

Fat Redistribution Syndromes Associated with HIV-1 Infection and Combination Antiretroviral Therapy

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Abstract

More than 15 years after the introduction of highly active antiretroviral therapy, HIV/HAART-associated lipodystrophy syndrome still shadows the indisputable efficacy of antiretroviral therapy. Several issues related to this complication (prevalence, diagnosis, pathogenesis, prevention, or clinical management) have not been completely clarified. However, in the last years, substantial progress has been made in elucidating some of these basic aspects. This includes a better knowledge of the pathogenic mechanisms underlying HIV/HAART-associated lipodystrophy syndrome such as genetic host determinants, the impact of HIV infection per se, as well as the contribution of antiretroviral therapy. In regard to treatment, we have learned that certain drugs are especially prone to cause HIV/HAART-associated lipodystrophy syndrome (i.e. thymidine analogues). Pharmacological interventions to treat this condition have yielded mostly disappointing results, and the only intervention which offers an immediate aesthetical improvement for patients with HIV/HAART-associated lipodystrophy syndrome is plastic surgery. Even under the most favorable conditions (ideal host genetic make-up, and the timely initiation of HIV therapy with less toxic drugs), current data show that HIV/HAART-associated lipodystrophy syndrome is a complication of HIV infection and/or antiretroviral treatment that we are unable to avoid. In the context of HIV-1-infected patients under long-term antiretroviral therapy, fat toxicity is still the dark side of the rainbow. (AIDS Rev. 2012;14:112-23)

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Key words

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Introduction

Highly active antiretroviral therapy (HAART)-associated lipodystrophy syndrome (HALS) is one of the most important and feared complications of antiretroviral therapy (ART) for HIV-1 infection¹. It was initially described in 1998², almost simultaneously to the encouraging

results of combination ART in reducing AIDS-associated mortality and opportunistic infections³.

Early reports of body shape changes included limb fat loss and trunk fat accumulation and were initially considered to be different manifestations of the same condition. Its frequent association with metabolic derangements, such as hyperlipidemia and insulin resistance, led to the consideration of HALS as a syndrome (i.e. a group of symptoms which consistently occur together).

A major problem that limits the definition of the syndrome is the absence of adequate diagnostic criteria for fat distribution abnormalities. Patterns of fat distribution in the general population are influenced by age, sex, and body weight, but these patterns are not well characterized. Currently, there is no consensus on a

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definition of HALS. The description of body fat changes relies on the patient's subjective perception and subsequent confirmation by a healthcare provider.

The most frequent feature observed in this complication is the loss of subcutaneous fat (lipoatrophy)⁴, which commonly occurs in the face, limbs, and buttocks, making it easily detectable by physical examination. When lipoatrophy is detected on clinical examination, the amount of fat loss is usually large ($> 30\%$)⁵. Lipohypertrophy, or fat accumulation, is less frequent than lipoatrophy⁴. Fat accumulation is usually observed in the abdomen, breasts, or dorsocervical region ("buffalo hump"). However, no association has been found between peripheral lipoatrophy and central lipohypertrophy, arguing against a single syndrome with reciprocal changes in fat⁴. Lipomatosis (localized or generalized lipoma) is not a frequent manifestation of lipohypertrophy, but can be observed in armpits, suprapubic regions, or other locations. These fat distribution abnormalities are often associated with hypertriglyceridemia, low HDL cholesterol, and insulin resistance².

In 2003, Carr, et al.⁶ carried out a rigorous attempt to define HALS objectively. By comparing patients with and without evident body fat changes, the HIV Lipodystrophy Case Definition (LDCD) established a diagnostic model that included age, sex, known duration of HIV infection, HIV disease stage, waist-to-hip ratio, anion gap, serum HDL cholesterol concentration, trunk-to-peripheral fat ratio, leg fat percentage, and intra-to-extra abdominal fat ratio. This model had approximately 80% accuracy for HALS diagnosis. Prospective studies confirmed its value and the increased sensitivity of LDCD scores for HALS diagnosis⁷. However, the complexity of the diagnostic model has limited its clinical usefulness.

Epidemiology

Limitations in the definition of HALS make it very difficult to accurately establish the prevalence of this condition. Several studies report diverse frequencies, probably reflecting differences in the diagnostic criteria and in the populations studied.

Considering studies in which a clinically-based diagnosis of HALS was used, the prevalence of HALS ranged from 13 to 70% in HIV patients receiving ART⁸⁻¹⁶. The wide range observed regarding HALS prevalence might be explained by differences in the study designs as well as the time of follow-up considered for each study.

