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REVIEW ARTICLE

Cardiovascular Disease in the Setting of Human Immunodeficiency Virus Infection

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Abstract: ***Background*:** Since the introduction of Antiretroviral Therapy (ART), the life expectancy and health quality for patients infected with Human Immunodeficiency Virus (HIV) have significantly improved. Nevertheless, as a result of not only the deleterious effects of the virus itself and prolonged ART, but also the effects of aging, cardiovascular diseases have emerged as one of the most common causes of death among these patients.

***Objective*:** The purpose of this review is to explore the new insights on the spectrum of Cardiovascular Disease (CVD) in HIV infection, with emphasis on the factors that contribute to the atherosclerotic process and its role in the development of acute coronary syndrome in the setting of infection.

***Methods*:** A literature search using PubMed, ScienceDirect and Web of Science was performed. Articles up to Mar, 2017, were selected for inclusion. The search was conducted using MeSH terms, with the following key terms: [human immunodeficiency virus AND (cardiovascular disease OR coronary heart disease) AND (antiretroviral therapy AND (cardiovascular disease OR coronary heart disease))].

***Results*:** Clinical cardiovascular disease tends to appear approximately 10 years before in infected individuals, when compared to the general population. The pathogenesis behind the cardiovascular, HIV-associated complications is complex and multifactorial, involving traditional CVD risk factors, as well as factors associated with the virus itself - immune activation and chronic inflammation – and the metabolic disorders related to ART regimens.

***Conclusion*:** Determining the cardiovascular risk among HIV-infected patients, as well as targeting and treating conditions that predispose to CVD, are now emerging concerns among physicians.

Keywords: Cardiovascular Disease (CVD), Human Immunodeficiency Virus (HIV), Antiretroviral Therapy (ART), Acute Coronary Syndrome (ACS), Coronary Heart Disease (CHD), atherosclerosis, cardiovascular risk.

1. INTRODUCTION

In 2015, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS), an estimated 36.7 million people were living with human immunodeficiency virus (HIV) worldwide, accounting for 1.1 million Acquired Immunodeficiency Syndrome (AIDS)-related illnesses by the same year [1]. Despite the documented beneficial effects of the introduction in the mid-1990s of highly active antiretroviral therapy (HAART) in the treatment of infected patients [2-7], HIV infection remains a leading cause of morbidity and mortality worldwide [5]. Nevertheless, it must be highlighted that Antiretroviral Therapy (ART) has significantly changed the HIV-related illnesses spectrum and the course of the disease, since it has evolved from a once fatal infection [8], accounting for high death rates due to AIDS [3, 9], into a chronic disease [4, 10-13]. Nowadays, Human Immunodeficiency Virus-infected Patients (HIV-IP) are living longer [2, 14-18] and with more quality of life from a physical health point of view [3, 5, 19]. Though, as this population becomes older - 50% of HIV-infected individuals who live in Europe and in the United States of America are aged 50 years or more [2] - the risk of non-AIDS morbidity and mortality is raising [6, 8, 20-23]. When compared to the general population, non-AIDS related complications tend to appear around a younger age (approximately 10 years before) in infected individuals, which suggests an acceleration of the ageing process in the course of the infection [18, 24]. Diseases that are increasingly more prevalent in the HIV-infected individuals include non-AIDS malignancies, liver and chronic kidney disease [9, 11, 15, 17, 21, 24] as well as clinical and subclinical Cardiovascular Disease (CVD) [2-4, 25-28]. In 2010, 19% of HIV-IP had been diagnosed with at least one CVD [29]. The increased risk of the cardiovascular

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complications previously mentioned appear to reflect the interplay of well-known cardiovascular risk factors that are overrepresented in the HIV-infected population [2, 11], such as smoking [11, 30, 31], the effects of the virus itself [7, 15] and the adverse metabolic complications of antiretroviral drugs (namely dyslipidemia, insulin resistance, diabetes and lipodystrophy) [3, 30-33]. Given the fact that HIV infection is an independent risk factor for cardiovascular illnesses [18], there is a need for early recognition of HIV-associated complications in the infected population, and particularly, of CVD [34]. Thus, the purpose of this review is to explore the new insights on the spectrum of cardiovascular complications in HIV-IP, with particular emphasis on Coronary Heart Disease (CHD) and Acute Coronary Syndrome (ACS), as well as the contribution of ART in this setting.

2. METHODS

A literature search using the databases of PubMed, ScienceDirect and Web of Science was performed. Articles up to Mar, 2017, with no lower date limitation, written in English, Spanish, Portuguese and French were selected for inclusion. The most recent articles were chosen whenever possible. The search was conducted using MeSH terms, with the following key terms: [human immunodeficiency virus AND (cardiovascular disease OR coronary heart disease) AND (antiretroviral therapy AND (cardiovascular disease OR coronary heart disease))].

