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Management of Metabolic Complications and Cardiovascular Risk in HIV-Infected Patients

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Abstract

As result of the great benefit of HAART, AIDS-related deaths have dramatically declined during the last decade in HIV-infected individuals. However, mortality due to non-AIDS conditions and particularly cardiovascular events seems to be on the rise in this population. Metabolic complications and other conditions responsible for increased cardiovascular risk are common in HIV persons. Moreover, antiretroviral medications and HIV itself might play a role in further increasing cardiovascular risk. As the HIV population is aging, a growing impact of cardiovascular events on survival can be expected. Therefore, early diagnosis and treatment of predisposing cardiovascular risk factors is warranted in this population. In this way, all HIV-infected individuals should be evaluated regularly for lipid abnormalities, hyperglycemia, arterial hypertension, overweight, renal disease, and smoking. The individual´s absolute risk for coronary heart disease must be defined, and comprehensive therapeutic measures should be undertaken in order to minimize future complications in subjects with significant cardiovascular risk. Lifestyle habits must be encouraged, including healthy diet and exercise. Switches in antiretroviral regimens using metabolic-friendly agents should also be considered for managing mild metabolic abnormalities in lipids and glucose, as long as suppression of viral replication is not compromised. The management of overt lipid disorders, diabetes, and hypertension basically must follow the guidelines applied to the general population and specific drugs administered, taking into account the potential for drug interactions with antiretroviral agents. In summary, efforts for reducing the increased cardiovascular risk characteristically seen in HIV-infected individuals are warranted, and preventable factors, including adequate management of metabolic abnormalities and hypertension, along with promotion of lifestyle habits and smoke cessation, should no longer be neglected. **(AIDS Rev. 2010;12:231-41)**

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Key words

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Introduction

The advent of HAART has led to a dramatic decline in mortality in the HIV population. The incidence of deaths shifted from more than 20% before 1996 to less than 2% ten years later[1]. The arrival of the newest antiretroviral (ARV) agents within the last few years has made feasible complete viral suppression in the majority of treated patients, with consequent benefits on the immune status and ultimately on survival. In this regard, mortality rates in HIV-infected patients who have experienced an acceptable CD4 recovery (> 500 cells/mm^3) on long-term ARV therapy currently resemble that of the general population[2].

Nevertheless, whereas mortality due to HIV-related events is sharply declining, non-AIDS conditions are emerging as significant causes of morbidity and mortality in this population. This is well established for liver disease in the subset of patients coinfected with

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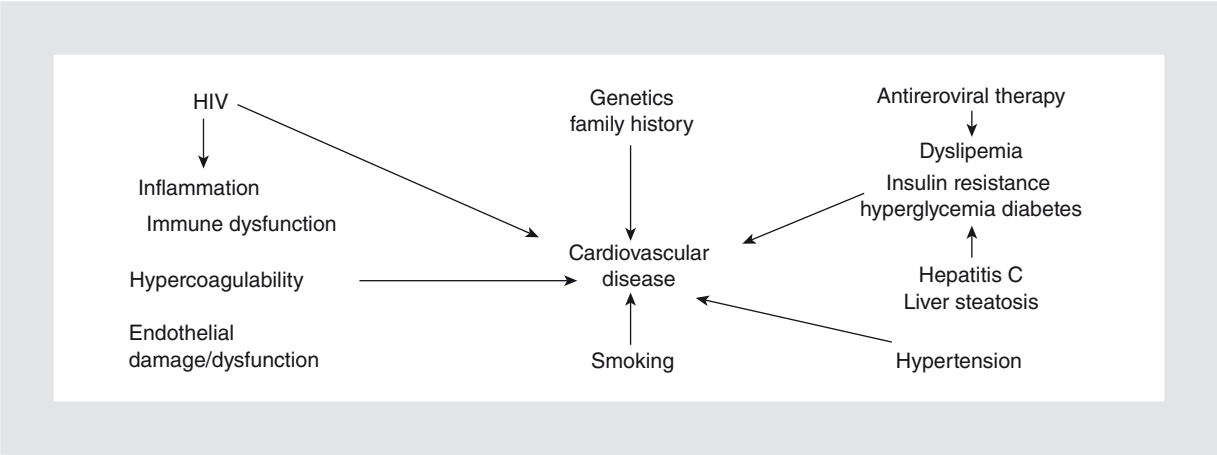

Figure 1. *Factors involved in cardiovascular disease in HIV infection.*

hepatitis viruses, mainly HCV. For the rest, cardiovascular disease (CVD) is emerging as the most important comorbidity and cause of death[3]. It is somewhat worrisome that HIV infection itself and some ARV medications may increase the rate of cardiovascular (CV) events. If so, control of HIV replication with ARV agents should be done, choosing agents with the lowest CV risk profile. When possible, ARV medications causing dyslipidemia, insulin resistance, diabetes mellitus, or hepatic steatosis must be discouraged. Moreover, early identification and proper management of traditional CV risk factors, such as smoking, overweight, or hypertension, is warranted[4,5]. As the prevalence of metabolic disorders is age-related, their incidence will be on the rise as the HIV population becomes older[5].

