



HIV and antiretroviral therapy-related fat alterations

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Abstract | Early in the HIV epidemic, lipodystrophy, characterized by subcutaneous fat loss (lipoatrophy), with or without central fat accumulation (lipohypertrophy), was recognized as a frequent condition among people living with HIV (PLWH) receiving combination antiretroviral therapy. The subsequent identification of thymidine analogue nucleoside reverse transcriptase inhibitors as the cause of lipoatrophy led to the development of newer antiretroviral agents; however, studies have demonstrated continued abnormalities in fat and/or lipid storage in PLWH treated with newer drugs (including integrase inhibitor-based regimens), with fat gain due to restoration to health in antiretroviral therapy-naïve PLWH, which is compounded by the rising rates of obesity. The mechanisms of fat alterations in PLWH are complex, multifactorial and not fully understood, although they are known to result in part from the direct effects of HIV proteins and antiretroviral agents on adipocyte health, genetic factors, increased microbial translocation, changes in the adaptive immune milieu after infection, increased tissue inflammation and accelerated fibrosis. Management includes classical lifestyle alterations with a role for pharmacological therapies and surgery in some patients. Continued fat alterations in PLWH will have an important effect on lifespan, healthspan and quality of life as patients age worldwide, highlighting the need to investigate the critical uncertainties regarding pathophysiology, risk factors and management.

Adipose tissue accounts for ~20–30% of total body weight in non-obese or overweight persons and for up to 50% in individuals with obesity and is a primary energy store with important endocrine and immunomodulatory functions. Most adipose tissue depots are comprised of white fat, which is responsible for energy storage and release in response to food intake and energy demand. In humans, brown and beige fat are minor components of adipose tissue and can dissipate energy as heat. White adipocytes sequester dietary lipids in adipose tissue depots to serve as energy stores during periods of fasting and prevent toxic lipid accumulation in other tissues such as muscle, liver, pancreas and heart¹. In addition, white adipocytes have a role in glucose and lipid metabolism and respond differentially to physiological cues or metabolic stresses by releasing adipokines and lipokines that regulate energy expenditure, appetite control, glucose homeostasis, insulin sensitivity, inflammation, immune function and tissue repair². Although adipose tissue is mainly comprised of adipocytes, it also contains mesenchymal stem cells (which can differentiate into adipocytes, myoblasts, osteoblasts and chondroblasts), immune cells (including M1 and M2 phenotype macrophages, CD4⁺ T cells and

CD8⁺ T cells) and fibroblasts, in addition to blood vessels and nerves.

Fat expands owing to excess energy supply either through hypertrophy (increased size of existing adipocytes) or hyperplasia (the formation of new adipocytes from mesenchymal stem cells in adipose tissue). In obesity, hypertrophic adipocytes have different biochemical properties to smaller adipocytes, including increased lipolysis, inflammatory cytokine production and reduced secretion of anti-inflammatory adipokines, such as adiponectin, that are also involved in insulin sensitivity¹. Such alterations in fat depots predispose to ectopic lipid accumulation and the development of comorbidities, including type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), sarcopenia, atherosclerosis and heart failure². During physiological ageing, fat is lost from lower limbs and increases in the trunk, alongside accumulation of senescent adipocytes that have altered adipogenic potential and increased secretion of proinflammatory cytokines³.

Fat alteration became a major concern in Western countries in the mid-1990s, when people living with HIV (PLWH) receiving combination antiretroviral therapy

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(cART) developed a condition of severe subcutaneous lipoatrophy (fat loss), which was termed lipodystrophy⁴. Some of these PLWH with lipodystrophy also had fat gain in the trunk and neck. Historically, these conditions were common in PLWH who were treated with older-generation thymidine analogue nucleoside reverse transcriptase inhibitors (NRTIs; such as zidovudine and stavudine)⁵ (BOX 1) and early protease inhibitors (PIs; such as indinavir and full-dose ritonavir). The toxic effects of thymidine analogue NRTIs on adipocytes led to the development of other antiretroviral agents with a lower risk of severe lipoatrophy, such as the NRTIs tenofovir disoproxil fumarate (TDF) and emtricitabine (also known as FTC). However, more recent studies have demonstrated fat alterations, mainly fat gain and changes in lipid trafficking and storage in individuals using these therapies, which are different from lipodystrophy and are compounded by the rising worldwide prevalence of obesity⁶. Moreover, first-generation thymidine analogue NRTIs can exert long-lasting effects, and fat alterations and metabolic dysregulation can be observed several years after regimen change⁷.

ART initiation and long-term treatment have been almost universally associated with weight and generalized fat gain, particularly in the trunk, leading to abdominal obesity (also known as visceral obesity)^{8,9}. Moreover, integrase strand transfer inhibitors (INSTIs) have been associated with weight gain and generalized fat gain in some PLWH¹⁰. The NRTI backbone agents used in these patients can also affect weight gain to varying degrees; TDF has been shown to result in less weight gain than other NRTIs in some studies^{10,11}, whereas tenofovir alafenamide (TAF; a newer formulation of tenofovir) has been associated with greater weight gain than TDF, abacavir or the non-NRTI (NNRTI) efavirenz in trials^{11,12}.

Mechanisms of fat alterations in PLWH are complex and result from the direct effects of HIV proteins and antiretroviral agents on adipocyte health, in addition to changes in microbial translocation and the immune response, increased tissue inflammation and accelerated fibrosis, although these mechanisms are only partly understood. In addition, the effects of HIV and antiretroviral therapies on fat differ between individuals. To this end, a central fat distribution, in particular within the visceral adipose tissue (VAT) depot (an 'apple' shape or android distribution) is generally associated with a less favourable metabolic phenotype, greater

inflammation and insulin resistance, and an increased risk of T2DM and cardiovascular diseases¹³. By contrast, a distribution where the subcutaneous adipose tissue (SAT) depot is preferentially expanded, particularly in the lower extremities ('pear' shape or gynoid distribution), is associated with a more favourable metabolic phenotype and insulin sensitivity¹³.

Fat alterations remain an issue in patients receiving contemporary cART, compounded by the rising rates of obesity globally, and particularly in North America. This Primer summarizes the characteristics and mechanisms of HIV-related and ART-related fat alterations, focusing on the current cART era, and discusses the management and critical research gaps in the field.

Epidemiology

HIV-associated wasting

Altered body composition in ART-naive PLWH before the onset of severe CD4⁺ T cell depletion was recognized early in the HIV epidemic and was characterized by lower lean and fat mass than people without HIV. In addition, wasting of lean muscle mass and fat was a hallmark of AIDS early in the epidemic^{14,15}. In these early cases, wasting was defined by a weight loss of >10% of pre-illness maximum weight or weight at <90% of ideal body weight for the patient's gender^{16,17}. In men with AIDS, the wasting syndrome was characterized by a disproportionate decrease in lean body mass with relative fat sparing, whereas women with AIDS had a progressive and disproportionate decrease in body fat relative to lean body mass at all severities of wasting¹⁸.

Wasting in PLWH was primarily caused by a profound caloric deficit, engendered by reduced energy absorption from gastrointestinal barrier dysfunction, opportunistic infections, reduced gastrointestinal transit time (leading to diarrhoea), increased protein turnover (leading to higher catabolism and impaired anabolism) and increased energy requirements^{19,20}. This negative energy balance reduced adipocyte lipid content and size, rather than damaging adipocyte bioenergetics or altering the stromal vascular fraction. As such, the mechanisms of this wasting are considered more similar to those of starvation than later descriptions of lipoatrophy early in the cART era. However, prior wasting disease was not without consequences. In ART-naive patients, peripheral fat reductions were generally greater in women than in men^{21,22} and ART-naive women with prior AIDS-defining illnesses (infections and cancers directly associated with AIDS-related immunodeficiency) had less fat than women without such illnesses²².

cART-related lipoatrophy and lipohypertrophy

In contrast to wasting, the clinical syndrome of lipoatrophy in patients receiving cART results from damage to adipocytes and stromal vascular cells. The lipoatrophy phenotype was first identified in PLWH who received cART triple-drug therapy, including one first generation PI and two NRTIs (either stavudine or zidovudine)²³. A high proportion of these patients, up to 80% in some surveys, reported a perceived striking and stigmatizing change in physical appearance during

Box 1 | Antiretroviral drugs

The most commonly previously or presently used drugs are indicated below.

Nucleoside or nucleotide reverse transcriptase inhibitors

- Zidovudine (ZDV), also known as azidothymidine (AZT)^a
- Didanosine (DDI)^a
- Stavudine (D4T)^a
- Lamivudine (3TC)^a
- Abacavir (ABC)^a
- Tenofovir disoproxil fumarate (TDF)
- Tenofovir alafenamide (TAF)
- Emtricitabine (FTC)

Non-nucleoside reverse transcriptase inhibitors

- Nevirapine (NVP)^a
- Efavirenz (EFV)^a
- Etravirine (ETR)

- Rilpivirine (RPV)
- Doravirine (DOR)

Protease inhibitors

- Saquinavir (SQV)^a
- Indinavir (IDV)^a
- Ritonavir (RTV)^a
- Nelfinavir (NFV)^a
- Lopinavir (LPV)
- Atazanavir (ATV)
- Darunavir (DRV)

Integrase strand transfer inhibitors

- Raltegravir (RAL)
- Dolutegravir (DTG)
- Elvitegravir (EVG)
- Bictegravir (BIC)

^aDenotes first generation antiretroviral molecules that were approved by the FDA between 1987 and 1998.

ART use at the same time that CD4⁺ T cell count and survival increased²⁴.

In some patients, lipoatrophy was observed in association with truncal fat accumulation. As previously mentioned, many early studies combined the two distinct phenomena of lipoatrophy and lipohypertrophy into a single 'lipodystrophy' phenotype, characterized by broad regional changes (generally reduced limb diameter and facial wasting with or without abdominal or truncal enlargement)^{25,26}. However, problems with this mixed definition include the conflation of two distinct syndromes, a reliance on relative proportions (for example, reductions in limb diameter suggest increased abdominal girth) and a lack of objective metrics. An objective definition of the mixed lipodystrophy phenotype, based on dual X-ray absorptiometry (DXA)-derived fat ratios, has not been validated for use in clinical practice^{4,27}. Thus, most prevalence studies are based on clinical evaluations of a patient's appearance using semi-quantitative clinical scores such as the Lipodystrophy Severity Grading Scale⁴.