3. CARDIOVASCULAR DISEASE IN HIV-INFECTED PATIENTS

In the years after the detection of the first cases of HIV back in the 1980s, the most frequent cardiovascular complications associated with the infection in developed countries were pericarditis, myocarditis caused by opportunistic infections [10], dilated cardiomyopathy, pericardial effusion, pulmonary hypertension and cardiac tumours [33]. However, with the increasing availability of ART and longer periods of exposure to the therapeutic regimen, opportunistic infections were controlled [4] and management of viral load was improved [15], hence changing the spectrum of cardiovascular complications in HIV-IP [35]. Consequently, this population is now presenting a substantially higher incidence and mortality rate due to arrhythmias, premature Coronary Artery Disease (CAD) and ACS, particularly myocardial infarction (MI) [10, 32] (Table **1**).

Still, cardiovascular involvement in treatment-naïve patients is important [15], which leads to the hypothesis that ART may not fully explain the increased risk of CVD seen in HIV-IP, and that the virus itself may play its role [36].

3.1. Major Cardiovascular Manifestations

As previously mentioned, the spectrum of CVD in HIV-infected individuals is broad and may affect the myocardium, pericardium, cardiac valves and/or pulmonary vascular beds [41]. The most frequent cardiovascular complications in this population include cardiomyopathy, pulmonary arterial hypertension, pericardial disease, cardiac tumours, arrhythmias, endocarditis, premature CAD and ACS, including MI [18, 36, 42].

Clinically symptomatic cardiomyopathy develops in 1%-2% of patients infected with HIV and usually occurs in the context of advanced AIDS stage [22, 41], being associated with the progressive development of congestive heart failure [15] and arrhythmia [43]. Cardiomyopathy occurs as a result of direct invasion of HIV into myocytes [42], which leads to a lymphocytic infiltrate of the myocardium with necrosis of adjacent cells [43]. Among HIV-IP, acute myocarditis is an important cause of cardiomyopathy [42] and a possible contributing factor to systolic dysfunction due to dilation of the cardiac chambers, namely, the left ventricle [41]. Factors that may explain the development of cardiomyopathy in the context of HIV infection are the cardiotoxicity of the virus itself [44] and some ART regimen drugs [34], nutritional deficiencies (namely vitamin B12, selenium, vitamin B1, carnitine, zinc, and β-carotene) [28] and the toxic effects of alcohol

Table 1. Summary data regarding the impact of human immunodeficiency virus (HIV) on cardiovascular disease, particularly CAD and ACS.

Follow-up	Size	Findings	References
5.9 years	82459 273350 HIV+ 55109 HIV-	Increased risk of MI among HIV+ patients (HR: 1.48; 95% CI: 1.27-1.72; $p < 0.0001$).	Freiberg *et al*. [20]
5.9 years	81322 33% HIV+	HIV+ veterans without major CVD risk factors had a 2-fold increased risk of MI compared with HIV- veterans without major CVD risk factors (HR: 2.0; 95% CI: 1.0-3.9; $p = 0.044$).	Paisible *et al*. [37]
6 years	74958 HIV+	The risk of MI was higher in both HIV+ men and women compared with the general population; Standardized mortality ratio: 1.4 (95% CI: 1.3-1.6; $p < 0.0001$) for HIV+ men and 2.7 (95% CI: 1.8-3.9; $p < 0.0001$) for HIV+ women compared with the general population.	Lang *et al*. [38]
(Data not presented in the original article [39])	618 HIV+ 383 HIV- men	HIV-infected men had a greater prevalence of coronary artery calcification (PR: 1.21; 95% CI: 1.08; $p = 0.001$) and any plaque (PR: 1.14; CI: 1.05-1.24; $p = 0.001$), than uninfected men.	Post *et al*. [40]

ACS: Acute coronary syndrome; CAD: Coronary artery disease; CI: Confidence interval; CVD: Cardiovascular disease; HIV: Human immunodeficiency virus; HR: Hazard ratio; MI: Myocardial infarction; PR: Prevalence ratio.
Adapted from Shahbaz *et al*. (2015) [39].

and/or illicit drugs [22]. To note, previous studies report a higher proportion of HIV-IP using illicit drugs when compared to HIV-uninfected patients [45, 46], as well as a higher prevalence of alcohol consumption [6].

Pulmonary hypertension affects an estimated 0.5% of individuals infected with HIV [41]. Though it is a rare condition, the mortality rate is high [28] and the 1-year survival rate is reported to range between 51% to 88% [42]. Its pathophysiology is thought to be related to the release of endothelin-1 and cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF) by HIV-stimulated host-cells, which ultimately causes endothelial damage and consequently smooth muscle and fibroblast proliferation [22, 42].

