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The pharmacological management of cardiovascular disease in people living with HIV (PLWH)

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Summary

Introduction: Cardiovascular disease (CVD) continues to be an essential cause of morbidity and mortality among people living with human immunodeficiency virus infection (PLWH). Since the bulk of cardiovascular risk (CVR) factors are shared between PLWH and the general population, prevention and treatment strategies are similar. However, there are CVR factors particular to PLWH, which need separate consideration. These factors are those HIV-dependent, those related to HIV-derived consequences, and combination antiretroviral therapy (cART)-dependent.

Areas covered: In this review, the authors discuss the management of CVD in PLWH, with a special interest in pharmacological treatment and drug-drug interactions with cART.

Expert opinion: In recent years, we have witnessed a decreased CVD morbidity and mortality in PLWH, which probably reflects an improvement in the management of CVR factors and CVD in these patients, partially thanks to new developments in antiretroviral therapy. Therefore, although there is still room for improvement, at present, the old desideratum of equalling PLWH and the general population in terms of CVD incidence and prognosis is a little closer.

Key words: people living with HIV, cardiovascular risk, cardiovascular disease, arterial hypertension, dyslipidaemia, triglycerides, colesterol, statins, diabetes mellitus, obesity, drug-drug interactions

1. Introduction

Since the beginning of combination antiretroviral therapy (cART), HIV-associated morbidity and mortality have drastically decreased among people living with HIV (PLWH). cART-associated immune reconstitution led to a dramatic decrease in opportunistic infections. At the same time, there has been a morbidity and mortality shift to age-associated comorbidities. Among them, at present, cardiovascular events are a significant cause of morbidity and are among the leading causes of death in PLWH [1]. There is overwhelming evidence that PLWHare at increased risk of cardiovascular events [2]. The assessment of cardiovascular risk (CVR) factors and their management is currently a crucial part of the care of PLWH. Strategies to reduce CVR include controlling HIV replication through cART and the identification and control of traditional CVR factors, such as smoking, arterial hypertension, diabetes mellitus, dyslipidaemia, and obesity [3].

2. Evaluation of cardiovascular risk

There are several models to estimate CVR. The most frequently used are the Framingham risk score, the American Heart Association / American College of Cardiology (AHA/ACC) Pooled Cohort Equations CV Risk Calculator (PCE), the SCORE (Systematic Coronary Risk Evaluation) and the Data Collection on the Adverse Effects of Anti-HIV Drugs (D:A:D) cohort risk calculator. In Europe, and particularly in the Mediterranean area, a local adaptation of SCORE called REGICOR is often used [3]. However, in PLWH, the usefulness of these calculators is not optimal. For example, the Framingham equation does not appropriately estimate the PLWH-associated CVR [4]. The D:A:D study collected prospective information from more than 32000 PLWH that did not have cardiovascular disease (CVD) at baseline. That prediction model evaluates the classic variables, such as age, gender, systolic blood pressure, smoking status, family history, diabetes, total cholesterol, together with HIV-specific variables suchlike, CD4 lymphocyte count, cumulative exposure to protease and nucleoside reverse transcriptase inhibitors, and current use of abacavir [5].

3. Primary prevention of cardiovascular disease

3.1 Arterial hypertension

3.1.1. Prevalence

Arterial hypertension has an estimated prevalence of 25% in PLWH according to a 2017 meta-analysis; it would increase to 34.7% in patients on cART and decreases to 12% in naïve patients, concluding that arterial hypertension among PLWH is associated with receiving cART, and increases with age, as in the general population. According to the Veterans Aging Cohort Study Virtual Cohort (VACS-VC), 32.8% of PLWH have had arterial hypertension, which iss uncontrolled in 25.4%, suggesting that the control of this pathology is suboptimal [6, 7].

3.1.2. Monitoring

The World Health Organization establishes as desirable the measurement of blood pressure (BP) at cART initiation. It also recommends routine BP monitoring without specifying the periodicity [8]. The European AIDS Clinical Society (EACS) recommends estimating CVD risk using the Framingham equation, or any other recommended scoring system and

repeating it annually [9]. The British HIV Association also recommends annual screening for hypertension, diabetes, dyslipidaemia, and chronic kidney disease in patients at increased CVD [10]. In Spain, the AIDS study group (GeSIDA) recommends the BP measurement at the first visit and annually after that if it is reasonable, increasing the periodicity in case of concurrence with other CVR factors [3]. Ambulatory blood pressure monitoring might help differentiate true arterial hypertension from isolated office hypertension [11].

3.1.3. Pharmacotherapy

The BP therapeutic target is systolic blood pressure (SBP) lower than 130 mm Hg and a diastolic blood pressure (DBP) lower than 80 mm Hg. The first recommendation should be lifestyle changes. Drug treatment should start when, after several months of lifestyle changes, the SBP is higher than 140 mmHg, or DBP is higher than 90 mmHg, especially when the 10-year CVR exceeds 10% **(Figure 1).** In patients under 55 years, the recommended starting drugs are angiotensin-converting enzyme (ACEi) inhibitors (e.g., lisinopril, ramipril, or perindopril) or angiotensin receptor blockers (ARB) (e.g., losartan, candesartan). In older or black people, the recommended starting antihypertensive is calcium channel blockers (e.g., amlodipine). If the target is not reached in 4-6 weeks, most guidelines suggest combining ACEi (or ARB) and calcium channel blockers. Whenever, despite all of the above, BP is not under control, the recommendation is to add a third drug (thiazide-type diuretic). If BP persists higher than the target, adding spironolactone (12.5 to 50 mg) is an option. It is also possible to use alpha or beta-blockers, but it would be convenient to refer to the specialist [7]. The European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) point out that combining two classes of antihypertensive drugs enhances BP reduction much more than increasing one agent's dose. ESH and ESC also prefer a single daily dose since it favours adherence and proper therapeutic compliance [12].