Although there is no consensus on how much fat must be lost to define HALS, a cut-off of limb fat loss

$> 10-20\%$ has been arbitrarily used. In general, results from clinical trials in antiretroviral (ARV)-naive patients initiating ART in absence of zidovudine or stavudine (Castle, STARTMRK, and ACTG 5224) report that around 6% of patients develop a significant loss of limb fat ($> 20\%$) by the second year of treatment¹⁷⁻¹⁹. The Gilead-934 trial²⁰ showed that 5% of patients receiving tenofovir/emtricitabine plus efavirenz developed $> 20\%$ limb fat loss between weeks 96 to 144 versus 20% in the zidovudine/lamivudine plus efavirenz arm.

At present, the number of new cases of HALS has significantly declined⁷, but the prevalence of this condition still remains very high. Some recent studies report prevalence rates of around half of patients attending out-patient consultations⁸. HALS is not only important due to its high prevalence, but also because of its limited reversibility once established⁹.

Risk factors for HIV/HAART-associated lipodystrophy syndrome

The main risks factors for lipoatrophy and lipohypertrophy are summarized in tables 1 and 2^{12,14,21-28}, respectively. There are certain treatment-related factors most consistently associated with HALS. Prolonged exposure to thymidine nucleotide reverse transcriptase inhibitors (tNRTI), specifically stavudine and to a lesser extent zidovudine, is associated with a greater risk of developing body fat changes, in particular subcutaneous fat loss^{4,27,29,30}. The role of other antiretroviral drugs is controversial, partly due to the lack of longitudinal objective data, but also due to the difficulty in establishing a causal relationship with combination regimens. The nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) drug family has been considered low-risk for the development of HALS. However, preliminary results of ritonavir-boosted protease inhibitor (PI/r) monotherapy simplification studies suggest that avoidance of any NRTI may be beneficial for fat recovery³⁰.

The first-generation of unboosted PI, particularly indinavir³¹, were initially considered as causative agents for HALS. However, the strength of the association was difficult to prove and was attenuated after adjustment for NRTI exposure. In fact, the consideration of exposure to boosted PI as a risk factor for the development of HALS has recently changed after the results reported by several studies, particularly the ACTG 5142 study²². In this study, fewer patients treated with ritonavir-boosted lopinavir (LPV/r) developed HALS ($> 20\%$ limb fat loss) at 96 weeks when compared to efavirenz-treated

Table 1. Risk factors associated with lipoatrophy in clinical studies

Study	Patients (n)	Host factors	HIV-1-associated factors	ART-dependent factors
Miller, et al. ¹⁴	1,348	Age > 50	CDC disease category C	Stavudine > 17 months PI use > 22 months
Heath, et al. ²¹	1,261		CDC disease category	Stavudine therapy duration
Lichtenstein, et al. ¹²	1,244	White race Age > 49 BMI < 24 kg/m ²	CD4 nadir < 100 cells/µl	Stavudine therapy Indinavir > 2 years
Haubrich, et al. ²²	753	Male sex Age Black race Baseline extremity fat		Efavirenz vs. lopinavir/r Stavudine vs. zidovudine Tenofovir vs. zidovudine
Saves, et al. ²³	614	Male sex Age		Stavudine therapy
Thiebaut, et al. ²⁴	581	Age Male sex		Treatment duration
Martinez, et al. ²⁵	494			Stavudine therapy Treatment duration
Mauss, et al. ²⁸	221	Hypertriglyceridemia	CD4 nadir < 200 cells/µl	Stavudine > 12 months NNRTI > 12 months
Joly, et al. ²⁶	170			Stavudine vs. zidovudine
Bogner, et al. ²⁷	115	White race Age > 40	Baseline HIV-1 viral load	Treatment duration

ART: antiretroviral therapy; BMI: body mass index; CDC: Centers for Disease Control and Prevention; NNRTI: nonnucleoside reverse transcriptase inhibitors; PI: protease inhibitor.

Table 2. Risk factors associated with lipo-accumulation in clinical studies

Authors	Patients (n)	Host factors	HIV-1-associated factors	ART-dependent factors
Miller, et al. ¹⁴	1,348	Age > 50	CDC disease category C	RTI use > 57 months Stavudine use > 17 months Indinavir use > 15 months
Heath, et al. ²¹	1,261			Stavudine duration PI use
Lichtenstein, et al. ¹²	1,244	BMI increased		Age > 50 Duration of treatment > 5 years
Saves, et al. ²³	614		CD4 increase	Saquinavir use Lamivudine use
Thiebaut, et al. ²⁴	581	BMI WTH ratio		Treatment duration
Martinez, et al. ²⁵	494	Female sex		Treatment duration
Joly, et al. ²⁶	170	Female sex Age (per 10 years older)		
Bogner, et al. ²⁷	115			Treatment duration PI use
Palacios, et al. ²⁹	80	Lipoatrophy		Stavudine use (per 6 month intervals)

ART: antiretroviral therapy; BMI: body mass index; CDC: Centers for Disease Control and Prevention; NRTI: nucleoside reverse transcriptase inhibitors; PI: protease inhibitor.

patients, regardless of the NRTI backbone used. Also, a low frequency of fat distribution abnormalities has been described in contemporary clinical trials when a PI/r plus non-tNRTI were used in ART¹⁸. Surprisingly, the use of ritonavir could potentially mitigate the negative effect on HALS development induced by stavudine, as shown in one clinical trial in which ritonavir-boosted atazanavir had a significantly lower incidence of lipoatrophy compared with unboosted atazanavir³².

