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Review

Drug therapies for HIV-related metabolic disorders

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ABSTRACT

Introduction: Human immunodeficiency virus (HIV) has become a chronic disease often associated with dyslipidaemia and insulin resistance. Combination antiretroviral therapy (cART) may contribute to metabolic disturbances, eventually leading to increased cardiovascular disease (CVR) in this population.

Escalating interventions to decrease CVR include promoting a healthy lifestyle, such as quitting smoking, diet and regular exercise. If they do not achieve the goals, a change of cART should be considered, followed by or used concomitantly with the use of chemical therapies.

Areas covered: The aim of this article is to review the available drug therapies for the treatment of metabolic disorders in HIV-infected patients and to examine their safety and effectiveness in this population. A review of the literature was conducted, highlighting the most relevant articles.

Expert opinion: Switching strategies can be useful but its expected benefit is not high. Therefore, chemical intervention is often needed. Statins have been proven to reduce CVR in the general population and in HIV-infected patients. Simvastatin is contraindicated in patients treated with boosted PI due to interactions; atorvastatin is safe at submaximal dose and needs close monitoring, while pravastatin lacks lipid-lowering potency, and rosuvastatin and pitavastatin are safe. Ezetimibe and fibrates are also safe and effective in HIV-infected patients and can be used in combination with statins. The management of glucose homeostatic disorders in HIV-infected patients follows the same guidelines as in the general population. However, there are specific considerations with respect to the interactions of particular medications with cART. When drug therapy is needed, metformin is the first-line drug. Decisions regarding second- and third-line drugs should be carefully individualized.

Keywords: Combination antiretroviral therapy, metabolic complications, cardiovascular risk, statins, fibrates, ezetimibe, metformin

ARTICLE HIGHLIGHTS

- Statins have a higher lipid-lowering potential than antiretroviral drug switching
- Statin use decreases cardiovascular risk in HIV-infected patients
- Rosuvastatin and pitavastatin are the most powerdul statins and have a good safety profile.
- Ezetimibe is an alternative or adjuvant drug for the treatment of hypercholesterolaemia
- Fibrates are safe and useful to control HIV-associated hypertriglyceridemia
- Glucose homoeostatic disorders in HIV-infected patients shold be manages as in the general population
- Potentially harmful interactions may arise when statins are used concomitantly with boosted protease inhibitors

1. Introduction

Combination antiretroviral therapy (cART) has led to a dramatic reduction in HIV-associated morbidity and mortality [1], resulting in older persons living with HIV/AIDS [2]. In this setting, cardiovascular disease has emerged as an important cause of morbidity and mortality in HIV-infected patients [3, 6]. Patients with HIV infection have an increased risk of both metabolic syndrome and cardiovascular diseases (CVDs), not only related to the influence of traditional risk factors, but also to other factors such as chronic inflammation and immune activation [7, 8,11, 12], immunodeficiency and possibly a direct action of certain antiretrovirals, whether or not associated with adipose tissue changes (fat redistribution, lipoatrophy, fat accumulation, or a mixed picture of both), and glucose homeostasis and lipid disorders [10, 13]. Consequently, managing metabolic changes in HIV, and in particular dyslipidaemia and insulin-resistance/diabetes, has become an increasing need for HIV caregivers.

Addressing metabolic disorders in HIV-infected patients is a three-step strategy including 1) lifestyle changes; 2) switching cART; and 3) drug therapies for CVR factors.

Therapeutic strategies and interventions designed to treat metabolic disorders include modification of risk factors, such as hypertension and increased lipid levels, through exercise and smoking cessation, adjustment of cART and addition of medications to treat hypertension, insulin resistance, and hypercholesterolaemia.

The aim of this article is to review the evidence available on the chemical therapies for treating these disorders, and to give recommendations regarding management of this important issue.

2. Switching strategies

Laboratory and clinical experience has shown that cART can induce severe and considerable adverse effects on lipid metabolism. Protease inhibitors (PIs) are the class of ART most commonly associated with the development of dyslipidaemia and, among them, ritonavir is the most representative drug. When combined with lopinavir, it conveys a high risk of CVDs in HIV-1-infected patients. Atazanavir has the least impact on lipid metabolism [14-15], and atazanavir/ritonavir and darunavir/ritonavir did not show significant differences in total cholesterol changes. Within the nucleoside reverse transcriptase analogues (NRTI) class, the effects on lipids are modest [16] . Tenofovir (TDF) is associated with lower elevations of total cholesterol, LDL and triglycerides than abacavir (ABC). TDF has a lipid-lowering effect per se [17].

Among non-nucleoside reverse transcriptase analogues (NNRTIs), nevirapine is associated with a better lipid profile than efavirenz (EFV) [18]. The use of nevirapine reduces the levels of total cholesterol and triglycerides and promotes an increase in HDL and a decrease in atherogenic risk. Integrase inhibitors, such as raltegravir, dolutegravir and elvitegravir, have a neutral lipid profile [17- 18]

When lipid disturbances appear, a strategy that has to be considered is changing specific antiretroviral agents, transitioning from PI-based or EFV-based regimens to a therapy based on an NNRTI (NVP, rilpivirine or etravirine), an integrase inhibitor, or even Atazanavir. However, switching a treatment regimen to improve the lipid profile may not produce the anticipated result because of the multifactorial nature of dyslipidaemia, since, in patients receiving treatment for HIV infection, lipid abnormalities may be caused by HIV itself, by antiretroviral therapy and/or by host factors. Switching should only be done when there are ART options that may result in a more favourable lipid profile and will maintain virologic suppression [19], and this strategy may be complementary to lipid-lowering drugs.