3.1.4. Drug-drug interactions (DDI)

Whenever starting an antihypertensive treatment, it is essential to assess the possible drug-drug interactions (DDI) with antiretroviral drugs. ACi and spironolactone have no DDI with antiretroviral drugs. ARB has few DDI; ritonavir- or cobicistat-boosted atazanavir (ATV) or darunavir (DRV) can increase concentration of valsartan due to inhibition of OATP1B1 and MRP2. Therefore, carefully monitoring BP is advisable, and decreasing the valsartan dose may be necessary when coadministered with boosted protease inhibitors. The only calcium channel blocker that can be administered, with caution, in patients with boosted ATV or DRV, is amlodipine. This drug is metabolized by CYP3A4, which is inhibited by ritonavir and cobicistat, with the consequent increase in blood amlodipine levels. The recommendation is to reduce amlodipine dose and monitor ECG, because both ATV and calcium channel blockers may lengthen the P-R interval [3, 13-16]. Diuretics are safe drugs except for indapamide. CYP P450 extensively metabolizes it, and thus, boosted ATV or DRV can potentially increase indapamide concentrations. Careful monitoring of clinical effect and tapping its dose could be needed. Efavirenz (EFV), etravirine (ETR), and nevirapine (NVP) can decrease indapamide concentrations [13].

3.2. Diabetes mellitus (DM)

PLWH on cART have a higher risk of developing insulin resistance and diabetes mellitus (DM) than uninfected patients, its prevalence ranging from 5% to 20% [17-20]. The estimated incidence is 5.72 cases per 100 per year, and in the follow-up of 3.12 cases per 1000 patients. Recent studies have reported an increase in type 2 DM prevalence over the past years despite improvement in cART safety [21].

There are risk factors associated with HIV infection in DM pathogenesis, such as inflammation (increased proinflammatory cytokines and free fatty acids), degree of immunosuppression, chronic infections, and cART. An independent factor in developing insulin resistance and type 2 DM (T2D) is the hepatitis C virus (HCV) co-infection due to a bidirectional interrelationship [18]. T2D favours steatosis and liver fibrosis, leading to an increase in intrahepatic tumor necrosis factor-alpha (TNF-α), whereas HCV infection causes insulin resistance, diabetes progression, and worse metabolic control [22]. Several studies show that PLWH coinfected with HCV and older than 40 years are three times more likely to develop type 2 DM than those without HCV infection [23]. Some studies found that tuberculosis was associated with an increased risk of T2D, although it could be a reversible cause of glucose intolerance [24]. Besides, other related factors are operating in PLWH, such as using different medications, like atypical antipsychotics, corticosteroids, opiates, low testosterone levels, and growth hormone resistance [25].

An essential factor is protease inhibitors (PI), and some nucleoside analogue reverse transcriptase inhibitors (NRTI). As seen in the Danish HIV cohort, patients treated with first-generation PI had an increased risk of developing T2D [26]. PI increases insulin resistance and reduces insulin secretion, as they block the GLUT-4 glucose transporter [27]. Several studies have shown that exposure to NRTI increases the risk of T2D [28, 29]. Above all, zidovudine and stavudine which associate with mitochondrial toxicity. Furthermore, cART- associated lipodystrophy increases inflammatory cytokines, such as TNF-a, contributing to insulin resistance. Furthermore, first-year antiretroviral treatment weight gain associates with a higher incidence of type 2 DM [21].

3.2.1. Diagnosis of DM

The diagnosis of DM in PLWH is similar compared to the general population and determined by repeated fasting blood glucose ≥ 7 mmol/l (126 mg/dl), oral glucose tolerance test (OGTT) at 2 h of ≥11.1 mmol/l (200 mg/dl), or glycosylated haemoglobin (HbA1c) ≥ 6.5% (≥48 mmol/L) [9]. A higher mean corpuscular volume or NRTI (such as abacavir) and a lower CD4 count may underestimate the measurement of HbA1c [30]. In turn, falsely high values associate with iron supplementation, vitamin C and E, and older age (age > 70: HbA1c + 0.4%). Therefore, the Infectious Diseases Society of America guidelines recommend the HbA1c cut-off point of 5.8% [31]. Assessment of glucose homeostasis is advisable at the beginning, 3-6 months post-change, and every 6-12 months in stable antiretroviral treatment. Assessment should include fasting blood glucose and or HbA1c levels, but tests may be deferred to every three years in patients under 45 years without CVR factors [31].

3.2.2. Pharmacotherapy

The objective of metabolic control is similar in PLWH and uninfected population, with HbA1c values ≤7%. Age, life expectancy, comorbidities, risk of hypoglycaemia, and costs are factors to individualize treatment [32]. The strategies for glycaemic control in PLWH with

diabetes are generally the same as in the general population, with some considerations. Lifestyle changes are the starting point. If these are insufficient, treatment with metformin is started at doses 500-850 mg QD, increasing to the maximum tolerated dose (2-3g/day) for 4-6 weeks. If the objective is still unreached yet (HbA1c > 6.5-7%), another drug must be added, such as a sulfonylurea, a thiazolidinedione, a Dipeptidyl peptidase 4 (DPP-4) inhibitor, an sodium-glucose co-transporter 2 (SGLT-2) inhibitor, Glucagon-like peptide 1 (GLP-1) agonist, or insulin. Whenever the patients need triple therapy or insulin, it is advisable to refer them to the endocrinologist [29].

Metformin is the first-line drug for type 2 DM which can reach a decrease of up to 1% in HbA1c. It is safe and effective and does not produce hypoglycaemia when given alone. It does not increase weight, and in PLWH favours the decrease of visceral fat [30]. Additionally, metformin has an independent CVD risk reduction benefit [33]. The most frequent side effects are gastrointestinal, such as nausea or diarrhoea. It should be avoided in patients with marked lipoatrophy as it may further decrease subcutaneous fat. Since dolutegravir (DTG) increases the area under the curve of metformin dose titration is advisable. Metformin can cause lactic acidosis. In cobicistat-treated patients, metformin dose adjustment is mandatory [34]. Mild to moderate renal impairment also conveys metformin dose adjustment too.