The role of nonnucleoside reverse transcriptase inhibitors (NNRTI) on HALS is controversial and data about the effect of these drugs on body fat are obscured by the concomitant use of tNRTI. In fact, nevirapine use may also exert a protective effect on HALS⁷ and a recently published trial comparing efavirenz with raltegravir (both with tenofovir/emtricitabine) showed a similar increase in limb fat at 96 weeks¹⁹.

Many non-pharmacologic factors have been associated with HALS development, but their etiologic role is unclear. In most studies, HALS is associated with increased age²⁰. Among immunologic factors, high CD4 counts^{21,33} but also a low CD4 nadir¹² have been associated with HALS. Female sex is associated with an increased risk for lipohypertrophy in some studies²⁴ but not in others³³. Ethnic factors, such as Caucasian and Asian race, have also been associated with HALS³².

Assessment of fat redistribution

Subjective assessment of HIV/HAART-associated lipodystrophy syndrome

Specific scores to measure the subjective perception of fat loss or accumulation have been developed. The Lipodystrophy Severity Grading Scale provides a standardized measurement of subjective lipoatrophy or lipoaccumulation, comparing patient perception with that of an experienced observer³⁴. But clinically, body fat changes are recognized late when a substantial amount of subcutaneous fat has been lost⁸.

Objective assessment methods of HIV/HAART-associated lipodystrophy syndrome

Anthropometric measurements are inexpensive and easy to take. Patient weight, height or body mass index, waist and hip girth, different limb circumferences, and skin folds have been used. These measurements are highly operator-dependent³⁵.

Bioelectrical impedance is also a cheap method to estimate total body water and subsequently total lean

body mass and adipose tissue³⁶. It does not discriminate distribution (regional, subcutaneous, or visceral) of fat.

Ultrasound provides regional adipose tissue thickness when measuring subcutaneous fat with good correlation with CT^{37,38}, but it is highly operator-dependent and without standardized reference points.

Dual-energy X-ray absorptiometry (DEXA) is an easy to use and popular low-cost, low-radiation assessment method. It provides the total fat content of trunk, limbs, or a determined area and is an excellent method to follow-up patients on treatment. Advantages of DEXA are good accuracy and reproducibility³⁹; DEXA does not discriminate between visceral or subcutaneous fat.

Computerized imaging techniques (CT) and magnetic resonance imaging (MRI) are the most accurate methods for qualitative and quantitative measurements of adipose tissue. When assessing fat content, these methods discriminate between subcutaneous and visceral adipose tissue, and measure the subcutaneous fat thickness and the total visceral adipose tissue expressed as an area from a single slice or even as a volume from multiple slices⁴⁰. Both CT and MRI are expensive and time consuming, and CT irradiates the patient.

Facial lipoatrophy

Facial loss of adipose tissue in cheek, supra-zygomatic, and temporal areas gives the patient a characteristic look. Facial lipoatrophy is present in 38-52% of people suffering from HALS. In order to standardize reproducible measurement for clinical purposes, two scales have graded lipoatrophy from 0 (absent) to 3 or 4 (severe), depending on cheek flattening or depression, nasogenian fold depth, and temporal and supra-zygomatic fat loss^{41,42}. Objective methods such as CT, MRI, or three dimensional laser scans are not useful in the clinical setting.

How can we diagnose HIV/HAART-associated lipodystrophy syndrome?

As HALS is a complex syndrome, attempts to find a single and useful diagnostic tool have failed. The more objective and reproducible techniques to quantify fat depots (DEXA, CT, MRI), but do not provide a diagnosis. Fat changes become evident only by repeating assessments in a longitudinal fashion.

Normal fat varies, depending on sex, age, and body mass index (BMI) and the pattern in the general

population is not well known. Fat mass index (FMI = fat mass kg/height [m^2]) has been suggested in a similar way to BMI. The normal FMI is 3-6 for men and 5-9 for women. The FMI varies from < 3 (severe fat deficit) to 21 (obesity grade III)⁴³. In order to assess whether fat distribution (trunk or peripheral) is balanced, a number of peripheral-to-central fat or limb-to-trunk fat ratios such as fat mass ratio (FMR = % trunk fat mass/% lower limb fat mass) have been proposed⁴⁴. An FMR > 1.96 in men and > 1.33 in women is diagnostic of lipodystrophy.

