



Nutrition and the HIV-associated lipodystrophy syndrome

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Abstract

HIV-associated lipodystrophy syndrome (HALS), comprising metabolic and morphological alterations, is a known side effect of highly active antiretroviral therapy (HAART). Evidence for the role of nutrition in the management of the systemic parameters of HALS is currently limited. In the present paper we review the current knowledge base surrounding HALS, focusing particularly on the role of nutrition in mitigating the systemic parameters of the syndrome. Reported prevalence of HALS was found to vary from 9 to 83% due to lack of a standardised definition, as well as variations in assessment methods and in the study population used. HALS is associated with both morphological (lipoatrophy, lipohypertrophy) and metabolic (dyslipidaemia, glucose intolerance, diabetes, hypertension, endothelial dysfunction and atherosclerosis) alterations, which may occur singly or in combination, and are associated with an increased risk of CVD. HAART-induced adipocyte inflammation, oxidative stress and macrophage infiltration, as well as altered adipocyte function and mitochondrial toxicity, have been shown to be central to the development of HALS. The adipocyte, therefore, represents a plausible target for treatment. Pharmacological and surgical treatment interventions have shown effect. However, their use is associated with numerous adverse effects and complications. Targeted lifestyle interventions may provide a useful alternative for managing HALS owing to their safety and tolerability. A Mediterranean-style diet has been found to be effective in improving the systemic parameters of HALS. Furthermore, the effects of *n*-3 PUFA supplementation are encouraging and future randomised controlled trials investigating the beneficial effects of *n*-3 PUFA in HALS are justified.

Key words: HIV-associated lipodystrophy syndrome; Highly active antiretroviral therapy; Nutrition therapy; Mediterranean diet; *n*-3 PUFA

Introduction

The number of individuals living with HIV/AIDS has increased globally⁽¹⁾, with a current estimated global prevalence of 33.3 million⁽²⁾. In the UK alone, the incidence of HIV/AIDS has almost doubled in the past decade and there are now an estimated 86 200 individuals living with HIV/AIDS⁽³⁾. This represents less than 1% of the global HIV/AIDS population, while Sub-Saharan Africa remains most severely affected by the HIV pandemic, with 67% of the global HIV/AIDS population located here⁽²⁾.

A significant turning point in the management of HIV came with the introduction of the nucleoside RT inhibitor (NRTI) zidovudine (ZDV), the first antiretroviral drug approved by the Food and Drug Administration in 1987⁽⁴⁾. For those with access to antiretroviral therapy (ART), HIV infection no longer represented an immediate

threat to mortality⁽⁵⁾, and was, in many cases, transformed into a chronic condition.

The development of subsequent antiretroviral drugs zalcitabine (ddC), didanosine (ddI) and stavudine (d4T) led to combination ART (cART), the first of which was ZDV and ddC⁽⁶⁾. cART, commonly referred to as highly active ART, consists of at least two antiretrovirals, most usually from one of three main drug classes: NRTI and nucleotide RT inhibitors (NtRTI), protease inhibitors (PI) and non-nucleoside RT inhibitors (NNRTI)⁽⁷⁾. NRTI and NtRTI interact with the substrate-binding site of the HIV RT enzyme⁽⁸⁾, which halts the production of new virions^(9,10). NNRTI bind specifically with a non-substrate-binding site of RT, disrupting the enzyme's catalytic site^(8,11); PI inhibit the protease enzyme, thus preventing the host cell from cleaving the viral proteins into active viral particles⁽¹¹⁾; fusion inhibitors

Abbreviations: ART, antiretroviral therapy; cART, combination antiretroviral therapy; CT, computed tomography; d4T, stavudine; HALS, HIV-associated lipodystrophy syndrome; LA, lipoatrophy; LH, lipohypertrophy; MI, myocardial infarction; *n*-3 LC-PUFA, *n*-3 long-chain PUFA; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NNRTI, non-nucleoside RT inhibitor; NRTI, nucleoside RT inhibitor; PI, protease inhibitor; REE, resting energy expenditure; T2DM, type 2 diabetes mellitus; ZDV, zidovudine.

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prevent viral capsid entry into the host cell by blocking the attachment, co-receptor binding and fusion of the viral particle⁽¹²⁾; C-C chemokine receptor type-5 (CCR5) inhibitors prevent viral entry into the host cell by inhibiting CCR5 signalling, which allows the virus to enter its target cell⁽¹³⁾; integrase inhibitors, a new class of antiretrovirals, inhibit the insertion of the HIV pro-viral DNA into the host cell genome⁽¹⁴⁾.

Shortly after the introduction of PI, which were in the context of sole use or cART, case reports of disorders of glucose metabolism⁽¹⁵⁾ and alterations in body fat distribution^(16–19) began to appear in the literature. HIV-associated lipodystrophy syndrome (HALS) was the term subsequently used to define these metabolic and morphological alterations, and was first described in 1998 by Carr *et al.*⁽²⁰⁾. Though ART, particularly PI and NRTI, are the main drivers of HALS, the virus itself and host genetics also contribute to its pathogenesis⁽²¹⁾.

HALS comprises peripheral lipoatrophy (LA) and central lipohypertrophy (LH)⁽²²⁾, which can occur together or separately⁽²³⁾, dyslipidaemia⁽²⁴⁾, insulin resistance⁽²⁵⁾, type 2 diabetes mellitus (T2DM)^(26–28), hypertension⁽²⁵⁾, endothelial dysfunction⁽²⁹⁾, and altered cytokine and adipokine production⁽²⁹⁾. Collectively these abnormalities have been associated with an increased risk of CVD in this population^(30–32). HALS has been associated with risk factors for premature CVD and premature myocardial infarction (MI)^(33–38).

Nutrition plays a key role in maintaining health in HIV infected individuals⁽³⁹⁾. According to a recent consensus statement from the American Dietetic Association⁽³⁹⁾, evidence on the role of diet in mitigating systemic parameters in HALS is limited. There are a number of studies that have generally investigated the area by cross-sectional analysis of diet and systemic parameters of HIV-positive adults with and without HALS. Existing evidence indicates the potential benefit of a diet high in fibre^(40,41) and Ca⁽⁴²⁾, which includes polyunsaturated fat⁽⁴³⁾, and which corresponds with a Mediterranean-style dietary pattern^(44,45) in lowering the risk of metabolic and morphological abnormalities in HALS.

In the present article, we aim to review the existing knowledge base surrounding HALS, including epidemiology, associated metabolic and morphologic complications, potential molecular mechanisms involved in its pathogenesis, as well as strategies used in the management of the condition, focusing particularly on the potential role of nutrition in mitigating the complications of the syndrome.

Prevalence and definition

The prevalence of HALS has been shown to vary widely from 9 to 83% depending on the assessment criteria used (Table 1). Furthermore, the study populations used to assess prevalence of the condition may also account for the observed differences in published prevalence.

The majority of studies recruit only HIV-infected individuals receiving ART or those receiving ART and ART-naive comparisons. Five studies compare those with HIV infection with those without HIV infection^(20,32,46–48), and only one of these compares prevalence rates between HIV-infected individuals receiving PI, those who were PI-naive and healthy men⁽²⁰⁾.

The methods used to identify HALS also greatly affect prevalence estimates. Currently used methods include patient self-report, physician examination/report, a combination of these, anthropometric indices, biochemical indices, dual-energy X-ray absorptiometry, computed tomography (CT) and MRI. Patient self-report and physician report are commonly used methods; however, the accuracy of these subjective methods has not been evaluated⁽⁴⁹⁾, and physician and patient assessments of HALS have been shown to vary⁽⁵⁰⁾.

Carr *et al.*⁽⁵¹⁾ showed that differences in the definition of the syndrome can contribute to a variation in prevalence of between 19 and 65%. Existing definitions include LA or LH^(48,52–62), LA alone^(20,61–75), LH alone^(61–68,70–78), or a combination of LA and LH^(52,54,55,61,62,64,66–68,71–75,79–85). The main definitions for the metabolic alterations associated with HALS (abdominal obesity, dyslipidaemia, raised blood pressure, insulin resistance and a pro-inflammatory, prothrombotic state) are the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III criteria⁽⁸⁶⁾, used by the majority of researchers^(24,25,32,47,73,87,88), the International Diabetes Federation (IDF) Guidelines⁽⁸⁹⁾ used in one study⁽⁷⁵⁾, a combination of NCEP and IDF used in three studies^(25,88,90), the 'Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition'⁽⁹¹⁾ used in one study⁽⁴⁶⁾, and the US National Institutes of Health Division of AIDS definition (2004 version)⁽⁹²⁾ used in one study⁽⁹³⁾. In addition to metabolic definitions, anthropometric techniques have been used in the identification of central adiposity in HALS⁽⁵⁹⁾. The use of anthropometry in detecting small changes in fat distribution in HIV patients is, however, limited, as it is associated with inter-individual differences in the measurement of fat distribution in HIV patients⁽⁹⁴⁾.