Relation between HIV infection and cardiovascular disease

Estimates from the World Health Organization on ischemic heart disease for 2030 predict that it will be among the first three causes of death in the HIV population in low-income countries[6]. Given the strong relationship between HIV and CV risk, their synergistic impact on survival must be viewed as a major health concern for the coming years[7].

In HIV-infected persons, all classical CV risk factors may be superimposed to different extents on the impact of unique HIV-related variables, such as ARV agents and HIV itself. Moreover, frequent comorbidities in HIV-infected individuals, such as chronic hepatitis C, may further contribute to increasing CV risk by several mechanisms (Fig. 1). Thus, active prevention, together with prompt diagnosis and management of CV risk factors, must be integrated as part of the routine HIV care. Only in this way would an amelioration in CV damage be expected for the current HIV population, otherwise largely free of risk for developing opportunistic conditions thanks to the tremendous success of ARV therapy[8,9].

Dyslipidemia is relatively common in the HIV population on ARV treatment, either as the only metabolic abnormality, or accompanying the lipodystrophy syndrome, in which there is fat redistribution and generally insulin resistance. High LDL-cholesterol increases the CV risk, whereas high HDL-cholesterol is a protecting factor. The role of hypertriglyceridemia as contributing to CV risk is still debated.

Certain ARV drugs are associated with dyslipidemia. One recent survey of 15 clinical trials examined the effect of first-line ARV therapy on lipids[10]. Higher serum levels of total cholesterol were associated with the use of fosamprenavir/ritonavir, lopinavir/ritonavir, and efavirenz when these drugs were combined with nucleoside reverse transcriptase inhibitors (NRTI) other than tenofovir[10]. Among the protease inhibitors (PI), atazanavir and darunavir seem to induce less lipid alterations[11,12]. Likewise, raltegravir and maraviroc appear to have minimal impact if any on lipids (Table 1). It must be noted that most of the variability seen in the influence of distinct ARV agents on lipid abnormalities does not seem to be explained by genetics[13].

Results from studies that have compared HIV-positive and HIV-negative individuals and that have adjusted for classical CV risk factors suggest that other conditions, such as ARV drugs and HIV itself, account for the increased CV risk in the HIV population[5,14,15]. The mechanism by which HIV infection itself may represents a potential risk for coronary heart disease (CHD) is unclear. From population-based studies, we know that the prevalence of CHD and myocardial infarction (MI) is

Table 1. Metabolic toxicity grading for antiretroviral agents

Antiretroviral class	Metabolic toxicity		
	Low	Moderate	High
NRTI	Lamivudine, emtricitabine, abacavir, tenofovir	Zidovudine, didanosine	Stavudine
NNRTI	Nevirapine	Efavirenz, etravirine	
PI	Saquinavir, atazanavir	Fosamprenavir, darunavir	Indinavir, lopinavir, tipranavir
Entry inhibitors	Enfuvirtide, maraviroc		
Integrase inhibitors	Raltegravir		

NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

increased in HIV persons compared to HIV-seronegative counterparts or the general population[5,14,16,17]. Moreover, markers of subclinical atherosclerosis, such as greater internal and common carotid artery intimamedia thickness, coronary plaques, ECG changes of ischemic heart disease, and altered parameters of peripheral artery disease, have all been found more frequently in HIV-infected persons than in controls[15,18-20]. Finally, several studies have shown that the carotid artery intimamedia thickness is greater in HIV patients than in HIV-seronegative individuals, regardless of the use of ARV therapy, the level of plasma viremia, or degree of immunodeficiency[21].

The mechanisms by which HIV infection may accelerate atherosclerosis are still under research. The growing data highlighting the consequences of persistent immune activation and inflammation in all HIV-infected persons, even in those with complete viral suppression on ARV therapy, along with the recognition of a chronic stage of hypercoagulability, may contribute to endothelial damage, with or without a direct involvement of viral injury (Fig. 1).

The SMART study has suggested that a characteristic scenario of persistent inflammation associated with uncontrolled viral replication has been linked to the pathogenesis of CV events in HIV persons[22]. A lower risk of CV disease was seen in patients after achieving sustained viral suppression[23]. Moreover, markers of inflammation and coagulation (IL-6 and D-dimer, respectively) increased after stopping ARV therapy in parallel with elevations in plasma viremia[24]. In the CASCADE study, a fourfold greater risk of death from CV causes was related to high plasma HIV RNA[25].