Abnormal fat distribution may also exist in ART-naïve HIV-infected patients with less limb and trunk fat than uninfected controls. But the decrease in limb fat is greater than the decrease in trunk fat, resulting in a higher FMR than uninfected controls⁴⁵. The FMR could be a valid method for one-time diagnosis of lipoatrophy^{43,44}.

Pathogenesis of HIV/HAART-associated lipodystrophy syndrome

Adipose tissue mass provides an indication of the average number and volume of adipocytes⁴⁶. The volume of fat cells reflects the balance between lipid synthesis (lipogenesis) and breakdown (lipolysis/fatty acid oxidation), whereas the number reflects the balance between cell production (pre-adipocyte replication/differentiation) and loss (apoptosis/adipocyte de-differentiation). Thus, HALS could be defined as an imbalance between the acquisition and loss of adipocytes and/or between the synthesis and breakdown of fat. There are at least three different pathogenic factors: host-, viral- and ARV-associated factors, with the complex interplay between them leading to the development of HALS.

Host factors: the role of genetics

Factors intrinsic to the host associated with HALS include age, gender, and ethnicity, without a clear biological explanation for their association⁴⁷. Genetic factors for HALS include polymorphisms in genes encoding for enzymes of the pyrimidine pathway, polymerase- γ , and cytokines such as tumor necrosis factor alpha (TNF- α), interleukins (IL) 1 β and 6 and resistin (Table 3)⁴⁷. Genetic variants within HLA in a Thai population, mitochondrial haplogroups, hemochromatosis, and matrix metalloproteinase 1 gene polymorphisms have been associated with HALS development⁴⁷. Multigene approaches suggest that genetic polymorphisms of genes involved in apoptosis

and adipocyte metabolism are related to HALS. However, to date most of these associations have not been replicated or data are controversial.

The pathogenic role of HIV-1 infection

HIV-1 infection *per se* can cause deleterious effects on fat. The HIV-1-infected patients naïve to ARV have less fat than age- and sex-matched uninfected controls⁴ and 1-3% of them present with HALS^{14,48}.

Deleterious effects of HIV-1 on adipocytes are exerted at least in part through viral proteins⁴⁹. *Tat* protein activates mononuclear cells to secrete IL-1 β , IL-6, IL-8, and TNF- α , and induces the expression of inflammatory cytokines and adhesion molecules and the release of monocyte chemoattractant protein (MCP)-1 by endothelial cells, thereby easing the transmigration of infected monocytes across endothelium⁵⁰. *Vpr* and *Nef* inhibit adipogenesis by a decrease in peroxisome proliferator-activated receptor (PPAR)- γ activity and promote insulin resistance⁵⁰.

Gene expression abnormalities in *ex vivo* fat samples from ART-naïve patients resemble those found in patients with HALS⁵¹.

The role of antiretroviral drugs

Mitochondrial dysfunction is the proposed mechanism via which some NRTI may exert deleterious effects on fat⁵² since it induces oxidative stress, leading to a reduction in leptin and adiponectin and an increase in MCP-1 and IL-6 production⁵⁰. The NRTI also increase the expression of genes involved in oxidative stress and apoptosis and impair adipocyte differentiation⁵³. Efavirenz also inhibits adipocyte differentiation⁵⁴.

First- and second-generation PI inhibit adipocyte differentiation and lipogenesis *in vitro*⁵⁰. This is caused by prelamin A accumulation due to the inhibition of ZMP-STE24, induction of nuclear architecture disruption, and sterol regulatory element-binding protein (SREBP)-1 mislocation⁵⁰. Some PI induce adipocyte apoptosis, insulin resistance, and oxidative stress and impair adipokine production⁵⁵. All these effects may be explained by endoplasmic reticulum stress induction and/or proteasome inhibition⁵⁰.

Interplay mechanisms of fat toxicity: mitochondrial dysfunction and inflammation

The NRTI toxicity involves mitochondrial dysfunction with mtDNA depletion due to the inhibition of host

Table 3. Genetic host factors associated with HIV/HAART-associated lipodystrophy syndrome

