncal lipoatrophy more difficult to identify for both the patient and the physician.

Lipoatrophy, especially of the buccal fat pads, can be very important for the body image of the patients, as it potentially contributes to stigmatization and a perception of being ‘recognizable as an HIV-infected patient’.\textsuperscript{21, 22} A study performed in Singapore\textsuperscript{23} showed that the body-shape changes affected the mood of 36% of patients and the work and/or social activity of 23% of patients, verifying that psychological effects are a cross-cultural phenomenon and that lipodystrophy is not a burden only for Western patients.

\subsection*{Risk factors/Aetiology}
- Several risk factors appear to be associated with lipoatrophy including treatment with thymidine analogues (thymidine analogues include stavudine and zidovudine, with stavudine being a greater risk factor\textsuperscript{24}).
- Several studies have suggested that exposure to nucleoside reverse transcriptase inhibitors (NRTIs) is a risk factor for development of
lipoatrophy, attributed to NRTI-induced inhibition of mitochondrial DNA polymerase gamma.\textsuperscript{17,25–27} Although some studies incriminated the combination of PIs with NRTIs, therapy consisting entirely of PIs did not lead to lipodystrophy,\textsuperscript{28} a finding that suggests that exposure to NRTIs may be the major risk factor.

- There have been some studies implicating race, sex or age (increased age, white race) in subsequent risk of lipoatrophy but the recent analysis of a subcohort of the ACTG 384\textsuperscript{29} did not demonstrate these associations in the multivariate analysis. This A5005s subcohort of the ACTG 384\textsuperscript{30} enrolled 334 subjects from 1998 to 1999 with follow-up until 2001. Three hundred and twenty-nine subjects had anthropometric measurements in triplicate. Subjects assigned to efavirenz ($n=110$) were compared with those assigned to nelfinavir ($n=99$); subjects assigned to zidovudine/lamivudine ($n=154$) were compared with those assigned to didanosine/stavudine ($n=180$). A subset of 157 subjects had serial DEXA scans. The analysis showed a higher baseline CD4 count associated with lipoatrophy\textsuperscript{29} and not a lower baseline CD4 count as previously suggested in studies of self-reported lipoatrophy.\textsuperscript{31} Despite this, a nadir CD4 count of $<200/\mu l$ is still mentioned as a risk factor although it is unclear because longitudinal studies\textsuperscript{32} show that CD4+ cell count, viral load and HAART use are independent predictors of body composition alterations in HIV-infected adults.

- It has also been suggested that coinfection with Hepatitis C increases the risk of lipoatrophy in HIV-infected individuals. In a cross-sectional study, lipoatrophy was associated more commonly with IR\textsuperscript{33} and lipoatrophy was observed more frequently in HIV-HCV patients in comparison with HIV patients (41\% versus 14\%; $P=0.003$). The value of the association with IR resistance should be interpreted with caution as multiple studies suggest an independent association between infection with either hepatitis B or C and development of diabetes or IR yet the Swiss cohort study was inconclusive regarding the association with coinfection of Hepatitis C or active Hepatitis B.\textsuperscript{34}

**Diagnosis**

Diagnosis of lipoatrophy is frequently based on patient's perception and this has been shown to correlate well with physical examination.\textsuperscript{17} Measurement of skin folds and limb circumference are practical and easy to perform in the clinic, provided that they are done by the same evaluator each time. Methods that can be used to measure fat directly include DEXA and MRI or CT scan. DEXA is better for limb fat which is mostly subcutaneous but cannot measure visceral fat and therefore cannot correctly estimate truncal fat, for which MRI or CT scan is necessary, making the process expensive and cumbersome.

Objective measurements of facial lipoatrophy are more difficult to perform. The FRAM study questionnaire\textsuperscript{16} asked patients to ‘evaluate
any changes in the amount of fat in their cheeks, just next to their nose and mouth’ and give changes a score from 1 to 6, ranging from severely increased to severely decreased. A similar scoring system from 1 to 7 was used for the health providers asked to evaluate the participants’ cheeks ranging from severely fat to severely wasted. A longitudinal score by both the patient and the doctor can be used in this case or substituted for serial photography, if the patient consents.