Many earlier surveys assessed a combined phenotype of lipoatrophy and/or lipohypertrophy in PLWH and estimated a worldwide prevalence of 13–70% from the mid-1990s to the early 2000s²⁸. Patient ethnicity did not appear to markedly influence the prevalence in PLWH, despite differences in susceptibility to VAT accumulation in the general population^{29,30}. In African countries/regions, lipoatrophy and/or lipohypertrophy were reported in ~25% of patients using ART, but prevalence ranged from 1–84%³¹, with higher values reported in women than in men, and in persons >40 years of age than in younger persons³². In the Asia-Pacific region, a severe phenotype, defined as disfiguring or obvious body shape changes on casual visual inspection, was reported in ~10% of PLWH using cART and was strongly associated with the use of stavudine and older PIs³³.

Lipoatrophy

Lipoatrophy prevalence has varied over time and geographical location owing to the improved knowledge of risk factors by HIV caregivers and the introduction of newer, less fat-toxic antiretroviral therapies. In general, a loss of ≥30% limb fat (evaluated using DXA) is required for lipoatrophy to become clinically evident³⁴ and early or subtle forms can be easily overlooked. Diagnosis is easier in women (who have higher initial amounts of limb fat) than in men (who can have minimal limb fat)³⁵. A prospective study and a clinical trial that delineated the natural history of lipoatrophy in PLWH treated with early thymidine analogue-containing cART reported a biphasic trend, with a general fat gain during the first 24–32 weeks after starting cART, in what is viewed as a 'return to health' phenomenon, followed by a median limb fat loss of 13.7% per year, which varied from 1.7% per year for zidovudine–lamivudine to 19% per year for stavudine–didanosine^{36,37}. The association of thymidine analogue NRTIs with lipoatrophy was further supported by its partial or total reversion when these drugs were replaced by less toxic NRTIs in some patients³⁸. In clinical trials of newer antiretroviral agents, the threshold of limb fat loss for the diagnosis of lipoatrophy is generally 10–20% and prevalence after 3 years of therapy is often 5–10% depending on the type or class of antiretroviral³⁹.

Owing to the high risk of lipoatrophy with thymidine analogue NRTIs, the WHO issued a statement in 2009 that recommends the avoidance of stavudine for HIV treatment⁴⁰. With the near-universal switch to TDF-based regimens in low-income countries, it is expected that the prevalence of lipoatrophy will decrease worldwide as older drug regimens are replaced with less toxic alternatives. However, despite the avoidance of both zidovudine and stavudine³⁸, the prevalence of lipoatrophy is still high among many long-term ART recipients owing to surviving historical cases²⁸.

Indeed, individuals who received thymidine analogue NRTIs as part of older cART regimens often have persistent fat alterations several years after therapy discontinuation^{41,42}. Long-term infected (median duration 12.2 years) and cART-treated PLWH in the AGEHIV cohort had higher waist and lower hip circumferences than people without HIV with similar demographic and behavioural characteristics⁴³. In addition, cumulative prior exposure to stavudine, zidovudine or didanosine was associated with persistent CT evidence of decreased SAT and increased abdominal VAT in the COCOMO study as well as a higher risk of hypertension, high total cholesterol and low HDL cholesterol^{44,45}. The increased VAT was greater with longer cumulative exposure to thymidine analogue NRTIs or didanosine and was observed at all time points after discontinuation of the drugs⁴⁴. Moreover, 22% patients from the APROCO cohort who were previously treated with thymidine NRTIs have persistent mixed lipoatrophy and/or lipohypertrophy and high rates of insulin resistance⁴⁶. Young adults who were infected with HIV during childhood and exposed to older-generation NRTIs are particularly susceptible to persistent lipoatrophy after discontinuation and have

a higher prevalence of fat alteration than age-paired persons from the general population^{38,47}.

Aside from the use of older NRTIs, other risk factors associated with lipotrophy include HIV-related factors, such as a low CD4⁺ T cell count (generally <100 cells/mm³) and high plasma HIV1 RNA levels (>10⁵ copies/ml) at cART initiation²⁸. For host-related factors, such as age, cut-offs have been established at more than 40 or 50 years and risk has been modelled for each 10 years (OR 1.32, 95% CI 1.07–1.63). A higher risk of lipotrophy is also associated with male sex and lower fat mass before therapy²⁸.

Lipohypertrophy

In the modern cART era, lipohypertrophy is generally observed in the abdomen and trunk⁴⁸. Up to 70% of PLWH receiving cART have increased abdominal fat, which is now the most common type of fat alteration in these patients^{37,44,49,50}, and risk factors include older age, female sex, elevated baseline triglycerides and higher baseline body fat percentage⁵¹. Generalized weight gain (see Generalized fat gain and obesity below) can be more difficult to distinguish from lipohypertrophy in persons with excess adiposity in the abdomen, chest, shoulder and nape of the neck (the android or ‘apple’ distribution) than those prone to accumulation in the hips, thighs and buttocks (the gynoid or ‘pear’ distribution). Mechanistically, lipohypertrophy is defined by regional increases in adipocyte size and/or number and it primarily affects the abdominal compartment, including disproportionate increases in VAT, dorso-cervical adipose tissue, breasts and supra-inguinal area, and diversely located lipomas^{28,52}; of note, these changes are different to those observed with generalized fat gain.

Although lipotrophy has been linked to specific ARTs, the independent risk of lipohypertrophy attributable to PI or NNRTIs use is difficult to assess as these agents were provided in combination with NRTIs⁴⁸. Some studies of later-generation PIs have reported little difference in the size of anatomical areas prone to lipohypertrophy compared with NNRTIs or INSTIs^{51,53}, with the possible exception of trunk fat gain with ritonavir-boosted atazanavir^{54,55}. Assessing disproportioned accumulation of adipose tissue, particularly in individuals with generalized weight gain and/or obesity, is aided by DXA and CT. Indeed, the imaging sub-study of the ACTG study A5257 demonstrated a mean CT-quantified VAT gain of 26% 96 weeks after treatment initiation, with a 13% limb fat gain and 20% SAT gain, which did not vary significantly between individuals randomized to receive raltegravir, ritonavir-boosted darunavir or ritonavir-boosted atazanavir⁵⁶. These findings suggest a disproportionate gain in VAT compared with SAT among persons receiving PIs or an INSTI in combination with newer-generation NRTIs. However, in a subsequent analysis, women had a greater increase in waist circumference on raltegravir versus PIs than men⁵⁷, suggesting sex differences in drug effects.

In long-term studies of ACTG participants, DXA-quantified lean mass began to decline at 96 weeks after ART initiation, which could result in sarcopenia in the

long term, relative to individuals without HIV, whereas trunk fat, associated with adverse metabolic outcomes, continued to accumulate at a faster rate than in individuals without HIV⁵⁸. Similarly, in studies from the Modena HIV Metabolic Clinic, DXA-quantified trunk fat continuously and steadily increased, whilst lean mass consistently decreased, in PLWH using long-term cART, which was observed in both men and women and across all age groups⁵⁹. As VAT gains of as little as 5% have been associated with an increased risk of metabolic syndrome⁶⁰ and trunk fat accumulation has been associated with short-term mortality risk in PLWH⁶¹, patients with increased trunk adiposity have an increased risk of cardiometabolic diseases and could benefit from the screening and treatment of cardiovascular and metabolic risk factors.

Generalized fat gain and obesity

Weight and generalized fat gain are almost universally described following cART initiation, involve limb and trunk fat, SAT and VAT, and occur during the first year of treatment on all regimens^{8,9,56}. In addition, the prevalence of obesity is increasing among PLWH, in particular in North America and in sub-Saharan Africa^{62,63}.

Weight gain following cART initiation could be attributable at least in part to a return to health phenomenon, with a concomitant gain in lean mass, but is clearly higher with some individual INSTIs, the newest antiretroviral class and TAF than with other ART molecules¹². In addition, weight gain is associated with personal factors, such as sex, genetics and ethnicity^{41,64}. Thus, a greater fat gain both in the peripheral and truncal depots, resulting in generalized fat gain, has been observed in some individuals receiving INSTIs, both in cohort studies and in clinical trials^{10,41,65–68}. Indeed, in a large analysis of more than 22,000 treatment-naive PLWH in the multi-site NA-ACCORD, individuals who initiated INSTI-based regimens gained an estimated mean 5.9 kg after 5 years of treatment, compared with 3.7 kg among individuals receiving NNRTI-based regimens and 5.5 kg for those receiving PI-based regimens⁶⁹. Smaller observational studies have also reported a greater weight gain in PLWH initiating INSTI-containing regimens than in those initiating NNRTI or PI regimens, which generally has been greater in women, black individuals, and in those with lower weight and CD4⁺ T cell counts before starting ART^{65,66,68,70}. The aetiology of weight gain with INSTIs is unclear and may include effects on thermogenesis, appetite or energy regulation, or perhaps reflect a direct effect or a greater antiretroviral efficacy of these drugs in adipose tissue^{71,72} or other metabolically active tissue.

In the prospective, randomized ADVANCE study, an increased incidence of obesity was observed in ART-naive PLWH in South Africa who initiated dolutegravir than in those who initiated an efavirenz-based treatment¹¹, affecting 7% of male patients and 20% of female patients initiating a dolutegravir–TAF–FTC regimen. Weight gain at 48 weeks was higher in women receiving dolutegravir–TAF–FTC (mean increase of 6.4 kg) than in those initiating dolutegravir–TDF–FTC (mean increase of 3.2 kg) and women had a

higher weight gain than men (mean increase of 4.7 kg for dolutegravir–TAF–FTC and 3.0 kg for dolutegravir–TDF–FTC); the reason for this sex difference is unknown¹¹. In addition, a pooled analysis of weight gain in eight randomized controlled trials of treatment-naïve PLWH initiating ART, comprising >5,000 participants, reported a higher weight gain at 96 weeks in those receiving TAF-containing regimens than in those receiving TDF, abacavir or zidovudine after adjusting for age, ethnicity, sex, baseline clinical factors and additional ART agents¹².