Sulfonylureas have a long track record of safety and efficacy, with an expected decrease of up to 1% in HbA1c. They increase weight and cause hypoglycemia. They are indicated in non-obese patients with severe hyperglycemia. There are no interaction studies with cART [35].

Thiazolidinediones offer an expected reduction of HbA1c of 1%. Pioglitazone has the benefit of reducing CVR since it increases HDL cholesterol and lowers triglycerides and liver fat levels. The disadvantages of using thiazolidinediones in PLWH are the possible increase in fracture risk in postmenopausal women, bladder cancer, and heart failure [36].

Incretins are a good option given their safety profile, and the few DDI expected with antiretroviral drugs, but there are no studies on PLWH. The different groups of incretins mimetics are: 1) GLP-1 agonists encompass liraglutide and exenatide. They have an injectable administration route. The advantages are a 1% reduction in HbA1c, weight loss, and that they do not cause hypoglycemia. Liraglutide reduces CVD mortality. The main side effect is gastrointestinal symptoms [30]. 2) DPP-4 inhibitors include linagliptin, saxagliptin, sitagliptin, and vildagliptin. They have fewer gastrointestinal side effects, and they do not increase body weight. Saxagliptin dose needs reduction if coadministered with boosted antiretrovirals [34].

Gliflozins are SGLT-2 inhibitors and include dapagliflozin, canagliflozin, and empagliflozin.Their advantages include weight loss, decrease in blood pressure, and they do not cause hypoglycaemia. Empagliflozin decreases CVD mortality in PLWH [37]. The most significant disadvantage is the risk of urinary and genital tract infections, around 5-10%, due to glycosuria [38]. There are no DDI described for dapagliflozin. Canagliflozin levels may increase when coadministered with ritonavir [34].

Insulin in PLWH has the same indications as in uninfected population, which are severe hyperglycaemia uncontrolled with oral antidiabetics or type 1 DM. Insulin does not interact with cART and reduces inflammation markers such as TNF-α. It does, however, increases body weight gain [35].

The choice of antidiabetic treatment should be made individually and considering other comorbidities. Antidiabetic treatment's efficacy is the same in PLWH compared with the uninfected population, including a worse response in Hispanics and African Americans [39].

3.3. Dyslipidaemia

3.3.1. Prevalence

Lipid abnormalities are common in PLWH treated with cART [40]. Untreated HIV infection increases CVR in a magnitude similar to or superior to other traditional risk factors [41]. This increase is likely due to inflammation, immune activation secondary to HIV infection, and increased insulin resistance [7, 42]. Besides, cART can induce the appearance of dyslipidaemia, particularly older medicines like first-generation PI. Moreover, due to DDI with cART components, lipid-lowering therapy becomes more difficult. The most frequently observed pattern in patients on cART is atherogenic dyslipidaemia characterized by low high-density lipoprotein cholesterol (HDLc), increased triglycerides (TG), and variable elevations of total cholesterol (TC), and low-density lipoprotein cholesterol (LDLc) [43, 44]. Heightened inflammation, highly atherogenic lipoproteins, and perhaps residual HIV replication contribute to atherosclerosis in PLWH, outlined by a high prevalence of vulnerable, rupture-prone coronary plaques [45, 46]. Expert groups recommend screening for dyslipidaemia at baseline, before initiating cART, within one to three months from starting a new regime, and every 6 to 12 months thereafter [30, 47].

3.3.2. Pharmacotherapy

Prevention strategies must include a strong focus on lifestyle optimization (improvements in diet, physical activity, and avoidance of tobacco use and exposure to second-hand smoke) to minimize future cardiovascular events. The approach to screen lipid abnormalities in PLWH is similar to that for the general population [42]. Statins continue to be the first-line therapy option, in terms of both safety and cost-effectiveness [43, 48]. However, the current guidelines for using these drugs in the general population are dissimilar, with substantial differences between American and European guidelines [46].

The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemia and statins for CVD prevention suggest evaluating the total subject CVR by using European SCORE tables and identifying the LDLc target for each level of risk. Then, calculate the percentage of required LDLc reduction to achieve that goal, and choose a statin that can provide this reduction. If the goal is not achieved with the maximum tolerable statin dose, combination with ezetimibe is recommended, and in those at "very high risk", the use of a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9) should be considered **(Table 1)**.

The American College of Cardiology/American Heart Association (ACC/AHA) [49] identify four statin benefit groups in which the potential for an ASCVD risk-reduction benefit exceeds the potential for adverse effects. These are: 1) individuals with clinical ASCVD; 2) individuals with primary elevations of LDLc ≥ 190 mg/ dL; 3) individuals aged 40-75 years with DM and LDLc 70–189 mg/dL; and 4) individuals without clinical ASCVD or DM who are 40-75 years of age with LDLc 70–189 mg/dL, and an estimated 10-year ASCVD risk of 7.5% or higher. In the latest guidelines, they consider a wide range of factors called "risk enhancers," including HIV.

