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Recent data on adipose tissue, insulin resistance, diabetes and dyslipidemia in ART-controlled HIV-infected persons

Jacqueline Capeau¹, Claire Lagathu¹, Véronique Béréziat¹, Bruno Fève^{1,2}

¹Sorbonne Université-Inserm, Faculty of Medicine, Centre de Recherche Saint-Antoine (CRSA), UMR_S938, ICAN, Paris, France

²Department of Endocrinology, CRMR Prisis, Saint-Antoine Hospital, GH APHP-Sorbonne Université, Paris France

Corresponding author: Jacqueline Capeau

Faculty of Medicine Sorbonne Université

27 rue Chaligny 75012 Paris, France

Phone: 33 668456988

Email: jacqueline.capeau@inserm.fr

Structured abstract

Purpose of review: Increased total body fat with truncal redistribution is common in antiretroviral-treatment(ART)-controlled persons living with-HIV(PLWH), leading to insulin resistance, prediabetes/diabetes and dyslipidemia. We address these topics here.

Recent findings: Most antiretrovirals are associated with gain in trunk fat, including visceral adipose tissue(VAT). Protease-inhibitors(PI) could inhibit white fat ability to dissipate energy (i.e. beiging) favoring fat gain. Expansion of VAT is associated with a pro-inflammatory profile linked to the tryptophan-kynurenine pathway and CD4 subtypes. ART-associated increased AT quantity leads to decreased AT density, insulin resistance and dyslipidemia that could be improved by lifestyle modifications.

PLWH present high level of insulin resistance, regardless of their treatment, and a higher prevalence of prediabetes, but not diabetes, than non-infected persons. Otherwise, HbA1c values appear inaccurate to diagnose prediabetes/diabetes in PLWH.

ART-related-dyslipidemia is characterized by elevated LDL-C and/or high triglycerides and reduced HDL-C. Whereas treatment with PIs generally results in worsened lipid values, treatment with integrase-strand-transfer-inhibitors is associated with a better profile. Tenofovir-alafenamide is associated with higher lipid levels than tenofovir-disoproxil-fumarate. Treatment of LDL-C-dyslipidemia could benefit, in statin-insufficiently controlled patients, from the class of proprotein-convertase-subtilisin-kenin-type-9(PCSK-9) inhibitors.

Summary: Lifestyle modifications are mandatory to reduce fat and improve dysglycemia/dyslipidemia. New drugs can efficiently control diabetes and LDL-C-dyslipidemia

Keywords

Adipose tissue, insulin resistance, diabetes, dyslipidemia, antiretroviral

1- Introduction

Antiretroviral-treatment (ART)-controlled persons living with HIV (PLWH) often present with central fat redistribution, characterized by increased visceral (VAT) and reduced subcutaneous adipose tissue (SAT). VAT expansion is associated with ectopic fat deposition in muscle, heart, liver, and pancreas, resulting in cardio-metabolic comorbidities(1).The prevalence of obesity is increasing worldwide, as a result of increased sedentary lifestyle and harmful food habits. This is also a concern for PLWH, even if they generally exhibit a lower prevalence of obesity than the corresponding general population.

Continuous ART, required to control HIV, results in potential ART-related outcomes altering AT and lipids. HIV, hidden within immune cells in fat reservoirs, releases viral proteins that can affect fat, and could act in synergy with some antiretrovirals(2).

Fat expansion and related cardio-metabolic outcomes are frequent in PLWH, mainly in relation to age and personal or environmental factors. Currently used antiretrovirals have less impact on glucose and lipid levels than first generation antiretrovirals (except fat gain induced by some integrase strand transfer inhibitors (INSTIs) and tenofovir alafenamide (TAF), see the paper by J Lake and J Trevillyan in this issue).

2- Current fat alterations in PLWH

The initial recognition of fat alterations in PLWH on ART began in the mid 1990s with highly prevalent facial and limb lipoatrophy, ultimately found to be a side effect of thymidine analogue reverse transcriptase inhibitors (tNRTIs). These drugs were replaced in the early 2000s in Western countries (and later in low-medium income countries) by ART with less effect on fat and lipoatrophy regressed in most lipoatrophic patients.