There are limited data comparing the benefits and risks of switching or modifying anti-retroviral therapy compared with lipid-lowering therapy, and all of them show that

switching has a moderate lipid-lowering capacity. A randomized, prospective study [20] in HIV-infected patients who had mixed hyperlipidaemia and who were being treated with their first antiretroviral therapy regimen compared the lipid-lowering effects of switching from a PI to an NNRTI (either nevirapine or EFV) with those of treatment with pravastatin or bezafibrate added to the current unchanged antiretroviral therapy regimen for up to 12 months. Both treatment strategies resulted in reductions in mean TG levels, with statistically significant differences favouring the lipid-lowering. An analysis from the D:A:D cohort [21] compared the effects of lipid-lowering therapy with switching from a PI- to an NNRTI-based antiretroviral regime. The results showed significant reductions in total cholesterol with both lipid-lowering treatments and antiretroviral therapy switching. Intervention with lipid-lowering treatments resulted in greater, although non-significant, mean reductions in total and LDL cholesterol levels, whereas switching to an NNRTI-based antiretroviral therapy resulted in a greater mean reduction in the HDL cholesterol level. Both strategies had similar reductions in serum TG levels and total cholesterol/HDL ratio. A more recent randomized open-label study evaluated the efficacy and safety of rosuvastatin versus boosted PI switching for the treatment of fasting dyslipidaemia in HIV-infected adults with increased CVR [22]. The study concluded that rosuvastatin was superior overall to PI switching in reducing fasting total and LDL cholesterol, with fewer adverse events.

3. Lipid-lowering therapies

3.1 Drugs for hypercholesterolaemia

Compared with uninfected individuals, the pattern observed most frequently in patients on cART is that of atherogenic dyslipidaemia characterized by low HDL cholesterol and high triglycerides, accompanied by varying elevations in total cholesterol and LDL cholesterol [9]. In patients without antiretroviral treatment, a characteristic pattern is usually observed with low CT and HDL cholesterol and elevated TG [9].

Statin therapy is well-established as a cornerstone of primary and secondary prophylaxis of CVDs in the general population, due its ability to decrease LDL cholesterol (LDL-C). Different statins are available, but all differ in their pharmacokinetic properties, drug interaction profiles, and risk of myotoxicity. Potential drug-drug interactions between statins and cART need to be considered when starting lipid-lowering therapy in the HIV population.

The intensity of efforts to prevent CVDs depends on the underlying risk of CVDs; drug treatment should be used by all those with established CVDs and among those with type 2 diabetes or 10-year CVD risk >10 %, irrespective of lipids levels. Statins should be considered in HIV patients with dyslipidaemia to achieve the LDL-c goals as define for high risk subjects. [16]

Target levels are suggested in figure 1, they are to be used as guidance and are not definitive.

The range of expected changes in LDL cholesterol with different statins is shown in table 1.

3.1.1 Simvastatin/Lovastatin: Simvastatin and lovastatin are metabolized by the liver through CYP450-3A , which is intentionally inhibited by boosters in PI-containing regimens, resulting in improved PI pharmacokinetics but also in increased systemic concentrations of these statins [23]. Different studies in HIV-infected patients have shown an increased risk of rhabdomyolysis and toxicity with simvastatin and lovastatin [24]. Therefore, simvastatin and lovastatin should not be given to patients taking boosted protease inhibitors. The toxicity profile of simvastatin when co-administered with non-PI-containing ART regimens is less clear [25].

3.1.2 Atorvastatin: Atorvastatin has been associated with a good therapeutic response and tolerability in different studies in HIV-infected patients on cART [26-28]. As it is metabolized by CYP 3A4, it is generally recommended to start with a low initial dose (10 mg), with further increases to achieve the LDL goal. Caution is needed when combined with fenofibrate [29]. Administration of atorvastatin in certain conditions (concomitant

administration with clarithromycin and lopinavir/ritonavir (LPV/r), or delavirdine) has been associated with an increased risk of rhabdomyolysis [30, 31].

3.1.3 Pravastatin: The effectiveness and safety of pravastatin has been reported in several studies [32], and since it is not metabolized by the CYP 450 system, it has proved to be safe [33]. However, pravastatin is not very potent, and not all patients will reach the target of the guideline lipid levels [34]. The often-needed combination of fenofibrate and pravastatin for HIV-related dyslipidaemia provides substantial improvements in lipid parameters and appears to be safe [34].

3.1.4 Rosuvastatin: Rosuvastatin has a good safety profile when given with PI, since it is not metabolized by CYP 3A4, only 10% of the administered dose is metabolized by CYP 2C9 and it is eliminated through faeces. It has generally been well-tolerated in clinical studies [35] and was found to be effective for the treatment of PI-associated hyperlipidaemia, without significant clinical or laboratory adverse events [36]. A trial that assessed, in HIV-seronegative healthy volunteers, the bioequivalence of rosuvastatin and LPV/r when administered alone and in combination, showed that LDL reduction was attenuated with LPV/r. Rosuvastatin AUC and C_{max} increased unexpectedly by 2.1- and 4.7-fold when co-administered with LPV/r [37]. In another trial, LPV/r levels were not affected by rosuvastatin, but rosuvastatin levels increased by 1.6-fold compared with data from healthy volunteers. Therefore, this combination should be used with caution [38]. Rosuvastatin is more potent than atorvastatin and substantially more potent that pravastatin in lowering LDL in HIV-infected patients [26, 27, 39].