Carr *et al.*⁽⁸²⁾ have attempted to objectively define HALS and developed an objective case definition for the syndrome based on age, sex, duration of HIV infection, HIV disease stage, waist:hip ratio, anion gap, serum HDL concentration, trunk:peripheral fat ratio, percentage leg fat, and intra-abdominal:extra-abdominal fat ratio. This definition is 79% sensitive and 80% specific for the diagnosis and intensity of the syndrome. However, the definition requires anthropometric variables from dual-energy X-ray absorptiometry and CT, reducing its utility in clinical practice⁽⁵⁰⁾.

Research has also focused on grading the severity of the components of HALS. The HIV Outpatient Study scale was



Table 1. Prevalence of the HIV-associated lipodystrophy syndrome (HALS)

Authors	Study design	n	Participants	Methods used to define HALS	Findings
Western Europe					
Bergersen <i>et al.</i> (2005) ⁽¹⁰³⁾	CS	308	HIV+, F	Anthro, Biochem	37.3% of patients on ART v. 10.9% ART-naive
Bernasconi <i>et al.</i> (2002) ⁽⁸⁰⁾	P	1359	HIV+, SHCS cohort	Self-report; physician report	43% had at least one sign of HALS; 28% LA; 30% LH
Boufassa <i>et al.</i> (2001) ⁽⁵²⁾	CS	685	HIV+, 70.5% M	Physician report	58.8% HALS
Chêne <i>et al.</i> (2002) ⁽⁵³⁾	RCT*	120	HIV+, 81% M	Physician report; Biochem	31% HALS after 30 months, 18% LA, 6% LH; 7% mixed
Elgalib <i>et al.</i> (2011) ⁽⁸⁸⁾	CS	678	HIV+, 74% M, CREATE cohort, 74% receiving ART	IDF (2005) ⁽⁸⁹⁾ and NCEP ATP III ⁽⁸⁶⁾ criteria	25% HALS (IDF, 2005); 24% HALS (NCEP ATP III); 68% metabolic syndrome
Fellay <i>et al.</i> (2001) ⁽⁸⁴⁾	CS	1160	HIV+, SHCS cohort	Physician report; according to Carr <i>et al.</i> (1998) ⁽²⁰⁾	47% with clinical and 27% with laboratory adverse events related to HALS
Galli <i>et al.</i> (2002) ⁽⁵⁴⁾	CS	655	HIV+, 72.1% M, LipolCoNa study	Self-report; retrospective and prospective physician reports	19.5% HALS
Galli <i>et al.</i> (2003) ⁽⁸³⁾	P	212	HIV+, F	Self-report; physician report	44.8% central LH; 42.9% peripheral LA; 33% mixed
Galli <i>et al.</i> (2003) ⁽⁵⁵⁾	CS	2258	HIV+, 70% M	Self-report; physician report	Adipose tissue alterations in 33.2%
Gervasconi <i>et al.</i> (1999) ⁽⁷⁶⁾	CS	306	HIV+, F	Self-report; physician report; DXA	10.4% HALS
Goujard <i>et al.</i> (2001) ⁽⁷⁷⁾	CS	143	HIV+, French PRIMO cohort	Physician report	Cumulative incidence HALS 5%; increased to 9% at 12 months and 26% at 24 months
Jericó <i>et al.</i> (2005) ⁽⁸⁷⁾	CS	710	HIV+, 72% M	Physician report; Biochem; NCEP ATP III ⁽⁸⁶⁾ criteria	17% metabolic syndrome
Martínez <i>et al.</i> (2001) ⁽⁷⁹⁾	P	494	HIV+, 76% M	Self-report; physician report	17% HALS
Mauss <i>et al.</i> (2002) ⁽⁶⁷⁾	CSOS	221	HIV+, 87% M, DAGNAE LipART cohort	Self-report; two physician reports	34% HALS; 18% LA; 8% LH; 74% mixed
Nguyen <i>et al.</i> (2008) ⁽⁶⁰⁾	P	5427	HIV+, 68% M, SHCS cohort	Physician report	33.9% HALS
Saint-Marc <i>et al.</i> (2000) ⁽⁶³⁾	CS	154	HIV+ M, LIPOCO cohort, ART experienced or ART-naive	Self-report; physician report	53.25% HALS; 15.89% LA; 4.21% LH; 18.22% mixed
Savès <i>et al.</i> (2002) ⁽⁸¹⁾	CS	614	HIV+, 80% M, APROCO cohort	Physician report	62% HALS
Seminari <i>et al.</i> (2002) ⁽⁶¹⁾	OB	504	HIV+, M, receiving ART	–	39.3% HALS; 23% LA; 20% LH; 25% mixed; 32% isolated metabolic alterations
Thiébaud <i>et al.</i> (2000) ⁽⁶⁴⁾	CS	581	HIV+, > 13 years, Aquitaine cohort	Physician report	38% HALS; 16% LA; 12% LH; 10% mixed; 54% metabolic abnormalities
Young <i>et al.</i> (2005) ⁽⁵⁸⁾	P	925	HIV+, ART-naive	Self-report; physician report	9% HALS
Eastern Europe					
Jevtovic <i>et al.</i> (2009) ⁽⁷³⁾	CS	582	HIV+, stable on ART	Self-report; physician report	29.1% HALS; 47% hyperlipidaemia; 9.6% T2DM
Africa					
Rwanda					
Mutimura <i>et al.</i> (2007) ⁽⁵⁹⁾	RT	571	HIV+, receiving ART for ≥ 6 months	Self-report; confirmed by physician	34% HALS; 9% LA; 19% LH; 72% mixed
van Griensven <i>et al.</i> (2007) ⁽⁷¹⁾	CS	409	HIV+, 21.5% M, stable on ART > 1 year	Self-report; physician report	34.2% HALS; 9.8% LA; 4.9% LH; 19.6% mixed
Dakar					
Mercier <i>et al.</i> (2009) ⁽⁷⁴⁾	OB	361	181 HIV+ cases and 180 HIV+ controls treated with ART for 4–9 years	Validated physician report of patients' self-report using Carr <i>et al.</i> (2003) ⁽⁸²⁾	31.1% HALS; 13.3% LA; 14.5% LH; 3.3% mixed
Benin					
Zannou <i>et al.</i> (2009) ⁽⁷⁵⁾	P	79	HIV+, 40.5% M, ART-naive	Self-report; physician report; Biochem; BIA; IDF (2005) ⁽⁸⁹⁾ criteria	Cumulative incidence HALS 30%; 9% LA; 24% LH; 2.5% mixed; 13% metabolic syndrome
Asia					
Asia-Pacific Region					
Han <i>et al.</i> (2011) ⁽⁹³⁾	OB	2072	HIV+ commencing ART	US NIH Division of AIDS (2004 version) ⁽⁹²⁾ definition (severity grade ≥ 3)	10.5% HALS
West India					
Pujari <i>et al.</i> (2005) ⁽⁷⁰⁾	CS	180	HIV+ cases and 126 HIV+ controls, receiving first-line ART for > 1 year	Self-report; physician report	46.1% HALS