2-1 Epidemiology

Importantly, tNRTI-related lipoatrophy is still present in some PLWH, with increased waist-to-hip ratio (WHR) reflecting increased waist (WC) and decreased hip circumferences (HC). These long-lasting alterations were associated, in the COCOMO cohort, with low AT density and impaired adiponectin production(3) and also with increased total cholesterol (TC) and low HDL-C(4). Increased WHR and/or lipoatrophy, reminiscent of stavudine use, are also associated with insulin resistance in long-term infected and treated PLWH from the APROCO cohort(5) and with incident diabetes among PLWH from the MACS cohort(6).

Over time, PLWH are gaining weight both in the truncal and limb compartments as shown in the European Modena cohort(7). In this cohort, the post-menopausal state was associated with greater fat mass. Peripheral lipoatrophy was diagnosed in one third of participants during the 2004-2014 period, more frequently among men. In addition, a CD4 nadir <200 cells/mm³ was associated with greater trunk fat mass on the long-term. This latter finding could possibly be explained by a high level of fat reservoirs, enhancing the effect of viral proteins on AT(2).

In a representative US population of PLWH evaluated during the 2009-2012 period (Medical Monitoring Project, MMP), 50-64 year old women were more likely to be obese than men (8.4% prevalence difference)(8). In the MACS and WIHS cohorts, including HIV-infected and non-infected men (MACS) and women (WIHS) with similar risk factors, BMI, HC and WC were greater in women than men and also higher in non-infected participants than in PLWH, both in men and women. However, the changes in these anthropometric variables did not differ according to the HIV status(9). BMI increased until age 60 and then plateaued, whereas WC and WHR continued to increase irrespective of HIV serostatus, indicating age-related truncal

fat redistribution. Moreover, in HIV-infected women, the rate of fat gain did not increase during/after menopause in contrast to HIV-negative women who experienced increased BMI and WC(10).

The impact of currently used PIs, NRTIs and non-NRTIs (NNRTIs) on fat gain appears mild. Currently used PIs are associated with modest fat gain: boosted atazanavir (ATV/r) with truncal fat and boosted darunavir (DRV/r) with increased VAT and SAT(11,12). Efavirenz (EFV) has not been previously associated with fat alterations. However, results from the ADVANCE trial suggest that EFV impaired weight gain among PLWH bearing the CYP2B6 genotypes leading to slow and intermediate EFV metabolism, and therefore to higher EFV concentrations(13). Tenofovir disoproxil fumarate (TDF) is also proposed to prevent fat gain. The role of INSTIs and TAF on fat gain is discussed in another paper in the present issue.

2-2 Mechanisms

Several lines of evidence suggest that the virus itself is probably involved into AT modifications. AT is an HIV/SIV (simian immunodeficiency virus) reservoir and SIV/HIV infection has been associated with features of adipose tissue aging. Thus, fat from SIV-infected macaques displayed markers of senescence. HIV proteins Tat and Nef released by infected immune cells could exert a bystander effect on adipose cells, enhancing senescence and impairing adipocyte differentiation and function(14).

PIs themselves can modify AT. Recently, inhibition of fat beiging, a process allowing dissipation of excessive fat through heat production, has been proposed to explain fat gain. The expression of the micro-RNA processing enzyme DICER and of the canonical brown and beige genes (UCP-1, PGC1alpha, PRDM16) were reduced in SAT of PLWH and negatively correlated with initial HIV infection severity and duration of PI use(11,15,16). These findings

suggest a PI-induced shift from a brown/beige to a white fat phenotype. As a result, fat is no longer dissipating energy as heat but rather retaining lipids and evolving toward hypertrophy and possible fat gain. This mechanism could also result from initial HIV infection severity, leading to increased fat reservoirs and AT dysfunction.

Decreased total and trunk fat was associated, in postmenopausal women from WHIS, with increases in the bone-derived hormone, undercarboxylated-osteocalcin, an indicator of bone health that mediates glucose metabolism and regulates fat mass(17). This draws attention to potential links between bone and AT metabolism in PLWH that need to be further explored.

Fat density, measured during CT scan imaging of VAT and SAT at L4-L5 level, can assess fat quality, in addition to quantity. It is proposed that, in the case of unhealthy expansion (hypertrophy), adipocytes become lipid engorged, of poorer quality and less dense. Fat density decreased over 96 weeks after ART initiation with ATV/r, DRV/r or raltegravir (RAL), each given with TDF/emtricitabine(FTC) as background. Coupled with increased SAT and VAT quantity, this suggests that unhealthy adipocyte hypertrophy occurs following ART initiation regardless of the molecule(18).

