Metabolic complications affecting adipose tissue, lipid and glucose metabolism associated with HIV antiretroviral treatment

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Abstract

Introduction: Efficient antiretroviral-treatment(ART) generally allows control of HIV infection. However, persons-living-with-HIV(PLWH), when ageing, present a high prevalence of metabolic diseases.

Area covered: Altered adiposity, dyslipidemias, insulin resistance, diabetes and their consequences are prevalent in PLWH and could be partly related to ART.

Expert opinion: At first, personal and lifestyle factors are involved in the onset of these complications. The persistence of HIV in tissue reservoirs could synergize with some ART and enhance metabolic disorders. Altered fat repartition, diagnosed as lipodystrophy, has been related to first-generation nucleoside-reverse-transcriptase-inhibitors(NRTIs) (stavudine zidovudine) and some protease inhibitors(PIs). Recently, use of some integrase-inhibitors(INSTI) resulted in weight/fat gain, which represents a worrisome unresolved situation.

Lipid parameters were affected by some first-generation NRTIs, non-NRTIs(efavirenz) but also PIs boosted by ritonavir, with increased total and LDL-cholesterol and triglycerides.

Insulin resistance is common in aging PLWH, often associated with abdominal obesity. Diabetes incidence, high with first-generation-ART (zidovudine, stavudine, didanosine, indinavir) has declined with contemporary ART close to that of the general population.

Metabolic syndrome, a dysmetabolic situation with central obesity and insulin resistance, and liver steatosis are common in PLWH and could indirectly result from ART-associated fat gain and insulin resistance. All these dysmetabolic situations increase the atherogenic cardiovascular risk.

1. Introduction

The aim of this review is to propose a narrative overview of the role of antiretroviral therapies (ART) in the onset of metabolic alterations and modified adiposity observed in persons living with HIV (PLWH). Due to the replacement of initial ART by newer molecules, ART effect on metabolic parameters and adiposity has markedly evolved. We present here rapidly some historical data, important since these first-generation drugs were still used recently in some countries and since they could present long-lasting effects. We also present effects related to contemporary ART, since, unexpectedly, some of them affect adiposity. These alterations have been only recently recognized and are not reviewed in the previous general reviews on the subject.

In high-income countries, most PLWH, when diagnosed, are at present controlled by antiretroviral treatment (ART) and, in low- and middle-income countries (LMICs), the proportion of treated-PLWH is increasing. As a consequence, PLWH are aging leading to an increased prevalence of age-related comorbidities, including metabolic disorders. Probably, in 2030, over 70% PLWH worldwide will be over 50 years (if HIV coverage by treatment is good, UNAIDS 2016, estimates). Since it is still not possible to cure HIV or to enhance patient's immune response to control the virus without ART, most patients require treatment.

Before 2000, PLWH received first-generation ART, as nucleoside analogue reverse transcriptase inhibitors (thymidine NRTIs, stavudine, zidovudine, didanosine) and protease inhibitors (PI, indinavir, ritonavir, nelfinavir) responsible for marked adverse events on lipid and glucose metabolism and on adipose tissue. These ART were replaced by newer molecules presenting a markedly lower metabolic toxicity.

However, some PLWH, previously treated with first-generation NRTIs, present long-lasting fat alterations with metabolic consequences[1]. Some contemporary ART as integrase inhibitors (INSTI), considered as metabolic-friendly, were recently associated with weight/fat gain. Therefore, there are remaining and evolving concerns regarding the effect of ART on metabolism and adipose tissue in PLWH.

As a consequence of the metabolic effects of some ART, increased prevalence of cardiovascular diseases (CVD), particularly atherosclerotic CVD[2] and diabetes, has been reported, but differ according to the calendar years and the geographic area. It is important to consider the metabolic profile of each patients to adapt ART. If required, classical lipid and glucose-lowering medications are prescribed.

2. Lipodystrophy and fat repartition

Altered amount and repartition of body fat was an unexpected side effect of first-generation ART, mainly stavudine and zidovudine, even if these drugs efficiently controlled HIV infection. It was no longer a real concern with second-generation NRTIs (as abacavir, lamivudine, emtricitabine, tenofovir, tenofovir alafenamide). However, residual adipose tissue toxicity of first-generation NRTIs and fat expansion associated with some INSTI reveal that in all ART classes, some molecules can impact adipose tissue. This suggests that this tissue could be sensitized/primed by HIV to ART effects.

2.1 Definition and role of ART (table 1)

2.1.1 Definition and role of NRTIs

ART tritherapy, associating two NRTIs (including stavudine or zidovudine) and one PI (often indinavir, nelfinavir, or full dose ritonavir) in the late 1990s led to the occurrence of a lipodystrophic syndrome in about 50% patients associating peripheral lipoatrophy with either central lipoatrophy or fat accumulation and, in some patients, fat accumulation at the neck level, called buffalo-hump. Due to replacement of the more adipose tissue-toxic ART, stavudine and zidovudine, these lipodystrophic phenotypes largely reversed and lipodystrophy was no longer considered as a major issue after 2000.