Table 1. Continued

Authors	Study design	n	Participants	Methods used to define HALS	Findings
South India Kalyanasundaram <i>et al.</i> (2012) ⁽⁶²⁾	CS	363	145 HIV+ on ART, 146 HIV+ ART-naive, seventy-two HIV-;	–	60.7% HALS; 51.1% LA; 22.7% LH; 22.7% mixed
Singapore Paton <i>et al.</i> (2002) ⁽⁶⁸⁾	CS	410	HIV+, receiving ART and ART-naive	Self-report	45.9% LA; 32.4% LH; 8.3% mixed
Thailand Puttawong <i>et al.</i> (2004) ⁽⁵⁷⁾	CS	278	HIV+, 60% M, ART and ART-naive	Self-report; physician report	17% HALS
Australia Carr <i>et al.</i> (1998) ⁽²⁰⁾	CS	295	HIV+, 116 receiving PI, thirty-two PI-naive, forty-seven healthy men	Self-report; physician report	64% HALS in PI recipients; 3% in PI-naive
Carr <i>et al.</i> (1999) ⁽⁹⁸⁾	CS	158	HIV+, 113 receiving PI, forty-five PI-naive	Self-report; physician report; DXA	83% HALS in PI recipients; 4% in PI-naive
Carr <i>et al.</i> (2003) ⁽⁸²⁾	CC	1081	HIV+, 85% M, ART and ART-naive	Self-report; physician report; Biochem; DXA; CT	9% LA; 6% LH
Carter <i>et al.</i> (2001) ⁽⁵¹⁾	CS	159	HIV+M, 76% receiving PI, 14% received PI in past, 2.5% ART-naive	Self-report; physician report; Biochem; Anthro; DXA	HALS prevalence varied (19–65%) depending on the definition
Miller <i>et al.</i> (2003) ⁽⁵⁶⁾	CS	1348	HIV+, 95% M, > 17 years, 20% AIDS, ART and ART-naive comparisons	Physician assessment	53% HALS; 20% LA; 6% LH; 27% mixed
Samaras <i>et al.</i> (2007) ⁽²⁵⁾	CS	788	HIV+, Lipodystrophy Case Definition cohort, ART and ART-naive	Self-report; physician report; Biochem; IDF (2005) ⁽⁸⁹⁾ and NCEP ATP III ⁽⁸⁶⁾ criteria	Metabolic syndrome: 14% (IDF, 2005); 18% (NCEP ATP III)
USA and Canada Heath <i>et al.</i> (2001) ⁽⁷⁸⁾	OB	1035	HIV+, 92% M, 62% receiving PI, 74% PI-naive	Self-report	50% HALS; 36% LA; 33% LH
Heath <i>et al.</i> (2002) ⁽⁶⁶⁾	P	366	HIV+, 89% M, ART-naive	Self-report; Biochem	Cumulative incidence LA 29%; 23% LH; 13% mixed; 9% dyslipidaemia
Jacobson <i>et al.</i> (2006) ⁽⁴⁶⁾	CS	477	HIV+ cases, HIV- comparison group from NHANES cohort, receiving ART	Physician report; Biochem; DXA; definition of metabolic syndrome†	24% metabolic syndrome
Lichtenstein <i>et al.</i> (2001) ⁽⁶⁵⁾	OB	1077	HIV+, HOPS cohort, receiving ART	Self-report; physician report	49% HALS
Lichtenstein <i>et al.</i> (2003) ⁽⁶⁹⁾	P	546	HIV+, receiving ART	Agreement between self-report and physician report	13.1% developed moderate/severe LA after 20 months
Mondy <i>et al.</i> (2007) ⁽³²⁾	PCS	471	HIV+, 66% M	Biochem; Anthro; NCEP ATP III ⁽⁸⁶⁾ criteria	26% metabolic syndrome
Sobieszczyk <i>et al.</i> (2008) ⁽⁴⁷⁾	CS	2393	HIV+, F, 1725 seropositive, 668 high-risk seronegative	Self-report; physician report; Biochem; NCEP ATP III ⁽⁸⁶⁾ criteria	33% metabolic syndrome
Tien <i>et al.</i> (2003) ⁽⁴⁸⁾	P	605	HIV+ cases, 210 HIV- controls, Women's Interagency HIV cohort	Self-report; physician report	48.6% HALS
van der Valk <i>et al.</i> (2001) ⁽⁸⁵⁾	RCT	175	HIV+, PI- or stavudine-naive	Physician report	17% HALS
Walmsley <i>et al.</i> (2008) ⁽⁷²⁾	P	68	HIV+, 85% M	Self-report; physician report; Biochem; DXA, photographs at baseline and every 6 months	77% HALS; 25% LA; 32% LH; 19% mixed
Multinational: EU, Australia, USA Worm <i>et al.</i> (2010) ⁽²⁴⁾	POB	33 347	HIV+, DAD study cohort	Biochem; modified NCEP ATP III ⁽⁸⁶⁾ criteria	Metabolic syndrome increased from 19.4 to 41.6% between 2000 and 2007

CS, cross-sectional; HIV+, HIV-positive; F, female; Anthro, anthropometry; Biochem, biochemical assessment; ART, antiretroviral therapy; P, prospective study; SHCS, Swiss HIV Cohort Study; LA, lipoatrophy; LH, lipohypertrophy; M, male; RCT, randomised controlled trial; CREATE, Cardiovascular Risk Evaluation and Antiretroviral Therapy Effects; IDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; LipoiCoNa, substudy of the Italian Cohort Naive Antiretrovirals; DXA, dual-energy X-ray absorptiometry; CSOS, cross-sectional observational study; APROCO, Antiprotéases Cohorte; OB, observational study; T2DM, type 2 diabetes mellitus; RT, randomised trial; BIA, bioelectrical impedance analysis; NIH, National Institutes of Health; HIV-, HIV-negative; PI, protease inhibitor; CC, case-control study; CT, computed tomography; NHANES, National Health and Nutrition Examination Survey; HOPS, HIV Out-Patient Study; PCS, prospective cross-sectional study; EU, European Union; POB, prospective observational study; DAD, Data Collection on Adverse Effects of Anti-HIV Drugs.

* Long-term follow-up of a randomised controlled trial.

† Based on the 'Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition'⁽⁹¹⁾.

one of the first methods used to assess the severity of HALS in different areas of the body, including the abdomen, arms, legs, hips/buttocks and face⁽⁶⁵⁾. Abnormalities in each area were graded from 'subtle' (noticeable only if looked for; no change in clothing fit), to 'moderate' (easily noticed by patient or physician; clothing has become tight or loose) and 'severe' (obvious to the casual observer; has required a change in clothing size). All changes were graded both subjectively (patient self-report) and objectively (physician examination)⁽⁶⁵⁾. Subsequently, Carr & Law⁽⁹⁵⁾ developed a severity grading scale based on their objective case definition of HALS; however, in the same paper they recommended abandoning the assessment of lipodystrophy severity, and suggested the lipodystrophy case definition score provided the best objective measure of severity. Recently, Fontdevila *et al.*⁽⁹⁶⁾ have developed a CT-validated grading system for determining the severity of facial LA based on the loss of facial bone and muscle structures. This grading system is recommended for use when comparing the efficacy of fat grafting procedures and, therefore, may not be ideal in routine clinical practice.

In the absence of a clear definition for HALS, the incidence and prevalence of the syndrome remain uncertain⁽⁹⁷⁾. It is clear that the definition and diagnostic criteria for HALS are poor, epidemiological data on its prevalence and incidence are also lacking, and as a result Guaraldi & Barabouitis⁽⁹⁷⁾ question whether HALS 'is over?'. In this paper, the authors suggest replacing the definition of HALS with the non-infectious co-morbidities that develop as a result of HIV infection.

Morphological alterations

In their original paper, Carr *et al.*⁽²⁰⁾ refer to lipodystrophy as 'fat wasting of the face, limbs and upper trunk'. Further research by the same authors acknowledged lipid accumulation as another feature of HALS⁽⁹⁸⁾. A review, published the same year, concluded that LA and LH are distinct entities with individual pathophysiological mechanisms underlying their development⁽⁹⁹⁾. Although these early findings separate LA and LH in the definition of HALS, recent findings conclude that the abnormalities associated with HALS, including LA and LH, can occur singly or in combination⁽²²⁾; for the purposes of the present review they will be discussed separately.

Lipoatrophy

LA, characterised by loss of subcutaneous fat⁽¹⁰⁰⁾, is distinctly different from the traditional HIV wasting syndrome, characterised by a disproportionate decrease in lean body mass⁽¹⁰¹⁾. LA, as a side effect of ART, is seen mainly in the face (facial LA) and the extremities (peripheral LA)⁽⁶³⁾. Fat wasting of the face usually presents as malar or temporal wasting⁽²²⁾. Peripheral fat wasting typically occurs in the

arms, shoulders, buttocks and legs⁽¹⁰²⁾. The latter type of fat wasting is often accompanied by prominent superficial veins, which contribute to the emaciated appearance observed in these individuals⁽¹⁰³⁾.

Initial reports attributed the development of LA to PI⁽²⁰⁾; however, it is now known that the use of NRTI such as d4T is more strongly linked with its development^(61,104). Some NRTI combinations, such as d4T and didanosine (ddI), are contraindicated as a result of their severe lipotrophic side effects⁽¹⁰⁵⁾. In addition to type of ART, a number of other risk factors for LA have been identified including older age⁽¹⁰⁵⁾, a decrease in BMI before ART⁽⁶⁹⁾, white race⁽⁶⁹⁾, use of PI for greater than 2 years⁽⁹⁸⁾, and factors relating to disease progression including lower CD4 cell count⁽⁶⁹⁾, duration and severity of HIV infection^(65,106) and prior diagnosis of AIDS⁽⁶⁵⁾.

Lipohypertrophy

LH is characterised by adipose tissue accumulation mainly in the intra-abdominal ('Crix belly')^(19,20,102,107,108) and dorsocervical ('buffalo hump') regions^(17,18,109). Other characteristic features of LH include breast enlargement, observed in both males and females^(59,68,77,80,81), accumulation of adipose tissue on the anterior region of the neck⁽¹¹⁰⁾, side of the neck^(59,68), under the axillae⁽¹¹⁰⁾ and in the suprapubic region⁽¹¹¹⁾, and localised or generalised lipomas⁽⁵⁶⁾. LH is distinct from simple visceral fat accumulation, as it is associated with a decrease, rather than an increase, in subcutaneous fat^(90,108). It is worth noting that abdominal LH is the most commonly identified lipohypertrophic change in HALS patients^(52,56,57,59,68,77–81,102).