Authors	Candidate gene	Polymorphism (risk alleles)	Sample size	HALS diagnosis	% HALS	Comments
Maher, et al. ¹¹²	TNF- α	238G/A	96	Clinical	36.5	Caucasian patients
Nolan, et al. ¹¹³	TNF- α	238G/A	220	Clinical	NA	Found in Caucasians
Tarr, et al. ¹¹⁴	TNF- α	238G/A	325	Clinical	25.2	
Asensi, et al. ⁷⁶	TNF- α	238G/A	243	Clinical	37.0	
Asensi, et al. ⁷⁶	IL-1- β	3954 C/T	243	Clinical	37.0	
Hulgan, et al. ¹¹⁵	Hemochromatosis gene (HFE)	187 C/C	96	DXA	46.0	
Hulgan, et al. ¹¹⁵	Mitochondrial haplogroup	H, U, T	54	DXA	44.0	Protective effect for mitochondrial haplogroup J
Ranade, et al. ⁷⁷	Resistin	rs3219177 C/T, T/T	104	Clinical, DXA	23.1	Caucasians
Zanone, et al. ⁷⁸	ApoC3	455 C/, T/T	255	Clinical	27.5	Lipoatrophy alone
	Fas	670 A/A				
	Adr β 3	T/T				
Zanone, et al. ⁷⁸	Adr β 2	16 A/A	255	Clinical	24.7	Lipohypertrophy
	Adr β 2	27 C/G, G/G				
Chiappini, et al. ¹¹⁶	PolG	E1143	197	Clinical	35.0	Case-control study
Domingo, et al. ¹¹⁷	Thymidylate synthase	Low expression TS genotype (*2/*2, *2/*3C and *3C/*3C	33	Clinical, DXA	51.5	Caucasians on d4T-based therapy
Wangsomboonsiri, et al. ¹¹⁸	HLA	HLA-B*4001	103	Clinical, DXA	54.4	Thai patients on d4T-based therapy
Montes, et al. ¹¹⁹	MMP-1	-16071G/2G	216	Clinical, DXA	38.0	d4T- and azathioprine-based therapy

HALS: HIV-1/HAART-associated lipodystrophy syndrome; TNF- α : tumor necrosis factor alpha; IL-1 β : interleukin 1 beta; HLA: human leukocyte antigen; DXA: dual X-ray absorptiometry; ApoC: apolipoprotein C3; Adr β : adrenergic receptor beta; d4T: stavudine; NA: not available; MMP-1: matrix metalloproteinase 1.

mtDNA polymerase- γ ⁵². Other mechanisms, such as oxidative mtDNA damage, heteroplasm mtDNA point mutations, multiple mtDNA deletions, and ADP/ATP translocase inhibition, can directly cause mitochondrial dysfunction, whereas TNF- α and PI may act as contributors⁵⁵.

Mitochondrial abnormalities will eventually lead to an increased production of reactive oxygen species (ROS), which has been linked to lipoatrophy⁵⁵. Down-regulation of uncoupling protein 2 may contribute to enhanced ROS production⁵⁵. The ROS are signaling molecules that control pre-adipocyte proliferation and adipocyte differentiation⁵⁵, and their generation may constitute an early and crucial event in HALS⁵⁵. Alternatively, events such as the collapse of membrane

potential, cytochrome C release, and ultimately apoptosis are influenced by mitochondrial bioenergetics⁵⁰. Excess adipocyte apoptosis was found in *ex vivo* fat samples from lipoatrophic areas⁵⁶.

HALS is linked to a chronic low-grade inflammatory state, which is observed in fat and at systemic level. At the systemic level, high free fatty acid (FFA) levels, increased insulin resistance, increased levels of C-reactive protein, and reduced levels of adiponectin are found⁵⁰. In subcutaneous adipose tissue (SAT), enhanced TNF- α , IL-6, and MCP-1 expression is reported⁵⁶. Enhanced expression of CD68, coupled with evidence of lipogranulomas⁵⁶, indicates increased macrophage infiltration. A complex cross-talk between adipocytes, pre-adipocytes, and inflammatory cells present within

SAT is therefore likely to be involved in the creation of this proinflammatory environment. Also, TNF- α and other proinflammatory cytokines are known to impair PPAR- γ expression and promote lipolysis⁵⁵. Antiretrovirals may contribute to fat inflammation and the role of NRTI has been demonstrated⁵⁷. Inflammation increases the expression of adipocyte nucleoside transporters and facilitates higher intracellular levels of NRTI⁵⁸. It may also enhance the deleterious effects of drugs, as is the case when stavudine is combined with C-reactive protein⁵⁸.

Lipohypertrophy: a growing paradox

Increased amounts of visceral adipose tissue (VAT) are often observed in HALS, although the mechanism by which this occurs remains unclear. VAT and SAT are different in terms of metabolism, gene expression, and inflammatory status⁵⁹. Adipocytes or other cells in SAT and VAT may in fact respond to the insults which cause HALS in an intrinsically different manner, thus resulting in atrophy in one area and hypertrophy in another. This is supported by studies showing that VAT and SAT adipocytes exhibit differential responses to PI, and greater resistance to zidovudine-induced mitochondrial toxicity⁵⁰. It could be that SAT constitutes the main target of HALS-related insults, and that VAT is simply a repository for fat that cannot be properly stored in SAT. This phenomenon could represent a kind of "secondary" lipotoxicity. A recent study showed that VAT from HALS did not exhibit impaired adipogenic gene expression, although it did share certain features with SAT such as impaired mitochondrial function and changes in inflammatory markers⁶⁰.