3.1.5 Fluvastatin: Metabolized by CYP2C9 and to a lesser extent by CYP3A4. Fluvastatin has demonstrated a significant reduction in total cholesterol and triglyceride levels and has proved to be well-tolerated [40]. It is recommended as a reasonable alternative to atorvastatin and pravastatin for patients with PI-based cART [41].

3.1.6 Pitavastatin: Pitavastatin has a particularly favourable pharmacokinetic profile, even in the setting of PI co-administration. There is a pharmacokinetic study that showed that concomitant use of pitavastatin and LPV/r was safe and well-tolerated in healthy adult volunteers. A 2014 study, in which HIV-uninfected subjects received pitavastatin 2mg or

4mg followed by either darunavir/ritonavir or EFV, demonstrated no significant interactions between the two antiretrovirals [42]. A randomized, double-blind trial, with 252 HIV-infected patients randomized to pitavastatin 4 mg daily vs. pravastatin 40 mg daily, showed a significantly greater LDL-C reduction with pitavastatin [43]. Given the promising pharmacokinetic profile of pitavastatin in HIV-infected individuals on cART, the REPRIEVE trial (ACTG A5332) – a randomized, double-blind trial of pitavastatin 4 mg versus placebo in 6,500 HIV-infected individuals for primary CVD prevention – is funded and beginning to enrol patients this year.

3.1.7 Ezetimibe: Ezetimibe is a cholesterol absorption inhibitor that impairs dietary and biliary cholesterol absorption at the brush border of the intestine, without affecting the absorption of triglycerides or fat soluble vitamins. It is indicated as an adjunctive therapy to diet and/or statins for the reduction of LDL cholesterol in patients with hypercholesterolaemia. Since ezetimibe does not have any interaction with the CYPA4 metabolizing enzymes, the risk of potential interactions with antiretrovirals is low [44, 45]. Ezetimibe as monotherapy is effective and safe in HIV-associated dyslipidaemia [44-46]. It has been well-tolerated and resulted in a significant decline in LDL cholesterol (> 20% with 10 mg/day of ezetimibe), and also total cholesterol and TG levels, while inducing an increase in HDL concentrations [44, 45, 47]. The combination of statins and ezetimibe has also proven to be an effective and safe lipid-lowering therapy in HIV-infected patients [42, 48, 49], even those with poor response to statins [44, 50].

Ezetimibe has no interaction with cART, including those PI-based regimes. The association of fenofibrate and ezetimibe has shown greater efficacy than pravastatin for the treatment of HIV-associated dyslipidaemia [46, 50, 51].

3.1.8 Niacin: Nicotinic acid is available in several formulations that include immediate-release (crystalline) and sustained-release formulations such as Niacor and Niaspan. Nicotinic acid and nicotinamide are the two common forms of the vitamin most often referred to as niacin. However nicotinamide does not have lipid-lowering properties. Niacin inhibits the hepatic production of very-low-density lipoprotein (VLDL) and consequently its metabolite LDL . On the other hand, it raises HDL cholesterol (HDL-C)

levels by as much as 30-35%, both by reducing lipid transfer of cholesterol from HDL to VLDL and by delaying HDL clearance .

In small studies, niacin use in HIV-infected patients was associated with reductions in total cholesterol and triglycerides [52-54]. Furthermore, niacin was found to be effective and safe, and the increase in glycaemia and insulin resistance observed with its use tended to be transient [53]. Common adverse events include headache, flushing, pruritus, rash, hyperuricaemia, and exacerbation of insulin resistance [52, 55].

3.2 Drugs for hypertriglyceridaemia

Hypertriglyceridaemia remains the most common lipid abnormality among patients who have HIV. The CVD risk implications from higher than normal triglycerides (TG) levels are even less clear, as TG has not consistently been shown to independently predict the risk of CVD [16] . However, patients with very elevated triglyceride levels are at increased risk of pancreatitis, and for such patients one goal of lipid-lowering therapy is to reduce the risk of this entity. Eating fish, reducing calories, saturated fat and alcohol intake reduce triglyceride levels but the clinical benefit of chemical treating of moderate hypertriglyceridaemia is uncertain. According to the European AIDS Clinical Society guidelines the clinical benefit of treating moderate hypertriglyceridaemia is when TG are very high (> 10 mmol/L or > 900 mg/dL) because of the increased risk of pancreatitis.

Since statins have mild or moderate effects on TG, fibrates represent the cornerstone of drug therapy for hypertriglyceridaemia and mixed hyperlipidaemia [47].

However, in HIV-1 patients, fibrates do not have the same efficacy as statins in preventing cardiovascular disease [47].

When treatment of hypertriglyceridaemia is needed, lipid guidelines recommend administration of gemfibrozil or fenofibrate [56, 57] and, between them, fenofibrate has a clear anti-atherogenic profile in patients with hypertriglyceridaemia [58]. Its basic action is to reduce TG, favouring greater VLDL catabolism [19, 59]. Moreover Fenofibrate has become the most commonly prescribed fibrate in HIV-infected patients because drug-drug interactions with antiretrovirals are unlikely and because some data suggested that it improves cardiovascular outcomes [40, 60-63]. It is metabolized by the CYP450 system,

but appears to affect only CYP4A enzymes and has not shown clinically relevant interactions with PIs [47]. Additionally Fenofibrate is safe, well-tolerated, and an effective treatment for hypertriglyceridaemia in HIV-infected patients [62, 64].Gemfibrozil is metabolized in the liver via uridine 5'-diphosphate-glucuronosyl transferase enzymes, which are induced by most PIs. This induction causes a decrease in its plasma concentrations, and this decrease might explain the low efficacy reported with the use of gemfibrozil [19].