Risk factors associated with the development of LH in the context of HIV and ART include age, female sex, having a BMI of greater than 25 kg/m²⁽²⁶⁰⁾, and having a low CD4 cell count^(65,69). The type of ART has also been shown to play a role in the pathogenesis of LH. Jacobson *et al.*⁽⁴⁶⁾ demonstrated that LH was observed in both patients who have and have not been exposed to PI, indicating that PI are not the only cause of LH. Thymidine analogues in particular have been shown to increase the risk of developing LH⁽⁷¹⁾. Novel drugs, such as the peptidic HIV-1 fusion inhibitor enfuvirtide, have also recently been implicated in the development of LH⁽¹¹²⁾. In addition to the type of ART, a longer duration of treatment has been associated with an increased risk of developing LH⁽⁷⁹⁾.

Metabolic alterations

Dyslipidaemia

Before the advent of ART, evidence suggested that HIV infection itself caused abnormalities of blood lipids^(113,114). One study investigating lipid abnormalities associated with seroconversion in men found that HIV infection was associated with a reduction in total

cholesterol, LDL and HDL⁽¹¹⁵⁾. Subsequent initiation of ART in the same subjects led to a significant increase in total cholesterol and LDL concentrations from baseline to follow-up, confirming the role of ART in the pathogenesis of dyslipidaemia in HIV⁽¹¹⁵⁾.

The prevalence of lipid disorders in HIV-infected individuals treated with ART has been shown to vary from 24 to 72%^(53,64,70,75,88,116,117). Characteristic lipid abnormalities associated with HALS include elevated total cholesterol and LDL, elevated TAG⁽²⁰⁾ and reduced HDL⁽¹¹⁸⁾. Early studies attributed the development of dyslipidaemia to PI therapy^(119,120). Subsequent studies have, however, shown that both NRTI and NNRTI are involved in the development of lipid abnormalities in HIV^(121,122). Furthermore, both *in vitro* and *in vivo* studies have demonstrated an association between cART and the development of more pronounced lipid abnormalities^(118,123). A recent UK study found that impaired postprandial TAG clearance in HIV patients receiving ART was exacerbated by a combination of NRTI and PI⁽¹²⁴⁾. A recent retrospective cohort study from Brazil found that PI increased serum TAG but not total cholesterol concentrations in 102 HIV-infected patients⁽¹²⁵⁾. In the same study NNRTI were associated with an increase in total cholesterol with no significant effect on TAG levels. Similarly, Walmsley *et al.*⁽⁷²⁾ in their prospective cohort study of HIV patients found that after 12 months of treatment with NNRTI, only total cholesterol concentrations increased significantly. Results pertaining to the duration of ART and risk of lipodystrophy are inconsistent, with some showing that increased duration increases risk of dyslipidaemia^(81,118), while other studies have shown no effect of duration on the risk of dyslipidaemia⁽³²⁾.

A number of factors have been identified which are associated with an increased risk of dyslipidaemia in patients receiving ART. Similar to the general population, dyslipidaemia in HIV has been shown to occur to a greater extent in female patients⁽¹²⁶⁾. Although African-Americans in the general population have been shown to have a lower prevalence of hypertriglycerolaemia⁽¹²⁷⁾, Foulkes *et al.*⁽¹²⁸⁾ found that exposure to PI induced the greatest increase in TAG concentrations in black compared with white and Hispanic populations. This may indicate a role for race/ethnicity in increasing the risk of dyslipidaemia in HIV. It is important to note, however, that this study had, according to the authors, limited power, making it difficult to detect small interaction effects within these racial/ethnic groups. A number of polymorphisms of genes including *APOA5*, *APOC3*, *APOE*, sterol-regulatory element-binding protein-1c (*SREBP1c*) and *TNF* have also been associated with an increased risk of dyslipidaemia in HIV-infected individuals^(129–133).

It has been suggested that the diagnosis of dyslipidaemia in HIV-infected individuals should be made using recommendations for non-HIV-infected individuals⁽⁹⁰⁾. For the general population, dyslipidaemia is diagnosed using

a fasting lipid profile and defined using the NCEP ATP III criteria. Ideally, fasting lipid profiles should be offered to patients before initiation of ART in order to gain an insight into the exact changes caused thereafter by ART⁽⁹⁰⁾. LDL levels are the primary target of the NCEP ATP III guidelines, which recommend that lifestyle modifications be trialled first, followed by statins, to lower LDL⁽⁸⁶⁾.

Glucose abnormalities

Before the ART era, the development of T2DM in HIV-infected individuals was attributed to the anti-microbial medication pentamidine⁽¹³⁴⁾ and was relatively uncommon⁽¹³⁵⁾. Following the introduction of PI, however, a greater number of reported glucose disorders began to emerge in HIV-infected individuals^(15,136,137).

Abnormalities in fasting blood glucose concentration have been found in up to 20% of patients^(64,72,74,88), while prevalence figures for impaired fasting glucose^(59,74,75,81,88) and impaired glucose tolerance^(57,72,73,81,98,116) have been shown to vary from 3.8 to 18% and from 7 to 37%, respectively. In comparison, the prevalence of impaired glucose tolerance and impaired fasting glucose in the general population is 8.4 and 6.3%, respectively⁽¹³⁸⁾.

Puttawong *et al.*⁽⁵⁷⁾ and Tomažič *et al.*⁽¹¹⁶⁾ identified the prevalence of insulin resistance in 30 and 38% of their HIV subjects, respectively. The prevalence of diabetes in the general population has been shown to be 9.8% for men and 9.2% for women⁽¹³⁹⁾, while in patients receiving ART, prevalence has been shown to range from 7 to 27%^(73,81,98,116). Although the aforementioned studies have shown a relationship between ART and glucose abnormalities in HALS, a number of studies have failed to show a relationship with either glycaemic parameters^(47,53,140) or insulin resistance⁽¹⁴¹⁾, highlighting the inconsistencies that currently exist in the literature.

Risk factors for the development of glucose abnormalities in the context of HIV and ART have been recently reviewed and were found to include older age, existing LA, non-white race, family history of T2DM, and disease factors, such as co-infection with hepatitis C⁽⁹⁰⁾. Furthermore, a recent study from Bangkok found that the risk of pre-diabetes in HIV-infected patients receiving ART increased with each 5 kg increase in body weight⁽¹⁴²⁾. In the same study, the NNRTI nevirapine was found to be protective for pre-diabetes. Both *in vitro* and *in vivo* studies have demonstrated the negative effect of PI on glucose homeostasis in HIV^(27,143,144). Results from the Women's Interagency HIV Study showed that longer-term exposure to NRTI increased the incidence of T2DM, indicating their role in increasing the risk of glucose abnormalities in HALS⁽¹⁴⁵⁾.

Diagnosis of glucose disorders in HALS is similar to the general population and has been made on the basis of guidelines from the International Diabetes Federation⁽⁸⁹⁾ and the American Diabetes Association⁽¹⁴⁶⁾. According to

these guidelines, fasting plasma glucose greater than 5.6 mmol/l is defined as impaired glucose tolerance and a value greater than 7 mmol/l is indicative of frank diabetes. The American Diabetes Association criteria for diagnosing abnormalities of glucose metabolism state that patients must present with symptoms (polyuria, polydipsia, weight loss) and a random glucose of greater than 11.1 mmol/l for a diagnosis of diabetes to be made. Furthermore, Wohl *et al.*⁽¹⁴⁷⁾ recommend follow-up with fasting blood glucose every 3–6 months for at-risk patients and those undergoing changes in their ART regimen.

Hypertension

Both LA and LH have been shown to be independently associated with hypertension in HIV-infected individuals receiving ART⁽¹⁴⁸⁾. As for the general population, hypertension in HIV patients is associated with an increased risk of CVD⁽¹⁴⁹⁾. A recent UK study of HIV patients with the metabolic syndrome found that raised systolic blood pressure was associated with risk factors such as being male, higher BMI and higher CD4 cell count and viral load^(88,150). Crane *et al.*⁽¹⁴⁸⁾ suggest that increased BMI may be involved in mediating hypertension associated with LH in HALS. When the authors adjusted for BMI, patients with LA had an increased risk of hypertension compared with those without anthropometric abnormalities⁽¹⁴⁸⁾. The role of ART in mediating hypertension is somewhat unclear. A study by Thiébaud *et al.*⁽¹⁵¹⁾ showed that ART was not independently associated with any negative effects on blood pressure; in fact, use of NNRTI was associated with a lower risk of hypertension in this group.