Elevated C reactive protein (CRP) has been recognized as an independent predictor of MI, also in HIV patients[26]. Some studies have suggested that inflammation, even in patients with viral suppression under ARV therapy, might persist as a pathogenic mechanism of endothelial dysfunction, which is generally assessed by flow-mediated dilation. This marker, which is also predictor of MI, is abnormal in most HIV subjects after adjusting for CV risk factors, being associated with high-sensitivity CRP values[27].

Inflammation has also been related to the aging process. The mean age of HIV persons is increasing. Continuous viral replication induces T-cell expansion and activation, leading to an accumulation of senescent T-cells. This effect has been associated with higher levels of IL-6, tumor necrosis factor (TNF), CRP, and D-dimer, which are all markers of CV disease. In a recent study conducted in HIV-positive women, carotid lesions and a diminished carotid distensibility significantly correlated with $CD4^+$ and $CD8^+$ T-cell activation. In addition, reduced carotid artery distensibility was related to an increased level of senescent $CD4^+$ and $CD8^+$ T-cells[28]. Thus, the role of inflammation in the pathogenesis of arteriosclerosis in HIV should be emphasized. The inflammatory process induced by HIV could be one of if not the main mechanism responsible for vascular damage in the HIV population.

With respect to immune dysfunction, a CD4 count nadir < 350 cells/mm^3 has been associated with increased arterial stiffness, which represents a potential risk factor for further CV disease[29]. Finally, a relationship between abacavir and increased risk of MI has been observed in both the D:A:D: and SMART trials, although not confirmed by others. Platelet hyperactivity and endothelial dysfunction have been suggested as possible pathogenic mechanisms[30,31]. Until further evidence is accumulated, tenofovir may be an appropriate alternative to abacavir in patients with substantial risk of CV disease.

Management of HIV-infected patients with elevated cardiovascular risk

A comprehensive evaluation of CV risk factors and diseases during the first medical visit must be performed, in order to assess the individual risk of each

Table 2. Monitoring of metabolic and cardiovascular risk factors in HIV-infected individuals

Evaluation	Data	At HIV diagnosis	Follow-up without HAART	Before start HAART	Follow-up on HAART
History	Family: – Premature CHD, diabetes, hypertension, dyslipidemia Patient: – Past and current diseases – Therapy – Lifestyle: diet, smoking, exercise, alcohol	X	annual	X	annual
Body composition	BMI, waist circumference, waist-to-hip ratio, clinical LD assessment	X	annual	X	annual
CV assessment	Blood pressure, ECG, Framingham score (CV risk)	X	annual	X	annual
Lipid profile	Fasting serum: total cholesterol, LDL-c, HDL-c and triglycerides	X	annual	X	every 3-6 months
Glucose	Fasting serum glucose; oral glucose tolerance test when indicated	X	annual	X	every 3-6 months
Renal function	eGFR urine analysis	X	annual	X	every 3-6 months

Assessment and monitoring should be more frequent in cases of severe dyslipidemia, elevated blood pressure, or elevated fasting blood glucose, and/or if medical interventions are instituted to correct these conditions.
CHD: coronary heart disease; Premature CHD: first-degree male relative < 55 years or first-degree female relative < 65 years; BMI: body mass index; LD: lipodystrophy; eGFR: estimated glomerular filtration rate (Cockcroft-Gault).

patient[8,9,32,33]. On this basis, preventive and therapeutic measures must be indicated, and periodic assessment done at regular intervals, i.e., every 3-6 months in subjects on ARV treatment and annually in patients not treated. Factors to be considered include age, smoking habits, diet, and exercise activity, as well as personal and family history of CHD, hyperlipidemia, diabetes, and hypertension. In women, the menopausal status is relevant. Baseline blood pressure, body mass index, and waist circumference should be recorded, together with laboratory measurements of glucose, lipids, and renal function (Table 2).

Prediction of CV risk

The medical information referred to above can be used to predict the patient's probability of developing CHD, hard CHD events (MI and death), and general CVD, according to standard multivariate risk models such as the Framingham Risk Score (FRS) (http://www.framinghamheartstudy.org/risk/index.html)[34]. Using the Framingham equation, which includes age, gender, total cholesterol, HDL-c, systolic blood pressure, and smoking, an individual can be stratified into three risk categories: low, medium, and high risk, corresponding to < 10, 10-20, and > 20% 10-year risk of CHD, respectively. The extent to which these models established for the general population can be applied to HIV persons is still under debate. In this context, the meaning of CV risk factors and response to specific treatments in HIV-infected subjects may not be accounted for in the same way as in persons without HIV disease. However, until more evidence is available, management strategies of CV risk proposed for uninfected persons should also apply to HIV patients.