Interestingly, the few studies of PLWH who switched from NNRTIs or PIs to INSTIs have reported mixed results. In a retrospective single-centre cohort study, there was no clear evidence of an overall increase in rate of weight gain following a switch to INSTIs in virologically suppressed individuals⁷³. Differences in gender (mainly men) and ethnicity (mainly white) could partly explain this result. By contrast, an analysis of 691 patients with virologic suppression in the ACTG A5551 or A5332 studies from 2007 to 2017 found that women, black people and persons aged ≥60 years experienced a greater rate of weight gain in the 2 years after a switch to an INSTI-based regimen than before the switch⁷⁴. Additionally, in the ANRS163 ETRAL study, 165 persons with viral suppression who switched from a PI to raltegravir and efavirenz had a 12% increase in DXA-assessed total, trunk and limb fat but not in lean mass after 96 weeks^{75,76}. The rate of weight gain is generally greater with dolutegravir than with elvitegravir or raltegravir, and among women, black people and those aged ≥60 years^{74,77}.

Ectopic fat depots

Clinically apparent lipohypertrophy is one facet of a broader condition of ectopic lipid deposition in PLWH, which is also often observed in the liver, epicardial tissue and skeletal muscle. Indeed, several studies have demonstrated increased epicardial fat in cART-treated PLWH, the volume of which is associated with VAT area, insulin resistance, traditional risk factors for atherosclerosis and the duration of cART^{78–80}. In addition, intramuscular fat accumulation has previously been reported in PLWH with lipoatrophy and/or lipohypertrophy⁸¹, and increased fatty infiltration of the thigh muscle was found to be associated with ageing independent of fat distribution⁸². Increased hepatic fat content has also been observed in PLWH with lipoatrophy⁸³ or in those with increased central adiposity⁸⁴. Interestingly, and unique to PLWH, a parabolic association between SAT and liver fat has been observed, indicating high levels of steatosis in people with lipoatrophy and in those with increased subcutaneous adiposity⁸³.

Mechanisms/pathophysiology

The mechanisms of fat alterations in PLWH are complex, multifactorial and only partly understood. The role of HIV itself is an area of increasing study, whereas the effect of ARTs has been proposed since the mid-1990s. Immune system activation, either locally or in the gut and with resulting inflammation, has also been proposed to affect adipocyte health.

Adipose tissue as a reservoir for HIV

Adipose tissue is an important HIV and simian immunodeficiency virus (SIV) reservoir, with the presence of latently infected CD4⁺ T cells and macrophages in both SAT and VAT depots from ART-naïve PLWH and SIV-infected macaques^{85–87}. Indeed, replication-competent HIV is present in both SAT and VAT CD4⁺ T cells from treated, aviraemic PLWH without clinical fat alterations, with a median latent HIV proviral DNA copy number equivalent to that in circulating and mesenteric lymph node CD4⁺ T cells. Additionally, SIV is detected within adipose tissue in ART-suppressed situations^{85–87} and HIV/SIV proteins can be detected in the plasma and tissues despite virus suppression^{88,89}. Furthermore, SIV DNA and RNA are present in stromal vascular fraction cells, sorted CD4⁺ T cells and CD14⁺ macrophages in SAT and VAT from SIV-infected macaques^{85,87,90}.

Role of the virus

As previously mentioned, many ART-naïve PLWH have decreased overall fat mass and can have fat alterations affecting both SAT and VAT compartments, suggesting that HIV infection per se can affect adipose tissue and induce metabolic disturbances^{22,91,92} (FIG. 1).

ART-naïve patients have a lower SAT volume and decreased whole tissue expression of *CEPBA* and *PPARG* (encoding the major transcription factors C/EBPα and PPARγ, respectively, which are important for normal adipogenesis and cellular function) compared with HIV-negative controls^{93,94}. Accordingly, the expression of pro-adipogenic genes is also reduced in SAT, including markers of lipid storage (*LPL* (encoding lipoprotein lipase) and *FABP4* (encoding the fatty acid transporter 4)) and adipokines with important endocrine function (for example, *LEP* (encoding leptin) and *ADIPOQ* (encoding adiponectin)), together with increased expression of proinflammatory cytokines such as IL-6 (REFS^{93,94}). In accordance with altered adipose tissue function and fat loss in PLWH, adiponectin and leptin circulating levels are decreased in ART-naïve PLWH⁹⁵.

In addition, fat from both cART-treated and ART-naïve PLWH has a decreased mitochondrial DNA (mtDNA) content and reduced expression of mitochondria-encoded proteins that are required for adequate adipocyte metabolic function^{93,94,96}. Mitochondrial dysfunction is associated with increased reactive oxygen species (ROS) generation by the respiratory chain, which can impair adipocyte function and normal lipid storage and release⁹⁷. Interestingly, these effects are not dependent on circulating virus levels, as long-term HIV non-progressors not receiving cART (that is, PLWH with very low circulating viral levels and preserved CD4⁺ T cell counts) demonstrate adipocyte mtDNA depletion and similar gene expression changes as observed in untreated PLWH with high viral levels⁹⁴.

Morphological and functional analysis of adipose tissue from ART-naïve macaques infected with SIV have revealed severe fibrosis in SAT and VAT characterized by collagen VI deposition and high expression of the profibrotic factor transforming growth factor-β (TGFβ)⁹⁸. This fibrosis negatively correlates with adipocyte size and adipogenesis, suggesting that HIV infection

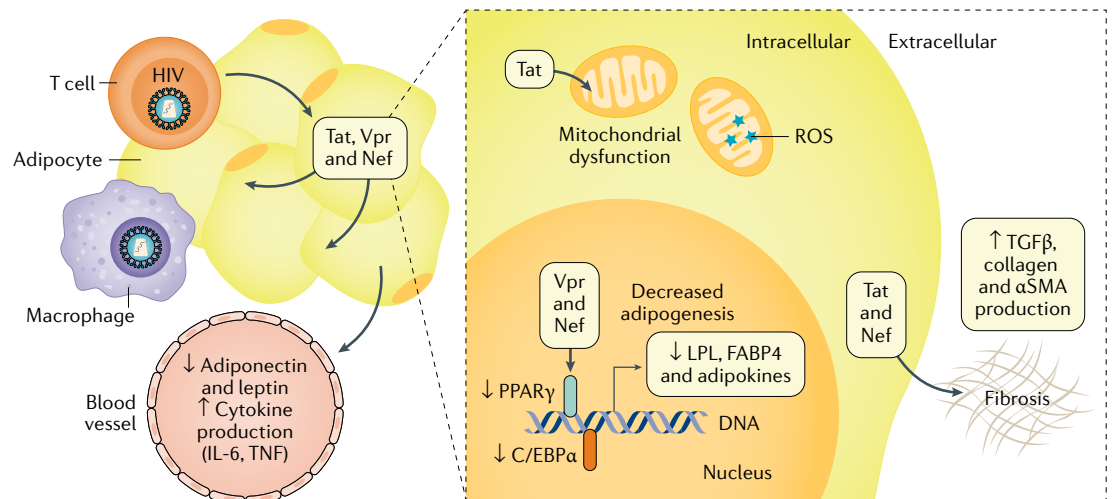


Fig. 1 | Effects of HIV on adipose tissue. HIV-infected T cells and macrophages can secrete viral proteins, such as Tat, Vpr and Nef, that affect proximal adipocytes, resulting in several cellular effects. These effects include mitochondrial dysfunction, increased production of extracellular matrix components leading to fibrosis, reduced adipogenesis, decreased production of adiponectin and leptin, and increased production of proinflammatory cytokines. α SMA, α -smooth muscle actin; C/EBP α , CCAAT/enhancer-binding protein- α ; FABP4, fatty acid binding protein 4; LPL, lipoprotein lipase; ROS, reactive oxygen species; PPAR γ , peroxisome proliferator-activated receptor- γ ; TGF β , transforming growth factor- β ; TNF, tumour necrosis factor.

per se could reduce adipose tissue expansion, at least in some depots. Although there are few data on adipose tissue fibrosis in treatment-naive PLWH, a longitudinal study in cART-treated PLWH with viral suppression found that adipose tissue fibrosis (assessed by changes in collagen VI and fibronectin deposition) decreased over 1 year in adults on cART with viral suppression⁹⁹.

Latently infected CD4⁺ T cells and macrophages present within adipose tissue are thought to release viral proteins locally within adipose tissue and into the circulation with locally detectable levels, despite suppression of plasma viraemia by cART. The accessory proteins Vpr and Nef and the regulatory protein Tat are the main proteins secreted by infected cells and can exert bystander effects on neighbouring adipocytes or precursor cells and affect adipose tissue metabolism^{100,101} (FIG. 2). In vitro studies have been used to evaluate how viral proteins affect adipocyte function, although it should be noted that these studies generally used viral protein concentrations observed in ART-naive patients but which could correspond to concentrations in adipose tissue. In these studies, Vpr and Nef have been shown to suppress the activity of the adipocyte master regulatory protein PPAR γ , leading to decreased expression of genes involved in the regulation of lipid storage (for example, *LPL* and *HSL* (encoding hormone sensitive lipase) and *FABP4* and *CD36*, involved in fatty acid transport)^{90,98,102–104}. The role of Tat is less clear than that of Vpr and Nef, as it can inhibit or promote adipogenesis depending on the cellular model used^{98,105,106}. In some studies, Tat has been shown to induce mitochondrial dysfunction, which likely occurs through mitochondrial membrane permeabilization and generation of mitochondrial ROS¹⁰⁷. In addition, Tat and Nef have been shown to promote the acquisition of a profibrotic phenotype characterized by the expression

of TGF β and α -smooth muscle actin (α SMA) and an increased production of extracellular matrix components such as collagen I, VI and fibronectin, leading to increased fibrosis, which corresponds with the in vivo data from macaques and cART-treated PLWH⁹⁸. Collectively, these data indicate that HIV infection can directly affect adipose tissue function and morphology through the action of viral proteins.

Role of adipose immune system

Adipose tissue contains cells of the innate and adaptive immune systems that defend against a range of pathogens, aid in the removal of apoptotic adipocytes and other cellular debris, and affect adipocyte regulation as well as energy storage and release. Research into obesity has established both the malleability and the importance of the adipose tissue immune environment for metabolic health and serves as a context to interpret adipose tissue changes in PLWH (FIG. 3). Obesity is accompanied by progressive accumulation of CD8⁺ T cells, CD4⁺ T helper 1 (T_H1) and T_H17 cells, and M1-phenotype proinflammatory macrophages (which are CD68⁺ and produce tumour necrosis factor (TNF), IL-12 and IL-23) in adipose tissue, with concomitant reduction of T_H2 and regulatory T cells^{108–111}. The mechanistic importance of these immune changes is demonstrated by animal studies showing that experimental depletion of adipose tissue CD8⁺ T cells improves tissue inflammation and insulin resistance in obesity¹¹⁰.