Carotid artery intima thickness

Arterial stiffness has been shown to be an independent predictor of cardiovascular morbidity and mortality in the general population⁽¹⁵²⁾. Exposure to ART in HIV-infected individuals is associated with thickening of the carotid artery intima and arterial stiffness^(153,154). Recent findings from the Women's Interagency HIV Study and the Multi-center AIDS Cohort found a significant association between HIV-related immunosuppression and increased carotid artery stiffness, independent from the impact of ART or other traditional atherosclerotic risk factors⁽¹⁵⁵⁾. These results suggest that disease factors may predict the development of arterial stiffness and subsequent atherosclerosis in HALS.

Endothelial dysfunction

Endothelial dysfunction is a critical initial step in the progression of atherosclerosis in HIV-infected individuals⁽¹⁵⁶⁾. A recent prospective study showed that the presence of lipodystrophy predicted endothelial dysfunction in

fifty-five HIV-infected patients, independent of other CVD risk factors⁽²⁹⁾. Contrary to initial findings, different classes of ART have been implicated in the pathogenesis of endothelial dysfunction in HALS⁽²⁹⁾. Currently, results appear conflicting, some showing that use of ART contributes to endothelial dysfunction⁽¹⁵⁷⁾, some showing no association between ART and endothelial function⁽¹⁵⁸⁾, and others showing improved endothelial function following treatment in previously ART-naïve subjects⁽¹⁵⁹⁾. Interestingly, recent *in vitro* work has shown increased oxidative stress and cellular senescence in human coronary artery endothelial cells following long-term exposure to ritonavir and lopinavir–ritonavir⁽¹⁶⁰⁾, highlighting a potential mechanism for PI-associated endothelial dysfunction. Larger long-term prospective studies are, however, required to determine the effect of ART on endothelial dysfunction *in vivo*.

Atherosclerosis

Patients with lipodystrophy have been shown to be at a higher risk of atherosclerosis⁽¹⁶¹⁾. Calza *et al.*⁽¹⁶²⁾ recently reviewed the link between HIV infection, ART and the development of premature atherosclerosis. Similar to the general population, the most commonly identified risk factors associated with atherosclerosis were age, smoking, increased BMI, hypertension and dyslipidaemia. Of nine studies, four found an association between the use of PI and premature atherosclerosis. Furthermore, three of five studies showed that HIV infection itself was associated with atherosclerosis. This, coupled with the association between risk of atherosclerosis and CD4 cell count⁽¹⁶³⁾, indicates that disease factors play an important role in the pathogenesis of atherosclerosis.

CVD

It has been well established that ART contributes to a 'metabolic syndrome' encompassing abdominal obesity, atherogenic dyslipidaemia, insulin resistance, endothelial dysfunction and inflammation, known as HALS. In recent years, therefore, research has begun to focus on the deleterious effects of ART on risk of CVD⁽¹³⁵⁾.

Early reports of CVD appeared in peer-reviewed literature shortly after the introduction of PI^(164,165). Evidence for the association between ART and increased risk of CVD is, at present, inconsistent. Some studies show no association between the use of ART and risk of CVD or cerebrovascular disease⁽¹⁶⁶⁾, while others show a positive association for PI^(30,118,167,168). Research has shown that between 5 and 31% of patients with HIV/AIDS are at risk for cardiovascular events^(73,169,170), and, similar to the general population, patients with the metabolic syndrome have a greater risk than those without⁽¹⁷⁰⁾.

Variations in observed risk could be explained by differences in the risk factors of the study population.

Commonly identified risk factors for MI or cardiovascular events include AIDS before ART initiation, age over 40 years, cigarette smoking⁽⁷³⁾, family history of CVD, diagnosis of dyslipidaemia, hypertension, lipodystrophy or T2DM⁽¹⁶⁷⁾ or pre-existing vascular disease⁽³⁵⁾. Unlike the general population, Bozzette *et al.*⁽³⁵⁾ showed that risk of serious cardiovascular events was lower for African-American subjects, indicating that race/ethnicity may also be a risk factor. It has also been found that the prevalence of CVD is higher for patients receiving a combination of PI and NNRTI⁽¹¹⁸⁾. In a recent review, Schafer *et al.*⁽¹⁷¹⁾ referred to studies which show an increased risk of CVD associated with recent, but not cumulative, use of abacavir, a NRTI. However, a recent 96-week randomised controlled trial did not find an association between the NRTI combination abacavir–lamivudine and cardiovascular morbidity and mortality in HIV-infected individuals⁽¹⁷²⁾. These researchers suggest that differences in results may be attributed to variations in pre-study viral load among patients. The increased longevity observed in the HIV population as a result of advanced drug therapy has also been associated with an increase in the incidence of CVD⁽¹⁷³⁾. Evidence indicates that disease progression and associated immune deficiency in HIV patients are associated with an increased CVD risk⁽¹⁵⁵⁾. Recent evidence that a low CD4 cell count was associated with an increased prevalence of carotid artery lesions in HIV patients further supports this finding⁽¹⁶³⁾. Paradoxically, interruption of ART has been shown to increase CVD risk⁽¹⁷⁴⁾, suggesting that HIV infection itself may play a role in increasing the risk of CVD. A recent treatment interruption trial in Thai HIV-infected patients demonstrated an association between markers of CVD, including increased vascular cell adhesion molecule-1, decreased adiponectin, and increased HIV RNA replication⁽¹⁷⁵⁾, which further supports this finding.

Currently, risk-prediction models such as the Framingham score are recommended for use in estimating CVD risk⁽¹⁶²⁾. The Framingham equations, developed over a decade ago for use in non-HIV-infected individuals⁽¹⁷⁶⁾, have been used to estimate CVD risk in HIV-infected subjects^(73,172,175); however, studies assessing the accuracy of this model in HIV-infected patients are limited⁽¹⁷⁷⁾. Friis-Møller *et al.*⁽¹¹⁸⁾, in a large prospective cohort, used CVD risk-scoring estimates for the general population to determine cut-offs to define HIV patients at ‘high risk’ of CVD. More recently, May *et al.*⁽¹⁷⁸⁾ have developed another risk model for predicting the risk of MI or death from CHD in HIV-infected men. These researchers use data from five cardiovascular cohorts of HIV-uninfected men and adapt the model for the known risk factors observed in HIV patients following initiation of ART. However, the authors state that only a modest change in CHD risk factors may be detected using the risk model. In addition, the model does not take into account changes in CHD risk attributable to lifestyle changes. To the best

of the current authors’ knowledge, this model has also not yet been evaluated.

Underlying molecular mechanisms

Altered adipocyte inflammatory status

Studies of human adipose tissue from HIV-infected patients receiving ART have demonstrated an increase in the expression of genes relating to inflammation. In particular, HALS has been associated with an increase in pro-inflammatory cytokine expression⁽¹⁷⁹⁾, in addition to increased systemic pro-inflammatory cytokine activity⁽¹⁸⁰⁾. Increased circulating levels of TNF- α , IL-6 and IL-1 β have been shown in both *in vitro*^(181,182) and *ex vivo* studies^(180,183,184). IL-6 has been shown to mediate insulin resistance and may modulate insulin signalling in adipose tissue⁽¹⁸⁵⁾. A large body of research has focused on the hypersecretion of TNF- α , which has a number of pathophysiological effects including mediating insulin resistance via reduction of insulin receptor kinase activity, inducing apoptosis and lipolysis^(186,187), and down-regulating insulin receptor kinase substrate (IRS)-1 and GLUT-4^(186,188). These effects may occur via a number of mechanisms including: a reduction in insulin signalling, attenuating the anti-lipolytic action of insulin⁽¹⁸⁹⁾; down-regulation of inhibitory G-protein-coupled receptors, leading to enhanced cyclic AMP levels⁽¹⁹⁰⁾; down-regulation of lipoprotein lipase⁽¹⁸⁶⁾; and down-regulation of the function and expression of perilipin, a lipid droplet-associated protein, which protects the adipocyte from the hydrolytic action of cellular lipases⁽¹⁹¹⁾. This increased cytokine production in HALS has also been suggested to induce a stress response in adipocytes, which may lead to physical damage of the cell^(181,192).

In addition to an increase in inflammatory cytokine production, HALS has been associated with a reduced expression of adiponectin in both plasma and adipose tissue⁽¹⁹³⁾. Adiponectin is a potent insulin sensitiser and, hence, its down-regulation contributes to insulin resistance⁽¹⁸²⁾. *In vitro* and *ex vivo* studies have shown reduced expression, secretion and release of adiponectin from adipose tissue^(181,183), while *in vivo* studies in HALS patients have identified the presence of hypoadiponectinaemia, which is a risk factor for cardiovascular impairment⁽¹⁹⁴⁾. Inhibition of adipocyte differentiation, such as that caused by PI, has been shown to down-regulate adiponectin expression⁽¹⁹⁵⁾. Furthermore, down-regulation of adiponectin expression by NRTI has been suggested to occur as a result of the reduction in fat mass associated with NRTI use^(196,197). Mallewa *et al.*⁽¹⁸⁸⁾ also refer to the negative feedback loop that exists between cytokines, whereby high levels of TNF- α and IL-6 may inhibit the expression of adiponectin, which may also account for the observed reduction in adiponectin in HALS.