Enlargement of the dorso-cervical fat pad (buffalo hump) is another distinct manifestation of hypertrophied fat in HALS patients⁶¹. Gene expression analysis and microscopic studies of buffalo hump have revealed the presence of brown adipose tissue features and an increased expression of cell proliferation marker genes, proving their lipomatous character⁶¹. Buffalo hump adipocytes have acquired some characteristics of brown fat, although not functional thermogenesis⁶¹. In rodent cell cultures, the expression of the specific brown fat marker gene, UCP-1, is increased in response to stavudine⁶². The delivery of fatty acids from lipoatrophic areas may also induce an increased proliferation of adipocytes in brown adipocyte-enriched areas, since UCP-1 is known to be activated by fatty acids present in brown fat cells⁶⁰.

Clinical consequences of HIV/HAART-associated lipodystrophy syndrome

Lipotoxicity

Lipotoxicity refers to the accumulation of fat in ectopic areas outside classical adipose tissue depots. This accumulation can cause toxic effects in muscle, liver, or pancreas. In HALS patients, insulin resistance, visceral obesity, and the release of FFA into the bloodstream induce nonalcoholic fatty liver disease⁶³.

The accumulation of lipid in skeletal muscle is considered a primary event in the pathogenesis of insulin resistance. There is a significant link between lipid accumulation in muscle and insulin resistance and with the extent of peripheral lipodystrophy⁶⁴. Protease inhibitors have been reported to inhibit glucose uptake in muscle, which may contribute to insulin-resistant states⁶⁴.

Patients with HALS frequently display alterations in glucose homeostasis due to peripheral insulin resistance, as well as reduced pancreatic insulin secretion⁵⁰. Impaired glucose tolerance in HALS patients is linked to reduced pancreatic β -cell compensation for decrements in insulin sensitivity, despite a simultaneous reduction in insulin clearance⁶⁵. The etiology of β -cell dysfunction in HALS is unknown, although it is thought that the effects of ARV and/or elevated FFA play a role⁶⁵.

Implications for cardiovascular health

HALS is associated with dyslipidemia, altered glucose tolerance, insulin resistance, and hypertension, all of which are reminiscent of the metabolic syndrome, a well-known cluster of cardiovascular risk factors⁶⁶. In addition, HALS has been linked to a heightened risk of subclinical atherosclerosis⁶⁷. In some cohorts, HALS has been identified more frequently among patients with coronary heart disease⁶⁸.

Quality of life, social and psychological impact

Changes in body morphology and facial lipoatrophy are stigmatizing and may severely impact quality of life, leading to psychological distress, decreased self-esteem, and increased anxiety and depression⁶⁹. The social effects include difficulties in finding clothing and impaired quality of social relationships, which can cause social alienation⁷⁰. Local fat atrophy may have

physical consequences, which include discomfort while sitting or pedal pain while standing. Sexual dysfunction has been observed in HALS patients because of their negative perception of self-image⁷¹.

Early senescence

The HIV-1-infected patients have higher than expected rates of diseases associated with the normal ageing process. The most prevalent include cardiovascular, cancer, liver, and kidney disease, neurological complications, osteopenia/osteoporosis, and frailty⁷². Ageing is physiologically associated with fat redistribution and may share common pathogenic mechanisms with most of these comorbidities, including oxidative stress and low-grade inflammation⁵⁵. Cellular insults by PI and tNRTI may lead to pre-adipocyte premature senescence⁵⁵.

Prevention and treatment of HIV/HAART-associated lipodystrophy syndrome

Prevention of lipoatrophy

Regimens without tNRTI contribute less to subcutaneous fat loss than regimens containing tNRTI^{22,33,73,74}. Ritonavir-boosted PI such as lopinavir²² or atazanavir¹⁸ led to higher increases in limb fat than the NNRTI efavirenz. The PI/r-containing NRTI-sparing regimens may lead to higher increases in limb fat as compared to standard triple regimens containing two NRTI⁷⁵.

Because the risk of developing lipoatrophy is inversely proportional to the CD4 cell count⁷⁶, it might be lower if initiating ART earlier. Several genetic polymorphisms have been associated with a higher risk of developing lipoatrophy⁷⁶⁻⁷⁸, but they are not yet ready for clinical use. Intense regular aerobic exercise, low-fat diets, and chronic metformin therapy might decrease subcutaneous fat and therefore increase the risk for lipoatrophy⁷⁹.

Prevention of lipohypertrophy

A net energy imbalance in favor of caloric consumption against its expenditure leads to fat storage. In HIV-infected patients with lipoatrophy, the subcutaneous fat compartment cannot adequately store fat and leaves the visceral compartment as the major repository for fat storage. Increased visceral fat may be present even if a patient is not considered obese, as defined by body mass index. Beyond caloric restriction, there

is no evidence that further modification of dietary factors may prevent lipohypertrophy⁸⁰. The use of inhaled corticosteroids in patients treated with PI may lead to Cushing's syndrome⁸¹.