This means that prescribers could consider initiating statin therapy for PLWH of the group four but with a risk score of 5%-7.5%.Guidelines suggest choosing the appropriate intensity of statin therapy to reduce CVD risk. A daily high-intensity statin therapy daily lowers LDLc by ≥ 50% on average. Moderate-intensity statin therapy lowers LDLc by 30%-50%, whereas low-intensity statin therapy lowers LDLc on average by < 30% **(Table 2).** The Expert Panel was unable to find evidence to support the continued use of specific LDLc and non-HDLc treatment targets. This guideline recommends using the new Pooled Cohort Equations (PCE) to estimate 10-year ASCVD risk **(Table 2)**. The treatment algorithm of dyslipidaemia in PLWH on cART is shown in **Figure 2.**

3.3.3. Hypertriglyceridaemia

Patients with TG levels > 5.4 mmol/l (≥ 500 mg/dl) are candidates for treatment with statins and omega-3 fatty acids and fibrates. Following EACS guidelines, statin treatment is recommended as the first-choice drug to reduce CVD risk in "high-risk" individuals with hypertriglyceridemia. In high-risk patients with TG levels > 2.3 mmol/l (> 200 mg/dl), the recommendation is treatment with fenofibrate combined with statins. In high-risk (or above) patients with TG levels from 1.5-5.6 mmol/l (135-499 mg/dl) despite statin treatment, n-3 omega-3 fatty acids (eicosapentaenoic ethyl 2-2 g/day) may be used in combination with a statin [50, 51].

3.3.4. Drugs for the treatment of dyslipidaemia

Statins reduce the liver cholesterol synthesis by competitively inhibiting the enzyme β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase rate-limiting step in cholesterol biosynthesis. Through their HMG-CoA reductase inhibitor activity, statins have pleiotropic immunomodulatory properties that contribute to their benefit in atherosclerosis beyond their lipid lowering effect [52].

Fibrates are agonists of peroxisome proliferator-activated receptors (PPAR), acting via transcription factors regulating lipid and lipoprotein metabolism. Consequently, fibrates are effective in lowering fasting TG levels [46].

Ezetimibe reduces the intestinal absorption of cholesterol. Its use is indicated in combination with statins in PLWH, which do not reach LDLc goals [9,46].

Omega 3 fatty acids are indicated in the treatment of severe hypertriglyceridaemia, with the risk of acute pancreatitis (TG> 900 mg/dL) in which the fibrates did not achieve the goal or are not tolerated. VLDL concentrations, serum lipids, and lipoproteins are decreased by n-3 fatty acids (2-4 g/day). The underlying mechanism is poorly understood, although it may be related, at least in part, to their ability to interact with PPAR and to decrease Apo B secretion [46].

Proprotein convertase subtilisin/Kexin type 9 (PCSK9). Alirocumab and evolocumab are fully human IgG1 monoclonal antibodies that bind with high affinity and specificity to PCSK9. PCSK9 binds to the hepatocyte LDLc receptor stimulating its degradation. The inhibition of PCSK9 increases the number of available LDLc receptors, allowing marked reductions in LDLc. They are currently indicated only in patients with familial hypercholesterolemia. However, they can be used in patients with established CVD who do not reach an LDLc < 100 mg/dl despite high statin doses, or when these are not tolerated or contraindicated [53, 54].

3.3.5. Drug-Drug Interactions

DDI are practically unavoidable in PLWH with comorbid conditions because of the life-long duration of cART. Thus, carefully checking for the potential DDI and the current guidelines for the use of antiretrovirals is mandatory. PI and non-nucleoside transcriptase inverse inhibitors (NNRTI) are metabolized by or affect the function of various cytochrome P450 (CYP) isoforms [29]. DDI of statins with other drugs are mainly due to alteration of their metabolism at the CYP450 enzyme system level, at their hepatic glucuronidation pathway, or at the transporters responsible for their tissue distribution. In patients treated with ritonavir-boosted PI, simvastatin is contraindicated. Atorvastatin and rosuvastatin should be started at low dose, whereas rosuvastatin should be started at low dose also in patients treated with NNRTI. Rosuvastatin and atorvastatin are preferred because there is evidence of their efficacy and safety in PLWH. Pitavastatin has no morbidity and mortality trial data to support its use but may have advantages of fewer DDI, higher HDL increase, and less effect on glucose homeostasis [55]. Fibrates are metabolized by glucuronidation with renal elimination. The combination of statins and fibrates is limited by the possibility of DDI, which mostly result in myopathy [56]. Potential DDI between antiretrovirals and lipid-lowering drugs and their main adverse effects [13] are described in **Table 3**.

3.4. Hyperuricaemia

The presence of elevated serum uric acid levels defines hyperuricemia. Two-thirds of the patients are asymptomatic and will not develop clinical manifestations such as gout or uric acid kidney disease [57]. Asymptomatic hyperuricaemia is a CVR factor in PLWH and the general population [58]. Therefore, values higher than 8 mg/dL (480 umol/l) need treatment. The prevalence of hyperuricaemia can be up to 42% in PLWH [59, 60], the annual incidence of gout being 0.5-2%, higher than the general population [61, 62]. The predisposing factors are the same as in the general population. HIV-specific factors contribute to hyperuricaemia, such as HIV infection itself and some antiretrovirals, such as didanosine and stavudine [63].

The management of asymptomatic hyperuricaemia should start with lifestyle measures. No studies endorse the pharmacological treatment of asymptomatic hyperuricaemia. If the patient presents symptoms or other comorbidities, the same treatment as in the general population applies [64]. The first-line treatment is allopurinol, presenting no DDI with new antiretrovirals. The most critical DDI occurs between colchicine and boosted antiretroviral drugs [13].

3.5. Overweight / Obesity

The proportion of overweight (BMI between 25–29.9 kg/m^2) and obesity (BMI > 30 kg/m^2) in the general population has increased in recent decades. There is also an increased prevalence of overweight and obesity in PLWH [65]. Risk factors are multifactorial, but the best known are older age, sedentary lifestyle, excess intake of paltry quality calories, and excess alcohol consumption. PLWH have a higher risk of abdominal obesity than the general population, which was notably intense with older age and low CD4 nadir [66, 67]. Obesity and visceral adiposity predispose to non-AIDS comorbidities, including CVD and liver disease, which are now among the leading causes of death in PLWH [68]. In recent years, some

studies have associated excess weight gain with specific cART. In the ADVANCE study [69], performed in Africa, the weight gain with DTG-containing regimens, especially in combination with tenofovir alafenamide (TAF), was significantly higher than with the EFV-based regime.