Adipose tissue macrophage infiltration, resulting in chronic low-grade inflammation, has also been suggested

to contribute to the development of HALS⁽¹⁹⁸⁾. Macrophage infiltration of adipose tissue has been shown to be greater in HALS patients compared with healthy controls⁽¹⁸³⁾. Recently, Hammond *et al.*⁽¹⁷⁹⁾ demonstrated an increase in adipose tissue macrophage count associated with thymidine NRTI treatment.

Altered adipocyte functionality

Microarray analysis of gene expression during adipogenesis has revealed numerous effects of ART on genes involved in adipocyte lipid and glucose metabolism⁽¹⁹⁶⁾. In a recent study, Sievers *et al.*⁽¹⁸⁴⁾ showed that NRTI caused a general decrease in the expression of genes involved in adipocyte differentiation and lipid and glucose metabolism within the cell (CCAAT/enhancer-binding protein- α (*C/EBPA*), *C/EBPB*, cyclo-oxygenase-3 (*COX3*), *GLUT4*, hexokinase-1 (*HEXOK1*), perilipin (*PLIN*), *SREBP1c*), and an increase in markers of cell proliferation and genes involved in mitochondrial transcription (*COX4*, lamin-B (*LAMINB*), lamin A/C (*LAMINA*), proliferating cell nuclear antigen (*PCNA*), PPAR- γ co-activator-1b (*PGC1B*)).

Similarly, a number of *in vitro* studies have demonstrated changes in gene expression following exposure of adipocytes to antiretroviral drugs. Both PI and NRTI have been shown to down-regulate the expression of adipocyte differentiation genes such as *Pparg*, *Cebpa*, adiponectin (*Adipoq*), leptin (*Lep*), the scavenger receptor CD36 (*Cd36*), adipocyte lipid-binding protein-2 (*Ap2*), fatty acid synthase (*fasn*) and acetyl-coenzyme A carboxylase (*Acc*)^(196,199). In particular, the NRTI d4T and ZDV have been found to cause a reduction in mRNA expression of adipogenic markers involved in lipid accumulation including fatty acid synthase, acetyl-coenzyme A carboxylase and adipocyte lipid-binding protein-2^(181,196,199,200). Pacenti *et al.*⁽¹⁹⁶⁾ demonstrated that NRTI modulate the expression of various transcription factors, such as *Aebp1*, *Pou5f1* and *Phf6*, which may play a role in determination of the adipocyte phenotype.

Adiponectin plays a role in glucose and lipid metabolism within the adipocyte⁽¹⁸²⁾ and a number of *in vitro* studies have shown a reduction in adiponectin expression following exposure of 3T3-L1 murine and Simpson–Golabi–Behmel syndrome (SGBS) human adipocytes to PI^(182,196,200). These alterations in gene expression correspond with findings of altered adipocyte function including reduced capacity of insulin to activate lipogenesis⁽¹⁹⁹⁾, decreased lipid accumulation⁽¹⁹⁹⁾ and reduced adipocyte lipid content^(181,182).

Two *ex vivo* studies have investigated gene expression in subcutaneous adipose tissue samples from HALS patients and found reduced nuclear mRNA expression of mitochondrial proteins (PGC-1 α), transcription factors (PPAR- γ) and adipocyte metabolic markers (GLUT-4, lipoprotein lipase)^(193,201). Further support for these findings comes from results by Kim *et al.*⁽²⁰¹⁾, which showed that the

expression of PPAR- γ increased after PI withdrawal. Moreover, mRNA expression of uncoupling protein-3 and preadipocyte factor-1, both inhibitors of adipocyte differentiation and metabolism, has been shown to be increased in HALS⁽¹⁹³⁾. As with the work of Sievers *et al.*⁽¹⁸⁴⁾, these findings suggest that ART impair mitochondrial biogenesis, adipocyte differentiation and metabolism, and are involved in the down-regulation of adipogenic transcription factors.

Mitochondrial toxicity

ART-mediated inhibition of mitochondrial DNA-polymerase- γ , leading to mitochondrial toxicity, has been suggested to not only be involved in cell death and loss of fat mass, but in the aetiology of alterations in adipose tissue function⁽¹⁷⁹⁾. As a result of these defects in adipose tissue function, the liver and skeletal muscles are exposed to increased concentrations of fatty acids, which has been associated with the development of the metabolic alterations seen in HALS⁽²⁰²⁾. Studies examining the effect of ART on mitochondrial toxicity are somewhat conflicting, with some showing limited or no effect of certain ART regimens on mitochondrial toxicity^(203,204), while others found effects for both single ART and cART^(179,199,205). According to Walker *et al.*⁽²⁰⁶⁾, mitochondrial toxicity is sometimes more pronounced with use of cART. A recent study examining the effect of switching from d4T to tenofovir found improvements in mitochondrial toxicity after just 1 month⁽²⁰⁷⁾. Mallewa *et al.*⁽¹⁸⁸⁾ suggest that these observed differences may be due to differing levels of affinity of the active metabolites of the drugs for mitochondrial DNA-polymerase- γ . Furthermore, PI and NRTI have been associated with increased oxidative stress, which has been shown to induce mitochondrial dysfunction in 3T3-F442A adipocytes^(208,209). This PI- and NRTI-associated mitochondrial dysfunction and oxidative stress have also been shown to trigger premature senescence in a number of cell models, including primary human fibroblasts⁽²⁰⁸⁾, human coronary artery endothelial cells and peripheral blood mononuclear cells⁽¹⁶⁰⁾. In the context of HIV and ART, it has been suggested that premature senescence may contribute to accelerated cellular ageing, which might increase the risk of premature CVD as observed in HALS⁽¹⁶⁰⁾.

Treatment

Pharmacological and surgical management

A number of pharmacological and surgical interventions have been used in the management of HALS. Pharmacological interventions include switching to more 'lipid-friendly' antiretrovirals⁽²¹⁰⁾, use of synthetic growth hormone analogues to reduce excess visceral adipose tissue⁽²¹¹⁾, statins to improve dyslipidaemia^(212–214) and

anti-diabetic drugs^(215–218) to improve glucose abnormalities. A number of adverse events are associated with these pharmacological interventions, which range from drug–drug interactions⁽²¹⁹⁾ to more serious side effects such as a higher virologic failure^(220,221) and increased risk of MI⁽²²²⁾ (Table 2).

To correct the morphological abnormalities associated with HALS, patients often undergo surgical procedures. These include liposuction⁽²²³⁾ and excisional lipectomy⁽²²⁴⁾ for LH and silicone gluteal prostheses⁽²²⁵⁾, facial fillers^(226–228), facial grafting⁽⁹⁶⁾ and fat transplantation⁽²²⁹⁾ for LA. Surgical interventions such as these are radical interventions and are associated with numerous adverse events, which often offset their success (Table 2).

Lifestyle interventions

Although pharmacological and surgical interventions have a role to play in the management of HALS, lifestyle interventions are increasingly being trialled as first-line strategies in the management in HALS, due to their greater safety and tolerability.

Exercise

A number of studies have investigated the role of exercise in improving the systemic parameters in HALS and have shown mixed results. One study failed to show an effect of exercise and resistance training in improving lipid parameters in HALS⁽²³⁰⁾, while four have shown a beneficial effect, particularly in reducing central fat accumulation and in increasing body weight and limb girth^(231–234).

A recent cross-sectional study investigated the effect of leisure time physical activity on central fat accumulation in adults receiving ART and showed a significant negative correlation between leisure time physical activity and central fat⁽²³⁵⁾. As for the general population, exercise in HALS patients has proven effective in improving lipid parameters and insulin resistance. Yarasheski *et al.*⁽²³⁶⁾ investigated the effect of exercise on dyslipidaemia and showed that progressive weight-lifting reduced serum TAG levels in eighteen men receiving ART. Furthermore, a recent study of twenty men receiving supervised strength and endurance training demonstrated increases in insulin-mediated glucose uptake and hence improved insulin sensitivity after 16 weeks of training⁽²³⁷⁾. Overall, it appears that exercise has a beneficial effect in improving lipid parameters and central adiposity in HALS.

Nutrition

Relatively little is known about the influence of diet on the metabolic complications of HIV and associated lipodystrophy⁽²³⁸⁾. There are a number of studies that have generally investigated the area by cross-sectional analysis of diet and systemic parameters of HIV-positive adults with and without lipodystrophy. Dietary fibre intake has been shown to be positively associated with metabolic health in HIV-positive adults^(40,41,43). In another study, fibre had no association⁽²³⁹⁾. A recent Brazilian cross-sectional study found that individuals with HIV who consumed more than two servings of dairy food per d had a lower BMI, waist circumference and blood pressure than those who consumed less than this amount⁽⁴²⁾.