However, recently, PLWH, long-term treated with thymidine NRTIs, were reported to still present alterations in body fat repartition, even if the drugs have been stopped years ago. Thus, young adults, infected since childhood, have a higher prevalence of metabolically detrimental fat distribution and dyslipidemia than age-paired subjects from the general population, even if their BMI is lower (in men) or similar (in women)[3]. PLWH from the AGEhIV cohort have higher waist circumference and lower hip circumference than well-paired non-infected individuals[4] and fat redistribution was associated with higher rates of hypertension[5]. In addition, in the COCOMO study, previous cumulative exposure to stavudine, zidovudine or didanosine is associated with long-lasting increased visceral adipose tissue (VAT) and decreased subcutaneous adipose tissue (SAT), as evaluated by abdominal CT scan, and related with excess risk of hypertension, high total cholesterol (TC) and low HDL[1].

2.1.2 Role of PIs

The role of PIs in the occurrence of trunk fat hypertrophy was less clear. However, in the ACTG5224s study evaluating ART-naïve patients, atazanavir boosted by ritonavir (ATV/r) was clearly associated with greater increase in VAT (26%) vs efavirenz (12%)[6] Accordingly, the effect of ATV/r on VAT was also observed in 4 other randomized trials evaluating initial therapy (for a review[7]). The role of other PIs is less clear[7]. However, in the ACTG5260s study, initiation of ART, including either ATV/r or darunavir/r (DRV/r) or raltegravir, was associated with similar increases in limb fat, trunk fat and VAT, VAT being preferentially increased (by 22-29%) as compared to limb fat (11-14%)[6].

2.1.3 Role of INSTI

In addition, this study clearly shows that the INSTI raltegravir led to increased weight and to global fat accumulation, in particular at the truncal level[6]. Interestingly women had greater VAT gain on raltegravir vs PI than men, and black vs nonblack individuals[8]. The association between dolutegravir or raltegravir vs elvitegravir use and weight gain was confirmed in observational cohorts of PLWH initiated with ART [9, 10, 11]. Weight gain following ART initiation could be attributable in part to a “return to health” phenomenon, but is also clearly associated with individual INSTI and with personal factors as sex and ethnicity [12].

In ART-experienced PLWH switched off PIs to a regimen containing an INSTI, results are less clear. In the ROCnRAL study, patients switched from PI/r to raltegravir+maraviroc did

not experience change in BMI or limb fat after 19 weeks but trunk fat tended to be increased (p=0.058)[13]. Switching a PI-containing regimen to dolutegravir or raltegravir resulted in a non-significant increased waist circumference together with decreased leptin levels suggesting decreased peripheral fat [14]. In the ANRS163 ETRAL study, 165 controlled PLWH switched off PI to raltegravir/etravirine increased by 12% total, trunk and limb fat after 96 weeks [15]. In the recent report evaluating on the long-term, 691 patients enrolled in A5551 or A5332 studies from 2007-2017, excess weight gain was observed following switch to INSTI. Change in rate of weight gain appears greater with dolutegravir than elvitegravir or raltegravir and was more prominent for women, blacks and persons aged over 60y[16].

2.2 Pathophysiology

2.2.1 Role of HIV

First, adipose tissue is now recognized as being a target of HIV, fat being a reservoir within CD4 T cells and probably macrophages[17, 18] and infected immune cells probably release viral proteins affecting proximal cells as adipose stem cells and adipocytes. We have recently reported that the virus, and its proteins Nef and Tat, induced adipose tissue dysfunction and increased production of extracellular matrix components, leading to increased fibrosis[19]. As a consequence, adipose tissue presents a dysfunctional phenotype with decreased adipogenesis, adipose dysfunction and increased inflammation[20]. Moreover, markers of gut barrier dysfunction in ART-naïve individuals predicted VAT increase with ART initiation[21].

2.2.2 Role of NRTIs

The major role played by stavudine, but also zidovudine, in the lipodystrophic phenotype has been clearly recognized, these drugs being involved in lipoatrophy but also in trunk fat hypertrophy[22]. Adipose tissue biopsies performed before 2000 revealed macrophage infiltration, inflammation, mitochondrial toxicity and dysfunctional adipose function[23, 24, 25]. Recently, similar alterations were reported in PLWH with abdominal obesity and a metabolic syndrome included in 2010-2012, suggesting the persistence of these alterations in such patients [26]. Thus, truncal obesity in PLWH is characterized by adipocyte hypertrophy together with reduced adipogenesis and increased inflammation with metabolic consequences[22, 26].

At the cellular level, stavudine and zidovudine were shown to induce mitochondrial toxicity though their ability to inhibit mitochondrial DNA (mtDNA) polymerase gamma. In addition,

they increase oxidative stress even if the mtDNA level is preserved. Due to the major role played by mitochondria in lipid oxidation, dysfunctional mitochondria could result in adipocyte loss and lipoatrophy[22] Also, mtDNA haplogroups may explain part of the genetic predisposition to lipodystrophy during ART[27]. Stavudine and zidovudine induce insulin resistance at the adipocyte level and therefore worsen the dysmetabolic profile[28].

The long-lasting effect of thymidine NRTIs is worrisome and the remaining fat alterations poorly investigated. The presence of HIV inside fat reservoirs as well as HIV- and ART-induced irreversible fat fibrosis could impair adipose tissue function and expansion leading to lipotoxicity and metabolic alterations. Whether mtDNA haplogroups are involved remains to be evaluated. Possibly, thymidine NRTIs can lead to the irreversible accumulation of mutations in mtDNA and therefore to earlier adipose tissue aging with mitochondrial dysfunction [29, 30]. Also, the strong toxicity induced by thymidine NRTIs could lead to exhaustion of adipose stem cells and therefore preclude the capacity of some fat depots to regenerate.