Initial treatment involves lifestyle changes, hygienic-dietary measures, exercise, and treatment of comorbidities. Currently, there are no data to support the need to change the cART regime. Drugs approved to treat obesity include orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion, and liraglutide. Only an endocrinologist or obesity expert can prescribe them. All of them may have adverse effects and potential DDI with antiretrovirals. Orlistat reduces dietary fat absorption and may affect antiretroviral absorption, especially lipophilic drugs. Persons with a BMI ≥ of 40 kg/m^2 or ≥ 35 kg/m^2 with obesity-related comorbidities or refractory to severe attempts at lifestyle changes are candidates for bariatric surgery. A multidisciplinary, specialist-led obesity programme should coordinate the joint efforts. Treatment monitoring after bariatric surgery and drug dose adjustment are warranted [9].

3.6. Canakinumab

The CANTOS study, a randomized, double-blinded trial of canakinumab for IL-1β inhibition in patients with a history of myocardial infarction and an elevated level of high-sensitivity C-reactive protein, showed a reduction of recurrent cardiovascular events compared with placebo, without decreasing the lipid levels [70]. Hsue et al. [71] conducted a small study to assess whether canakinumab reduced immune activation and inflammation of the atherosclerotic plaque in PLWH over 40 years with established CVD and at least one risk factor. In addition to the classic blood parameters, they used fluorodeoxyglucose-positron-emission tomography/computed tomography (FDG-PET/CT) to assess bone marrow activity and arterial inflammation. During a 12-week follow-up, they observed no change in CD4 T-cell count and HIV RNA levels, but a significant decrease in inflammatory biomarkers.

4. Acute cardiovascular disease

4.1. Acute coronary syndromes (ACS)

There is a high prevalence of coronary heart disease among PLWH, in part due to increased life expectancy and access to cART, but also to a high prevalence of traditional CVR factors (smoking, diabetes, hypertension, hyperlipidemia). HIV infection itself also causes microbial translocation and immune activation, which leads to an increase in cytokines and coagulation factors (D-dimers, fibrinogen, Factor VII, tissue factor, von Willebrand factor), together with platelet activation; which results in inflammation, coagulation disorders and the consequent atherosclerosis. On the other hand, it is known that cART can be the cause of dyslipidaemia, insulin resistance, hypertension and endothelial dysfunction [72].

In addition to coronary obstruction, coronary microvascular dysfunction plays a fundamental role in myocardial ischemia. When this dysfunction occurs, it is not possible to satisfy the metabolic demand of the myocardium due to an alteration in the regulatory mechanisms of coronary blood flow. One of these regulatory mechanisms are ion channels. Changes in coronary ion channels expression or activity (due, for example, to arterial

hypertension, dyslipidemia or diabetes mellitus) can lead to changes in vascular tone, hypoxia and tissue death [73].

The treatment and prevention of ACS in PLWH are based on general population guidelines but with attention to DDI for example, between clopidogrel or prasugrel and boosted PI [74]. The algorithm for revascularization therapy is also the same as in the general population; percutaneous coronary intervention is a safe and effective option. However, some studies associate an increased risk of recurrence and new revascularization in PLWH [75]. Despite all this, in long-term studies, no increase in the cardiovascular death rate was observed [74, 76].

4.2. Peripheral arteriopathy

Peripheral arterial disease (PAD) is a useful marker of systemic atherosclerosis and a powerful predictor of cardiovascular morbidity and mortality [77]. Multiple studies [78-80] have related the presence of PAD with HIV through different diagnostic methods; however, there are controversies about its prevalence in PLWH. PLWH are at increased risk of subclinical atherosclerosis in association with classical CVR factors [81], besides the negative impact of individual cART on lipid metabolism and the direct effect of HIV on the arterial wall [77]. The data collected suggest that a sustained low CD4 count (< 200 cells/mm^3), obesity, and advanced age, are independent risk factors for PAD in PLWH [82-84]. The prevalence of asymptomatic PAD in cohorts of relatively young PLWH is superimposable to that observed in the uninfected middle-aged adult population [85, 86].

The clinical manifestations, diagnosis, and management of PAD in PLWH are the same as in the general population [87]. Recognizing that most PAD is due to atherosclerosis, recommendations from the 2016 ACC/AHA and 2017 ESC/ESVS address the same risk factors as in coronary artery disease (CAD) [88, 89]. Both guidelines issue recommendations for smoking cessation, statin therapy, glucose control, and blood pressure management [90, 91]. Although older cART regimens might result in more adverse metabolic effects and might contribute to CVR, early, continuous use of modern cART regimens could help minimize the risk of myocardial infarction by maintaining viral suppression and decreasing immune activation [92].

Antiplatelet therapy with aspirin (range 75-325 mg/day) or clopidogrel alone (75 mg/day) is recommended to reduce myocardial infarction, stroke, and vascular-related death in patients with symptomatic PAD. The European guidelines suggest clopidogrel may be superior to aspirin. The U.S. guidelines state that aspirin or clopidogrel therapy may help reduce cardiovascular events, although the strength of this recommendation relies on an abnormal vs. borderline ankle-brachial index (> 0.90 and ≤ 1.40). The European guidelines recommend avoiding antiplatelet therapy in patients with asymptomatic PAD unless they have another indication, such as CAD. Dual antiplatelet therapy (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization [93]. Anticoagulation is not an indication to reduce the risk of cardiovascular ischemic events in patients with PAD. Vorapaxar, a thrombin receptor antagonist, in combination with antiplatelet therapy, received a recommendation in the U.S. guidelines. Although referenced in the text, the European guidelines do not make

specific recommendations regarding vorapaxar, recognizing some benefit but at the cost of significant bleeding [93]. The use of ACEi or ARB can help reduce the risk of cardiovascular ischemic events in patients with PAD and are the first-line therapy in patients with PADs and hypertension [90]. There is no specific recommendation for PLWH. The U.S. and European guidelines concur that outcomes are similar between endovascular and surgical approaches. Both address factors that may favour an endovascular strategy, including comorbidities and the absence of suitable autologous veins for bypass grafts. Revascularization is a reasonable treatment option for the patient with lifestyle-limiting claudication with an inadequate response to guideline-directed management and therapy [90].