Early studies of subcutaneous fat from PLWH receiving cART with lipotrophy reported greater adipocyte apoptosis, fibrosis and expression of the inflammatory markers IL-12, p40, IL-6, IL-8 and macrophage inflammatory protein 1 α (MIP1 α) than in tissue from individuals without HIV, which was thought to be principally due to the effects of NRTIs on adipocyte function¹¹².

High levels of these cytokines inhibit adipocyte insulin signalling by reducing gene expression of IRS1, phosphoinositide 3-kinase p85 α and GLUT4 (REFS^{113–118}). Despite the increased inflammatory and macrophage activation markers (for example, MIP1 α) in adipose tissue from PLWH, findings on adipose tissue macrophage density have been varied^{112,118}. One study reported greater apoptosis, fibrosis and macrophage infiltration, reduced expression of the genes encoding adiponectin and leptin, and higher IL-6 and TNF in PLWH with peripheral lipoatrophy using a PI-based cART regimen compared with people without HIV¹¹⁸. By contrast, another large study found that macrophage density did not differ between PLWH and individuals without HIV or by lipoatrophy status in PLWH, although macrophage density was slightly higher in individuals receiving zidovudine and stavudine than in those receiving abacavir and tenofovir¹¹². In this study, PLWH with clinically evident lipoatrophy had higher HIV-DNA levels within circulating CD14⁺CD16⁺ monocytes than in PLWH without lipoatrophy, but the mechanisms linking this monocyte viral reservoir with fat alteration have yet to be elucidated¹¹².

In the current cART era, several studies have reported a profound shift in the adipose tissue T cell profile towards a CD8⁺ cell predominance in both PLWH and macaques with SIV infection^{86,119,120}, which is intriguing given the CD8⁺ T cell infiltration in obesity and the higher rates of metabolic disease in PLWH^{46,121–123}. Interestingly, among PLWH seen in a European metabolic diseases clinic with a range of fat alteration phenotypes, circulating CD8⁺ T cell activation was higher in both patients with lipoatrophy and in those with central fat accumulation than in patients without clinically apparent fat redistribution¹²⁴. In addition, CD8⁺ T cells in SAT from PLWH without clinically apparent lipodystrophy have increased antigen receptor clonality¹²⁰, a finding which is also reported in animal models of obesity¹²⁵. This finding could reflect local T cell expansion, although some studies have reported a lack of Ki-67 (a marker of proliferating cells) expression and high CD57 (a marker of late differentiation or senescence and an indicator of reduced replicative capacity) expression on CD8⁺ cells from adipose tissue of SIV-infected macaques, which could reflect minimal in situ proliferation^{87,126,127}. Interestingly, the distribution of CD4⁺ and CD8⁺ T cell subsets (naive, central memory, effector memory and effector memory RA⁺ T cells) was similar in SAT from PLWH without clinically evident lipodystrophy, suggesting that the accumulation of CD8⁺ T cells occurs in a relatively stochastic manner, as opposed to accumulation of one broad subset¹²⁸. Furthermore, the same study found the SAT of PLWH with T2DM to be markedly enriched for CD4⁺ T effector memory cells and T effector memory RA cells co-expressing CD57, CX₃CR1 and GPR56 compared with the SAT of non-diabetic PLWH, a phenotype which is reported to have antiviral specificity^{129–132}.

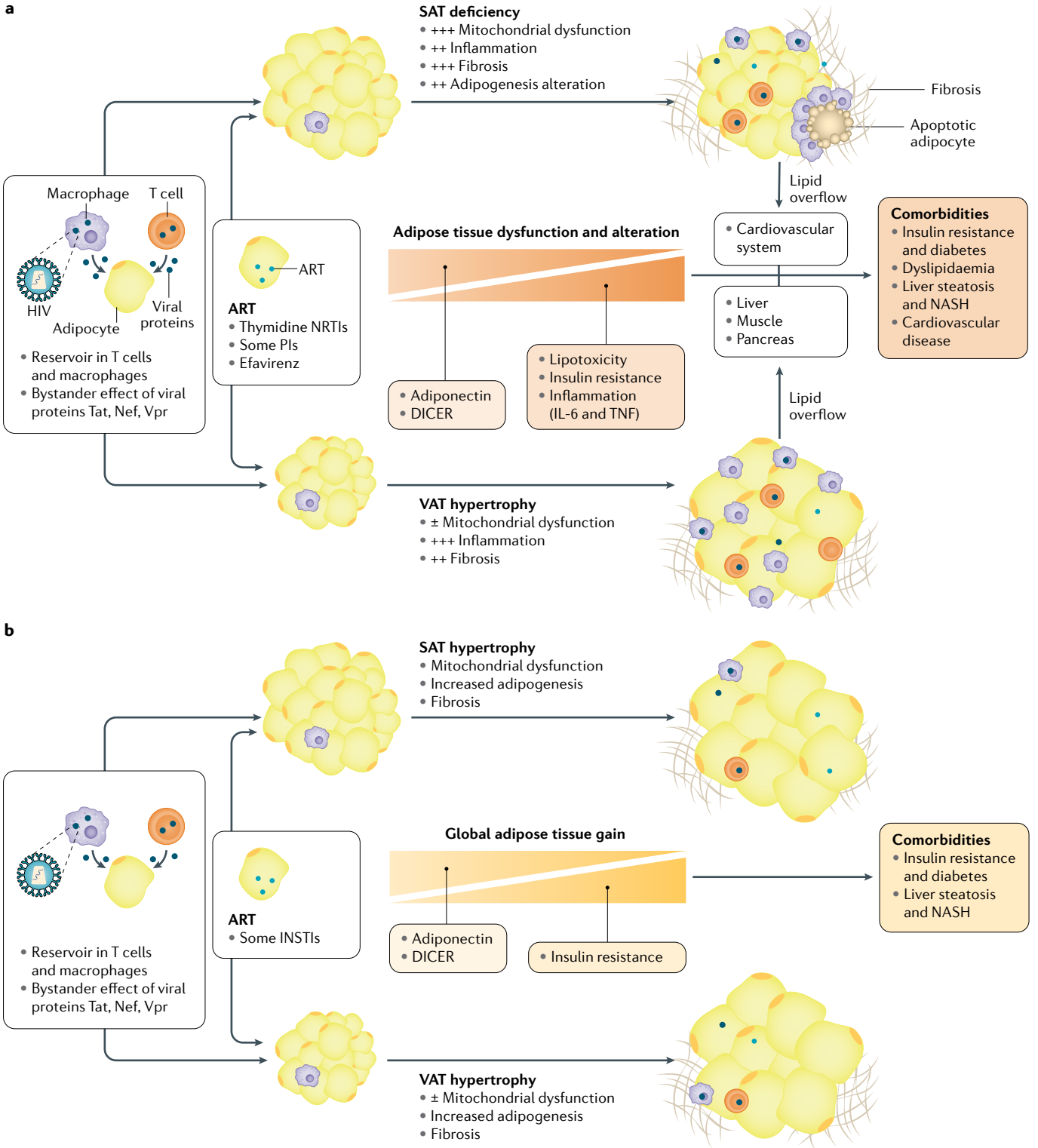
Role of ART

Several studies have examined SAT morphology and function in PLWH and lipodystrophy receiving cART (FIG. 2a). The main features in lipoatrophy-prone SAT

were a markedly decreased gene and protein expression of pro-adipogenic transcription factors, including PPAR γ , C/EBP α and SREBP1, and of their target genes, such as *GLUT4* or *LPL*, compared with HIV-negative controls (although the molecular mechanism of this is unknown), leading to decreased adipocyte differentiation and resulting in impaired fatty acid and glucose metabolism^{23,133}. Furthermore, probably due to impaired adipogenesis, the expression of adiponectin and leptin (markers of mature adipocytes) was reduced^{100,133}. In addition, chronic low-grade inflammation has been observed in lipoatrophic SAT from PLWH, characterized by increased gene and protein expression of proinflammatory markers (such as IL-6 and TNF). These proinflammatory markers are secreted by infiltrating immune cells and stressed adipocytes and are associated with increased fibrosis, TGF β expression and increased adipocyte apoptosis^{118,134–136}. SAT loss owing to thymidine NRTIs is accompanied by a shift to a proinflammatory and profibrotic state, which does not fully resolve following the removal of these agents⁴⁸.

Loss of limb fat was more prevalent with older thymidine analogues (for example, zidovudine or stavudine) than with newer NRTIs (for example, lamivudine, abacavir and tenofovir), and there is evidence that the mtDNA haplogroup may influence susceptibility^{9,137–143}. Older thymidine analogue NRTIs seem to inhibit mtDNA polymerase- γ most strongly, resulting in reduced mtDNA replication and content per cell^{144,145}, including substantial reductions in the mtDNA content of adipocytes^{138,146,147}. Reduced mtDNA levels are probably responsible for the reduced metabolic flexibility of lipoatrophic adipose tissue^{138,148}. The mtDNA haplogroup may influence susceptibility to NRTI-induced lipoatrophy^{142,146,149}, with mitochondrial haplogroups H, I and K conferring a greater risk of lipoatrophy and haplogroups T and W being protective against lipoatrophy^{140,141,150}. Variation in mtDNA among haplogroups is speculated to influence energy production efficiency, ROS generation and adipocyte apoptosis. Haplogroup H, in particular, is believed to be tightly coupled to ATP production and, consequently, to more ROS generation, whereas haplogroup T is partially uncoupled to ATP production, leading to less ROS production^{140,141,150}. Oxidative stress has also been proposed to underlie thymidine analogue NRTI-related mitochondrial toxicity by inducing mtDNA depletion and subsequent mitochondrial energy deficiency, leading to adipocyte loss and tissue atrophy¹⁵⁰.

In comparison to SAT, only a few studies have evaluated the alterations of VAT in ART-treated PLWH. A study comparing PLWH with lipoatrophy and central fat accumulation with healthy controls found similar mtDNA depletion and abnormal increases in mitochondrial protein levels in VAT and SAT from PLWH, whilst transcript levels of adipogenesis marker genes, such as *PPARG* and *ADIPOQ*, were unaltered in VAT but were decreased in SAT¹⁵¹. Moreover, SAT from PLWH with lipoatrophy had increased glucose uptake, possibly a compensatory mechanism for reduced stores on PET compared with healthy controls, whereas VAT glucose uptake was the same irrespective of HIV status¹⁵².