The FRS has not been specifically validated in the HIV population. In fact, pathogenic mechanisms involved in CV risk in HIV-infected patients might presumably not be adequately considered within standard risk evaluation methods. According to the D:A:D study, MI rates seen in ARV treated and untreated HIV-infected individuals were higher and lower, respectively, than those predicted by the FRS. Nevertheless, it predicted CV events at increased rates in parallel with time on ARV treatment[35]. Based on these findings, FRS may be useful for an initial estimation of CV risk in HIV individuals, although more precise models should be investigated for this population. The D:A:D five-year estimated risk calculator, developed from a population of HIV-infected patients, includes time of exposure to indinavir, lopinavir, and abacavir, as well as classical CV risk factors such as age, gender, current and previous smoking, diabetes, family history of CVD, systolic blood pressure, total cholesterol, and HDL-c (www.cphiv.dk/tools.aspx). This model has been shown to be more accurate than the Framingham score to predict risk of MI, CHD, and CVD in HIV patients[36].

Table 3. Management of hyperlipidemia: goals and elective therapy

Risk	LDL-c goal	Drug start	Non-HDL-c goal	First-line treatment*	Second-line
High CHD, CHD equivalent, DM2 or 2+RF 10YR > 10%	< 100	≥ 100†	< 130	Rosuvastatin‡ 5 mg qD Atorvastatin§ 10 mg qD	Gemfibrozil¶ 900 mg qD Fenofibrate** 250 mg qD Nicotinic ac.†† 1000 mg qD Ezetimibe‡‡ 10 mg qD
Moderate ≥ 2 RF and < 10%	< 130	≥ 160	< 160	TLC§§, consider statin	Fibrate, nicotinic acid, ezetimibe
Low 0 - 1 RF	< 160	≥ 190	< 190	TLC	Statin, fibrate, nicotinic acid, ezetimibe

TLC: treatment of lifestyle changes; CHD: coronary heart disease; CHD equivalent: peripheral arterial disease, carotid artery disease or abdominal aortic aneurysm; DM2: diabetes mellitus type 2; 10YR: ten-year risk; 2+RF: two or more risk factors (cigarette smoking, hypertension (BP > 140/90 mmHg), low HDL < 40 mg/dl, family history of premature CHD (first-degree relatives, men < 55 y, women < 45 y) and age (men ≥ 45 y, women ≥ 55 y); LDL and non-HDL-c data are in mg/dl.
*First-line treatment should always include lifestyle changes even in high-risk persons.
†If 10YR < 20% initiate drug therapy at 130 mg/dl or more.
‡Rosuvastatin (Crestor®): initiate at 5-10 mg, raise if goal not achieved. Max. 40 mg qD.
§Atorvastatin (Cardyl®, Prevencor®, Zarator®): initiate at 10 mg, raise if goal not achieved. Max. 80 mg qD.
¶Gemfibrozil (Lopid®, Trialmin®): 900 mg qD, maximum 1,500 mg/d.
**Fenofibrate (Secalip®, Liparison®): 250 mg qD.
††Nicotinic acid/laropiprant (Tredaptive®): initiate at 1,000/20 mg qD for 4 weeks, then 2,000/40 mg qD. If discontinuation is 7 or more days, reinitiate.
‡‡Ezetimibe (Ezetrol®): 10 mg qD.
§§TLC: exercise, diet, low alcohol intake, viscous fiber, and stanol/sterol containing foods.

Strategies intended to minimize CV risk in HIV patients should address lipid alterations, diabetes, and abnormal blood pressure, as well as modifiable risk factors (i.e. smoking, overweight, sedentary habits, and excessive alcohol consumption), without compromising viral suppression. In addition, virologic control achieved by ARV therapy may also decrease the risk of noninfectious comorbidities, including CV disease. In patients with > 20% 10-year risk or with prior CVD, the risk of CVD events and cardiac death will usually be higher than the risk of progression to AIDS or death in HIV patients.

Lifestyle interventions

Counseling on healthy diet habits, regular exercise, and quitting smoking should be performed in a first step to minimize CV risk. Dyslipidemia, excessive weight, high blood pressure, and glucose abnormalities have been shown to improve after diet and exercise[37-39].

Smoking cessation leads to a decrease in CVD and risk of malignancies[40]. Smoking prevalence in HIV patients is generally high, ranging from 45 to 70%[41-43]. Several studies have demonstrated a higher rate of smoking in HIV persons compared to uninfected controls[43,44]. Thus, aggressive interventions aimed to stop smoking are warranted[45,46]. Strategies based on specific counseling and pharmacologic approaches should be further investigated[46,47]. Among the drugs used for smoking cessation, it should be noted that bupropion is metabolized by cytochrome P450; thus, potential interactions with certain ARV agents must be taken into account.