Strategies for the management of HIV/HAART-associated lipodystrophy syndrome

Management of lipoatrophy

Once lipoatrophy has developed, subcutaneous fat could potentially recover, although recovery is slow and incomplete either due to irreversible damage of adipose tissue or due to persistency of unknown or unavoidable factors contributing to fat loss, or a combination of these factors. There is no evidence showing that diet or exercise can improve lipoatrophy^{79,80,82}.

Modification of successful ART may increase the risk of virologic failure⁸³, and potentially adds the risk of toxicity from new drug(s). When switching from PI, metabolic complications such as dyslipidemia and insulin resistance seem to be partly reversible, whereas the morphologic alterations appear to be unchanged. When NRTI are switched, a modest improvement in lipoatrophy has been reported, but dyslipidemia appears unaffected⁸⁴. Switching from stavudine to zidovudine⁸⁵, reducing stavudine dose⁸⁶, and discontinuing ART^{57,87,88} have been associated with limb fat gain, but these cannot be considered as reasonable options to improve lipoatrophy in clinical practice. Switching from tNRTI to either abacavir or tenofovir or to nucleoside-sparing regimens is associated with a 200-800 mg increase in limb fat after one year (Fig. 1 A, B, C)^{31,89-92}. In ARV-naive HIV-infected patients, PI/r-containing regimens have shown higher increases in limb fat mass compared with regimens containing NNRTI²². Whether this difference might translate into any clinical benefit for the management or prevention of lipoatrophy is currently unknown.

Pharmacological interventions to treat lipoatrophy have shown controversial results. Thiazolidinediones induce adipocyte differentiation and increase subcutaneous fat mass⁹³. However, a meta-analysis of six placebo-controlled trials of thiazolidinedione therapy for HIV lipoatrophy revealed that pioglitazone therapy was more effective than placebo to increase limb fat mass, whereas rosiglitazone was not significantly better than placebo⁹⁴. Another more comprehensive meta-analysis confirmed the lack of clinically significant effects of both pioglitazone and rosiglitazone in