A comprehensive review on the methods used in the assessment of body composition in HAART-associated lipodystrophy has been published.35

Treatment
Several approaches to treatment have been attempted with variable success.

- Prevention: Since several studies have shown better outcomes in terms of lower limb fat mass changes in patients on non-stavudine containing regimens, avoiding thymidine analogues where possible is a potential preventive option. These compared regimens of stavudine versus tenofovir both in combination with efavirenz and lamivudine26 and tenofovir/emtricitabine versus lamivudine/zidovudine both in combination with efavirenz,36 although the studies were not always designed to evaluate only the lipoatrophy outcome.

- Dietary interventions: Two studies,37,38 recently published, randomized a diverse group of HIV patients diagnosed with lipodystrophy to a diet intervention and a control group. Diet intervention appeared to improve perceived weight loss as well as quality-of-life (not statistically significant), and although mood states were not significantly improved between the two groups, the control group showed deterioration in mood status, compared with the intervention group, that was concluded to be clinically significant. Better studies, possibly separating lipoatrophy from lipo-hypertrophy from mixed phenotypes, are needed to clarify if dietary interventions have consistent effects on HIV lipodystrophy and if these effects are more important than the constant support offered by frequent contact with a health provider.

- Change of antiretroviral regimen: Changing an established antiretroviral regimen in order to improve lipoatrophy appears to be less effective. Modest improvement of lipoatrophy after substituting stavudine with either abacavir or tenofovir is possible39–41 with results sustained at more than 2 years. At the end of 2 years, though, lipodystrophy was still evident.42 Switching from a PI to a non-nucleoside reverse transcriptase inhibitor (NNRTI) or abacavir did not result in improvement in lipoatrophy.43, 44

- Thiazolidinediones: Thiazolidinediones are insulin-sensitizing agents used in the treatment of diabetes. They have been shown to be effective in reducing visceral fat in studies with patients with congenital forms of
lipodystrophy. The results of thiazolidinedione use in the context of HIV lipoatrophy are conflicting and their use is not currently recommended, although they may have a role in a subgroup of patients. In three studies comparing rosiglitazone with placebo\textsuperscript{44–46} no convincing improvement in lipoatrophy was observed, although some of the studies might have been biased by random allocation of more patients treated with stavudine to the treatment group. Small but randomized studies of HIV patients who already had abnormal glucose metabolism showed a modest effect of rosiglitazone compared with placebo,\textsuperscript{46,47} but this might be a metabolically different subgroup of the HIV population.

- **Recombinant human growth hormone (rhGH):** Human growth hormone has been tried but although it appears to affect the mechanisms underlying lipodystrophy, it has a negligible effect on facial lipoatrophy.\textsuperscript{48–51}

- **Leptin therapy:** A recent randomized, placebo-controlled, double-blinded, crossover study performed in seven HIV positive patients with lipoatrophy\textsuperscript{52} r-metHuLeptin replacement at physiological doses in HIV + leptin-deficient patients with HAART-induced lipoatrophy showed that r-metHuLeptin improved IR, high-density lipoprotein and truncal fat mass. There was no description of effects on facial lipoatrophy.

- **Antioxidants/mitochondrial cofactors:** No firm conclusion regarding antioxidants and mitochondrial cofactors has been reached from available studies.\textsuperscript{8} Uridine, a pyrimidine nucleoside, appears promising since \textit{in vitro} it protects adipocytes from the toxic effects of thymidine analogues. A recent trial\textsuperscript{53} randomized 20 patients with HAART-associated lipoatrophy to either a dietary uridine supplement (36 g three times a day for 10 consecutive days/month) or placebo, for 3 months. Total limb fat, intra-abdominal fat and total body fat all increased in the uridine group, while lean body mass remained unchanged. Interestingly, high-density lipoprotein-cholesterol concentrations decreased in the uridine and increased in the placebo group, whereas fasting serum insulin concentrations did not change. Uridine supplementation was well tolerated did not affect virological control.