Pericardial disease is also a frequent condition in HIV-IP. Unlike cardiomyopathy, pericardial effusions may occur at any point in the course of HIV infection [22], being caused by *Mycobacterium tuberculosis*, fungi, viral and other opportunistic microorganisms [41]. In patients with AIDS, it may also be due to metastatic invasion of non-Hodgkin's lymphoma and/or Kaposi's sarcoma which are the most common cardiac tumours in HIV-infected individuals [22]. As in the general population, individuals living with HIV infection are at a higher risk of developing metastatic and secondary, rather than primary cardiac tumours [28].

In the context of arrhythmias, several medications used in the treatment of HIV infection are related to QT interval prolongation [42] and *torsades des pointes* [28] which can lead to sudden cardiac death [47]. Hence, it is advisable, as in the general population, to perform an electrocardiogram in HIV-IP [35] to assess the presence of ST segment variations and the corrected QT (QTc) interval [10, 15] before starting HAART [35]. The monitoring of these parameters is particularly important when ART is combined with other drugs with a potential QTc interval prolongation effect [15] (Table **2**).

Finally, among the HIV-infected population, infective endocarditis (mainly caused by *Staphylococcus aureus* and *Streptococcus viridans*) [18] is a manifestation seen almost exclusively in those individuals who concomitantly use drug injections [48] as a result of the side effects of prolonged ART therapy [2, 11, 17, 25, 26].

3.2. Pathophysiology of CVD in HIV Infection

The mechanisms proposed to explain the pathogenesis of serious non-AIDS events and the increased cardiovascular risk in HIV-IP are multiple and include, among other causes, viral direct effects (persistent immune activation [2], systemic inflammation [49, 50], endothelial dysfunction and increased thrombotic activity), as well as indirect metabolic disorders, such as dyslipidemia, lipodystrophy and insulin resistance, elicited by the infection itself and as a result of the side effects of prolonged ART therapy [2, 11, 17, 25, 26].

Table 2. Drugs commonly used by HIV-infected patients with potential QTc interval prolongation effect.

Medication	Use in HIV
NNRTIs (In interaction with other classes of drugs, *e.g*. calcium channel antagonists, warfarin, β-adrenoceptor antagonists, nifedipine, quinidine, corticosteroids and theophylline)	HAART
PIs Ritonavir (may significantly increase the QTc interval when taken with saquinavir)	
Antibiotics Erythromycin Trimethropim/sulfamethoxazole Ciprofloxacin Clarithromycin Pentamidine Pyrimethamine Fluroquinolones Amphotericin B Azole antifungals	HIV-related infections and opportunistic infections
Psychotropic agents Tricyclic antidepressants Phenothiazines Haloperidol	Psychotic disorders
Antihistamines Astemizole Terfenadine	Allergic reactions
Methadone	Maintenance treatment of opioid dependency

HAART: Highly active antiretroviral therapy; HIV: Human immunodeficiency virus; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; PIs: Protease inhibitors; QTc: Corrected QT. Adapted from Fisher *et al*. (2011) [28], Conte *et al*. (2013) [22] and Pham & Torres (2015) [10].

3.2.1. The Role of Traditional Risk Factors

As has been documented by previous studies, traditional CVD risk factors that contribute to the pathogenesis of cardiovascular conditions appear to be more common in the HIV-infected population [2, 11, 21]. Triant [51] observed a greater incidence of hypertension (HIV: 21.2 *vs*. non-HIV: 15.9%; $p < 0.001$), diabetes (HIV: 11.5 *vs*. non-HIV: 6.6 %; $p < 0.0001$) and dyslipidemia (HIV: 23.3 *vs*. non-HIV: 17.6 %; $p < 0.0001$) in HIV-positive patients compared to a control group of HIV-negative individuals.

Dyslipidemia in the HIV infection setting is usually characterized by low high-density lipoprotein (HDL)-cholesterol [52] and increased triglyceride concentration [18, 53, 54]. On the other hand, HIV is an independent risk factor for diabetes [52], a well-known component of the metabolic syndrome [55].

Others determinants of CVD that appear to be overrepresented in HIV-IP are lifestyle factors (cigarette smoking, sedentary life, stress) and abdominal obesity [21].

3.2.2. The Role of the Virus: A Guilty on its Own

Besides the onset of immunodeficiency, HIV seroconversion is characterized by hyperactivation of both adaptive and innate immune systems [23, 36, 56] and chronic inflammation [23, 56]. The continuous immune activation might lead to a permanent T-cell, monocyte and macrophage-related state of inflammation [57] that is not completely reversed under maintained virological suppression with combined ART [2, 17, 23, 49, 51, 58-61]. Hence, the persistent virion production at low levels enables the inflammatory state to carry on indefinitely [23]. This permanent state of immune activation and inflammation observed in HIV-IP may be due to various factors, including: (1) homeostatic drive which might explain the impaired immunological and inflammatory response even after the reduction of the initial stimulus [17], (2) compromised gut mucosa barrier by rapid depletion of local CD4+ T-cells caused by the virus [6, 23], resulting in subsequent translocation of microbial products [57, 62] like lipopolysaccharides [19, 23], that set a persistent state of antigen stimulation [52] and might enhance the activation of monocytes and macrophages [11, 14, 19, 23, 62-64], (3) residual non-detected viremia [19, 23] and (4) proinflammatory effects of ART drugs [17].