4.3 Stroke

In addition to traditional risk factors, several factors increase the risk of stroke in PLWH, such as a low CD4 count and high viral load [94]. The use of ritonavir-boosted PI is also associated with an increased risk of stroke, even after adjusting for other CVR factors, although these data come from observational studies [95, 96]. As for the treatment and management approach, current recommendations follow the national guidelines in the absence of specific data for PLWH. Management measures include HIV treatment and control of classic CVR factors, such as smoking cessation and lifestyle change [96-99]. Endovascular treatment is the gold standard in acute stroke treatment [100]. Retrospective studies have shown that PLWH are not at increased risk of dying after thrombolysis. Statins and antiplatelet therapy are the pillars of secondary stroke prevention of atherosclerotic ischemic stroke. The LDL goal is < 70 mg/dl. Unfortunately, several studies suggest that statins are underused in PLWH [98].

5. Expert Opinion

The massive implementation of cART in PLWH has caused a relentless shift in HIV-associated diseases from AIDS-defining conditions to age-associated comorbidities. There is substantial evidence that age-associated comorbidities are more prevalent in PLWH than in age- and sex-matched uninfected people. On the other hand, data regarding its premature occurrence in PLWH are not entirely convincing. Among the most prevalent age-associated comorbidities in PLWH, CVD has a substantial impact on PLWH-associated morbidity and mortality.

Rational management of CVR makes knowledge of the factors which increase that risk imperative. Factors involved in CVD pathogenesis in PLWH can be divided between those shared with the general population and represented by traditional CVR factors such as host- and environment-dependent factors, and non-modifiable ones such as the individual genetic background. However, there are CVR factors specific for PLWH, those which are HIV-dependent, including the consequences thereof, such as chronic inflammation and immune activation, and those related to lifelong exposure to antiretroviral drugs.

CVR estimation in PLWH is still an unresolved issue. Its assessment in the general population through estimation scores often does not accurately predict CVR in PLWH. Inaccuracy is most likely is due to the weight of HIV-associated factors, which are not usually reckoned by general population-derived scores. Consequently, specific scores for PLWH have

been developed, such as the D:A:D cardiovascular risk score, which is not very often used in clinical practice. Such controversy made several experts suggest the routine use of image techniques to accurately assess CVR in PLWH.

Primary and secondary CVD prevention and acute CVD management in PLWH are no different from those of the general population management. However, some singularities of PLWH derived from the excess CVR conferred by untreated HIV infection itself, associated inflammation and immune activation, and cART- dependent metabolic disturbances of atherogenic potential may add some distinctive traits. Among these singularities, there is a higher prevalence of traditional CVR factors in PLWH. Nonetheless, lipid-lowering therapy and other drugs used to reduce CVR usually show less than expected efficacy in PLWH, partially due to DDI with antiretroviral drugs and the fear thereof. Besides, HIV physicians, non-expert or untrained in metabolic disturbances management, had to take charge of CVR handling. Therefore, their therapeutic attitude was less aggressive than that of metabolic disease experts. Opportunely, the training has changed in recent years together with more expedite consultation of endocrinologists and metabolic disease specialists.

Nevertheless, the singularities of CVD in PLWH have been relentlessly vanishing. The HIV factor has almost disappeared thanks to early and efficacious cART, which leads to more than 90% undetectability in unselected populations. The development of new antiretrovirals which are easy-to-take, with lower DDI potential and metabolically friendly, has rendered the cART contribution almost anodyne. However, there is a paramount concern related to some antiretroviral drugs' potential impact with an associated excess weight increase and its deleterious consequences in patients treated with them.

For the reasons mentioned above, CVR and CVD management in PLWH has improved in recent times and now closely resembles its management in the general population. This easier and better management has a reflection in cohort data, showing a decreasing incidence of CVD morbidity and mortality in PLWH.

Currently, in terms of CVD management, the most important pending issues are CVR assessment methods and the control of HIV consequences such as chronic inflammation and immune activation. Most probably, it is the improvement in both areas, which will lead to further advances in the management of CVD in PLWH. In John Hunter's words, the mastery over what he called "unhealthy inflammation" (Treatise of the Blood, Inflammation, and Gun-Shot Wounds. London Richardson, 1794) will pave the way to further improvements.