2.2.3 Role of PIs

It has been also shown that cervical fat presented a phenotypic modification of white towards brown adipose tissue which could be related to PIs use[31, 32]. Recently, a role for decreased expression of the *dicer* gene was also involved in the PLWH lipodystrophy[33]. Dicer is an endonuclease that regulates microRNAs and has evolved as a viral mechanism to enhance host HIV infectivity, but may also have unintended metabolic consequences[34]. The expression of *dicer* was strongly and negatively associated with the duration of PI use and its decrease could be related to PI use.

In vitro studies reported that some PIs altered adipocyte function and induced insulin resistance. One possible mechanism is the ability of these molecules to inhibit the enzyme ZMP-STE24 involved into the maturation of the nuclear matrix protein prelamin-A into lamin-A[35, 36]. Accumulation of prelamin A, which keeps a farnesyl anchor inserted in the nuclear membrane, resulted in altered adipocyte function and insulin resistance [36, 37]. Such alterations are also observed in patients with genetic forms of lipodystrophy due to mutations in the gene encoding lamin A/C, called laminopathies, with central fat redistribution, neck fat accumulation, peripheral lipoatrophy and insulin resistance, resembling the HIV-related lipodystrophic phenotype [38]. We have also shown that abnormal lamin network precludes the maturation and intranuclear localization of the transcription factor SREBP-1c required for lipogenesis [36], therefore linking adipose dysfunction and altered lipid metabolism. Different

PIs present different efficacy to inhibit the enzyme ZMP-STE24 and induce prelamin-A accumulation. The newer ones, atazanavir and darunavir, has milder effects than indinavir, lopinavir and ritonavir [35, 39].

2.2.4 The role of other ART

Among non-NRTI (NNRTI), efavirenz was shown in vitro to alter adipocyte function and increase inflammation while nevirapine exerted beneficial effects [40].

The mechanisms by which some INSTI lead to a global increase in adiposity [15] remain unknown.

2.3 Consequences and management

The long-lasting lipodystrophic phenotype associated with previous use of thymidine NRTIs results in a higher risk of hypertension, high TC and reduced HDL[1, 5]. Truncal adiposity is clearly related to a dysmetabolic phenotype with increased risk of CVD and diabetes and also of liver steatosis. The fat gain observed with INSTI has been linked, in a few studies, with increased insulin resistance [15]and diabetes [41].

The stigmatizing facial lipoatrophic phenotype initially observed was treated by plastic surgery, either by injection of patient's abdominal fat into cheeks (Coleman technique) or by injection of polylactic acid to regain cheek volume. Surgery of buffalo hump had disappointing results. To manage increased abdominal fat, restricted diet and exercise are safe and efficient options. Switch strategies off INSTI allowed weight loss in some patients. In the case of severe obesity, bariatric surgery is an efficient option to lose weight et decrease metabolic complications [42].

3. Dyslipidemia

Abnormal lipid levels have been reported early in ART-naïve PLWH, and related to the inflammatory context associated with acute infection. When patients are initiating ART, the level of TC, LDL and triglycerides generally increases due to decreased inflammation and also to a specific effect of ART. In addition, a number of other conditions, such as personal factors, familial backgrounds, age and sex will impact the level of lipid parameters. Some factors are clearly related to environment (diet, alcohol, weight), other to genetic features, and also to the use of some drugs. In addition, a number of diseases are associated with secondary dyslipidemias (cholestasis, hypothyroidism, nephrotic syndrome, diabetes…)

3.1 Definition

In the situation of inflammatory dyslipidemia, as observed in ART-naïve patients with acute infection, triglycerides are increased while TC, LDL and HDL are decreased[43]. This dyslipidemia, with normal or low levels of TC and LDL is nevertheless associated with increased cardiovascular risk. In ART-controlled patients, the presence of low-grade chronic inflammation is often reported. It could reduce the increased level of TC or LDL due to ART and reassure on the cardiovascular risk.

LDL-related dyslipidemia, defined by an increased level of TC and LDL, has to be evaluated in conjunction with other personal risk factors as sex, age, familial backgrounds of cardiovascular diseases, hypertension, smoking and type 2 diabetes. The guidelines for CV risk evaluation differ according to the countries and often use CVD risk scores including LDL. LDL-linked dyslipidemia results in markedly increased risk of atherogenic cardiovascular diseases.

Otherwise, increased triglycerides and decreased HDL define another type of dyslipidemia called atherogenic dyslipidemia, often seen in diabetic patients, associated with increased risk of CVD. It is defined by triglycerides (mg/dl) to HDL (mg/dl) ratio higher than 3.5 for men and 2.5 for women [44].

3.2 Prevalence and role of ART (table 2)

3.2.1 Prevalence

The prevalence of dyslipidemia is generally high in aging PLWH, as compared to the general population. However, in most studies, dyslipidemia has a global definition: increased level of LDL and/or of triglycerides and/or decreased level of HDL and/or the use of a lipid-lowering drug (statin, fibrate).

Thus, the prevalence observed in PLWH from the AQUITAINE cohort, median age of 50.5 years, was of 36.2% [45]. Accordingly, an increased prevalence of dyslipidemia has been reported in LMICs [46]. In the APROCO-COPILOTE study, we evaluated, 352 long-term infected and treated patients, aged 49 years: the prevalence of LDL-related and atherogenic dyslipidemias was respectively 28% and 9% [47].