Combination fibrate-statin therapy should be used with great caution because of the risk of myopathy [65]. In clinical studies with HIV-uninfected patients, serum levels of statins increase 1.9- to 5.7-fold in gemfibrozil-treated subjects, but are unchanged in fenofibrate-treated subjects [66]. Association of simvastatine and gemfibrozil can be especially harmful because a great increase of statin blood concentration in patients on cART and may be avoided. However in a randomized trial of fenofibrate, there was a low incidence of myopathy, whether or not patients were concomitantly taking a statin [67]. Thus, fenofibrate is the preferred fibrate in patients who require combined therapy with a statin [67]. In many studies, the combination of pravastatin and fenofibrate appears to be safe and effective in improving HIV-associated mixed dyslipidaemia [35, 68]. Similarly, the combination of atorvastatin and gemfibrozil was safe in a small study in HIV-infected subjects . When used in combination with fibrates, pravastatin and fluvastatin may be the preferred statins [69]. The co-administration of fenofibrate and fish oils and niacin is also safe and effective in treating HIV-dyslipidaemia [70, 71]. When fibrates are used, periodic monitoring of serum creatinine, creatine kinase, and transaminases is warranted [40, 72, 73]. The range of expected changes in triglycerides is shown in table 2.

Fish oil: Fish oil contains two medically relevant long-chain polyunsaturated fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), collectively known as omega-3 fatty acids. Fish oil is an attractive supplement because of its desirable anti-inflammatory properties, reduction of cardiovascular atherogenic effects, and lack of drug-drug interactions with antiretroviral therapy. The ability of fish oil to reduce elevated

TG concentrations in HIV-uninfected patients has been observed in different studies in uninfected individuals [74].

Omega-3 fatty acids have been successfully employed to treat hypertriglyceridaemia in HIV-infected individuals (71, 74-76). This ability to reduce TG levels ranges from 25% to 45%, and may have a benefit of atherogenic cardiovascular disease risk reduction through a combination of anti-inflammatory and anti-platelet actions [71, 75, 76, 77]. No interaction has been observed between fish oil and antiretrovirals. For HIV-1 patients, the use of fish oil associated with fenofibrate showed additive effects in reducing TG [71, 75, 76]. Since fish oil has antiplatelet effects, patients concomitantly using drugs that affect bleeding time should be monitored for adverse effects.

3.3 Other potential lipid-lowering drugs

Studies have shown that HIV-infected patients with lipoatrophy have low levels of leptin. Therefore, the use of recombinant methionyl human leptin could be associated with reduced insulin resistance and increased HDL levels [78]. Based on the potential lipid-lowering and immunomodulatory properties of tetradecylthioacetic acid (TTA), some studies [79] suggest that TTA combined with dietary intervention could be an interesting therapeutic approach in HIV-infected patients on cART, potentially resulting in both hypolipidaemic and anti-inflammatory effects. Acipimox, a drug with sustained action and a structure similar to niacin, has been associated with decreased insulin resistance and significantly reduced levels of TG in HIV-1-infected adults [80]. In a double-blind study, the use of cholestin was able to reduce the levels of TC and LDL cholesterol without modifying HDL and TG, and without showing adverse effects [81]. The use of L-carnitine resulted in a significant reduction in serum triglycerides in patients with HIV-associated dyslipidaemia [82].

4. Drugs for glucose homeostatic disorders

Diabetes Mellitus (DM) and HIV infection are independently associated with an increased risk of atherosclerosis. [83] Whether HIV infection is associated with increased DM risk relative to uninfected controls has been debated. In the more recent ART era, HIV seems to be associated with similar to decreased DM incidence compared to controls. [84]

Diabetes is diagnosed by WHO criteria: fasting plasma glucouse (FPG) 7 or more mmol/L or oral glucose tolerance test (OGTT) 2-h value 11 or more mmol/L or HbA1c equal or more than 6'5%. HbA1c values in treated HIV- positive persons, particularly when on Abacavir, tend to underestimate type 2 diabetes.

Treatment goals are prevention of hyper-/hypoglycaemia, glucose control (HbA1c< 6'5-7%) without hypoglycaemia, fasting plasma glucose 4-6 mmol/L and prevention of long-term complications. Target levels are shown in figure 1. If modification of lifestyle measures is insufficient to reach the goals drug therapy should be started. [16]

4.1 Metformin: The first-line medication for diabetes mellitus (DM). It increases insulin sensitivity in peripheral tissues. Advantages of metformin include a 1-2% decline in HbA1c, a long track record of safety and efficacy data, including no hypoglycaemia when given alone, no weight gain, and low cost. It has also demonstrated improvements in insulin sensitivity [85], reduction in visceral fat in HIV-infected individuals [86], and it may provide an independent CVD risk reduction [87]. Adverse effects include gastrointestinal side effects, such as diarrhoea and bloating. Lactic acidosis is a very rare side effect and it is contraindicated in situations associated with an increased risk of lactic acidosis (for instance, when thymidine analogues or didanosine form part of the cART). Metformin may also worsen lipoatrophy [88], and therefore it has to be administered with caution in patients with this condition.

Special attention should be paid when metformin is co-administered with dolutegravir, as it increases metformin concentration by organic cation transporter 2 blockade at renal level.

If patient does not reach the goal after lifestyle modification and metformin, there are several additional options, whether or not combined with metformin, although the data for other antidiabetic drugs in HIV-infected individuals are very limited.