Dyslipidemia

The results of the D:A:D study clearly show that the prevalence of lipid disorders in HIV-infected patients is higher among those on ARV treatment (23-54%) than in ARV-naive individuals (8-15%). In both groups, hypertriglyceridemia (triglyceride > 200 mg/dl) is more frequent than hypercholesterolemia (total cholesterol > 240 mg/dl). Among subjects on ARV treatment, triglycerides and cholesterol elevations are greatest in association with the use of protease inhibitor/nonnucleoside reverse transcriptase inhibitor (PI/NNRTI) regimens (54 and 44%, respectively), followed by PI regimens (40 and 27%, respectively), and NNRTI-containing combinations (32 and 23%, respectively)[41].

Assessment of dyslipidemia must be done before starting ARV therapy, every six months thereafter, and after switching to a new ARV regimen. Fasting levels of total cholesterol, HDL-c, and triglycerides, together with calculation of LDL-c values using the Friedewald equation (LDL cholesterol = total cholesterol [TC] – HDL cholesterol – triglycerides/5) should be determined. In cases of triglycerides 400 mg/dl, a direct measurement of LDL-c must be performed, and predisposing conditions should be ruled out (i.e. alcohol abuse, hypothyroidism).

The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) issued evidence-based guidelines on lipid management in 2001[48]. Dyslipidemia is defined as TC ≥ 200 mg/dl, LDL-c ≥ 130 mg/dl, triglycerides ≥ 150 mg/dl, HDL-c < 40 mg/dl, and TC/HDL ratio ≥ 6.5. The guidelines propose distinct strategies

Table 4. Lipid-lowering drugs and relative efficacy

Active drug	Brand	Dose	LDL	HDL	TG	Non - HDL - c*
Atorvastatin	Cardyl® Prevencor® Zarator®	10, 20, 40, 80 mg qD	↓	↑	↓	↓
Rosuvastatin	Crestor®	5, 10, 20, 40 mg qD	↓↓	↑	↓	↓↓
Ezetimibe	Ezetrol®	10 mg qD	↓			
Fenofibrate	Secalip® Liparison®	250 mg qD	↓↓	↑	↓↓	
Gemfibrozil	Lopid® Trialmin®	600 BID, 900 mg qD, max. 1.5 g/24 h	↓	↑	↓↓↓	
Nicotinic acid and laropiprant	Tredaptive®	0-4 weeks 1 g qD > 4 weeks 2 g qD	↓	↑↑	↓↓	↓

LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglyceride; qd: once daily.
*Non-HDL-cholesterol goals are 30 mg/dl higher than LDL-c goals.

for treating lipid abnormalities according to the individual CV risk and LDL-c. Variables assessed for estimating CV risk include age, smoking, total cholesterol and HDL-c, family history of premature CHD, blood pressure, and menopausal status in women. Therapeutic indications are made regarding the time for initiating specific lifestyle recommendations and prescription of lipid-lowering drugs in order to achieve LDL-c goals (Table 3).

Distinct drugs are suggested for the different profiles of hypercholesterolemia and/or hypertriglyceridemia (Table 4). An update of ATPIII, on the basis of five major clinical trials of statin therapy published subsequently, was reported in 2004[49]. It includes diabetes in the high-risk category, given the benefit of LDL-lowering therapy in this particular population. The metabolic syndrome is also considered as a secondary target to be addressed.

Until further data are available for the HIV population, guidelines from the Infectious Disease Society of America (IDSA) and the Adult AIDS Clinical Trial Group (ACTG), as well as from the European AIDS Clinical Society (EACS) recommend that the management of dyslipidemia in HIV-infected patients must follow the NCEP guidelines[32,33]. Potential drug interactions with ARV agents must be taken into account.

In patients with low-to-moderate dyslipidemia, recommended lipid goals may be achieved with diet, exercise, and keeping normal weight[37]. Diet should be based on reducing saturated fat and cholesterol and increasing fiber-containing meals. If not effective, a change of ARV regimen may be considered, provided that antiviral efficacy is not compromised. Options for ART modification include: (i) replacing PI/r by NNRTI, or by another PI/r known to cause less metabolic disturbances; and (ii) replacing stavudine or zidovudine by tenofovir. Switching PI/r to NNRTI, darunavir/r or atazanavir is generally followed by an improvement in the lipid profile[11,12,50,51]. Other drugs without a significant impact on lipids, such as raltegravir and maraviroc, should also be considered (Table 1). When these measures are not enough or adherence to lifestyle counseling becomes difficult, lipid-lowering drugs should be prescribed.