3.2.2 Role of NRTIs

Regarding NRTIs, zidovudine and stavudine increase TC, LDL and triglycerides levels, this increase being higher with stavudine than zidovudine. Abacavir has a mild effect while didanosine, lamivudine and emtricitabine have no effect[43]. Interestingly, tenofovir is

associated with decreased lipid parameters, TC, LDL, HDL and triglycerides [48]. Since tenofovir exerts adverse effects on the bone and the kidney, a derived molecule has been introduced, tenofovir alafenamide (TAF), with no effect on lipid parameters (and also on bone and kidney). When patients are switched from tenofovir to TAF, the level of LDL, HDL and triglycerides is increased and if they are switched back to tenofovir this level is decreased again [49, 50], indicating the specificity of the effect of tenofovir.

3.2.3 Role of PIs

Contemporary PIs are used with a boosting dose of ritonavir, able to inhibit PI degradation by hepatic cytochrome P450-3A4 and therefore to increase PI circulating level. Some PIs, as ritonavir and lopinavir, exert a strong effect on lipid parameters and increase LDL and triglycerides. The other PIs have no or mild effect by their own, but since they are boosted with ritonavir, they still affect lipid levels. In darunavir-treated patients, when the boosting agent was changed from ritonavir to cobicistat, decreased levels of TC, LDL and triglycerides and increased levels of HDL were observed in the group of patients with TC> 200 mg/dL [51].

3.2.3 Role of other ART

Among the NNRTIs, efavirenz increases the level of LDL and triglycerides and also HDL while nevirapine exerts minor effects on LDL and favorable effects on HDL and therefore is considered as lipid-friendly. The other NNRTIs have minimal effects on lipid parameters.

The classes of the CCR5 inhibitor (maraviroc) and of integrase inhibitors (raltegravir, dolutegravir and elvitegravir) are considered as neutral on lipid parameters [43](for a review see [52]).

Therefore, in ART-naïve subjects, ART initiation has been associated with increased level of TC, LDL, HDL and triglycerides. This has been observed with all PIs boosted with ritonavir and also with efavirenz, part of the effects being due to decreased inflammation as a result of HIV control and part to the specific effects of ART. As well in ART-controlled patients, switches from some ART to another have clearly confirmed the dyslipidemic effect of some molecules in the different classes [43].

3.3 Pathophysiology

Regarding PIs, some studies suggested that their rapid effects on lipid parameters could originate at the liver level. In the liver of mice exposed to ritonavir, excess fatty acid synthesis

and hepatic steatosis occur after ritonavir exposure, associated with intra-nuclear accumulation of SREBP-1c. Moreover, in the liver and hepatocytes, PIs appear to inhibit the proteosomal degradation of pre-secretory apolipoprotein B, an LDL component, and to enhance its secretion in the presence of oleic acid [43, 53, 54]. Regarding NRTIs, their effect on lipid metabolism is seen after a longer period and could be an indirect manifestation of impaired adipose tissue function and resulting insulin resistance [43]. The mechanism of the lipid-lowering effect of TDF remains unknown.

3.4 Consequences on CVD and management

The elevation of LDL has been clearly associated with increased CDV risk in these patients, in particular risk of myocardial infarction, with a major role for lopinavir/r but also recently for darunavir/r in the DAD cohort [6]. However, atazanavir/r appears to be neutral regarding this risk. This could be due to the higher level of unconjugated bilirubin, observed in these patients, since bilirubin exerts a potential anti-oxidant effect which could protect the vessels. Regarding INSTI, a very recent work proposed that INSTI-based regimen was associated with a lower CVD risk than non-INSTI regimen in PLWH initiating ART in the US [55].

Lipid parameters are part of the annual check-up of ageing PLWH. If LDL is over the objectives (which vary from 2.6 to 5 mmol/l (100 to 190 mg/dL) according to the patient' number of risk factors), at first, a switch off PIs can be proposed. If the objectives are not reached, in addition to a cholesterol-low diet, a statin is prescribed.

In the case of increased triglycerides: a diet with reduced sugar and alcohol intake is proposed. If the triglycerides level is lower than 10 mmol/l, the clinical benefit of a treatment is uncertain.

4. Diabetes and insulin resistance

The high occurrence of type 2 diabetes seen with first-generation ART has been mostly resolved with newer ART. However, insulin resistance is still prevalent, possibly as a result of previous fat alterations and of ongoing gain weight observed worldwide and truncal adiposity associated with aging.

4.1 Definition

Insulin resistance is defined by the decreased effect of insulin on its main targets, the liver, adipose tissue and muscles, leading to increased insulin secretion to maintain normal

glycemia. If the pancreas cannot secrete enough insulin, glycemia gradually increases and could reach the threshold of 7 mmol/l, defining diabetes.

Clinically, the gold-standard test, the euglycemic hyper-insulinemic clamp, required to diagnose insulin resistance, is rarely performed and generally the HOMA-IR index is used: fasting glycemia (mmol/L) x fasting insulinemia (mU/L)/22.5. A value over 2.5 indicates insulin resistance, a situation common in the general population, associated with age and increased truncal fat. Long-term insulin resistance, with a progressively defective insulin secretion, could lead to type 2 diabetes.