4.2 Sulphonylureas: Sulphonylureas (e.g. glipizide and glyburide) stimulate insulin release from pancreatic β-cells. Advantages of this group of drugs include a 1% HbA1c decrease, a long track record of safety and efficacy data, proven decreases in microvascular events, and relatively low cost. Adverse effects include weight gain (2–4 kg), risk of hypoglycaemia, high failure rate and drug interactions since they are metabolized mainly by CYP2C9, and this isoenzyme may be induced by PI with a resulting decrease in efficacy of the sulphonylurea.

4.3 Thiazolidinediones: Thiazolidinediones (rosiglitazone and pioglitazone) work by improving target cell response to insulin. Their advantages are no hypoglycaemia, a potential independent CVD risk reduction benefit [89], an increase in high-density lipoprotein, a decrease in triglycerides, and a reduction of liver fat [90]. Although this remains uncertain, some studies observed a non-confirmed beneficial effect on lipoatrophy, with improvement in peripheral fat mass [91]. Disadvantages include high cost, weight gain, fluid retention and worsening heart failure, macular oedema, osteoporosis/fracture, and possibly increased risk of bladder cancer [92, 93]. In patients with lipoatrophy and type 2 diabetes mellitus, pioglitazone may be a preferred option. However, the potential benefits needs to be weighed against the possibility of side effects, especially the decrease in bone mineral density and fracture risk, which may be higher in HIV-infected individuals [94]. Rosiglitazone use has been associated with decreased bone formation in HIV-infected patients, but did not alter bone resorption or total bone mineral density in a double-blind placebo-controlled trial [95]. Furthermore, rosiglitazone has been associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular cause [96].

4.4 Incretins: Glucagon-like peptide 1 (GLP-1) regulates glucose homeostasis by decreasing β-cell workload and improving β-cell response. GLP-1 enhances glucose-dependent insulin secretion. GLP-1 also regulates gastric emptying, decreasing insulin

demand, reduces postprandial glucagon secretion, and increases satiety [97]. There are two therapeutic classes available: GLP-1 analogues and dipeptidyl peptidase 4 (DPP-IV) inhibitors.

Currently available GLP-1 analogues include exenatide, liraglutide, and exenatide long-acting release. The benefits of GLP-1 analogues are absence of hypoglycaemia risk, weight loss, and preservation of β-cell mass/function. Their disadvantages include gastrointestinal side effects and high cost. Post-marketing trials are under way to examine possible increased risk of pancreatitis, thyroid cancer, and pancreatic cancer [98]. There are no data for HIV-infected individuals. DPP-IV inhibitors (sitagliptin, saxagliptin, vildagliptin, and linagliptin) have similar advantages to GLP-1 analogues, and disadvantages that include a relatively small reduction in HbA1c (0.5%), gastrointestinal side effects, possible hypersensitivity reaction, and high cost. Although a possible CVD risk reduction benefit with gliptins has been reported, the benefit has not been shown in subsequent studies [99, 100].

Concerns regarding gliptin use in HIV-infected individuals have been raised, since gliptins have molecular targets on immune cells. However, a small study revealed no changes in CD4 or HIV RNA among treated HIV-infected patients taking sitagliptin.

There is a study concluding that sitagliptin has beneficial systemic and adipose anti-inflammatory effects in cART-treated HIV-infected adults with impaired glucose tolerance [101]. Large-scale, long-term studies should determine whether gliptins are able to decrease CVR and events in HIV-infected adults. Saxagliptin interacts with strong cytochrome P450 3A4/5 inhibitors (e.g. ritonavir), and its dose should be reduced when such drugs are used.

4.5 Gliflozins: Sodium-glucose transport protein 2 (SGLT2) inhibitors, such as dapagliflozin and canagliflozin, block the reabsorption of glucose in an insulin-dependent fashion, and glucose is then excreted in the urine. The advantages include weight loss, the lowering of blood pressure, and absence of hypoglycaemia. The disadvantages include consequences of glycosuria (urinary tract infection and genital fungal infections), and potentially increased cardiovascular risk, particularly within the first 30 days of initiating canagliflozin

[102]. No interactions between cART and dapagliflozin are expected. However, if UDP-glucuronosyltransferase enzyme inducers (e.g. ritonavir) are co-administered with canagliflozin, clinicians could consider increasing the dose to 300 mg. There are no studies with HIV-infected patients.

4.6 Meglitinides: Repaglinide and nateglinide are short-acting medications that increase insulin release. They offer the advantages of less risk of hypoglycaemia than sulphonylureas and more flexibility with dosing. However, they are expensive, require frequent dosing, and only have a modest effect on HbA1c. They have not been studied in patients with HIV infection.

4.7 Insulin: Insulin is the preferred second-line medication for patients with HbA1c ≥ 8.5%. The major advantage of insulin is that it can produce significant reductions in HbA1c. However, insulin may cause hypoglycaemia, is associated with weight gain, and the insulin analogues (e.g. glargine or detemir insulin) are costly. Recently, concern was raised about mitogenic effects of long-acting insulin, due to binding with the insulin-like growth factor 1 receptor. However, several large studies showed no effect of long-acting insulin on cancer incidence [103].

Considering all these options, the choice of treatment for diabetes should follow the recommendations in the general population using a two-step model: 1) lifestyle modifications; 2) metformin should be considered as first-line therapy in those without a contraindication, particularly in those with central lipohypertrophy in whom reductions in visceral adipose tissue may be enhanced. In patients with lipoatrophy or non-overwight and type 2 diabetes mellitus, sulfonylureas may be a preferred option, since metformin may exacerbate lipoatrophy. If target is not reached with one drug a combination of 2 agents should be used.