If therapy with lipid-lowering drugs is needed, statins or fibrates are indicated, depending on the lipid profile and potential for drug interactions. Predominant hypercholesterolemia or high triglyceride levels should initially require statins or fibrates, respectively (Table 4). Reductions in lipid levels achieved by lipid-lowering therapy are greater in non-HIV infected patients than in HIV-seropositive individuals[52]. Response to any therapeutic lipid-lowering strategy must be evaluated after 3-6 months by repeating a fasting lipid profile.

Statins are inhibitors of the hydroxymethylglutaryl coenzyme A reductase, being of choice for decreasing high LDL-c. To a lesser degree, they may increase the HDL-c fraction and decrease triglycerides. Additionally, they have been associated with a favorable effect on the endothelial function, which might provide a benefit regarding CV risk.

Lovastatin and simvastatin are highly metabolized through the cytochrome P450 (CYP3A4), which is inhibited by most PI. Thus, their concomitant use is contraindicated in order to avoid serious side effects of statin overexposure such as rhabdomyolysis. Rosuvastatin and atorvastatin provide higher efficacy than pravastatin in decreasing LDL-c. Due to partial metabolism of atorvastatin by CYP3A4, it must be used with caution when coadministered with PI, with hepatitis and

Table 5. Diagnosis of diabetes mellitus and its preceding stages

Test	Fasting plasma glucose (mg/dl)		Oral glucose tolerance test: 2-hour value (mg/dl)
Impaired fasting glucose	100-125	and	< 140
Impaired glucose tolerance	< 126	and	140-199
Diabetes	≥ 126	or	≥ 200

Repeated abnormal values before diagnosis.

myositis being potential toxicities. Rosuvastatin is the most potent statin in reducing LDL-c and triglycerides, with serum levels being only slightly modified when associated with PI[53,54]. Thus, it may be the statin of choice in several scenarios, particularly when using PI. With respect to NNRTI, the statin metabolism is induced by efavirenz, which may compromise their activity[55].

Statins should be initiated at the lowest dose established for each agent. Subsequent adjustments of dosing can be done according to response, and potential side effects must be closely monitored during follow-up, especially elevations in creatine phosphokinase and abnormal liver parameters. Of note, statins may improve abnormal baseline transaminase levels in patients with steatohepatitis[56]. Although the mechanism is not well defined, the removal of lipids from the liver using statins might explain the benefit on liver function. In subjects with moderate hypertriglyceridemia (200-500 mg/dl) and two or more CV risk factors, a statin should be prescribed.

Triglycerides > 500 mg/dl require the use of fibrates, such as gemfibrozil and fenofibrate, especially in order to prevent pancreatitis. They are metabolized by CYP4A, and therefore no relevant interactions with ARV drugs are expected. Gemfibrozil is generally initially recommended due to its efficacy in reducing triglycerides, together with a proven benefit on CV risk. When concomitant hypercholesterolemia is present, statins can be added to fibrates, provided that potential rhabdomyolysis is closely monitored[57].

When comparing the effect on the lipid profile of switching ARV drugs versus the use of lipid-lowering agents, a significantly greater decline in triglycerides has been observed in patients treated with PI using pravastatin or bezafibrate than switching to nevirapine or efavirenz[58].

Fish oil supplementation is a good source of omega-3 fatty acids, and has shown to diminish triglycerides in HIV patients[59,60]. It is well tolerated, although potential effects on platelets must be checked, especially in subjects treated with drugs that may favor bleeding.

Ezetimibe is indicated in severe hypercholesterolemia, generally associated with statins. It decreases the gastrointestinal absorption of cholesterol and is well tolerated, having no CYP450 interactions with ARV agents. In HIV patients, the drug has provided a significant reduction in LDL-c, without significant changes in triglycerides[61,62]. CK levels should be checked, due to potential rhabdomyolisis.

Lipodystrophy

The incidence of fat distribution abnormalities has substantially diminished following the abandoning of the oldest nucleoside analogs and PI. In the prevention of lipoatrophy, the best strategy is avoidance of thymidine analogs. Glitazones have been tried to treat fat loss, without confirmed efficacy. Surgical interventions of facial lipoatrophy with permanent fillers offer cosmetic improvement, but the durability is still uncertain. Diet and exercise are recommended to reduce abdominal fat accumulation. Pharmacological approaches with growth hormone and metformin decrease visceral adipose tissue, but may impair subcutaneous lipoatrophy and efficacy in the long term has not been demonstrated. Surgery can be indicated for buffalo humps and local lipomas.

Glucose abnormalities

New-onset diabetes mellitus is diagnosed in 5-10% of HIV persons[63]. Impaired glucose tolerance (IGT) and early insulin resistance are particularly prevalent in HIV patients (10-25%), mostly in those receiving PI[64].