- **Surgery and injection of exogenous material for facial contour restoration:** There are limited good quality data on the effects of surgical solutions for lipoatrophy and the studies have focused on facial lipoatrophy since it is perceived as the most debilitating. Bioabsorbable fillers, including Poly-l-lactic acid (PLLA—in the UK Sculptra\textsuperscript{®,} Sanofi Aventis)\textsuperscript{54} and Hyaluronic acid (Restylane\textsuperscript{®,} Perlane\textsuperscript{®} and other trade names in different countries), have been tried. PLLA appears to improve facial appearance and Hospital Anxiety and Depression Scale scores, with an improvement sustainable for at least 18 months in a randomized, open-label, comparative, single-centre study\textsuperscript{54} with mild nodularity at the injection site in 9 out of 30 subjects (30%) and injection site induration in 1 out of 30 subjects (3%). Anaphylaxis with PLLA injections has been reported.\textsuperscript{55} Hyaluronic acid, synthetic non-animal stabilized or rooster comb-derived, has been used for both wrinkle improvement and for treatment of
HAART lipoatrophy. Mild side-effects from non-HIV studies include redness, bruising and swelling, with hypersensitivity reactions noted at 0.6%. Non-bioabsorbable, permanent, fillers have also been tried, including the synthetic reticulate polymer poly-Alkyl-Imide (Bio-Alcamid®-Polymekon, Milan, Italy), a substance that is claimed is easy to remove if needed, which would be an attractive option if spontaneous improvement of lipoatrophy occurs in the future. Lipofilling and submalar silicone implants have been tried in small studies as well. The potential side-effects of granuloma formation and the local migration of particles have to be considered. Finally, autologous fat transplants with or without dermal graft skin transfer has been attempted but concerns over disfiguring facial lipohypertrophy at the graft site at the same time as recurrent fat accumulation at the harvest site have recently been raised and there may be difficulties in identifying enough fat tissue to transplant in patients suffering from severe lipoatrophy.

**Lipohypertrophy**

**Characteristics**

Accumulation of fat tissue has been reported since the advent of HAART. Areas where fat increases include the abdomen, where it represents visceral adipose tissue, the dorsocervical area (‘buffalo hump’), the anterior neck, the areas under the axillae, both male and female breasts and the suprapubic area. Lipomas can also develop on the trunk or extremities. Unlike simple obesity visceral fat deposition is associated with decreased not increased subcutaneous fat. As with lipoatrophy, lipohypertrophy is common and may change with time in an individual. Estimates about the prevalence of lipohypertrophy vary but it may be between 30 and 40%. In a cohort of 452 individuals assessed at baseline and again 1 year later the prevalence of central fat deposition defined as a waist-to-hip ratio of >0.95 for men and of >0.85 for women at baseline and then 1 year later were 44 and 52%, respectively.

**Risk factors/Aetiology**

In the cohort mentioned above, the risk of developing new fat deposition during the year of follow-up was higher among women ($P < 0.001$) and among participants with greater body fat levels ($P = 0.005$) and higher triglyceride levels ($P < 0.001$). Other risk factors were thought to be low CD4 count at the beginning of treatment, white race, increased age and also longer duration of antiretroviral treatment (which could be a marker for longer duration of HIV infection). Lipohypertrophy has been observed in patients who have and have not been exposed to PIs making it unlikely that they play a significant role in its pathogenesis.
Diagnosis
Central lipohypertrophy is defined as a waist-to-hip ratio of >0.95 for men and of >0.85 for women. Of note, an elevated waist-to-hip ratio may be the result of either increased weight circumference or decreased hip circumference. For that reason, an elevated abdominal circumference at action level 2 (for men ≥102 cm and for women ≥88 cm) is considered a better proxy. As described above regarding lipoatrophy, DEXA scanning cannot be used for lipohypertrophy diagnosis. Only CT scan and MRI offer useful information about the degree of abdominal obesity.