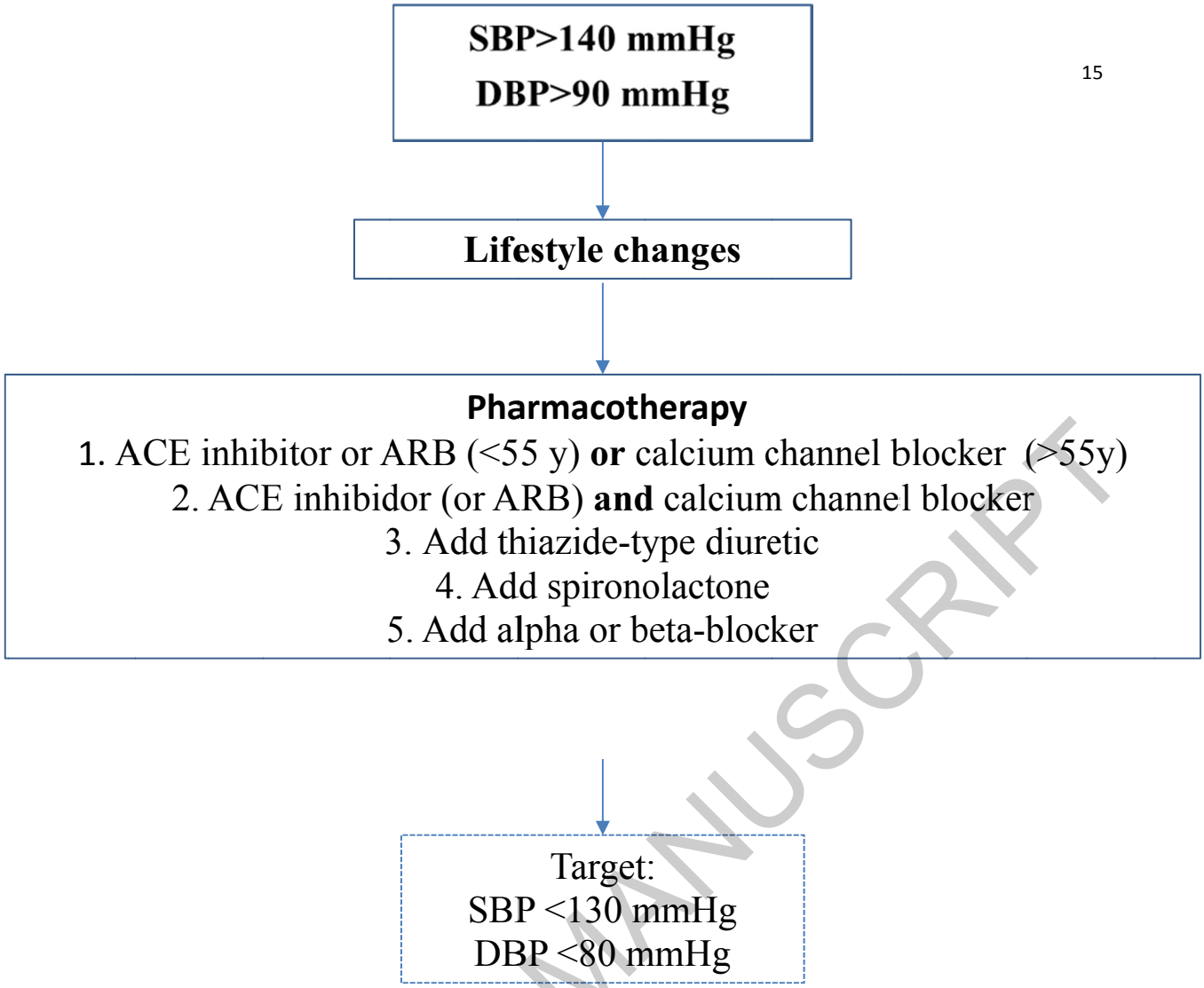

Figure 1. Arterial hypertension: definition, target and management.[9]