Table 2. Adverse events associated with the pharmacological and surgical management of the HIV-associated lipodystrophy syndrome

Intervention	Associated adverse event(s)
Pharmacological	
Switch strategies	
Switch from one PI to another, for example, atazanavir	Higher virologic failure ⁽²¹⁷⁾
Switch from PI to NRTI, for example, abacavir	Higher virologic failure ⁽²¹⁶⁾
Synthetic growth hormone analogues	
Growth hormone-releasing hormone: tesamorelin (Egrifta™)	Arthralgia, erythema and pruritis at site of injection; abdominal pain, swelling, myalgia; worsening glycaemic control ⁽²⁰⁷⁾
Lipid-lowering drugs	
Statins	Pharmacokinetic interaction with PI ^(209,210,215)
Niacin	Glucose intolerance; transient increases in insulin resistance ⁽²⁴⁸⁾
Anti-diabetic drugs	
Metformin	Increased risk of lactic acidosis when taken with NRTI ^(213,214)
Rosiglitazone	Increased postprandial lipaemia; increased risk of myocardial infarction ^(214,218)
Pioglitazone	Pharmacokinetic interaction with PI ⁽²¹⁴⁾
Surgical	
Lipohypertrophy	
Ultrasonic liposuction	Relapse/recurrence of abdominal lipohypertrophy common ⁽²¹⁹⁾
Excisional lipectomy	High rate of recurrence of dorsocervical fat pad ⁽²²⁰⁾
Lipoatrophy	
Silicone gluteal prostheses	Painful postoperative period ⁽²²¹⁾
Facial fillers	Granuloma formation; local migration of particles ⁽⁹⁰⁾
Fat transplantation	Operative risks and facial fat hypertrophy ⁽²²⁵⁾
Facial grafting	Fat resorption ⁽⁹⁶⁾

PI, protease inhibitor; NRTI, nucleoside RT inhibitor.

The authors of this study suggest that Ca intake may be involved in mediating these changes. In most cross-sectional studies no association was found between saturated fat^(41,239,240), total fat^(41,239,240) or other fat subclasses⁽²³⁹⁾, with the exception of *trans*-fatty acids⁽⁴¹⁾, and metabolic health in HIV-positive adults. Samaras *et al.*⁽²⁴¹⁾ in their study of men with HALS showed that saturated fat intake was significantly positively associated with percentage body fat. Weak evidence suggests that polyunsaturated fat intake is positively associated with insulin sensitivity in HIV-infected individuals⁽⁴³⁾. Contrary to these findings, Samaras *et al.*⁽²⁴¹⁾ demonstrated that fat subtype did not relate to fasting insulin, insulin resistance, total cholesterol, HDL, TAG, glucose or adiponectin concentrations in HALS.

Turčinov *et al.*⁽⁴⁵⁾ cross-sectionally investigated the diets of 136 HIV-positive Croatian adults on ART. Adherence to a Mediterranean diet was assessed by a 150-item questionnaire and a point scale that stratified subjects as having low or moderate to high adherence. Although HALS was not an inclusion factor in the study, it was determined that Croatians who did not smoke and moderately or highly adhered to the Mediterranean diet were least likely to have LA and LH. In another cross-sectional study, adherence to a Mediterranean-style diet was positively correlated with HDL and marginally negatively correlated with TAG levels⁽⁴⁴⁾.

Interestingly, a negative association between total and supplemental vitamin E intake and diastolic blood pressure has been shown among HIV-positive adults⁽²³⁹⁾. Two association studies have shown that dietary energy intake is not associated with metabolic dysregulation among HIV-positive adults^(41,239), and one has shown significant positive associations⁽²⁴⁰⁾.

A number of intervention studies have investigated the effects of diet in mitigating the metabolic and morphological abnormalities of HALS (Table 3). Barrios *et al.*⁽²⁴²⁾ showed that adherence to a low-fat diet for 6 months reduced total cholesterol by 10% and TAG by 23% among HIV-positive adults with hyperlipidaemia. Contrary to these findings, Ng *et al.*⁽²⁴³⁾ in a recent pilot randomised controlled trial found that HIV-infected individuals who adhered to a low-fat diet did not have reduced cholesterol levels and in fact had increased TAG levels after 1 year. The same authors found that HIV-infected individuals adopting a modified Mediterranean diet had significantly increased cholesterol levels after 9 and 12 months, while serum TAG levels in the same individuals remained unchanged over the same period⁽²⁴³⁾. In a case report, Roubenoff *et al.*⁽²⁴⁴⁾ found that a moderate-fat, low-GI, high-fibre diet, in combination with exercise, reduced total and trunk fat, LDL, fasting glucose and insulin resistance in one male HALS patient. Similarly, another study found that a low-fat diet and aerobic exercise significantly reduced body weight, body fat and waist:hip ratio in HALS patients⁽²³⁰⁾. One study investigated the effect of altering the fatty acid composition of the diet from

medium- to long-chain fatty acids in HALS, and showed improvements in lipid profile after 3 months⁽²⁴⁵⁾. Owing to conflicting results, further randomised controlled trials are necessary before dietary recommendations can be made in this area.

A number of studies have examined the effect of supplements, such as L-acetylcarnitine, uridine and niacin, on the metabolic and morphological abnormalities in HALS. L-Acetylcarnitine has been suggested to be involved in regulating fatty acid oxidation⁽²⁴⁶⁾ and in one study of HALS subjects supplementation with 4 g/d resulted in increased lipid oxidation, decreased intramyocellular TAG content, decreased plasma NEFA and lower insulin sensitivity compared with controls after 8 months⁽²⁴⁷⁾. Three interventions have trialled dietary uridine supplementation, which has been shown *in vitro* to prevent and treat mitochondrial toxicity⁽²⁴⁸⁾. One study showed no effect on changes in fat or blood mitochondrial DNA levels⁽²⁴⁸⁾, while the other two studies showed conflicting results – one finding no significant increase in limb fat mass following 24 weeks of supplementation⁽²⁴⁹⁾, while the other showed a significant increase in subcutaneous fat mass following 3 months of supplementation in lipotrophic patients⁽²⁵⁰⁾. Both studies used the same level of supplementation. Niacin, which has been shown to modulate lipoprotein metabolism and inhibit TAG synthesis⁽²⁵¹⁾, was used in one study examining the effect of combination therapy with diet, exercise and niacin in patients with highly active ART-associated dyslipidaemia. Treatment with a low-saturated fat diet, exercise and niacin significantly increased HDL concentrations, and total cholesterol:HDL ratio compared with controls after 24 weeks⁽²⁵²⁾.

An interesting set of studies by Kosmiski *et al.*^(253–255) has shown that lipodystrophy in HIV is associated with an increase in resting energy expenditure (REE) per kg lean body mass. Furthermore, 3 d of eu-energetic feeding, which normally would not induce a change in REE, resulted in a significant increase in REE among HIV-positive adults with lipodystrophy compared with HIV-positive adults without lipodystrophy and healthy controls⁽²⁵³⁾. The same researchers found that 3 d of hypo-energetic feeding induced a significant drop in REE and 3 d of hyper-energetic feeding induced a significant increase in REE in HIV-positive adults with lipodystrophy compared with HIV-positive adults and healthy controls^(253,255). The group concluded that lipodystrophic subjects have higher REE per kg lean body mass than non-lipodystrophic subjects, that short-term over-feeding increases REE among lipodystrophic subjects and that short-term energy restriction reduces REE among lipodystrophic subjects. The authors suggest that hypermetabolism associated with lipodystrophy, and a form of adaptive thermogenesis invoked to dissipate energy that cannot be stored in a normal manner underlie these observations.