4.2 Prevalence and role of ART (table 2)

4.2.1 Prevalence of insulin resistance

Insulin resistance was one of the first metabolic complications reported with highly active ART associating two first-generation NRTIs and one PI in the late 1990s as a result of indinavir use together with stavudine and zidovudine [56, 57]. Accordingly, patients with limited capacities to face this high level of insulin resistance presented an increased incidence of diabetes.

At present, in particular in aging patients, the occurrence of insulin resistance remains high, probably due to a remaining effect of first-generation thymidine NRTIs on fat distribution in addition to age and increased weight. Thus, in the APROCO-COPILOTE study, insulin resistance was diagnosed in 36% of patients, all having received first generation NRTI and PI, median age 49 years, normal BMI and a waist-to-hip ratio of 0.95[47]. In ART-naïve patients, initiation with atanazavir/r or darunavir/r resulted in a rapid 2-fold increase in insulin resistance [58].

4.2.2 Studies of ART effect on insulin sensitivity in healthy controls

Studies performed with healthy volunteers evaluated the ability of ART to modify insulin sensitivity after 2-4 weeks, by using the euglycemic hyper-insulinemic clamp. At first, lopinavir/r and atazanavir/r, but not unboosted atazanavir, were found to increase insulin resistance [59, 60]. Recent studies evaluated in young lean male controls the effect of lopinavir/r vs raltegravir and reported that lopinavir/r increased insulin resistance but not raltegravir [61]. As well, darunavir/r or elvitegravir boosted by cobicistat had no effect on insulin sensitivity by contrast to lopinavir/r [62]. However, these studies are far from the real-life situation of aging, often overweight and HIV-infected patients.

4.2.3 Role of INSTI in insulin resistance of PLWH

Integrase inhibitors were initially considered as metabolic friendly. In the SPIRAL study, in which ART-controlled patients were switched from a PI/r regimen to raltegravir, insulin sensitivity was increased [63]. As well, switching patients taking PIs to dolutegravir or raltegravir was associated with decreased insulin resistance [14]. However, in the ACTG A5260s study, ART-naive patients initiated with raltegravir presented a rapid 2-fold increase in insulin resistance similar to that observed with ATV/r and DRV/r [58].

In a retrospective study evaluating the patients either initiated with or switched to dolutegravir, the HOMA-IR increased similarly in patients treated with dolutegravir or other treatment but 50% PLWH were overweight or obese and baseline HOMA-IR was over 2 in 70% of them[64]. In the ETRAL study, patients switched off PI to raltegravir/etravirine increased insulin level, indicating increased insulin resistance [15]. Some case reports on diabetes occurrence in patients initiated with INSTI have been reported [41, 65]. Therefore, more studies are required to clarify the impact of INSTI on insulin sensitivity and diabetes.

4.2.4 Prevalence of diabetes

Regarding diabetes, its prevalence has markedly evolved with calendar years, in particular as a result of ART modification. It also markedly differs according to the countries/geographic origin. The first alert regarding an increased incidence of diabetes occurred in the late 1990s after the introduction of indinavir and full dose ritonavir. In the 2000s, in the MACS cohort from USA, with subjects having a BMI of 26 kg/m^2, the diabetes incidence was 47/1000 patient year of follow-up (PYFU) in PLWH versus 14/1000 PYFU in paired non-infected controls [66], ritonavir being a risk factor. More recently, the incidence of diabetes remains high at 15.5/1000 vs 8.5/1000 PYFU in respectively infected and non-infected subjects with a high BMI of 27-28 kg/m^2. Worldwide, in the D:A:D cohort, or in Europe, the incidence of diabetes is lower at 4-5/1000 PYFU in accordance with a lower BMI of 21-23 kg/m^2. In the French APROCO-COPILOTE study, we observed a high incidence of diabetes of 14/1000 PYFU before 2000 when the patients received indinavir, stavudine or didanosine, and a marked decrease after 2005, close to the level of the general population, in parallel with replacement of stavudine and indinavir[67]. Accordingly, in Denmark, the high incidence of diabetes observed before 2000, is no longer observed after 2000 [68]. Incidence remains slightly higher than in the general population in the Netherlands and Italy [4, 69]. A recent meta-analysis clearly illustrates the effect of the geographic diversity [70]. When considering 44 studies, the pooled incidence rate of overt diabetes worldwide was 13.7/1000 PYFU with

marked differences between North American countries (19.1/1000 PUFY) and Europe (8.0/1000 PYFU). This could result from the regional differences in adiposity. As well, the global cumulative incidence was 4.9% worldwide, higher in American (6.1%) and lower in European studies (3.8%). The main factors associated with incident prediabetes or diabetes were, as expected, older age, family history of diabetes, Black or Hispanic origin, overweight/obesity, central obesity, dyslipidemia, metabolic syndrome, increased fasting glycemia, but also lipodystrophy/lipoatrophy and certain ART. This latter aspect has been evaluated in about 15 studies with patients from various geographical origins: the results confirm the association of some ART with diabetes. Recently, due to aging and the overall increased adiposity (as in the general population), the incidence of diabetes is increasing.

In LMICs, since PLWH have received, even recently, the toxic NRTIs (stavudine, zidovudine and indinavir), the prevalence of diabetes is high when compared to the general population. Globally, this prevalence is rather low in South-East Asia, PLWH being young and with a low BMI [71]. In Africa, in a large cohort of South-African patients, the crude incidence of diabetes was 13.2/1000 PYFU, close to that of North-America [72]. Stavudine and zidovudine are consistently associated with increased incidence of diabetes. By contrast, tenofovir and emtricitabine seem to be protective [71].