Treatment
As with lipoatrophy, several treatment options have been tried.

- Prevention/exercise/dietary interventions: General interventions including increasing the level of exercise and weight reduction may be beneficial. Resistance exercise can be effective in reducing central fat accumulation. Discussion on dietary intervention in lipoatrophy applies to lipohypertrophy as well.

- Metformin: A study of metformin with or without rosiglitazone showed that although metformin was effective in improving insulin sensitivity it failed to reduce visceral fat. In view of the possible side-effects of the medication, metformin therapy cannot be recommended for the sole indication of lipohypertrophy.

- Growth hormone: rhGH appears to be successful in treating central adiposity in a 12 week induction/24 week maintenance double-blind, placebo controlled multicentre trial. At 12 weeks, induction therapy resulted in significant reduction in visceral adiposity (−32.6 versus 0.5 cm; P < 0.001) compared with placebo. The effect of rhGH should be balanced against its side-effects—generally thought to be mild (arthralgias, myalgias, hand numbness, mastalgias), its potential to cause hyperglycaemia and diabetes in predisposed individuals (patients with impaired fasting glucose or glucose tolerance have been generally excluded from growth hormone studies) and its cost. Research in similar molecules is actively pursued.

- Thiazolidinediones do not appear to be effective for managing lipohypertrophy in the HIV population and are not recommended.

- Surgery: Because the central fat deposition is visceral, a surgical approach would not be effective. Surgery has been used to correct buffalo humps but results are limited by fat reaccumulation in some patients.

Disorders of glucose metabolism

Characteristics/epidemiology
In 1997, the FDA issued an advisory warning of hyperglycaemia developing in patients treated for HIV infection with PIs. Since then
many publications have described disorders related to abnormal glucose metabolism in the context of HIV infection including IR/impaired glucose tolerance and frank diabetes. The disease is thought to be a continuum with IR predicting future glucose intolerance and diabetes mellitus.

The epidemiology of the impaired glucose tolerance is currently unknown. Exact estimates of incidence and prevalence are lacking for large HIV populations. Studies assessing the prevalence in populations receiving PIs estimate the prevalence of all abnormalities between 8 and 46%. Abnormalities described include IR but there is a large heterogeneity in both the populations and the endpoints used. Many studies assess glucose abnormalities using nothing more sophisticated than fasting and random glucose levels. In a cohort of HIV-infected patients receiving combination antiretroviral therapy 35% had impaired glucose tolerance. In a cross-sectional study of patients taking PIs 7% had diabetes mellitus with impaired glucose tolerance found in an additional 16%. Contradictory results produced by well-designed studies may reflect preferential screening practices, especially when self-reporting of diabetes is used. Caution should be exercised when interpreting results from healthy volunteers as well as results at relatively short endpoints that can contradict results from longer studies.

Most recently, the Nutrition for Healthy Living (NFHL) study evaluated the association of the Quantitative Insulin Sensitivity Check Index with demographic, socioeconomic, body composition, lipid, liver function, HIV-associated factors (CD4 cell count, viral load, type of HAART and years infected), and injection drug use in a cohort of 378 non-diabetic participants and found no significant difference in the prevalence of IR in the NFHL study versus the National Health and Nutrition Examination Survey III (51% versus 47%; \( P = 0.27 \)).

**Risk factors/Aetiology**

While it is still unclear if HIV increases the risk of IR, factors traditionally quoted as playing a role include indinavir, lopinavir and ritonavir that have been found to induce IR over a short treatment course. The same is not true for atazanavir or amprenavir and the mechanism quoted is interference with the glucose transporter 4. Other risk factors are important for the general population as well and include hepatitis C coinfection with the caveats mentioned above, older age, family history of diabetes, lipoatrophy, non-white race and use of stavudine. Stavudine affects glucose disposal and mitochondrial handling in healthy, non-diabetic individuals and a mechanism involving changes in mitochondrial DNA has been proposed to be responsible. Recently, data on zidovudine/lamivudine including
regimens appear to suggest that the combination of zidovudine/lamivudine reduces peripheral glucose uptake at 3, 12 and 24 months and is associated with delayed reduced limb fat, limb fat-to-total ratio and visceral abdominal adiposity. These findings warrant further research.