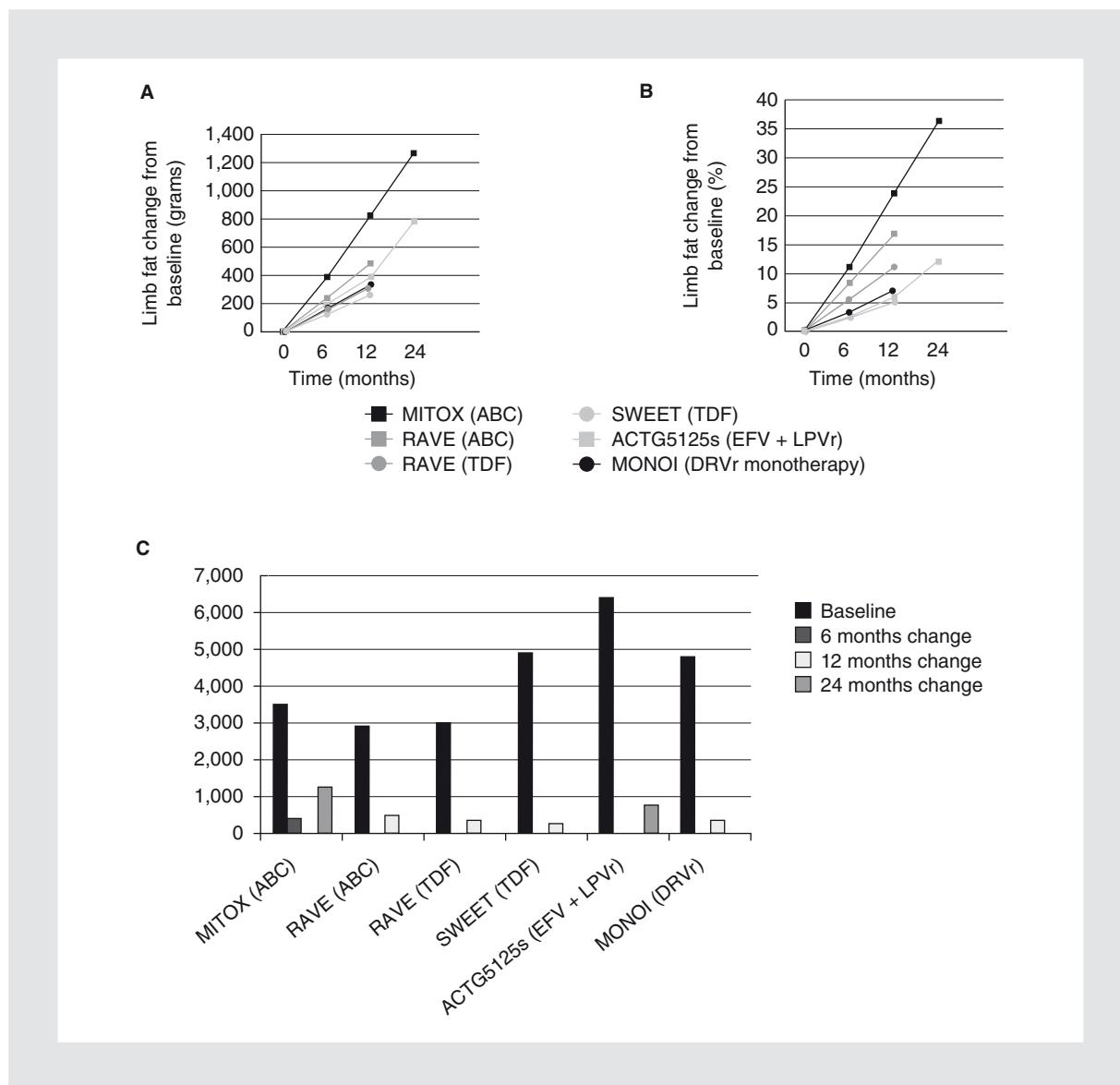


Figure 1. Dynamics of limb fat at baseline and during different antiretroviral switching strategies.

MITOX (abacavir, ABC): Switch from either stavudine or zidovudine to abacavir^{98,92}; RAVE (abacavir, ABC): Switch from either stavudine or zidovudine to abacavir¹¹⁰; RAVE (tenofovir, TDF): Switch from either stavudine or zidovudine to tenofovir¹¹⁰; SWEET (tenofovir, TDF): Switch from the fixed-dose combination zidovudine/lamivudine to the fixed-dose combination tenofovir/emtricitabine⁹¹; ACTG5125s: Switch from either stavudine or zidovudine plus didanosine or lamivudine to efavirenz (EFV) plus lopinavir/ritonavir (LPV/r)⁹⁰; MONOI: Switch from nucleoside reverse transcriptase analogues (approximately 60% of patients taking either abacavir plus lamivudine or tenofovir plus emtricitabine)³¹.

HIV-infected patients with HALS⁹⁵. Uridine⁹⁶ and pravastatin⁹⁷ have been reported to improve HALS in small randomized clinical trials, but these effects have not been confirmed^{98,99}.

Facial filling has proven to be an aesthetic only but highly satisfactory procedure¹⁰⁰. Transplantation of autologous fat is more time consuming than injections of gel fillers and may not be feasible in cases of severe lipoatrophy. However, fat is less expensive and as durable as gel fillers¹⁰¹.

Management of lipohypertrophy

Low-caloric or low-fat, high-fiber diets and aerobic or resistance exercise have shown benefits on central fat accumulation^{66,79}. Diet and exercise might worsen lipoatrophy in HIV-infected patients with a low BMI. It remains unproven that switching or discontinuing ARV drugs may have a benefit in reducing VAT^{66,87}.

Growth hormone deficiency is associated with visceral adiposity in the general population¹⁰² as well as

in HIV-infected patients with HALS¹⁰³. Growth hormone has been used at doses of 0.33 to 6 mg daily⁶⁶. With doses of 4 mg every day or every other day^{104,105}, patients with abdominal lipohypertrophy experienced 10-20% reduction in VAT and 6-7% reduction in subcutaneous fat. Body fat effects were lost when growth hormone dose was reduced or discontinued. The reduction in VAT as well as the frequency and intensity of adverse events were directly proportional to the growth hormone dose used. Arthralgia, myalgia, edema, and glucose intolerance or diabetes are not uncommon side-effects of growth hormone therapy.

Tesamorelin is a growth hormone-releasing hormone analogue that mimics closely the physiological dose and function of growth hormone, but with potentially fewer side effects. Two large randomized, double-blinded, placebo-controlled trials have¹⁰⁶ reported 11-15% reductions in VAT after six months of tesamorelin use, although this effect was lost upon therapy discontinuation. Tesamorelin may infrequently induce injection-site reactions (2% of patients) and growth hormone-related side effects such as arthralgia or edema, but it was not associated with glycemic abnormalities.

Superficial, localized fat accumulation in HIV-infected patients has been successfully treated with surgical interventions. Liposuction has been used to remove fat from the anterior neck, enlarged breasts, and subcutaneous abdominal compartment¹⁰⁷⁻¹⁰⁹, but it cannot remove intra-abdominal fat. Approximately 25% of patients will develop a recurrence of lipohypertrophy after liposuction¹⁰⁸.

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Conflicts of interest

The authors do not declare any conflict of interest.

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