Diagnosis (Table 5), prevention and management of type 2 diabetes, as well as impaired fasting glucose (IFG) and IGT, are based on the same criteria used in the general population, which include evaluation and treatment of other CV risk factors[65,66].

Both IFG and IGT are associated with increased CV risk, and also enhance the likelihood of overt diabetes up to sixfold. As in the general population, lifestyle measures and control of other CV risk factors are indicated for managing IFG and IGT, and the ideal body mass index should be aimed at in cases of overweight and obesity[65,66]. More aggressive measures should be added for overt diabetes.

Table 6. Management of type 2 diabetes

Date	HbA1c	Recommendation
At diagnosis		Lifestyle interventions ± metformin†
First visit*	> 7%	Add another drug‡
Second visit*	> 7%	Add insulin therapy

HbA1c: hemoglobin A1c.
*Every 3 months or earlier if necessary. If HbA1c < 7% check every 6 months at least.
†Consider metformin as first line drug. Start at half dose and increase every 7-10 days to avoid gastrointestinal adverse effects (maximum 2,500 mg/d). Consider pioglitazone as first-line monotherapy if lipoatrophy.
‡Sulfonylurea (other than chlorpropamide or glibenclamide) or pioglitazone (more experience in HIV patients).

Management of type 2 diabetes must focus on glucose control (HbA1c < 6.5-7% without hypoglycemia, or fasting plasma glucose 70-110 mg/dl) (Table 6). Fasting glucose levels should be checked at the start of or after changing ARV therapy, and every six months thereafter. Whereas serum glucose is an accurate marker for managing glucose disorders in HIV patients, glycosylated hemoglobin may underestimate plasma glucose levels in this population. The reasons for this discordance are higher mean corpuscular volume and abacavir use[67].

If diet and exercise are not sufficient to achieve treatment goals, administration of oral antidiabetic drugs should be considered (Table 7). Metformin and pioglitazone reduce insulin resistance and are of choice in overweight and lipoatrophic patients, respectively. Both agents can be administered together. When glucose control is not possible with oral therapy, insulin should be indicated, beginning with 10 IU of long-acting insulin at night, and further increased by 2 IU every 72 hours until glucose control is achieved. Metformin can be combined with insulin. Consistent data regarding the use of other antidiabetic agents (i.e. sulfonylureas, glinides, α-glucosidase inhibitors) in HIV patients on ARV treatment are not available. Additionally, serum lipids and blood pressure must be controlled. Angiotensin-converting enzyme (ACE) inhibitors are of choice among antihypertensive agents in diabetic patients. Acetylsalicylic acid should also be prescribed (75-150 mg/day). Screening for macro- and microvascular disease should be performed regularly, including monitoring of nephropathy and retinopathy.

Hypertension

The prevalence of hypertension in HIV patients is around 25%[68,69]. When treating hypertension in this population, physicians should follow the current recommendations available for the general population. The European Societies of Hypertension and Cardiology, and the 7-Joint National Committee from the USA, have both issued guidelines on hypertension management[70,71]. The therapeutic approach in hypertensive individuals depends not only on blood pressure levels, but also on the CV risk. More intense measures are needed in parallel with the increase in CV risk. Diagnosis of hypertension is based on the average of at least two blood pressure readings made at different visits. Although infrequent at middle age, secondary hypertension should always be ruled out.

Table 7. Oral antidiabetic drugs

Type	Active agent	Initial dose	Maximum dose	Comments
Biguanides	Metformin	500-750 mg qd/bid	2,500 mg/d	Of choice in overweight patients Side effects: gastrointestinal symptoms, may worsen lipoatrophy, lactic acidosis (rare) Contraindicated in renal insufficiency
Thiazolidinediones	Pioglitazone	15 mg qd	45 mg qd	If lipoatrophy Side effects: fluid retention, cardiac failure, weight gain
Sulfonylureas	Glipizide Gliclazide	5 mg qd 80 mg qd	20 mg bid 160 mg bid	May be considered for non-overweight patients
Glinides	Repaglinide	0.5 mg tid	5 mg tid	
α-glucoside inhibitors	Acarbose	50 mg tid	200 mg tid	
DPP-4 inhibitors	Sitagliptine Vidagliptine	100 mg qd 50 mg bid	100 mg qd 50 mg bid	

DPP-4: dipeptidyl peptidase 4; qd: once daily; bid: twice daily; tid: thrice daily.