**Diagnosis**

The currently accepted and used definitions follow the American Diabetes Association Criteria, according to which impaired fasting (≥8 h) glucose is any measurement between the values of 100 (5.5 mmol/l) and 125 mg/dl (6.9 mmol/l), impaired glucose tolerance is defined as a 2-h post-glucose between 140 (7.7 mmol/l) and 199 mg/dl (10.9 mmol/l) and diabetes mellitus as a fasting glucose of more than 126 mg/dl (6.9 mmol/l) or 2-h post-glucose standardized 75 g load tolerance test (OGTT) value of 200 mg/dl (11 mmol/l). For a diagnosis of diabetes, patients must have symptoms (polyuria, polydipsia, weight loss) and a casual glucose more than 200 mg/dl (11 mmol/l) or a fasting glucose ≥126 mg/dl (6.9 mmol/l) or a 2-h post-glucose by OGTT ≥200 mg/dl (11 mmol/l). There is no universally accepted measure of IR. A fasting blood glucose level should be performed on diagnosis and before initiation of HIV therapy. Recommendations about follow-up vary thereafter, with many authorities recommending monitoring a fasting blood glucose every 3–6 months for patients that have risk factors or undergo changes of their treatment regimen.

**Treatment**

Treatment practices should be the same as in the non-HIV population. Lifestyle modifications are especially important in the context of HIV because of the probable increased cardiovascular risk. Substitution of an NNRTI for a PI in order to increase insulin sensitivity is not evidence based. Metformin can be a useful addition to the antidiabetic armamentarium, but caution is advised when NRTIs are prescribed because of the risk of lactic acidosis. Metformin can improve IR in the context of lipodystrophy. Thiazolidinediones (rosiglitazone and pioglitazone) can also be used in this context but concerning data about the impact of rosiglitazone on total cardiac risk have recently emerged.

**Dyslipidaemia**

**Characteristics**

Lipid abnormalities were initially noted in HIV patients before the advent of HAART. These lipid abnormalities are associated with many
chronic infections and are not unique to HIV. They include elevations of the total triglycerides (TG), raised levels of very low-density lipoprotein (VLDL) and low levels of HDL. Low-density lipoprotein (LDL) is also decreased.

Since HAART became available, a new combination of lipid abnormalities has appeared, including low HDL, high TG and high LDL. This combination of lipid abnormalities tends also to be associated with IR. Because patients receiving HAART appear to be at increased risk for cardiovascular complications, it is desirable to assess and treat the hyperlipidaemia when the HIV disease is initially controlled. As with glucose abnormalities, exact figures for the incidence and prevalence of dyslipidemia in the context of HIV infection are not available. A French study that followed an inhomogeneous group of 925 patients prospectively for a median of 25 months found that 70 patients (8%) experienced high TG. A prospective population study from Canada quotes a cumulative incidence of dyslipidaemia of 9% within 31 months. The Paediatric AIDS Clinical Trials Group 219C (PACTG 219C) is a prospective cohort study designed to examine long-term outcomes in children born to HIV-infected women. From PACTG 219C, 13% of infected children in a recent analysis had hypercholesterolemia compared with 4.8% of uninfected children.

**Risk factors/Aetiology**

- Most PIs, with the exception of atazanavir, are associated with high LDL and TG. The development of dyslipidaemia during PI use appears to be exposure (dose and time) related. The different PIs vary in their effect on lipids, whether boosted with ritonavir or not. An analysis of the AIDS Clinical Trial Group Studies (ACTG) showed that race/ethnicity is also a highly significant predictor of plasma lipids in fully adjusted models. The effect of PI exposure appears to differ across race/ethnicity. Black/non-Hispanic, compared with White/non-Hispanics and Hispanics, have lower plasma TG levels overall, but the greatest increase in TG levels when exposed to PIs.