Thus, SAT but not VAT from lipodystrophic PLWH has an increased metabolic rate (that is, higher rates of glucose transport and lipid oxidation), suggesting a greater metabolic flexibility for SAT and a capacity for expansion for VAT^{152–154}. Molecular analysis of SAT from PLWH and lipoatrophy found reduced expression of the microRNA-processing enzyme DICER, which is associated with the downregulation of brown and beige adipose tissue genes implicated in mitochondrial

biogenesis such as *UCP1* and *PPARGC1A*^{154,155}. This phenotypic change could, in part, explain cART-related increased oxidative stress and mitochondrial toxicity, which could also contribute to the metabolic dysregulation observed in adipose tissue of PLWH. DICER expression was strongly and negatively associated with the duration of PI use¹⁵⁶ (FIG. 2). In addition, the duration of cART and PI use was linked with the reduced expression of brown and beige fat genes that are involved

◀ **Fig. 2 | Pathophysiological mechanisms involved in HIV-related and ART-related adipose tissue alterations and dysfunction.** Subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) alterations are often observed among people living with HIV. Some insults to adipose tissue could result from HIV infection. HIV is present in certain T cells and macrophages within adipose tissue. HIV proteins, such as Tat, Nef and Vpr, released by HIV-infected immune cells within adipose tissue, can exert bystander effects on proximal adipose cells. **a** | Some alterations can be related to individual antiretroviral therapy (ART) molecules among the different classes, in particular thymidine nucleoside reverse transcriptase inhibitors (NRTIs), some protease inhibitors (PIs) and non-NRTIs (NNRTIs) such as efavirenz. The development of a profibrotic, proinflammatory and anti-adipogenic environment is more likely in SAT than in VAT. In some cases, adipocyte death occurs with surrounding macrophages. Adipocyte stress and dysfunction as a result of mitochondrial dysfunction, decreased adiponectin and DICER expression, and increased release of proinflammatory cytokines such as IL-6 and tumour necrosis factor (TNF) by adipocytes and immune cells could lead to adipocyte insulin resistance and storage deficiency, ultimately driving lipid overflow. Thus, SAT deficiency, combined with VAT hypertrophy, may convey lipotoxicity, lipid accumulation in the liver, heart, vessels, muscles and pancreas, and related comorbidities such as type 2 diabetes mellitus, liver steatosis and non-alcoholic steatohepatitis (NASH), and atherosclerotic cardiovascular diseases. **b** | Alterations at the adipose tissue level induced by some integrase strand transfer inhibitors (INSTIs) appear partly different. These molecules can induce adipocyte hypertrophy with increased adipogenesis together with increased fibrosis and mitochondrial dysfunction, which could result in global fat gain with increased SAT and VAT depots as well as in increased peripheral fat. Insulin resistance and liver steatosis are expected outcomes. +++, a major effect; ++, an important effect; +, a mild effect; ±, the effect is minor or absent.

in thermogenesis, which could mediate metabolic complications¹⁵⁶. Finally, rodent models have shown that thymidine analogue exposure induces greater mtDNA depletion in SAT than in VAT, whereas in vitro exposure of adipose tissue to older generation PIs increases lipolysis and decreases glyceroneogenesis (a metabolic pathway that recycles free fatty acids to triglycerides) in SAT but not in VAT^{153,157}.

As previously mentioned, some PLWH have hypertrophy of dorsocervical adipose tissue (DCAT; referred to as a 'buffalo hump'), with a prevalence of up to 25% in PLWH in the 1990s¹⁵⁸. Interestingly, DICER expression in SAT is inversely associated with excess DCAT accumulation¹⁴⁹. Similar to PLWH with clinical fat alteration, DICER adipocyte-specific knockout mice have reduced white adipose tissue depots (lipoatrophy), whitening of brown adipose tissue depots, insulin resistance and local inflammation^{159,160}. However, although hypertrophied DCAT from PLWH has increased fibrosis gene expression, studies show less inflammation and less disruption of adipogenesis than expected from hypertrophied depots¹⁶¹, suggesting that DCAT has different characteristics to other fat depots¹⁶². The downregulation of DICER in SAT of PLWH may favour a shift to a proinflammatory and profibrotic state, limiting the capacity for fat browning and storage. Taken as a whole, lipohypertrophy, including the enlargement of DCAT, in PLWH has been hypothesized to result, in part, from impaired energy storage in atrophied, inflamed and fibrotic SAT^{100,163}.

A number of in vitro studies have been conducted to investigate the individual effect of ART on adipocytes, although results from these studies need confirmation with clinical data in PLWH. These studies revealed effects of PIs and NRTIs on adipogenesis, insulin signalling, adipokine secretion and adipocyte apoptosis^{23,163}. As previously mentioned, thymidine analogue NRTIs

induce mitochondrial toxicity, in part, by inhibiting the mtDNA polymerase- γ ^{138,146,149}. The effect of PIs on adipose tissue could result from the inhibition of ZMPSTE24 (which cleaves prelamin A to lamin A), which could lead to defects in lamin A maturation and organization and, consequently, to SREBP1 nuclear mislocalization and reduced adipogenesis¹⁶⁴. Moreover, ZMPSTE24 inhibition leads to the accumulation of senescence-associated prelamin A, also observed in circulating immune cells and in adipose tissue of PLWH^{161,165,166}, causing cellular senescence and adipocyte dysfunction. PIs could also lead to enhanced endoplasmic reticulum stress owing to high ROS production, which could also have adverse effects on adipocyte function²³. Many of these cellular alterations are absent or less severe with modern PIs (such as atazanavir or darunavir)^{167,168}. Among NNRTIs, efavirenz can affect in vitro adipogenesis and *ADIPOQ* expression whilst increasing the expression of proinflammatory markers¹⁶⁹.

Early in vitro studies suggested that the INSTIs elvitegravir and raltegravir do not alter adipogenesis of cultured adipocytes^{170–172}; however, more recent studies of SAT and VAT from INSTI-treated macaques displayed increased fibrosis, adipocyte size and adipogenic marker expression (*PPARG* and *CEBPA*) compared with untreated animals. Similarly, SAT and VAT from INSTI-treated PLWH had a higher level of fibrosis than SAT and VAT from non-INSTI-treated patients. Data from in vitro studies support the biopsy data, as dolutegravir and, to a lesser extent, raltegravir increased extracellular matrix production and lipid accumulation in human adipose stem cells and/or adipocytes⁷². Despite their pro-adipogenic effect, INSTIs have also been shown to promote oxidative stress and insulin resistance⁷² (FIG. 2b).

Changes in gene expression, such as reduced expression of brown and beige fat genes (*UCP1*, *PPARGC1A* and *PRDM16*)¹⁵⁶, has also been reported in SAT from INSTI-treated PLWH and could favour adipocyte hypertrophy. In addition, SAT from PLWH who have been switched to raltegravir/maraviroc exhibited decreased expression of gene pathways linked to immune function and activation¹⁷³. One hypothesis would be that, in PLWH, INSTIs could alleviate adipocyte stress by promoting hypertrophy and expansion, resulting in fat gain, but may also lead to increased oxidative stress, fibrosis and insulin resistance.

INSTIs can also have direct or indirect effects on food intake through effects on MC4R in the hypothalamus¹⁰, on thermogenesis and energy regulation¹⁵⁶, and on the hormonal milieu (as indicated by the protective level of the anti-Müllerian hormone against raltegravir-induced fat gain in women with reproductive activity)⁷⁶. Moreover, the notable heterogeneity of weight gain in PLWH who received INSTIs raises the possibility of genetic susceptibility in energy signalling or storage pathways. Further clinical studies are needed to explore the effects of INSTIs on adipose tissue health and globally in vivo.

Adipose tissue can impair the efficacy of cART, which can contribute to viral persistence. Indeed, adipocytes can sequester substantial amounts of ARTs inside

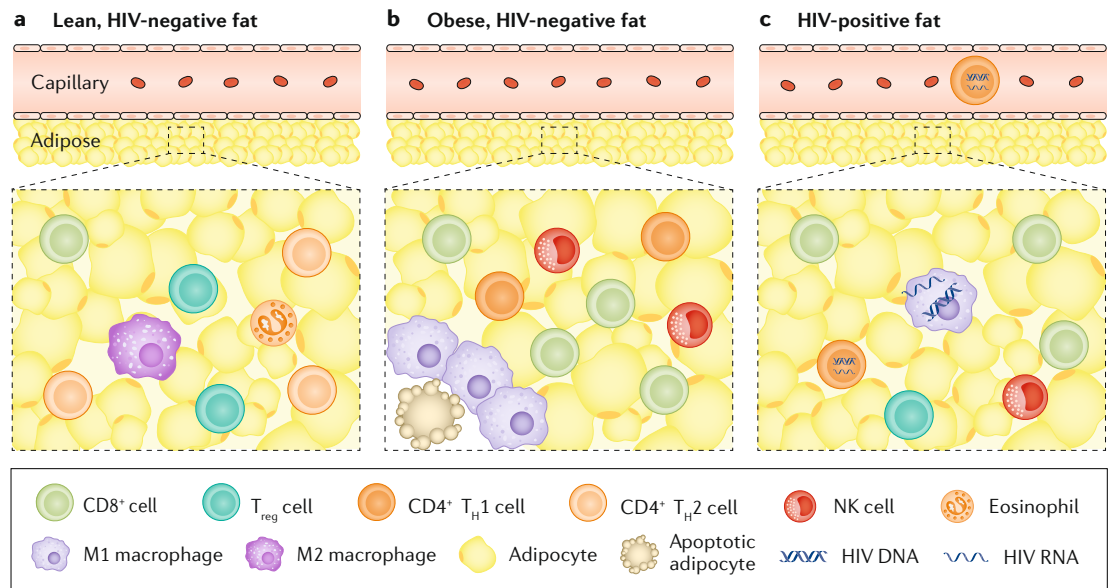


Fig. 3 | Alterations of immunity in adipose tissue from HIV-infected individuals with fat redistribution as compared with lean and obese non-infected individuals. **a** | Adipose tissue from lean individuals is comprised of adipocytes and a stromal vascular cell fraction in which CD4⁺ T cells predominate over CD8⁺ T cells and are typically polarized towards a T helper 2 (T_H2) cell cytokine profile. The adipose tissue also contains macrophages characterized by an anti-inflammatory (M2) phenotype, regulatory T (T_{reg}) cells and eosinophils with few natural killer (NK) cells. **b** | Obese adipose tissue is characterized by hypertrophic and more heterogeneous adipocytes, an increased proportion of CD8⁺ T cells with more oligoclonal T cell receptor repertoires, CD4⁺ T cells polarized towards a T_H1 cell cytokine profile and fewer T_{reg} cells. In animal models, the influx of CD8⁺ T cells in obesity promotes recruitment and activation of macrophages with a proinflammatory (M1) phenotype, some of which surround apoptotic adipocytes. There are fewer eosinophils and more NK cells. **c** | Adipose tissue from (non-obese) persons with HIV, irrespective of the presence of clinically apparent lipodystrophy, demonstrates several similarities but also notable differences with obesity. In HIV and in simian immunodeficiency-infected macaques, adipocytes are similar in size to those in lean, HIV-negative persons but can demonstrate greater heterogeneity and impaired adipogenesis and lipid metabolism. There is a marked enrichment in CD8⁺ T cells over CD4⁺ T cells but few infiltrating macrophages. The CD4⁺ T cells are predominantly CD69⁺, the T_H1/T_H2 cell balance is similar to that in lean, HIV-negative persons, and the number of T_{reg} cells may be similar or increased. In HIV and SIV, a notable exception is the presence of latently HIV/SIV-infected CD4⁺ T cells capable of producing viral proteins and RNA virus.