2-3 Consequences

VAT expansion is associated with ectopic fat deposition in liver, muscle, heart (epicardial fat), vessels and the pancreas, with deleterious cardiometabolic outcomes(1,11). Increased abdominal fat, as evaluated by WHR, was associated with pro-inflammatory products of the tryptophan-kynurenine pathway, which could be a potential source of inflammation in HIV(19). Increased VAT was also related to reduced PBMC telomere length in PLWH, independently of smoking and age, suggesting involvement of VAT in accentuated aging(20). Body fat parameters were associated with hypogonadism in HIV-infected men <50y,

inversely related to free testosterone and the estrone+estradiol/testosterone ratio, and were also associated with multimorbidity and frailty. Therefore, body fat mass, multimorbidity and frailty are associated with each other and contribute to male hypogonadism in PLWH(21).

Decreased SAT and VAT density, in favor of unhealthy fat hypertrophy, has been associated with increased HOMA-IR and triglyceride (TG) levels and decreased HDL-C, thus linking unhealthy AT to insulin resistance and dyslipidemia(22). Moreover, SAT of diabetic and non-diabetic PLWH was found to be enriched in CD4 and CD8 T effector memory (TEM) subsets compared to those present in blood, which could contribute to local tissue inflammation. The level of CD4/CD8 TEM subsets was even higher in SAT from diabetic as compared to non-diabetic PLWH(23). In diabetic subjects, SAT was enriched in a population of CD4 T cells expressing CX3CR1, GPR56 and CD57 which could exert anti-viral activities locally against HIV, CMV and other viruses (24).

In addition, in well-controlled PLWH, higher amounts of VAT was associated with higher atherosclerotic coronary plaque and coronary artery calcium score (CAC) while the reverse was seen with increased SAT(25), linking VAT and cardiovascular outcomes.

Apart from cardiometabolic comorbidities, altered AT distribution is associated with neurocognitive outcomes. In the MACS cohort, increased BMI and higher WC were associated with lower cognition and greater cognitive decline both in PLWH and in HIV-negative men(26).

2-4 Interventions

Lifestyle modifications are strongly encouraged: exercise, regardless of its intensity, resulted in reduced total and visceral AT in PLWH(27).

3- Insulin resistance, prediabetes and diabetes

The high occurrence of diabetes noted with first-generation ART mostly resolved with newer ART(28). However, since some INSTIs and TAF can increase BMI, this could increase the risk of prediabetes/diabetes.

3-1 Insulin resistance

In routine clinical practice, insulin sensitivity and identification of insulin resistance is usually accomplished by calculating the HOMA-IR index, using fasting glucose and insulin levels. While this is far less accurate than an insulin clamp, HOMA-IR is often elevated in PLWH (>2), and is associated with increased truncal fat. This finding raises concerns about the possible evolution towards diabetes.

In ViiV healthcare trials(29), HOMA-IR was evaluated in PLWH initiated with dolutegravir-including therapies. In the SPRING-1 trial of ART-naïve PLWH initiated with DTG vs EFV, 80% of PLWH had HOMA-IR>2 at baseline, with further increase during follow-up. In the switch SWORD and STRIVING trials, baseline HOMA-IR was >2 in 65-75% with a mild increase in the 2 arms over time. Even if 33% of the subjects were overweight and 17% obese, this high level of initial HOMA in ART-naïve and ART-controlled PLWH is worrying. In the TANGO study, patients were switched to dolutegravir/lamivudine (DTG/3TC) or remained under a TAF-containing regimen (elvitegravir/cobicistat, EVG/c, in most cases). Again, baseline HOMA-IR was elevated (median 2.8 and 2.6, respectively) and mildly decreased or increased during follow-up(30). HOMA-IR is generally lower in European cohorts with lower BMI. Thus, in the ETRAL study, evaluating aging PI-treated PLWH switched to RAL/etravirine, median BMI was <25 kg/m² but median HOMA-IR was 1.7 in men, 1.9 in women, and increased in

relation with weight gain in men and peri/post-menopausal women(31). High values of HOMA-IR reported in most studies, at least in Western countries, could be related to ART, but probably less so than an elevated BMI, trunk fat accumulation and age.

3-2 Diagnosis of prediabetes and diabetes.