Table 8. Antihypertensive drugs and dosing

Class	Drugs	
ACE inhibitors	Enalapril (5-20 mg), Perindopril (2-8 mg), Ramipril (1.25-10 mg)	
ARBs	Losartan (50-100 mg), Candesartan (8-32 mg), Telmisartan (20-80 mg), Valsartan (80-320 mg)	
Calcium antagonists	Amlodipine (5-10 mg), Nifedipine (30-120 mg)	
Diuretics	Hidroclorothiazide (12.5-50 mg)	
Beta-blockers	Carvedilol (6.25-25 mg), Atenolol (50-100 mg), Nebivolol (5 mg)	
Combinations	**Brand**	**Dose (qD)**
Enalapril/Nitrendipine	Eneas®	10/20 mg
Trandolapril/Verapamil	Tarka®	2/180 mg
Amlodipine/Valsartan	Copalia®, Exforge®, Imprida®, Dafiro®	5/160 mg, 10/160 mg
Olmesartan/Amlodipine	Sevikar®	20/5 mg, 40/5 mg, 40/5 mg, 40/10 mg

Initiate at low dose. If blood pressure goal is not achieved, switch to or add another drug class. Before achieving maximum doses, add another drug class.
ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers.

Proper management of hypertension should always include modification of lifestyle habits, weight loss if needed, advice for incorporating low total and saturated fat in the diet, dietary sodium reduction to 2.5 g/day, aerobic physical activity, and moderation in alcohol consumption. Antihypertensive drugs must be prescribed if blood pressure is not controlled after several months on lifestyle changes, or at diagnosis when CV risk and/or blood pressure values are significantly high. Blood pressure goal is achieved when levels decline below 140/90 mmHg, or below 130/80 in diabetic patients. Five major classes of antihypertensive agents are available, which can be used alone or in combination (Table 8). Criteria for treatment and other related aspects are summarized in table 9.

Table 9. Classification of arterial hypertension, therapy goals and drugs recommended

Risk	Initiation regimen
Low and moderate	Single
High and very high	Combination
If BP goal not achieved	
Switch to any other class	
Add another class	

	Blood pressure (mmHg)				
Other risk factors, OD or disease	**Normal SBP 120-129 or DBP 80-84**	**High normal SBP 130-139 or DBP 85-89**	**Grade 1 HT SBP 140-159 or DBP 90-99**	**Grade 2 HT SBP 160-179 or DBP 100-109**	**Grade 3 HT SBP ≥ 180 or ≥ 110**
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1-2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS, OD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

Associated pathology	Preferred drug	Observations
Renal dysfunction, DM	ACEI , ARB	Avoid BB
Metabolic syndrome	ACEI , ARB , CA	Carvedilol and Nebivolol
Atrial fibrillation	BB, CA	ACEI , ARB if paroxysmal
Heart failure	Diuretics, BB, ACEI , ARB	In preferred order
Peripheral artery disease	CA	
Previous MI	BB, ACEI , ARB	
Angina	BB, CA	
Blacks	Diuretics, CA	Avoid RAA system drugs

BP: blood pressure; DM: diabetes mellitus; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CA: calcium-antagonist; BB: beta-blocker; RAA: renin-angiotensin-aldosterone.

Associated comorbidities must be taken into account when deciding which drug to use, being particularly cautious with calcium-channel blockers, which may interact with ARV agents.

Finally, it must be remarked that the goals achieved after diverse therapeutic approaches are additive. A reduction in risk of CHD by 20-25% is expected when total cholesterol is decreased by 1 mmol/l (39 mg/dl), or systolic blood pressure falls 10 mmHg, or low-dose acetylsalicylic acid is used. Of note, the risk of CHD decreases the most (by 50%) after smoking cessation. All these interventions together could reduce the absolute risk by more than 80%. So, it is crucial to address all CV risk factors in order to maximize the benefit.

Summary

Metabolic abnormalities and other classical CV risk factors are frequent in HIV patients. As the incidence of CV disease increases with age, its prevalence is expected to rise in the future, given the success of ART treatment in reducing AIDS events and mortality. Therefore, early detection and management of CV risk factors is warranted in HIV patients in order to prevent CVD.

The pathogenesis of CVD in HIV patients is multifactorial. Together with traditional risk factors, inflammation associated to HIV infection seems to play a role. The benefit of ART therapy by suppressing viral replication is recognizable on CVD. However, metabolic abnormalities associated to the use of some ARV agents must be addressed properly. When feasible, switch strategies to regimens including more lipid-friendly agents must be encouraged in an attempt to ameliorate CV risk. In general, the newest ARV drugs show a better metabolic profile than the older compounds.

All HIV patients should be checked regularly for metabolic and other CV risk factors. The management of lipid abnormalities, diabetes, and hypertension should be encouraged in all HIV patients, following guidelines for the general population. The absolute risk for coronary heart disease must be assessed for each individual, and adequate multiple therapeutic measures must be planned. Lifestyle changes, together with pharmacological interventions, should be advised when needed, and potential drug interactions with ARV agents must be taken into account. The benefits of different interventions are additive, so small favorable changes in different targets may ultimately provide a substantial decrease in the absolute CV risk.

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