the adipocyte lipid droplet, which renders the therapy ineffective¹⁷⁴. Adipocytes have consistently been shown to reduce the antiviral efficacy of TDF and TAF in vitro and analysis of adipose tissue from treated PLWH suggests that INSTIs penetrate adipose tissue, whereas the penetration of NRTIs is restricted⁷¹. Obesity has been reported to affect ART plasma exposure but without consequence on immunovirological control¹⁷⁵.

Role of gut dysbiosis and inflammation

Gastrointestinal dysbiosis (a microbial imbalance or maladaptation characterized by underrepresentation of typically dominating species and overrepresentation of normally outcompeted or contained species) is emerging as an important contributor to adipose tissue dysfunction in PLWH. Alterations in the human gut microbiome have been linked to increased risk of obesity¹⁷⁶, cardiovascular disease¹⁷⁷, hypertension¹⁷⁸ and T2DM^{179,180}, among other conditions.

HIV infection alters the architecture of the intestinal wall and the composition of the gut microbiome in PLWH, which persists despite effective viral suppression using cART and has detrimental effects on mucosal immunity, systemic inflammation and metabolic function^{181,182}.

The intestinal mucosa undergoes villous atrophy, increased enterocyte apoptosis, impairment of tight junctions, impaired B cell function, decreased IgA production and depletion of T cells (especially T_H17 cells)¹⁸³, which can occur as soon as 2 weeks after infection in SIV-infected macaques¹⁸⁴. During the acute infection phase, HIV replication depletes 80–90% of gut CD4⁺ T cells, which promotes mucosal inflammation, affects the immune response to translocating bacteria and leads to increased activated circulating CD8⁺ T cells^{185–189}. In addition, microbial dysbiosis, predominantly characterized by reduced diversity within the microbiota (similar to the findings in individuals with obesity), is evident before the onset of marked immunosuppression in HIV infection¹⁸⁷ and persists in chronic infection^{190–198}. Specifically, members of the Proteobacteria phyla in the Enterobacteriaceae family, including *Salmonella*, *Escherichia*, *Shigella*, *Klebsiella* and *Serratia* species, are enriched in viraemic, untreated PLWH compared with HIV-negative individuals, whereas Bacteroidetes and Firmicutes are reduced¹⁹⁹, although findings have varied between studies^{195,200,201}. cART initiation does not seem to restore the microbiota to a pre-infection community composition²⁰² and could actually further reduce diversity^{192,196}.

The translocation of microbial products promotes VAT inflammation²⁰³, impairs adipocyte energy handling and has been shown to contribute to the accumulation of visceral fat in the general population²⁰³; this mechanism has also been suggested in PLWH²⁰⁴. Indeed, the translocation of lipopolysaccharide (LPS) across the gut wall promotes adipose tissue inflammation²⁰³ owing to the activation of adipose tissue macrophages via the CD14 receptor, causing a shift from an M2 to an M1 phenotype, and increases IL-6, TNF and other inflammatory cytokine production²⁰³. Circulating and locally produced VAT TNF promotes further loss of tight junction integrity and gut barrier dysfunction in a cyclic fashion²⁰⁵. Indeed, in ART-initiated PLWH from the ACTG A5257/A5260s study, gut integrity was associated with VAT gain and higher baseline intestinal fatty acid-binding protein levels were associated with increases in VAT, total body fat and BMI after 96 weeks²⁰⁴.

A potential role for circulating LPS endotoxaemia in adipose tissue expansion is evidenced by animal studies demonstrating that a 4-week LPS infusion increases body weight and VAT to the same extent as a 4-week high-fat diet regimen and increases insulin resistance and expression of inflammatory transcripts in adipose tissue²⁰³. LPS stimulates the proliferation of pre-adipocytes through a CD14-dependent mechanism²⁰⁵, possibly through activation of JAK/STAT and AMPK via cytosolic phospholipase A2 (REF.²⁰⁶).

In addition, higher levels of LPS absorbed via chylomicrons among persons on high-fat diets is hypothesized to increase adipocyte lipid uptake in obesity²⁰⁶, although a similar link between LPS inclusion in lipid droplets and adipocyte hypertrophy in the context of HIV-related dysbiosis and gut barrier dysfunction requires further investigation. It should be noted that, although gut dysbiosis and impaired mucosal barrier function have been observed in PLWH, the mechanistic linkages and the directionality of this association are not fully understood^{195,207}.

Diagnosis, screening and prevention

Diagnosis and clinical assessment

The diagnosis of fat alterations in PLWH is primarily based on clinical assessment, patient medical history and patient self-report²⁰⁸. Indeed, both regional and generalized accumulation or loss of fat mass beyond what is expected for age-related changes in body composition according to local standards is sufficient for diagnosis (FIG. 4). Diagnosis of lipoatrophy or lipohypertrophy may lead to a need for screening for additional health problems, such as T2DM and dyslipidaemia, owing to the well-described associations between these metabolic disturbances and the presence of lipoatrophy and/or lipohypertrophy.

In general, the diagnosis of lipoatrophy, particularly of the face and periphery, is performed via visual inspection. Skinfold thickness measurement can be used for research purposes but is rarely used in clinic practice owing to its poor additional clinical usefulness.

Lipohypertrophy specifically refers to localized abnormal fat accumulation on physical examination or imaging, most frequently of the VAT, breasts, DCAT and/or as discrete accumulations under the skin (lipomas). Lipohypertrophy can occur in one or more regions simultaneously, with or without concurrent peripheral lipoatrophy. Importantly, the clinical assessment of lipohypertrophy can be complicated by concomitant obesity in PLWH. Obesity is traditionally defined as a BMI >30 kg/m²; however, low muscle mass and increased VAT to BMI ratios^{209–211}, both of which are common in PLWH, can lead to underestimations of regional and generalized adiposity. A personal history or family history of obesity and diffuse fat distribution can support the diagnosis of generalized obesity in PLWH, whereas the diagnosis of lipohypertrophy can be supported by regional truncal or visceral fat accumulation. Of note, lipohypertrophy is typically clinically visible at least 1–2 years after the commencement of cART²¹². Although most standardized lipohypertrophy definitions include radiographic assessment of fat quantity⁴, the use of imaging is generally restricted to research settings^{213–215}. In addition, cohorts used to generate the definitions of lipohypertrophy were predominantly comprised of PLWH who received early-generation NRTIs and, therefore, had a high prevalence of lipoatrophy with concomitant lipohypertrophy²¹⁶, meaning that the validity of these definitions in the present ART era is unknown. Of note, the gain of fat reported with INSTI use is generalized in most patients and is not defined as lipohypertrophy.



Fig. 4 | Manifestations of ART-associated fat alterations. Facial lipoatrophy related to thymidine nucleoside reverse transcriptase inhibitors (part a). Limb lipoatrophy related to thymidine nucleoside reverse transcriptase inhibitors (part b). Abdominal lipohypertrophy (part c). Buffalo hump (part d). Fat gain leading to obesity in a patient treated with an integrase strand transfer inhibitor (parts e and f). ART, antiretroviral therapy.

In clinical practice, body weight and BMI should be tracked at least once per year in PLWH. In addition, as BMI can underestimate adiposity in PLWH, measurement of waist circumference is also recommended at least annually^{217,218}. A minimum waist circumference of ≥ 94 cm in women and ≥ 95 cm in men correlates with a VAT area of ≥ 130 cm², which is a validated threshold for increased cardiometabolic risk^{219,220}, although these values have not been validated in PLWH. The causes of lipohypertrophy are not fully understood and are likely multifactorial. Generalized obesity and central lipohypertrophy can overlap in an ageing population with traditional and HIV/ART-specific risk factors, which can confound the diagnosis of lipohypertrophy.

Prevention

HIV seeding into fat is believed to occur early in HIV infection, and initiation of cART during acute HIV infection, which has been shown to decrease other HIV tissue reservoirs^{221,222}, could limit HIV-induced adipose tissue dysfunction. In addition, the use of ARTs with better adipose tissue penetration, such as INSTIs, might also help reduce reservoir size and, potentially, HIV-associated fat depot disturbances. However, the use of INSTIs should be balanced against evidence that some INSTIs increase fat mass^{11,59}. Earlier cART initiation also avoids progression of HIV disease, the severity of which has been associated with the presence of lipodystrophy^{4,33,223} and with greater weight gain following ART initiation^{12,65}.

The avoidance of older ARTs that can induce lipotrophy and central lipohypertrophy is also warranted to try and prevent fat alterations, whenever possible. In addition, close monitoring of weight gain and aggressive lifestyle interventions, such as healthy diet and regular exercise, could prevent the aggravation of lipohypertrophy by obesity and monitoring of waist circumference could allow earlier introduction of therapies to reduce VAT in PLWH. With improved understanding of how to reduce chronic inflammation, immune activation and gut barrier disruption in PLWH, new opportunities to prevent the contribution of these factors to lipodystrophy may emerge.