4.3 Pathophysiology

Regarding insulin resistance, stavudine and zidovudine have been shown to induce insulin resistance in cultured adipocytes [28] as was indinavir [35, 36]. Other PIs also induce insulin resistance in cultured adipocytes or endothelial cells as lopinavir and ritonavir, with a milder effect for boosted atazanavir and even milder for boosted darunavir [39, 73]. Insulin resistance would lead to increased release of free fatty acids by adipose tissue, resulting in insulin resistance in the liver, heart, pancreas and the muscles, a process called lipotoxicity [74].

In addition, PI were shown to be toxic on beta-cell function. Exposures to ritonavir, lopinavir, atazanavir, or tipranavir resulted in increased apoptosis and reduced insulin-secretory capacity in insulinoma cells and human pancreatic islet cells [75]. PIs impaired beta-cell function by increasing oxidative stress and apoptosis [76]. Diabetes can result from the association of PI-induced insulin resistance and impaired secretion.

Personal and familial factors are also important risk factors for type 2 diabtes: in addition to age and BMI, the non-Caucasian geographic origin, sedentarily, antecedents of gestational diabetes and the presence of type 2 diabetes among first-degree relatives

4.5 Management

Insulin resistance is not routinely screened. Aging-PLWH need to be evaluated annually for glycemia. A confirmed fasted value over 7 mmol/L indicates diabetes. Glycemia between 5.6 and 7 mmol/l should be considered as a prediabetes condition. The care and follow-up of prediabetes and diabetes are similar to those in the general population, with lifestyle and dietary intervention being particularly important to decrease insulin resistance. Attention is required to avoid drug interactions: co-administration of dolutegravir leads to increased, and potentially toxic, plasma concentrations of metformin.

5. Metabolic syndrome, metabolic liver diseases and other comorbid situations

5.1 The metabolic syndrome

5.1.2 Definition

The metabolic syndrome (MetS) is a complex of interrelated risk factors for CDV and diabetes. These factors include dysglycemia, raised blood pressure, elevated triglycerides, low HDL and central adiposity. The association and clustering of these factors have been associated with the presence of insulin resistance [77].

There are several definitions issued from the American guidelines (NCEP-ATPIII) or from the international guidelines (IDF). To find a consensus, a harmonized definition has been proposed in 2009 by the presence of at least 3 out of the five following criteria [77]:

- abdominal obesity defined by a waist circumference over 80 cm in women and 94 in men in Europe, 88 cm in women and 102 cm in men in North America. These values differ for Asian and South American subjects.
- elevated triglycerides ≥ 1.5 g/L or 1.7 mmol/l
- elevated blood pressure systolic ≥ 130 and/or diastolic ≥85 mmHg
- reduced HDL ≤ 0.4 g/l or 1.0 mmol/L for men and ≤ 0.5 g/l or 1.3 mmol/L for women
- glycemia ≥ 5.5 mmol/L

5.1.2 Prevalence and role of ART

In a meta-analysis investigating a total of 65 studies across five continents comprising 55,094 PLWH aged 17–73 years, the overall prevalence was, with ATPIII-2001 definition, 16.7%, with IDF-2005, 18% and, with ATPIII-2004-2005, 24.6%. This prevalence varied

significantly by participant age, duration of HIV diagnosis, severity of infection, NNRTIs use and calendar year [78]. In the D:A:D study group, the prevalence was of 19.4% in 2000/2001 and increased to 41.6% in 2006/2007[79].

Use of PI has been associated with the development of MetS in a systematic review and meta-analysis of 9 papers with a 2.1 relative risk [80]. In a retrospective study of 266 PLWH, treatment with NRTI and PI increased the chance of developing MetS by around 2.4 times [81].

5.2 Metabolic liver diseases

The presence of a metabolic liver disease is also a common situation in PLWH. The presence of steatosis is considered as a consequence of metabolic disorders. This situation called NAFLD (non-alcoholic fatty liver disease) has been reported in about 35% of HIV-monoinfected individuals [82] in a meta-analysis of 10 studies. The risk factors for NAFLD were high BMI, waist circumference, diabetes hypertension, high triglycerides and high CD4 but not duration of ART. However, a role of ART has been reported with first-generation ART. Indeed, at first, the main potential mechanism of ART-related steatosis was mitochondrial toxicity leading to microsteatosis reported with stavudine, didanosine or with older NRTIs, is some but not all studies [83, 84, 85, 86]. As well efavirenz was associated with steatosis while raltegravir was able to decrease it [87]. Recently, moderate-to-severe NAFLD was observed in 8.5% of PLWH and cumulative exposure to zidovudine was associated with higher odds of NAFLD, despite a mean time since discontinuation of 9.4 years [88].

NAFLD can also evolve towards inflammation (NASH, non-alcoholic steatohepatitis) and even fibrosis and cirrhosis with a risk of hepatocellular carcinoma. Patients with high BMI, fasting glucose and increased AST level were at increased risk of significant liver fibrosis [82]. Therefore, metabolic disorders, increased trunk fat, insulin resistance and diabetes, which could result from the effect of ART, are key risk factors for NAFLD, independently of HIV parameters.