To diagnose prediabetes/diabetes recent recommendations advise criteria based on glycated hemoglobin (HbA1c) values, respectively $5.7\% < \text{HbA1c} < 6.4\%$ (39-47 mmol/mol) for prediabetes and $\text{HbA1c} > 6.5\%$ (>48 mmol/mol) for frank diabetes In the CICADA study from Tanzania, the prevalence of diabetes was 13% using HbA1c and 6% using oral glucose tolerance test (OGTT) with only partial overlap among participants identified by the two tests(32). In Thailand, authors diagnosed dysglycemia using fasting glucose, 2h post-prandial glucose and HbA1c levels: the agreement between the three estimations was weak and conversely HbA1c underestimated prediabetes prevalence (33). In African PLWH, HbA1c also underestimated the prevalence of diabetes(34), in particular in those with sickle cell disease(35). These studies underline the inadequacy of using HbA1c to diagnose prediabetes/diabetes in several populations, inasmuch as this parameter can vary with hemoglobin variants, presence of hemolysis, red globular volume and treatment with some NRTIs.

3-3 Prevalence of prediabetes and diabetes

At present, the prevalence of diabetes is generally not different between PLWH and controls, but the BMI of PLWH is generally lower. In a study performed in Finland in 2017(36), the prevalence of diabetes was 13.2% in PLWH, a figure not different from 14.5% in the general population but with a lower prevalence of obesity: 18.2% vs 23.9%.

Importantly, fasting glucose was higher in PLWH but HbA1c lower, further stressing the concerns about using HbA1c to diagnose prediabetes/diabetes in PLWH. Of note, the risk of dysglycemia for a given BMI was higher in PLWH than in the general population. In the MMP group of US PLWH, the prevalence of diabetes was higher by 13% in women than men >65y(8). In the MACS cohort, the risk for incident diabetes was evaluated in pre-diabetic subjects between 1999 and 2019. PLWH had a 40% higher risk of becoming diabetic than non-infected individuals, even if they were younger and with a lower BMI. Longer use of stavudine and resulting increased WHR could explain this increased risk(6). In PLWH from the Asia-Pacific region, with a median age of 35 years, diabetes incidence was quite elevated at 10.8/1000 persons-year-of-follow-up and associated with later years of follow-up 2014-2017 as compared to 2011-2013, in addition to classical risk factors (age, sex, BMI)(37).

3-4 Mechanisms

In the APROCO cohort, 11% of long-term infected and ART-controlled PLWH, median age 49 years, were diabetic. Diabetes was associated independently with increased inflammation and oxidative stress(5). In PLWH from the MACS, history of AIDS was linked to incident diabetes, which may reflect continued immune system dysregulation and inflammation as drivers for diabetes(6).

In the WIHS cohort, women experienced increased levels of HbA1c only if they gained $\geq 5\%$ weight on INSTI(38). Up to now there is no indication of an increased risk of diabetes, over that related to weight gain, in INSTI-treated PLWH.

In the MACS and the WIHS cohorts, plasma lipidomic profiles revealed that eleven lipid species were associated with the risk of diabetes. Most of them were elevated in ART-treated PLWH, which suggests a specific link between lipid metabolism and HIV and the

possibility that ART-related plasma lipidomic alterations may precede the development of diabetes(39).

3-5 Consequences

In the MACS cohort, abnormal glucose metabolism was associated with declines in gait speed and grip strength, regardless of HIV serostatus. Improved glucose control is an intervenable target to prevent progression of physical function limitation and the occurrence of frailty(40).

In 2936 US veterans with HIV, 628 had depression. They had a 24% increased risk of diabetes, and more severe depression was associated with higher risk of developing diabetes(41).

3-6 Treatment

Even if not tested in dedicated clinical trials, PLWH can benefit, in addition to the conventional antidiabetics (metformin and sulfonylurea), from GLP-1 (glucagon-like peptide-1) receptor agonists, and SGLT2 (sodium-glucose co-transporter-2) inhibitors that, in addition to decreasing glycemia, also decrease weight and cardiovascular risk(1), and also preserve kidney function in the case of SGLT2 inhibitors. The antidiabetic class of DPP4 inhibitors has an anti-inflammatory effect on adipose tissue(11).

4- Dyslipidemia

ART-induced alterations in lipid levels are common in PLWH. In addition to ART, dyslipidemia results from personal factors such as age, familial history, sex, diet, and alcohol intake. Increased LDL-C or triglycerides (TG) and decreased HDL-C, are related to different metabolic

situations. LDL-related dyslipidemia is independent from increased TG and decreased HDL-C as evaluated by the TG:HDL-C ratio (mg/dl) >3.5 for men and 2.5 for women, a type of dyslipidemia often seen in diabetic patients and associated with insulin resistance(28).