Prediabetes conditions as impaired glucose tolerance (OGTT: 7’8- 11 mmol/L and HbA1c 5.7-6’4%) and impaired fasting glucose (FPG 5.7-6.9 and HbA1c 5.7-6’4%) increase CVD morbidity and mortality and increase the risk of developing DM by 4-6 fold. These persons

should be targeted for lifestyle intervention, and their CVD risk factors must be evaluated and treated.

5. Metabolic syndrome

Metabolic syndrome (MS) is a well-known cluster of cardiovascular risk (CVR) factors. The proposed common criteria for the clinical diagnosis of metabolic syndrome are based on the presence of three of the following five criteria: abdominal obesity; triglycerides ≥150 mg/dL (or drug treatment for elevated triglycerides); HDL cholesterol <40 mg/dL and <50 mg/dL for men and women, respectively (or drug treatment for reduced HDL-C); blood pressure ≥130/≥85 mm Hg or on medication for hypertension; and fasting glucose ≥100 mg/dL or on medication for hyperglycaemia.

The aetiologies of the metabolic abnormalities are not completely understood. The role of cART and the separate effect of HIV on patients who are surviving longer may contribute to the increased incidence of the development of MS [104]. HIV can cause lipid abnormalities, including elevated triglycerides due to a combination of hepatic very-low-density lipoprotein overproduction and reduced triglyceride clearance, and low HDL due to poor nutritional state and weight loss. In a large cohort of HIV-infected cART-naive persons [105], apart from the traditional factors such as age and BMI, HIV-associated factors such as low CD4-cell count and lack of virologic suppression were associated with an increased risk of developing MS.

Furthermore, specific cART regimens show associations with individual components of MS. Proposed mechanisms for PIs are that they can induce insulin resistance by inhibiting the glucose transporter 4 and by reducing peroxisomal proliferator-activated receptor activity, and for NRTIs that they can cause mitochondrial toxicity that leads to fat cell apoptosis, elevated free fatty acids and eventually insulin resistance and hypertriglyceridaemia [104, 105, 106]. Evidence also suggests a link between MS and PIs, and specifically an increased risk for LPV/r [107, 108]. The use of stavudine [108, 109] or didanosine [107] is also considered a risk factor for MS.

The goal of treatment for metabolic abnormalities associated with MS and HIV infection is to prevent microvascular and macrovascular complications with target-driven interventions, while maintaining the highest quality of life possible [104, 110]. Therapeutic strategies and interventions designed to treat MS include modification of risk factors such as hypertension and elevated lipids through exercise and smoking cessation, adjustment of HAART, addition of medications to treat hypertension, insulin resistance, hypercholesterolaemia, and treatment of psychological impact of adipose tissue changes and lipodystrophy [104].

Lifestyle modification is the first line of treatment for MS, especially insulin resistance and glucose intolerance, and must be considered on a case-by-case basis.

In this setting, research [113-115] has shown that medical treatment for hyperglycaemia as part of MS may start with agents that stimulate insulin secretion, sulphonylureas (glyburide) and meglitinides (repaglinide), to improve beta-cell function. Another medication that can be prescribed is metformin, which decreases hepatic production of glucose and increases muscle sensitivity to insulin [116].

Statins, including pravastatin, fluvastatin, and rosavastatin, are prescribed for HIV-infected patients with dyslipidaemia. Gemfibrozil and fenofibrate significantly reduce triglycerides, more moderately reduce LDL cholesterol and can be used when a patient is taking PIs. In addition, current treatment options for MS include switching antiretroviral agents [104]. Evidence suggests that switching a PI to certain NRTIs or NNRTIs in virally suppressed patients does not affect antiviral efficacy and may partly reverse metabolic changes [118].

6. Hypertension

Exposure to ART is significantly associated with increased systolic and diastolic blood pressure levels, and increased risk of hypertension, regardless of study-level sociodemographic differences [119]. Blood pressure should be tested and can be controlled with angiotensin-converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARB), as indicated in figure 1 [104]. Some ACE inhibitors may not be the best

choice for patients with HIV infection due to their potential side effects. Captopril has been associated with Kaposi sarcoma, hepatic toxicity, neurotoxicity, muscle pain, weakness, and diarrhoea . The ARB class of drugs will compete with other medications that are metabolized by cytochrome P450 isoenzyme, and should be used with caution in combination with antiretroviral medications. Calcium channel blockers diltiazem and dihydropyridine should be used with caution in combination with antiretroviral medications, due to decreased clearance of active drug, potentially increasing the effects of calcium channel blockers [113].

7. Obesity

Obesity, defined as a body mass index (BMI) at or above 30, has reached epidemic proportions.[120] Overweight (BMI 25–29.9) or obese status, specially abdominal obesity (>102 cm in men and >88 cm in women or waist-hip index >0,9 for men and >0,85 for women, are risk factors for diabetes, hypertension, cardiovascular disease and malignancy in HIV-negative adults[121-122]. The confluence of obesity and HIV infection likely exacerbates risk for co-morbidities such as diabetes, cardiovascular disease, and other conditions, highlighting the need to aggressively manage obesity and its related co-morbidities in the aging HIV-infected populace.

Investigators examining the trend toward obesity in HIV-infected patients have reported frequencies of overweight/obesity ranging from 45–61% [123-125]. The studies that have evaluated change in weight status during the ART era have also noted a gradual trend for increasing BMI during the course of treatment [126].

Treatment decisions for these patients must consider the paradigm shift from HIV as a disease of wasting to one with an increasing prevalence of obesity. Diagnosis and nutrition/physical activity interventions should be used for prevention and treatment of obesity in HIV individuals.