The presence of MetS can impact on the liver. In a matched cohort of HIV-monoinfected patients with or without MetS, the prevalence of significant liver fibrosis (≥ F2) was higher in patients with MetS compared to those without MetS. In multivariable analysis, obesity and HOMA-IR were independent factors of significant fibrosis whereas HIV parameters and ART were not [89].

5.3 Other comorbid conditions

Abdominal obesity is strongly associated with CDV risk and mortality.

Also, poorer neurocognitive functions have been associated with increased waist circumference among PLWH from the CHARTER study. In the MACS, VAT was strongly associated with regional brain atrophy [7], and total and central obesity found to predict cognitive decline[90].

The presence of MetS in PLWH also favors hand osteoarthritis [91].

Multimorbidity, the accumulation of multiple serious chronic conditions, may amplify morbidity and mortality with detrimental effects on the muscle, as sarcopenia, and physical function impairment leading to frailty [7].

6. Conclusion

Diagnosed PLWH are, at present, generally well-controlled by ART and are aging, with a high and increasing proportion being over 50 years. This situation is obvious in high-income countries but also prevalent in LMICs, which represent the majority of older PLWH worldwide at present and even more in the next future. These subjects present a high prevalence of age-related metabolic diseases affecting adipose tissue, lipid and glucose metabolism and responsible for an increased prevalence of comorbidities as CVD, diabetes and liver complications.

These situations have a multifactorial origin, including personal and familial factors and the persistent presence of HIV in the reservoirs, but, obviously, ART is playing a role.

While some first-generation ART molecules from the different classes, NRTI, NNRTI and PI, had a markedly deleterious impact on adipose tissue, lipid or glucose metabolisms, the replacement of these molecules by newer ones, within the same classes, allowed to minimize the metabolic adverse effects of ART. At present, the contemporary ART have generally no or mild effects on lipid and glucose metabolisms. However, it is important to consider the metabolic profile of each ART to individualize the treatment according to patient's personal risk factors. Recent warnings were raised regarding the class of INSTI, considered as metabolic friendly, with unexplained fat gain and possibly impaired glucose metabolism.

Moreover, while the prevalence of diabetes in PLWH is close to that of the general population, dyslipidemia, CVD, metabolic syndrome and liver metabolic diseases are still more prevalent in PLWH than in the general population with possible deleterious consequences as neurocognitive decline, frailty and multimorbidity. Their close management is mandatory and follows the guidelines proposed for the general population.

7. Expert opinion

To evaluate the role of ART in the occurrence of metabolic disorders is a major issue. This role has been clearly shown for different ART, even if the mechanisms involved are poorly understood. However, there are a number of concerns regarding clinical studies performed so far. PLWH receive several ART at a given time and have been often long-term exposed to a number of first-generation ART, with possible residual effects. Drug adverse effects differ according to the ART class but also to the individual molecule. In addition, HIV is still present in tissue reservoirs. The patient often presents other viral co-infections, a residual altered immune status, gut dysbiosis and stigmata of HIV infection severity, all these parameters resulting in chronic low-grade inflammation which can impact on metabolic and adipose tissue parameters.

To evaluate ART effects, in vitro studies used cell models [22, 92]. However, the results are only indicative since cell culture cannot recapitulate the organ complexity in particular regarding adipose tissue, the liver or arterial wall. ART are often highly linked to plasma proteins and therefore the unbound fraction is generally lower than that present in in vitro conditions but the exposure to ART is shorter than in vivo. The synergistic action of HIV proteins and ART is generally not addressed by in vitro models.

Regarding animal models, some mouse models expressing part of HIV have been engineered but do not present all PLWH characteristics. Simian models, as macaques infected with SIV, present an infection very similar to humans and are controlled by ART. However, these models are expensive and cannot recapitulate all the complex situations present in PLWH.

Therefore, clinical studies are relevant to study ART effect in PLWH. However, in ART-naïve patients initiated with ART, interpretation of metabolic modifications needs to consider at the same time the control of HIV infection with restoration of immunity, and the effect of given ART. When controlled patients are switched from an ART-regimen to another, they receive in general 2 or 3 drugs together, have been long-term treated with different molecules and present different stigmata of infection severity (evaluated by CD4 nadir and count, CD4/CD8 ratio, viral load) which complexify the study.

The ultimate goal is to have highly efficient ART devoid of metabolic (and other) metabolic effects. Indeed, aging of PLWH is now considered as a major issue, since most ART are efficient to control infection. Therefore, the main goal is to promote long-term healthy aging

by using ART with no or minor side effects. It would be important to address the adverse effects of ART in the real life setting in aging PLWH. Due to the complexity of each patient (age, sex, personal and family history, coinfections, severity of HIV infection, history of previous ART) large studies with careful evaluation of all metabolic parameters would be required to clearly identify the metabolic ART side effects.

We need to understand the pathophysiology of ART-related metabolic alterations. Overall, at present, a special focus is raised on adipose tissue and we need to address the effect of INSTI on that tissue. It is important to consider that, in addition to ART, HIV in the reservoirs is also involved in the metabolic alterations. As well, coinfections with CMV, altered gut microbiota, and personal factors, such as diet and sedentarily, result in a state of low-grade inflammation associated with insulin resistance and lipotoxicity. To consider together all these alterations is required to progress in the comprehension of these disorders. Since a number of ART reveal a dysmetabolic potential in some patients only, to identify the at-risk groups and to perform careful analyses in these group would be an important goal.