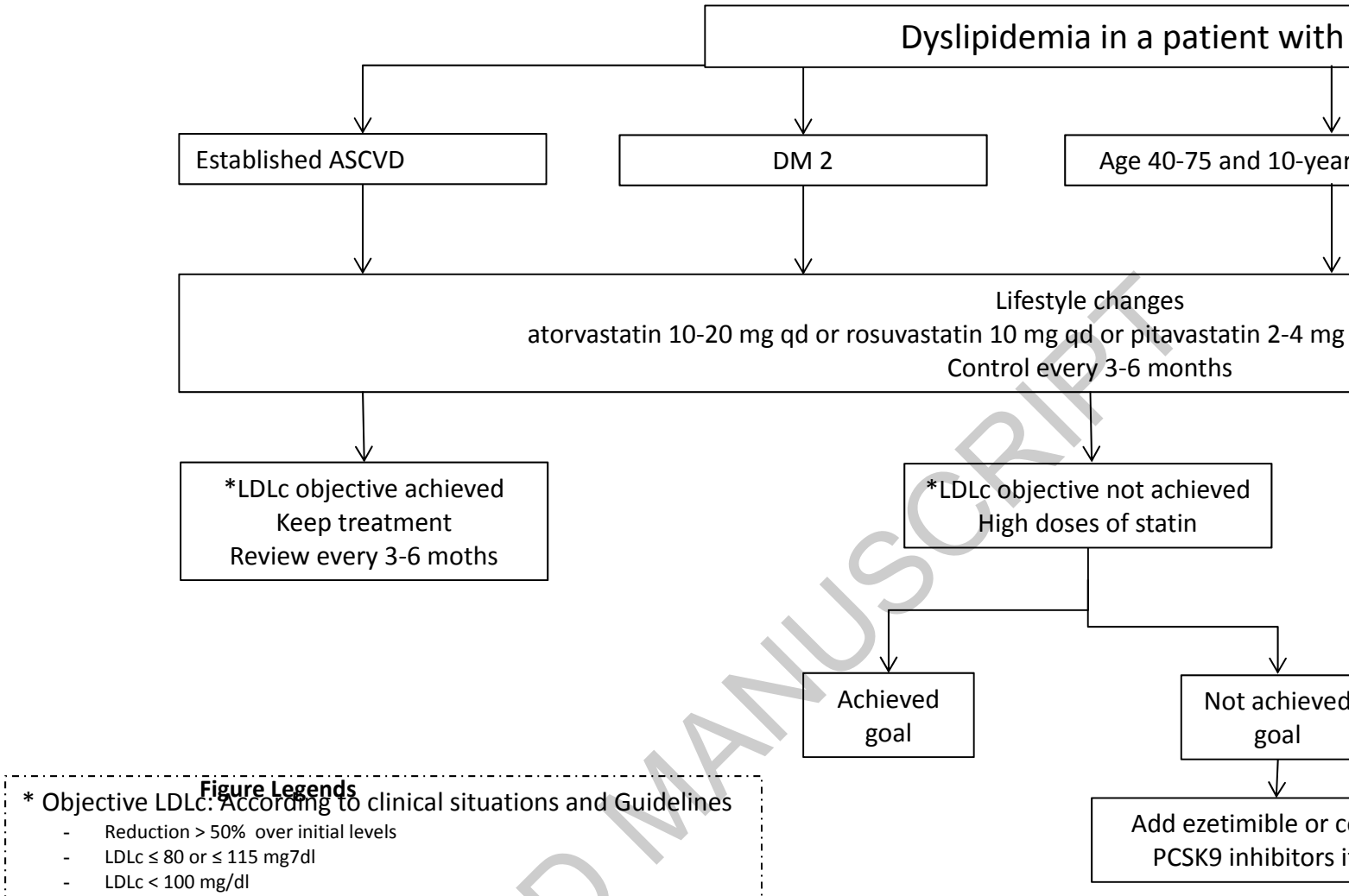

Figure 1. Algorithm for the diagnosis and management of arterial hypertension in people living with HIV (PLWH) [9]

ASCVD = atherosclerotic cardiovascular disease , DM = diabetes mellitus, LDLc = low-density lipoprotein cholesterol , TG

Figure 2. Management of dyslipidemia in people living with HIV on combination antiretroviral therapy (cART) [9][49]

Table 1: Dyslipidaemia treatment strategy in PLWH according to lipoproteins goals and risk level [46]

Risk Level	LDL Goal	Non HDL-C Goal	
Very high			
ASCVD established			High i
T1DM (> 20 years)	LDL < 55 mg/dL (1.4 mmol/L)		
DM with target organ damage	LDLc reduction of ≥ 50% from baseline	< 85 mg/dL (2.2 mmol/L)	PCSK9 in
SCORE > 10%			PCSK9 inhibito
Severe CKD (eGFR < 30 mL/min)			
High			
Markedly elevated single risk factor	LDLc < 70 mg/dL (1.8 mmol/L)		
DM duration ≥ 10 years	LDLc reduction of ≥ 50% from baseline	< 100 mg/dL (2.6 mmol/L)	
Moderate CKD (eGFR 30-59 mL/min)			High i
Moderate	LDL < 100 mg/dL (2.6 mmol/L)		
SCORE 1-5%		< 130 mg/dL (3.4 mmol/L)	M

PLWH: people living with human immunodeficiency virus infection. ASCVD: atherosclerotic cardiovascular disease. CKD: chronic kidney disease. DM: diabetes mellitus. eGFR: estimated glomerular filtration rate. LDLc: low-density lipoprotein cholesterol. HDLc: high-density lipoprotein cholesterol. PCSK9: proprotein convertase subtilisin/kexin type 9. SCORE: Systematic Coronary Risk Estimation. T1DM: type 1 DM.

Table 2: Statin treatment strategy in PLWH according to target groups and ASCVD risk score [49]

Groups	10-year ASCVD risk	Statin therapy
ASCVD established LDLc ≥ 190 mg/dl	Not necessary	High Intensity
Type 1 & 2 DM 40-75 years	≥ 7.5 ≤ 7.5	High intensity Moderate Intensity
Primary prevention and LDLc < 190 mg/dl 40-75 years	≥ 7.5	Moderate Intensity

PLWH: people living with human immunodeficiency virus infection. ASCVD: atherosclerotic cardiovascular disease. LDLc: low density lipoprotein cholesterol. DM: diabetes mellitus.

Table 3: Potential DDI among antiretroviral therapy and lipid-lowering drugs and derived side effects [9][13]

DRUG CLASS	DRUG	ATV	DRV	COBI	RTV	EFV	NVP	ETR	RPV	RAL	DTG	MVC	Side E
Statin	Atorvastatin	↑	↑	↑	↑	↓	↓	↔	↔	↔	↔	↔	Gastroin symp headache, rhabdor (rare), a hepa
	Fluvastatin	↔	↔		↔			↑		↔		↔	
	Pravastatin	↑	↑	↑	↔	↓	↔	↔	↔	↔	↔	↔	
	Rosuvastatin	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	
	Pitavastatin	↑	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	
	Simvastatin	X	X	X	X	↓	↓	↓	↔	↔	↔	↔	
Intestinal cholesterol absorption inhibitor	Ezetimibe	No DDI with cART anticipated											Gastroin symp
PCSK9-inhibitor	Evolucumab	No DDI with cART anticipated											N

ATV: Atazanavir. DRV: Darunavir. COBI: Cobicistat. RTV: Ritonavir. EFV: Efavirenz. NVP: Nevirapine. ETR: Etravirine. RPV: Rilpivirine. RAL: Raltegravir. DTG: Dolutegravir. MVC: Maraviroc. PCSK9: proprotein convertase subtilisin/kexin type 9. DDI: drug-drug interactions. cART: antiretroviral therapy.

Legend

↑ Potential elevated exposure of the non-ARV drug

↓Potential decreased exposure of the non-ARV drug

↔ No significant effect

X These drugs should not be co-administered

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*** Literature review that concludes that HIV should be considered a vascular risk by itself**

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***Interesting review on stroke in PLWH, which includes both a management and pathogenesis section of HIV vasculopathy**

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*** Statement from the American Heart Association that reviews the pathophysiology and management of all items of cardiovascular disease at PLWH.**

Highlight Box

- Management of CVR and CVD in PLWH has improved in recent years.
- Consequently, CVD morbidity and mortality have decreased in recent years
- Assessment of CVR in PLWH is still an unresolved issue, since the score derived from and used in the general population does not accurately work for PLWH
- CVR factor management in PLWH is essentially the same as in the general population
- The particularities of CVR and CVD in PLWH include addressing chronic inflammation and immune activation, potential DDI between cART and drugs for metabolic disturbances, and the metabolic toxicity of cART
- CVD management in PLWH is essentially superimposable to that of uninfected people