8. Fat redistribution syndromes

Fat redistribution syndromes include lipoatrophy, lipohypertrophy, and mixed syndromes. So far, their epidemiology has changed greatly and currently their clinical relevance has been decreasing with the advent of newer, more fat-friendly antiretroviral drugs.

Basically, the drugs used for the treatment of fat redistribution have been those employed for the treatment of metabolic abnormalities. However, most approaches have rendered disappointing results. The therapeutic strategies for these syndromes have recently been updated [127]. These strategies have included modification of host-dependent factors, including those related to HIV-1 infection and those associated with cART. Preventive and medical strategies have been associated with moderate success.

9. Cardiovascular disease prevention

More than 10% of patients with HIV infection experience cardiovascular manifestations. Cardiovascular prevention is required in more than one half of HIV-infected/treated patients to complete the effectiveness of modern antiretroviral therapy. As the life expectancy of HIV patients improves continuously, this proportion is also likely to increase in the future [128].

Patients should be assessed by CVD risk in the next 10 years annually with the Framingham equation or whatever system local National Guidelines recommends and advised on diet and lifestyle. Modifiable risk factors should be identified and treated as mentioned above. Smoking cessation results in about 50% less risk of ischemic heart disease and it is additive to other interventions.

Acetylsalicylic acid showed benefit in persons with established CVD or older than 50 years with 10-year CVD risk superior to 20%. In persons without a history of CVD (including diabetics) evidence is less compelling [129-130].

10.Conclusion

Cardio-metabolic risk factors are of increasing concern in HIV-infected individuals, particularly with the advent of cART and the subsequent rise in longevity. Management strategies recommended are similar than in general population with some especial considerations. CVD risk should be assessed in these patients and all of them be advised

on diet and lifestyle. Once identified modifiable risk factors caregivers should consider the need of drug treatments.

Switching cART strategies can be useful but its expected benefit is not high. Therefore, chemical intervention is often needed. Statins have been proven to reduce CVR in the general population and in HIV-infected patients. Simvastatin is contraindicated in patients treated with boosted PI due to interactions; atorvastatin is safe at submaximal dose and needs close monitoring, while pravastatin lacks lipid-lowering potency, and rosuvastatin and pitavastatin are safe. Ezetimibe and fibrates are also safe and effective in HIV-infected patients and can be used in combination with statins. The management of glucose homeostatic disorders in HIV-infected patients follows the same guidelines as in the general population with specific considerations with respect to the interactions of particular medications with cART. When drug therapy is needed, metformin is the first-line drug. Decisions regarding second- and third-line drugs should be carefully individualized. Other CVR factors such as hypertension and obesity should be identified and treated.

11.Expert Opinion

Metabolic disturbances are among the most common complications arising in patients living and ageing with HIV infection. In fact, metabolic disturbances were noticed shortly after the introduction of PIs in antiretroviral therapy back in 1996. Early concerns about their presence in the setting of early surviving patients were soon translated into observations of coronary heart disease events, and this link raised the hypothesis that this class of drugs was associated with an increased risk of cardiovascular disease, a hypothesis supported by large cohort studies. However, the issue proved to be more complex, since in non-infected patients it soon became apparent that metabolic disturbances and their consequences in terms of cardiovascular disease were a multifactorial disease with at least three well-known factors. First, host-dependent factors, such as genetic background, and above all environmental factors, with the utmost importance for lifestyle factors, such as smoking and diet. Second, HIV-dependent factors, since it was noticed from the pre-

cART era that HIV itself was able to induce lipid changes which, in the absence at that time of ART, had a meaning that was difficult to elucidate. Third, ART-dependent factors, such as the insulin resistance and lipid disorders noticed after the introduction and massive implementation of cART. At first, PIs were blamed for both kinds of disorders, but later the list of guilty parties was enlarged to include NRTIs, especially thymidine analogues, and even EFV, which was initially thought to be a metabolically friendly drug. During the 1990s and the early years of the 21st century, when dyslipidaemic NRTIS and metabolically harmful PIs were commonly used, it became apparent that cardiovascular disease was one of the most common causes of death among those not directly related to HIV infection, in HIV-infected patients.

Therefore, the need to address the management of metabolic disturbances in the setting of HIV infection became a need for caregivers, and a great deal was learned about the use of lipid-lowering agents and drugs to correct glucose homeostatic disorders. At the same time, much was learned about the specific lipid profile for most antiretroviral drugs. At that time, the management of metabolic disorders in the context of long-treated, long-surviving HIV-infected population included mainly two strategies which are still currently valid, often used, and mutually complementary, i.e. switching to more lipid-friendly cART regimes in virologically controlled patients and/or chemical therapy for dyslipidaemia and/or insulin resistance. As a general rule, HIV caregivers have taken advantage of these studies undertaken in an uninfected population, and these findings have been applied to the HIV population, always taking into account the specificities of HIV-infected patients, especially those relating to cART and their potential to have drug-drug interactions. The fact is that strategies devised to control metabolic disturbances in particular and cardiovascular risk in general were quite successful, since mortality due to cardiovascular disease has decreased in recent years compared with the early years of cART.

Among those factors which are modifiable to control metabolic disturbances, some of them are host-dependent, mainly lifestyle factors such as exercise and healthy diet, and c-ART-dependent factors are also modifiable. This is exemplified in the third era of the management of HIV infection by the appearance of new drugs and drug classes, such as

second-generation NNRTIs, integrase inhibitors, and the most commonly used NRTIs (TDF, ABC and 3TC/FTC) which have little impact, if any, on the metabolic profile of HIV-infected patients. However, this promising development has been counteracted by the fact that the HIV-infected population is becoming increasingly older, with an associated high burden of comorbidities and associated polypharmacy. This will undoubtedly have an impact not only on the chance of developing metabolic disturbances but also on the strategies designed to control them effectively.