Management

Adopting a healthy lifestyle is the most effective and safest means to prevent and treat abdominal obesity in PLWH. This lifestyle should form part of the routine management strategy for all PLWH, particularly as overweight and obesity is increasingly common in the general population^{62,224}. Judicious use of pharmacotherapy, including approved weight-reducing drugs and tesamorelin in appropriate individuals, can be effective, although patients should be carefully monitored as the long-term benefits and adverse effects remain uncertain.

Lipotrophy

Facial lipotrophy in patients treated with thymidine NRTIs is only partially reversed when patients undergo medication switching to remove the responsible drugs and may take months or longer to become clinically apparent^{225,226}. Some patients with persistent

lipotrophy may benefit from plastic surgery. Initially, the patient's SAT was injected into the cheeks using the Coleman technique, but injection of poly-L-lactic acid has the highest efficacy in published studies and is FDA approved. In addition, poly-L-lactic acid is less frequently associated with local infection and poor patient satisfaction, is more durable and may improve quality of life (QOL). Calcium hydroxyapatite, which is also FDA approved, and hyaluronic acid, among other products, are also used but have less supporting evidence²²⁷; re-injection may be required within 1–2 years and can need further repetition^{41,228}.

Abdominal obesity

The most common type of fat alteration in the current cART era in PLWH is central adiposity. Management of central adiposity in the general population is complicated and has an uncertain long-term efficacy. This management includes adopting a reduced-calorie diet and a sustained exercise programme, and can decrease total fat and VAT quantity in the short term as well as the risk of developing T2DM and cardiovascular disease²²⁹. Similarly, the management of abdominal obesity in PLWH is also challenging. PLWH with abdominal obesity should undertake regular exercise and consume a healthy diet, although the long-term efficacy of these strategies in this population remains to be proven. Medication switching from a PI associated with abdominal obesity to either a non-NRTI or a PI with fewer associated fat mass complications is generally not effective in reducing VAT²¹². Whether INSTI-associated weight gain is related to increased clinical risks or is reversible is unknown. Accordingly, it is important to evaluate the reversibility of the effect of INSTIs and propose switching from these drugs as a therapeutic strategy.

Pharmacological therapy. Pharmacotherapy for the treatment of generalized obesity is effective in the general population but the long-term benefits of weight-reducing drugs remains controversial as their ability to substantially reduce VAT is uncertain and adverse effects are common²³⁰.

The GLP1 agonist liraglutide is effective in reducing weight in individuals with obesity with or without T2DM²³¹ and is associated with a reduction in the frequency of cardiovascular events in patients with T2DM²³². However, this drug class has not been evaluated in PLWH. The insulin-sensitizing drug metformin causes a 10% reduction of VAT in PLWH with lipohypertrophy but is associated with worsening peripheral lipotrophy in patients with mixed body shape phenotypes (that is, those with both lipotrophy and lipohypertrophy)²³³. Whether metformin is effective in PLWH with glucose homeostasis abnormalities and abdominal obesity but without peripheral lipotrophy has not been assessed. One study of recombinant leptin significantly decreased VAT in PLWH²³⁴. Testosterone replacement can decrease total fat mass in the general population but has an uncertain effect on reducing VAT and may increase cardiovascular disease risk in men >65 years of age²³⁵. In one study, testosterone replacement in hypogonadal male

PLWH decreased DXA-derived trunk fat although there was no change in VAT assessed using CT, reflecting the need for accurate imaging modalities to assess therapeutic responses²³⁶. The treatments described above are not generally recommended for the management of abdominal obesity in PLWH.

Modulation of the growth hormone axis

HIV-negative (non-infected) persons with endocrine disorders associated with abdominal obesity, including growth hormone deficiency (GHD) and hypogonadism, can benefit from growth hormone (GH) replacement. GH treatment has also been studied in people with abdominal obesity without GHD^{237–239}. However, these studies are limited by short durations and infrequent use of accurate abdominal fat assessments. Indeed, although GH treatment reduced VAT in patients with GHD and abdominal obesity, follow-up has generally been too short to determine whether this effect is sustained and whether the risk of cardiovascular disease is reduced²⁴⁰.

Despite the limitations of these studies, owing to the short-term benefits of treatment in seronegative persons with GHD and the documented abnormalities of the GH/insulin-like growth factor 1 (IGF1) axis in treated PLWH²⁴¹, GH replacement has also been studied in PLWH. GH/IGF1 disturbances in PLWH include a reduction in mean overnight GH levels resulting from decreased GH pulse amplitude, pulse width and trough GH levels, with no change in pulse frequency, and decreased GH response to GH-releasing hormone-arginine stimulation. Furthermore, they are closely related to increased visceral adiposity^{242,243}. In these studies, recombinant human GH significantly decreased VAT in the short-term compared with placebo^{244,245}; however, glucose homeostasis was impaired and higher SAT reductions were observed in patients with baseline lipoatrophy than in those without lipoatrophy. These limitations were not affected by changing dosing schedules^{229,245}. In addition, although VAT decreased with treatment, it returned to baseline levels following drug cessation. Based on the results of these trials, GH is not approved for the treatment of abdominal obesity in PLWH.

Other therapies targeting the GH pathway have been evaluated for the treatment of abdominal obesity in PLWH. GH-releasing factor (GHRF) has been shown to restore physiological control of GH secretion, maintain normal negative feedback of IGF1 on GH release, and limit GH-related toxicities in PLWH and lipohypertrophy²⁴⁶. In addition, synthetic GHRF was associated with increased baseline IGF1 levels within the normal range and with reductions in DXA-assessed trunk fat, albeit with a non-significant reduction in CT-assessed VAT of 9%, in male PLWH with increased VAT (CT-assessed VAT of 180 cm²)²⁴⁷.

Tesamorelin, a synthetic human GHRF²⁴⁸, was demonstrated to decrease DXA-trunk fat by 9.2% and CT-assessed VAT by 15.7% compared with placebo in treated PLWH with abdominal obesity (diagnosed using anthropometric parameters associated with increased VAT in seronegative individuals²¹⁹),

impaired fasting glycaemia or diet-controlled T2DM. Importantly, SAT did not change between groups. No participants with baseline impaired fasting glycaemia developed T2DM. Interestingly, tesamorelin did not affect glucose homeostasis in HIV-seronegative persons without T2DM²⁴⁹.

In a pooled analysis of two studies of tesamorelin in PLWH with abdominal obesity^{250,251}, VAT decreased by 15.4% in patients treated with tesamorelin, with an increase in IGF1 levels within the physiological range, reduced baseline triglycerides and a reduced total cholesterol to HDL cholesterol ratio in those who received tesamorelin compared with placebo²⁵¹. In addition, a minimal increase in HbA_{1c} of unknown significance occurred in patients who received tesamorelin. Furthermore, QOL was reduced in persons on placebo and remained unchanged in treated participants²⁵¹. During the 26-week extension phase of the trial, treated persons maintained the VAT reduction and improvements in trunk fat, waist circumference, triglycerides and IGF1. By contrast, VAT and trunk fat returned to baseline levels within 3 months in individuals who received tesamorelin during the first phase of the trial, but who switched to placebo during the extension phase. Adverse events were similar between groups^{251,252}. Overall, ~66% of tesamorelin-treated PLWH achieved a significant reduction of VAT. Further studies of tesamorelin have demonstrated that improvements in metabolic parameters (including triglyceride and adiponectin levels) and inflammatory markers (including a reduction in tissue plasminogen activator levels) were more likely to occur in tesamorelin responders than in non-responders^{253,254}. Moreover, tesamorelin has also been shown to reduce liver fat and pretreatment elevated transaminases in responders^{255,256}. Indeed, one study showed a significant reduction of hepatic fat and prevention of progression of fibrosis, without improvement in existing fibrosis, in treated PLWH with hepatic steatosis²⁵⁷. This finding is important as liver fibrosis is a predictor of mortality in persons with NAFLD, an emerging non-AIDS complication in PLWH²⁵⁸. Although participants in this trial were not selected for the presence of increased VAT, VAT was increased in all participants and decreased with treatment; 60–70% of all participants were receiving INSTI-based regimens, but it was not possible to differentiate responses between individuals who had previously received other cART regimens versus those only on currently recommended first-line drugs.

Tesamorelin is the only drug approved for the reduction of excess abdominal fat in PLWH with lipohypertrophy and is licensed in the USA, Canada and several other countries. Follow-up studies will clarify whether supraphysiological IGF1 levels are associated with increased cancer risk, as has been suggested for people without HIV²⁵⁹. However, the risk of cancer with tesamorelin may be low, as IGF1 generally increases within the normal range, and GH replacement in seronegative persons with GHD showed no association with malignancy if IGF1 levels remained within normal age-related ranges²⁶⁰. Tesamorelin discontinuation is recommended in PLWH if IGF1 levels increase persistently by more

than three standard deviations (Theratechnologies). In addition, tesamorelin cessation should be considered if de novo impaired glucose tolerance or T2DM develops. The long-term effects of tesamorelin on cardio-metabolic outcomes, the optimal treatment duration and options for the long-term maintenance of decreased VAT are unknown.

Surgery for weight reduction and buffalo hump

Bariatric and metabolic surgery for individuals with severe obesity in the general population leads to improved long-term survival and QOL as well as to sustained weight loss and amelioration of obesity-related comorbidities²⁶¹. Studies of bariatric surgery for severe generalized obesity (BMI >40 kg/m²) in PLWH are limited to small series and have reported uncertain effects on VAT. However, bariatric surgery might be effective for weight loss and to decrease metabolic complications in some patients²⁶². After bariatric surgery, some cART-treated PLWH can have a detectable viral load and decreased exposure to some antiretroviral drugs and should be closely monitored after surgery²⁶³. The role of surgery specifically to remove excess VAT is unclear, with potential beneficial effects on weight but not metabolic health or adipokine secretion^{264,265}.

Surgical lipectomy for functional or clinical indications of enlarged DCAT has been reported in small series with acceptable results and with at least 2 years of follow-up, although caution is urged because of increased recurrence rates^{266–268}.

Quality of life

PLWH must be engaged in the cascade of HIV care to fully benefit from cART. In 2014, the Joint United Nations Program on HIV and AIDS set up the ‘90-90-90’ targets to be achieved by 2020 (90-90-90: treatment for all) (that is, 90% of PLWH diagnosed early after infection, 90% linked and retained in care, and 90% receiving and adhering to effective therapy). In 2018, ~79% of PLWH knew their HIV status, 78% of those who knew their HIV status were accessing treatment and 86% of PLWH who were accessing treatment were virally suppressed, therefore keeping them alive and well and

preventing transmission of the virus²⁶⁹. Therefore, major progress has been made but there is still an important gap to reach the objectives.