Despite weak support from observational studies, a number of intervention trials focusing on the role of *n-3*

Table 3. Intervention trials investigating the effect of nutrition in the HIV-associated lipodystrophy syndrome (HALS)

Reference	Study design	n	Subjects	Type of intervention	Duration	Outcome
Diet						
Barrios <i>et al.</i> (2002) ⁽²⁴²⁾	PI	230	HIV+, dyslipidaemic, receiving ART	Low-fat diet	6 months	TC, TAG and weight ↓ significantly in subjects with good compliance. Patients receiving protease inhibitors had a slightly greater decline in lipid levels than those not on protease inhibitors
Kosmiski <i>et al.</i> (2007) ⁽²⁵³⁾	CT	28	HIV+, 82% M, nine HALS +, ten HALS -, nine healthy controls	3 d eu-energetic feeding followed by 3 d overfeeding.	6 d	REE ↑ significantly in HALS + but not control groups
Kosmiski <i>et al.</i> (2007) ⁽²⁵⁵⁾	CT	30	HIV+, 77% M, eleven HALS +; ten HALS - (all receiving ART); nine healthy controls	3 d eu-energetic feeding followed by 3 d hypoenergetic feeding	6 d	REE significantly higher in HALS + compared with HALS - and healthy controls. Energy restriction caused significant decline in REE in HALS +
Ng <i>et al.</i> (2011) ⁽²⁴³⁾	Pilot RCT	48	HIV+	Modified Mediterranean diet v. low-fat, low-cholesterol diet	1 year	Mediterranean diet: no change in TAG, significant ↑ serum TC Low-fat diet: ↑ TAG levels, no change in TC
Roubenoff <i>et al.</i> (2002) ⁽²⁴⁴⁾	CR	1	HIV+, M, receiving ART	Moderate-fat, low-GI, high-fibre diet + exercise three times per week	4 months	↓ Total and trunk fat, LDL, TC, fasting glucose and insulin resistance
Terry <i>et al.</i> (2006) ⁽²³⁰⁾	RCT	30	HIV+, 67% M, HALS, receiving ART	Low-lipid diet + aerobic exercise	3 months	Body weight, body fat and WHR ↓ significantly
Vázquez <i>et al.</i> (2006) ⁽²⁴⁵⁾	CR	1	HIV+, M, HALS, receiving ART	Eu-energetic substitution of MCT for long-chain fatty acids	3 months	↑ Lean mass, ↓ fat mass, improvement in lipid profile
Wohl <i>et al.</i> (2005) ⁽²⁵⁸⁾	OLRT	26	HIV+, hypertriglycerolaemic	Diet (↓ total and <i>trans</i> -fat, ↑ fibre) + aerobic exercise	16 weeks	Significant ↓ BMI at week 16
Supplements						
Benedini <i>et al.</i> (2009) ⁽²⁴⁷⁾	RIT	9	HIV+, 56% M, receiving protease inhibitors/NRTI, nine healthy controls	2 g L-acetylcarnitine per d	8 months	↓ Intramyocellular TAG content; ↓ plasma NEFA; ↓ respiratory quotient; ↑ % leg fat
Balasubramanyam <i>et al.</i> (2011) ⁽²⁵²⁾	RDBPCT	191	HIV+, hypertriglycerolaemic	Diet + exercise + niacin (2 g/d)	24 weeks	Significant ↑ HDL
Calmy <i>et al.</i> (2010) ⁽²⁴⁹⁾	PR	45	HIV+, M, lipoatrophic patients	36 g uridine t.d.s.	24 weeks*	No significant ↑ in limb fat mass
McComsey <i>et al.</i> (2007) ⁽²⁴⁸⁾	POL	14	HIV+, 79% M, receiving ART, lipoatrophic patients	36 g NucleomaxX (uridine) t.d.s. every other day	32 weeks†	Lipoatrophy scores by patient and physician improved significantly at weeks 16 and 32 compared with baseline. No changes in fat or blood mitochondrial DNA levels
Sutinen <i>et al.</i> (2007) ⁽²⁵⁰⁾	RDBPCT	20	HIV+, 85% M, ten cases, ten controls, receiving ART, lipoatrophic patients	36 g uridine supplement t.d.s.	3 months	Significant ↑ total limb fat, intra-abdominal fat and total body fat from baseline to 3 months in intervention group. Non-significant ↓ in HDL in intervention group

PI, prospective intervention; HIV+, HIV-positive; ART, antiretroviral therapy; TC, total cholesterol; ↓, decrease; CT, control trial; M, male; HALS +, HIV patients with HALS; HALS -, HIV patients without HALS; REE, resting energy expenditure; ↑, increase; RCT, randomised controlled trial; CR, case report; GI, glycaemic index; WHR, waist:hip ratio; MCT, medium-chain TAG; OLRT, open-label randomised trial; RIT, randomised intervention trial; NRTI, nucleoside RT inhibitor; RDBPCT, randomised double-blind placebo-controlled trial; PR, prospective randomised trial; t.d.s., ter die sumendum (three times per d); POL, prospective open label study.

* 10 d per month for 24 weeks.

† 16-week intervention followed by 16-week washout.



long-chain PUFA (*n*-3 LC-PUFA) in mitigating the metabolic abnormalities in HALS patients have been pursued. In the pre-ART era, intervention trials investigating the immunomodulatory effects of EPA and DHA as an adjunct therapy in HIV patients were pursued⁽²⁵⁶⁾. Their hypothesis was based on the immunomodulatory effects of EPA and DHA previously documented. Evidence strongly supports a role for *n*-3 LC-PUFA in HIV therapy, but in lipid lowering rather than immune regulation.

In a study of 120 HIV-positive adults on ART, 8 weeks of supplementation with 6 g *n*-3 LC-PUFA per d induced a 25.5 and 38.7% reduction in plasma TAG concentrations among moderate and severe hypertriglycerolaemics, respectively⁽²⁵⁷⁾. Similarly, plasma TAG concentrations decreased by 25% following 4 weeks of supplementation with 1750 mg EPA and 1150 mg DHA per d among fifty-two HIV-positive adults with moderately raised TAG⁽²⁵⁸⁾. In a study of 100 HIV-positive adults with hypertriglycerolaemia, fish oil supplements taken at 6 g/d for 8 weeks reduced TAG concentrations by 46%, fenofibrates reduced TAG concentrations by 58%, and the combination of fish oil and fenofibrates by 65.5%⁽²⁵⁹⁾. Manfredi *et al.*⁽²⁶⁰⁾ showed that rates of TAG normalisation were non-significantly different, at 25.9 and 34%, between HIV-positive subjects with raised TAG supplemented with ethyl esters of *n*-3 LC-PUFA or treated with pharmaceutical lipid-lowering therapy, respectively. Salmon oil, administered at 3 g/d, significantly reduced TAG concentrations after 12 to 24 weeks of supplementation in fifty-eight HIV-positive adults on ART⁽²⁶¹⁾. The TAG-lowering effects of the *n*-3 LC-PUFA among HIV-positive adults are supported by three smaller prospective studies^(262–264), although Virgili *et al.*⁽²⁶⁵⁾ showed no significant effect among nine HIV-positive subjects receiving 1120 mg EPA and 720 mg DHA daily for 6 weeks. A review of 237 hospital charts from HIV-positive adults with hypertriglycerolaemia showed that the use of *n*-3 LC-PUFA supplements was associated with a 32% reduction in TAG concentrations⁽²⁶⁶⁾. Furthermore, at baseline 11% of subjects used these dietary supplements, whereas at 6 months 25% of subjects used the supplements⁽²⁶⁶⁾. This demonstrates an enthusiasm and acceptance of these dietary supplements by HIV-positive adults with hypertriglycerolaemia. The effects of *n*-3 LC-PUFA on lipoprotein concentrations in HIV-positive adults are unclear, with no effect⁽²⁶²⁾, 11% raised HDL⁽²⁶⁶⁾ and 22.4% raised LDL⁽²⁵⁸⁾ reported.

EPA and DHA have been shown to have anti-inflammatory effects *in vitro* via their role as PPAR- γ ligands⁽²⁶⁷⁾ and modulation of the NF- κ B signalling system^(268,269). Despite the strength of evidence to support anti-inflammatory effects of EPA and DHA *in vitro*, studies investigating the effects of *n*-3 LC-PUFA supplementation on cytokine production in HIV-positive adults are limited. One study found no effects on the concentration of the soluble TNF- α receptor following 6 months of dietary supplementation with a product containing 1.7 g *n*-3 LC-PUFA

and 7.4 g arginine⁽²⁷⁰⁾. Another study demonstrated that among ten subjects consuming a bar containing 1.96 g *n*-3 LC-PUFA, PGF-1 α secretion was decreased, and IL-1 β and IL-6 secretion increased, from peripheral blood mononuclear cells⁽²⁷¹⁾. Overall, *n*-3 LC-PUFA appear to have beneficial TAG-lowering effects; however, their role in modulating inflammation in HALS remains to be elucidated.

Conclusion

There is a clear disparity in the reported prevalence of HALS owing to lack of a standardised definition, use of different methods for diagnosing the syndrome, as well as variations in the study population. It has been suggested that the search for a standardised definition for HALS should be abandoned and instead replaced with a description of the non-infectious co-morbidities associated with HIV, a condition that is slowly and globally acquiring chronic disease status. HALS is associated with fat maldistribution and metabolic complications such as dyslipidaemia, insulin resistance, hypertension, endothelial dysfunction and atherosclerosis, which lead to a rise in the incidence of CVD among this population group. Alterations in adipocyte inflammatory status and functionality, as well as mitochondrial toxicity, have been shown to underlie the development of HALS. Although current pharmacological and surgical interventions are effective in the treatment of HALS, their use is not without limitations. Targeted lifestyle interventions, such as exercise, may provide a useful alternative for managing non-infectious co-morbidities in HIV patients. Diet, particularly in the context of what we currently consider cardioprotective, appears to offer a safe, tolerable and effective treatment strategy for HALS, with evidence accumulating to supporting the use of *n*-3 LC-PUFA in future interventions.

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