Therefore, in the future a landscape for continuing metabolic disturbances may be foreseen, and this landscape will hopefully not only be populated by lipid-neutral antiretroviral drugs but also by better lipid-lowering drugs and drugs to correct glucose homeostatic disorders.

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Figure Legend:

Figure 1: Algorithm for management of HIV-related metabolic disorders

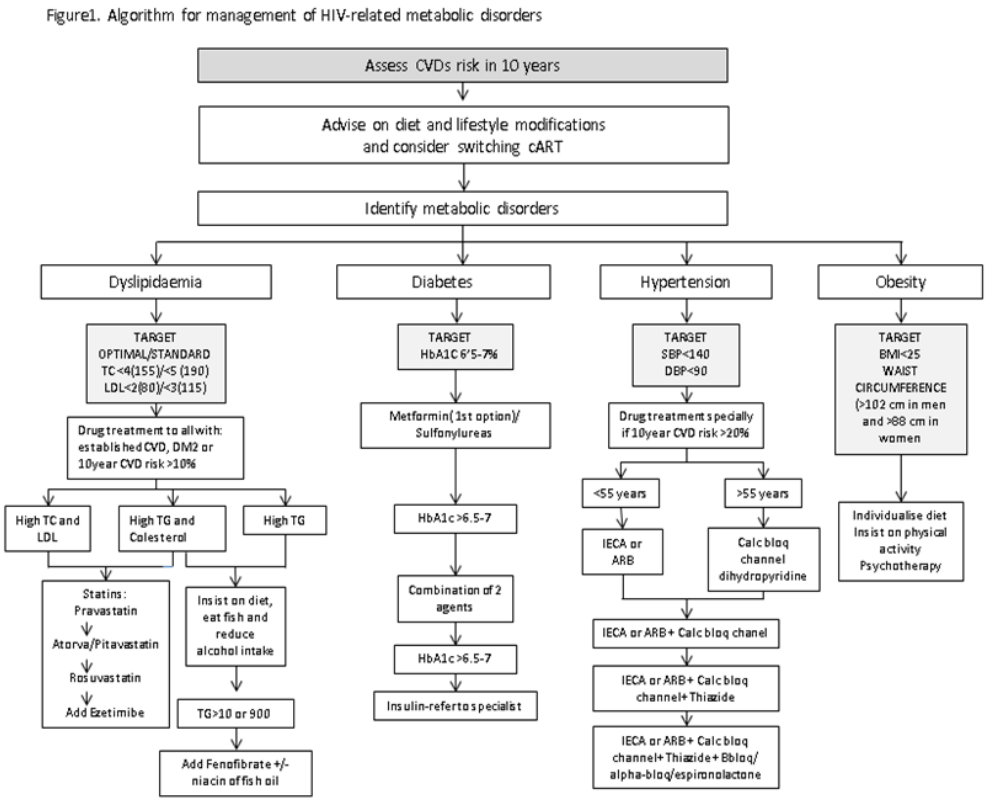

Table 1. Range of expected LDL cholesterol reduction (%) with different statins at different

Expected LDL cholesterol reduction (%)	Pravastatin	Fluvastatin	Lovastatin	Simvastatin	Pitavastatin	Atorvastatin	Rosuvastatin
20-25%	10mg	20mg	10mg				
26-30%	20mg	40mg	20mg	10mg			
31-35%	40mg	80mg	40mg	20mg	1mg	10mg	
36-40%				40mg	2mg	20mg	5mg
41-50%					4mg	40mg	10mg
51-55%						80mg	20mg
Special considerations in HIV	Appropriate Low power	Appropriate Low power	Better avoid	Better avoid	Appropriate intermediate power	Appropriate Hihgt power Use carefully at higt doses	Appropriate Hihgt power

Table 2. Average effects of different classes of triglyceride-lowering drugs on serum lipids

FIBRATE	Effective dose/day	Effect on TG	Effect on TC	Effect on LDL-c	Effect on HDL-c
Bezafibrate	400mg	- 30%	- 15%	- 20%	+ 10- 20%
Fenofibrate	200mg	- 30%	- 15%	- 25%	+ 10 – 20%
Gemfibrozil	900mg	- 40%	- 10%	- 15%	+ 10 – 20%

TG = triglycerides, TC = total cholesterol, LDL-c = Low density lipoprotein cholesterol, HDL-c = High density lipoprotein cholesterol

Table 3. Characteristics and efficacy of interventions for glucose homeostastic disorders

Intervention	HbA1c reduction	Adverse effects	Evidence	Comments
Lifestyle modifications	1-2%		I	
Metformin	1-2%	Diarrhoea, meteorism	I	Dolutegravir increases metformin concentrations
DPP-IV inhibitos	0,75%	Rinofaringitis, angioedema	III	Saxagliptin interacts with CYP3A4/5 inhibitor, reduce saxagliptin dose when used with CYP3A4/5 inh
GLP-1 analogues	0,75-1%	Nausea, vomit, pancreatitis	III	
Piglitazone	0,5-1,4%	Oedema, CHF, fractures	I	When used with CYP2C8 inhibitors rosiglitazone/pioglitazone levels may increase
Insulin	limitless	Hypoglycaemia, weight gain	I	

Sulfonylureas	**1%**	**Hypoglycaemia, weight gain**	**I**	