One objective in the field of HIV infection is to cure the virus, which would lead to empty the reservoirs and allow stopping ART. However, HIV-and ART-induced adipose tissue fibrosis is possibly an irreversible scar. At least, the reduction of these reservoirs could help to reduce some metabolic alterations. Moreover, the field of ART is continuously evolving with the search for new ART and new classes devoid of metabolic (and other) toxicities. evolving Gut dysbiosis is probably playing an important role with decreased metabolic-friendly butyrate producing bacteria [93]. Discovery of efficient prebiotic/probiotic agents to reverse dysbiosis is an important goal. CMV coinfection participates to low grade inflammation and cure of CMV could be beneficial. Thus, multiple targets can be reached to erase or decrease metabolic and adipose tissue alterations.

Research on adipose tissue and insulin resistance is a priority since fat alterations are strongly involved into metabolic disorders and impact the CV system, the liver and even the brain [90].

The priority at present is to understand the mechanisms involved in the INSTI effects on fat and possibly on insulin sensitivity, since INSTI are at present the most used ART class, recommended in ART-naïve and ART-experienced PLWH.

8. Article highlights box

- PLWH are aging and present a high prevalence of metabolic diseases including increased adiposity, insulin resistance, diabetes and dyslipidemias leading to enhanced CVD, metabolic liver complications and multimorbidity.
- Antiretroviral molecules are able to control HIV in most patients but not to cure the disease. Therefore, HIV remains in the reservoirs with potential deleterious effects and ART needs to be continuously given.
- Some molecules from different ART classes, NRTI, NNRTI, PI and INSTI, differently affect adipose tissue, glucose and lipid metabolism.
- While first-generation ART molecules exerted major adverse effects on fat, glucose and lipid metabolism, newer drugs have mild or no effects. This could result from a reduced level of HIV infection severity and/or from the different toxicities of each individual molecule.
- The class of INSTI is considered as metabolic friendly but a recent warning was raised on its effect on adiposity and glucose metabolism.

Table 1: effects of the most prescribed different ART molecules on fat

Name of ART	abbreviation	lipoatrophy	Peripheral fat gain	Central fat gain	references
stavudine	D4T	+++		++	1, 22
zidovudine	ZDV, AZT	++		+	1, 22
didanosine	DDI	+/-		+/-	1, 22
lamivudine	3TC	0		0	22
abacavir	ABC	0		0	22
tenofovir	TDF	0		0	22
emtricitabine	FTC	0		0	22
tenofovir alafenamide	TAF	0		0	22
efavirenz	EFV	+/-	+/-	+	22, 95
nevirapine	NPV	0		0	22
rilpivirine	RPV	0	+/-	0	95
etravirine	ETR				
indinavir	IDV	+/-		+	22
ritonavir	RTV	+/-		+	22
lopinavir/ritonavir	LPV/r	+/-		+	22
atazanavir/ritonavir	ATV/r	0	+	++	6, 7, 22
darunavir/ritonavir	DRV/r	0	+	++	6, 22
maraviroc	MVC				
raltegravir	RAL	0	+	++	6, 8, 11, 14, 15, 16
dolutegravir	DTG	0	+ (+?)	++ (+?)	10, 11, 14, 16, 64
elvitegravir/cobicistat	EVG/COBI	0	+	+	11, 16

0: absence of an effect, empty cases when no information is available.

Table 2: effects of the most prescribed different ART molecules on lipid and glucose metabolism

Name of ART	Abbreviation	TC	LDL	HDL	TG	HOMA-IR	diabetes	references
stavudine	D4T	++	++		++	++	++	22, 43, 52, 67, 70, 71
zidovudine	ZDV, AZT	+	+		++	++	++	22, 43, 52, 67, 70, 71
didanosine	DDI					+	++	22, 70, 71
lamivudine	3TC	0	0	0	0	0		22, 43, 52, 70
abacavir	ABC	+	+		+	0		22, 43, 52
tenofovir	TDF	-	-	-	-	0	- -	22, 43, 48, 49, 50, 70, 71
emtricitabine	FTC	0	0	0		0	-/0	48, 52, 70, 71
tenofovir alafenamide	TAF	0	0	0		0		49, 50
efavirenz	EFV	++	++	+	++	+	+	22, 43, 52, 70, 94, 95, 96
nevirapine	NPV	+	+	++		0	-	22, 43, 70, 97
rilpivirine	RPV	+/-	+/-	+/-	+			95
etravirine	ETR	+/-	+/-	+/-	+			15, 96
indinavir	IDV	+	+		+	+++	++	22, 67, 70
ritonavir	RTV	+	+	-	++	++	+	22, 51, 66, 70
lopinavir/ritonavir	LPV/r	++	++	-	+++	++		22, 43, 52
atazanavir/ritonavir	ATV/r	+/-	+/-	+/-	0	+/-	+	22, 43,

								52, 58, 70, 97
darunavir/ritonavir	DRV/r	+	+	-	+	+/-		22, 43, 52, 58, 94
maraviroc	MVC	0	0	0	0	0		22, 43
raltegravir	RAL	0	0	0	0	+/-	+/-	15, 22, 41, 43, 58, 65, 94
dolutegravir	DTG	0	0	0	0	+/-		94
elvitegravir/cobicistat	EVG/COBI	0	0	0	0			97

0: absence of an effect, empty cases when no information is available.

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