Notably, the ‘90-90-90’ targets are public health objectives and fail to address the health of PLWH as defined by the WHO as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. Indeed, some individuals argue that there is an urgent need to contend with other challenges, including non-communicable diseases, mental health and HIV-related discrimination, and have proposed a fourth ‘90’ of achieving good health-related QOL (HRQOL) among 90% of those successfully treated for HIV²⁷⁰ (FIG. 5).

Several QOL changes have been reported in PLWH. Indeed, PLWH with viral suppression have reported high levels of fatigue or energy loss, insomnia, sadness or depression, sexual dysfunction, and changes in body appearance, among other symptoms²⁷¹. Lipoatrophy and lipohypertrophy have been associated with depression in adults as well as in older children and adolescents^{272,273}. In addition, one cross-sectional study comparing >3,000 PLWH with >7,000 members of the general population in the UK reported that HRQOL scores were significantly lower in PLWH and remained low in those with viral suppression²⁷⁴.

After the advent of effective cART in the mid-to-late 1990s, lipodystrophy was generally considered as an unavoidable adverse effect of life-saving therapies. Of the fat alterations in PLWH, facial lipoatrophy is particularly stigmatizing and is suggestive of the use of anti-HIV drugs^{275,276}. However, studies specifically assessing the effect of fat alterations on HRQOL are scarce, particularly in children (BOX 2), and the available QOL instruments do not allow a comparative assessment across countries, studies and populations. The most frequently used instruments used to assess QOL (such as the Short Form 36 (SF-36)²⁷⁷, the EuroQoL 5 Domains (EQ-5D)²⁷⁴ or the Medical Outcomes Study in Health Survey (MOS-HIV)²⁷⁸) do not specifically assess the effect of body composition changes; however, some QOL assessment tools specifically include questions regarding lipodystrophy, such as the lipodystrophy-specific Assessment of Body Change and Distress (ABCD)²⁷⁹ and the HIV/AIDS-Targeted Quality of Life (HAT-QoL)²⁸⁰. Assessing HRQOL is challenging as it is subjective, multifaceted and includes psychological, physical, social and personal outcomes²⁸¹. Interestingly, although most data from Brazil, Europe and the USA have suggested a negative effect of lipodystrophy on QOL^{282–285}, this effect was not observed in one cross-sectional, hospital-based evaluation in Ethiopia²⁸⁶. By contrast, one study in Spain indicated that lipodystrophy is associated with social isolation, even years after the HIV diagnosis²⁸⁷. The negative effect of body fat changes seems to be even more critical in women whose self-perception of these changes was closely associated with a decrease in QOL^{288,289}. However, one review of 23 studies demonstrated that the use of facial fillers and autologous fat transfer (Coleman intervention) were associated with improved QOL patient scores in PLWH²⁸¹.

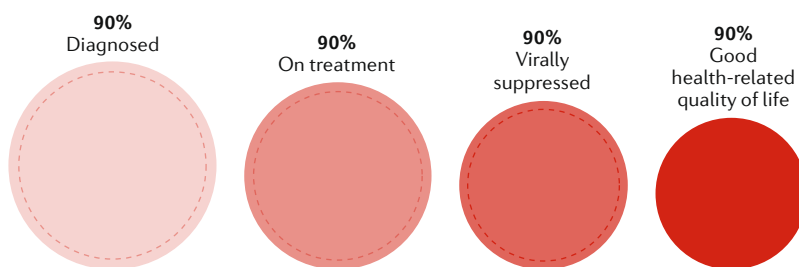


Fig. 5 | **The ‘fourth 90’: proposed revision to the UNAIDS 90-90-90 targets.** The Joint United Nations Program on HIV and AIDS set up the ‘90-90-90’ targets to be achieved by 2020 (90% of people living with HIV diagnosed early, 90% linked and retained in care, and 90% receive and adhere to effective therapy). Lazarus et al. argue that there is an urgent need to contend with other challenges, including non-communicable diseases, mental health or HIV-related discrimination, and have proposed a fourth ‘90’, that of achieving good health-related quality of life among 90% of those successfully treated for HIV²⁷⁰. Adapted from REF.²⁷⁰, CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

Outlook

Despite advances in our understanding of the pathogenesis, consequences and treatment of fat alterations in PLWH, there is still much to be learned and new challenges have arisen that must be addressed in future research studies.

Effect of HIV on adipose function

Systemic inflammation and bacterial translocation in the gut lymphoid tissue, which may be influenced by changes in the gut microbiome, are likely important mechanisms for adipose dysfunction in PLWH. Improved understanding of the molecular mechanisms underlying these pathways could lead to targeted strategies to treat fat alterations in PLWH. In addition, the recognition of adipose tissue as a reservoir for HIV could have important consequences for the functional cure of HIV infection. Future studies that aim to alter the gut microbiota in PLWH, reduce bacterial translocation or affect systemic inflammation should also determine their effects on adipose function, including adipokine and cytokine secretion and free fatty acid uptake and release. In addition, strategies to eradicate HIV should also focus on HIV persistence in adipose tissue. Conversely, strategies aimed at decreasing fat mass and improving adipose function in PLWH should also assess the potential effects on the HIV reservoir in fat.

Effect of cART on fat

Although the metabolic adverse effects of antiretroviral therapies have improved markedly over the past 20 years, newer, well-tolerated medications, such as INSTIs and TAF, have been shown to lead to more weight gain than other agents. This finding poses challenges in the clinical care of PLWH given the efficacy, low toxicity and popularity of these medications. Accordingly, research evaluating the magnitude of these changes is important in addition to determining which patients are most likely to be affected (for example, the use of early biomarkers or demographic or clinical data) and the clinical consequences. Furthermore, strategies investigating the effect of switching from INSTIs or TAF on adipose volume and function in virally suppressed PLWH who have substantial fat alterations should be evaluated.

Understanding the changes in adipose tissue during the first 2 years after cART initiation and evaluation of the strategies to prevent this weight gain are also critical research topics. Prevention strategies could include patient counselling before cART initiation and other behavioural approaches, adjunctive medications or avoidance of ARTs most associated with weight gain in those at the highest risk. In addition, it has been suggested that HIV and some ARTs can induce fat fibrosis; thus, determining the reversibility of this fibrosis and, if partial, the possible remaining irreversible scar of adipose tissue, is essential.

Ectopic fat in HIV and its health consequences

As previously mentioned, ectopic expansion of fat deposits can also occur disproportionately in PLWH. Pancreatic and myocardial fat deposits in PLWH have not been well studied and require further research.

Box 2 | Fat alterations in children with HIV

Although children with HIV are commonly affected by body fat changes, studies assessing the effect of these changes using quality-of-life (QOL) tools are scarce. Disfigurement²⁹⁴, HIV status disclosure²⁹⁵ and stigmatization are commonly reported concerns in observational cohorts. Indeed, disclosure concerns have been suggested as a relevant target for interventions to decrease HIV-related stigma and increase health-related QOL in children. Body fat changes that affect the growth and well-being of children are well known and have a significant impact on the mental health of older children and adolescents, leading to poor self-image, depression and subsequent poor adherence to therapy²⁷³. However, QOL tools have not been specifically used to assess the effect of body fat changes in children. Every effort should be made to use antiretroviral therapies with no or limited fat toxicity. Owing to the delay of almost 5 years in the commercialization of a new drug and its license for use in children, children have been neglected with regard to drug innovation and have been exposed to offending drugs and, therefore, to drug-related adverse events²⁹⁶.

By contrast, liver fat (NAFLD or non-alcoholic steatohepatitis) continue to be a major focus of research, with several on-going trials (NCT03129113, NCT03913351, NCT03669133 and NCT02196831).

Adipose alterations in an ageing HIV population

In the general population, ageing is associated with increases in VAT, losses in SAT and accumulation of fat in ectopic sites. These fat changes are thought to be a major source of inflammation and immune activation and have a similar phenotype to those seen in PLWH. For older (generally >50 years of age) PLWH, these fat changes have been associated with physical frailty and cognitive decline^{290–292}, suggesting that reversing fat alterations in older PLWH could also reduce the burden of these ageing-related comorbidities. Based on this hypothesis, trials investigating the effects of tesamorelin (NCT02572323), the GLP1 analogue liraglutide (NCT02743598) and exercise (NCT02663934) on cognitive function in PLWH are ongoing.

Fat changes in low-/middle-income countries

Most cases of HIV are in low-income and middle-income countries. In these countries, improvements in health care, sanitation and food availability have led to increases in lifespan among the general population, although urbanization and adoption of the Western (high-calorie) diet have led to increasing rates of obesity and obesity-related conditions²⁹³. In the context of these changes, PLWH in low-income and middle-income countries are surviving for longer where cART is available and are increasingly receiving new medications that are associated with weight gain (such as INSTIs). The next phase of research into this area will involve understanding both the global burden of obesity in PLWH and its consequences.

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Author contributions

Introduction (J.C. and J.R.K.); Epidemiology (P.D., J.C. and J.E.L.); Mechanisms/pathophysiology (J.R.K. and C.L.); Diagnosis, screening and prevention (J.E.L.); Management (J.F.); Quality of life (A.C.); Outlook (T.T.B.); Overview of the primer (J.R.K. and J.C.). J.R.K. and C.L. contributed equally to the development of this Primer.

Competing interests

J.R.K. has received research support from Gilead Sciences and served as a consultant to Gilead Sciences and Theratechnologies. J.E.L. receives research support from Gilead Sciences and has served as a consultant to Gilead Sciences and Merck Sharp & Dohme. P.D. has received educational grants from and served as a consultant to Gilead Sciences, Johnson & Johnson, Merck Sharp & Dohme, and ViiV Healthcare. A.C. received unrestricted educational grants (to the institution) from BMS, Gilead, Merck Sharp & Dohme and ViiV Healthcare. J.F. has served on speakers' bureaus from Gilead Sciences, Merck Sharp & Dohme and ViiV Healthcare, and has served as a consultant to Theratechnologies up to 2015. T.T.B. has served as a consultant to Gilead Sciences, Merck, Theratechnologies and ViiV Healthcare. J.C. has received research support (to the institution) from Janssen, Merck Sharp & Dohme and ViiV Healthcare, and educational grants from BMS, Gilead Sciences, Janssen, Merck Sharp & Dohme and ViiV Healthcare. C.L. declares no competing interests.

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