4-1 Prevalence

Recent studies report the prevalence of dyslipidemia in different groups of PLWH and corresponding general population. In a Finish population, elevated TG:HDL-C was found in 27% of PLWH as compared to 18% in the general population, in agreement with the higher prevalence of dysglycemia(36). In the French APROCO cohort, LDL-related dyslipidemia was found in 28% and high TG:HDL-C in 9% of PLWH(5). In the CARMA-ENDO study, including HIV-infected and non-infected women from British Columbia, a higher proportion of PLWH (63%) than HIV-negative (40%) had dyslipidemia, mainly low HDL-C or high TG, despite a young median age (43.5 years)(42). In the US MMP group, women >50y were more likely to have high TC and LDL-C than men: respectively 9.9 and 5.1% for age 50-64y and 18.8 and 15.6% for age ≥65y(8).

4-2 Mechanisms

In the APROCO cohort, LDL-related dyslipidemia was associated with oxidative stress, while elevated TG:HDL-C ratio was associated independently with inflammation and oxidative stress(5). In the MACS cohort, lower levels of the atheroprotective small HDL-particles were associated with greater systemic inflammation. This may be a potential mechanism contributing to increased cardiovascular risk among PLWH(43). These results enlighten the potential role of inflammation/oxidative stress as drivers for dyslipidemia, in addition to ART and individual factors.

INSTI use has been consistently associated with globally improved lipid parameters in switch situations (decreased LDL-C and TG, often improved HDL-C). However, PLWH were often switched off PI to initiate INSTI. The beneficial effect could result from stopping the PI and/or INSTI initiation. In the TANGO study, PLWH switched to DTG/3TC (8% initially PI-treated) were compared to PLWH taking TAF (mainly EVG/c/TAF). Over 48 weeks, DTG/3TC treatment decreased TC, LDL-C and TG levels as compared to the TAF arm(30). The difference between the two arms could result from the INSTI, cobicistat or TAF use.

In the WIHS, comparing women switched or not to an INSTI, HDL-C level was decreased only in those INSTI-treated and gaining $\geq 5\%$ weight, stressing weight-related rather than INSTI-related changes(38).

The different effect on lipids of TAF vs TDF, previously identified in clinical trials, was confirmed in the real life setting in several studies: switching TDF to TAF increased TC, LDL-C, HDL-C and TG while the LDL-C/HDL-C ratio remained stable(44, 45). When TAF was switched back to TDF, lipid levels returned to previous values(46).

4-3 Treatment

Statins remain the first option to decrease LDL-C. If insufficiently decreased, ezetimibe is an efficient and safe second-line option. However, in PLWH insufficiently controlled or intolerant to statins, evolocumab, a proprotein convertase subtilisin-kenin type-9(PCSK9) inhibitor, was well tolerated and further reduced LDL-C by 60% at 24w versus placebo. It also reduced other atherogenic lipid levels(47). It can be considered for lowering atherogenic lipoproteins in PLWH with high cardiovascular risk.

4-4 Consequences

A lipidomic profiling of 211 lipid species in 937 patients, HIV-infected or not, from the MACS and WIHS cohorts revealed that 12 species were associated with risk of carotid artery plaque and conventional blood lipids, most of them being elevated in ART-controlled PLWH suggesting a link both with HIV infection and ART(48).

5- Conclusion

Fat alterations and fat gain observed in PLWH are often associated with insulin resistance and dysglycemia, raising concerns for the possible latter occurrence of diabetes. Recent ART combinations are involved into metabolic disturbances, mainly due to their weight gain effect, with mild direct effects on glycemic and lipid parameters. Strategies to control AT and metabolic alterations favor lifestyle modifications to reduce weight. Efficient anti-diabetic and hypolipidemic drugs are now available to lower glycemia and LDL-C to reasonable targets.

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7- Bullets

- Aging long-term ART-controlled persons-living with HIV often present fat redistribution with truncal fat inflation.
- Increased ART-related adipose tissue quantity is associated with unhealthy decreased density, resulting in insulin resistance and dyslipidemia.

- Insulin resistance is common in PLWH, whatever antiretrovirals, and could result in prediabetes, which incidence is increased as compared to non-infected controls.
- HbA1c values are often used to diagnose prediabetes/diabetes but appear inadequate in PLWH, being lower than expected according to glycemia.
- PI use is associated with worsened lipid values (increased LDL-C and triglycerides, often reduced HDL-C) while integrase-strand-transfer inhibitors appear more lipid friendly.

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