- NNRTIs also appear to have an effect on hyperlipidemia, producing increases in levels of LDL and TG. Because NNRTIs have the potential of also increasing HDL, the ratio of total cholesterol to HDL may be preserved.

**Diagnosis**

Diagnosis of dyslipidemia in the context of HIV should follow the recommendations for non-HIV-infected patients. A fasting lipid profile should ideally be offered before initiation of antiretroviral therapy. Fasting lipid profiles should be repeated before and after interventions until the cholesterol goal is reached and monitored periodically thereafter.
Treatment
Guidelines on the management of dyslipidemia in adults with HIV were published by the Infectious Diseases Society of America and the Adult AIDS Clinical Trials Group in 2003 and a new version is expected in late 2007. Assessment of risk factors according to the National Cholesterol Education Programme Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATPIII) guidelines is used to guide treatment goals. When appropriate, Framingham calculations are used. In summary, lifestyle modifications such as a low-fat diet, increased exercise, reduced alcohol consumption and smoking cessation should be encouraged. Secondary causes of hyperlipidemia must be identified and corrected when possible. In the cases of patients where the above are not successful, changing the anti-retroviral therapy or instituting lipid controlling medications may become necessary.

- Changing from PIs or NNRTIs to boosted atazanavir can be effective. During a 24 week open-field, prospective, observational cohort study including 33 patients, non-HDL cholesterol decreased by 22% but HDL and LDL cholesterol profiles did not change significantly. Comparable results were observed at the 48 week cutoff of the SWAN study, where HIV-positive patients with virologic suppression who were receiving stable PI-based regimens with or without ritonavir were switched to atazanavir for reasons of regimen simplification. At week 48, the percentages of patients with LDL cholesterol levels of ≥100 mg/dl (2.56 mmol/l) but <130 mg/dl (3.33 mmol/l), ≥130 mg/dl (3.33 mmol/l) but <160 mg/dl (4.10 mmol/l), ≥160 mg/dl (4.10 mmol/l) but <190 mg/dl (4.87 mmol/l) and ≥190 mg/dl (4.87 mmol/l), were 40, 15, 5 and 2%, respectively, for the atazanavir-treatment group, compared with 24, 24, 17 and 11%, respectively, for the comparator PI group. Use of lipid-lowering agents was observed to be higher among patients receiving the non-atazanavir PI regimen (14% versus 8%; P = 0.05).

- Changing from PIs to NNRTIs in NNRTI naïve patients might be inferior to treating with statins and it produces different results for efavirenz and nevirapine.

- Lipid lowering medications: Statins that have substantial interaction with the p450 (CYP) 3A4 isoenzyme should not be used. For patients taking PIs, simvastatin and lovastatin should be avoided, but atorvastatin, fluvastatin and combination pravastatin (with or without fenofibrate) have been used. Pravastatin and fluvastatin are least likely to have drug interactions. An interesting recent study showed that HAART-inhibited endothelial-cell mediated healing and promoted neointima formation after angioplasty in rats but these effects were attenuated by cotreatment with rosuvastatin. A fibric acid derivative, either gemfibrozil or fenofibrate can be used for primary high hypertriglyceridaemia and Niacin might be used
for mixed dyslipidaemia. Ezetimibe appears to be effective and well tolerated so far. 104

**Summary/conclusions**

HIV not only affects the immune system but both the virus and its treatment appear to have profound effects on endocrine pathways. Clinicians need to be aware of these and of ways to avoid and treat metabolic complications. Although not covered in this review, HIV also significantly affects bone metabolism and other endocrine pathways. This devastating epidemic is slowly entering the chronic disease phase, especially in developed countries. While that is happening, we have the opportunity to apply established research paradigms in epidemiology and endocrinology and gain a greater understanding of human metabolism.

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