The permanent state of inflammation in HIV-infection also causes an interaction with coagulation factors, which usually leads to endothelial dysfunction and a hypercoagulation state [2, 11, 65], increasing the risk for the occurrence of cardiovascular events [56].

On the other hand, HIV is directly implicated in the development of well-known traditional CVD risk factors. In treatment-naïve patients, the levels of viremia are directly related to elevated serum concentrations of triglycerides and low levels of HDL cholesterol [7], which is supported by Gibellini *et al*. [66], that report alterations in lipoproteins and their concentrations determined by the virus, inducing an accelerated development of atherosclerosis.

Ultimately, increased levels of activated T-cells and monocytes, as well as inflammatory and coagulation markers, are ongoing conditions in HIV-IP [6], even with continuous successful ART regimens [56, 58, 60, 67]. However, despite the well-documented systemic inflammation in HIV-IP, there has been no proved benefit of adding anti-inflammatory drugs to ART on improving clinical CVD endpoints [68].

3.2.3. The Role of Antiretroviral Therapy

According to the 2016 recommendations from the European AIDS Clinical Society (EACS), ART must be initiated in all HIV-infected persons with primary infection, with the indication to immediate treatment in the following cases: (1) CD4+ count less than 350 cells/μL, (2) age ≥ 50 years, (3) concomitant neurological diseases, (4) presence of severe or prolonged symptoms, and (5) acute infection, which is defined by the detection of p24 antigen and/or Human Immunodeficiency Virus-ribonucleic Acid (HIV-RNA) in the absence of HIV antibody [69].

This therapeutic regimen is composed of a minimum of 3 antiretroviral drugs from different classes combined [22, 70]. The classes that compose ART are protease inhibitors (PIs), Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), integrase inhibitors [36, 47] and C-C chemokine receptor 5 (CCR5) inhibitors [71, 72] (Table **3**).

Currently used ART regimens usually consist of combinations of two NRTIs with either one protease inhibitor, one non-nucleoside reverse transcriptase inhibitor or one integrase inhibitor (raltegravir) [10, 36, 70, 72] (Table **4**).

Table 3. Classes of antiretroviral therapy (ART) drugs and related adverse cardiovascular effects.

Class	Mechanism of Action	Drugs	Cardiovascular Effects
Protease Inhibitors (PIs)	Inhibit the viral protease that catalyses the cleavage of viral proteins essential for virus maturation.	Amprenavir Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir Tipranavir	Cardiotoxicity due to induction of dyslipidemia by mediating the expression of proinflammatory cytokines, increasing apoptosis and diminishing proliferation of peripheral adipocytes, contributing to biosynthesis of triglycerides in the liver, and promoting insulin resistance and lipodystrophy.

(Table 3) Contd…

Class	Mechanism of Action	Drugs	Cardiovascular Effects
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Inhibit reverse transcriptase, the enzyme involved in conversion of single-stranded HIV RNA into double-stranded DNA.	Abacavir Didanosine Tenofovir Emtricitabine Lamivudine Stavudine Zidovudine	Cardiotoxicity due to direct effect on mitochondrial enzymes, inhibition of nucleoside transport, inhibition of nucleoside phosphorylation and generation of reactive oxygen species in the mitochondria.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Inhibit reverse transcriptase, the enzyme involved in conversion of single-stranded HIV RNA into double-stranded DNA.	Efavirenz Etravirine Nevirapine Rilpivirine	Pharmacological interaction with other classes of drugs, *e.g*. calcium channel antagonists, warfarin, beta-adrenoceptor antagonists, nifedipine, quinidine, corticosteroids and theophylline.
Integrase inhibitors	Inhibit the viral integrase enzyme that catalyses the insertion of proviral DNA into the host genome.	Raltegravir	No specific cardiovascular side effects or drug interactions reported so far.
Entry and fusion inhibitors	Inhibit viral entry into host cells. Inhibit binding of HIV envelope glycoprotein to the CCR5 co-receptor.	Maraviroc Enfuvirtide	No specific cardiovascular side effects or drug interactions reported so far.

CCR5: C-C chemokine receptor 5; DNA: Desoxyribonucleic acid; Glut-4: Glucose transporter type 4; HIV: Human immunodeficiency virus; RNA: Ribonucleic acid.
Adapted from Fisher *et al*. (2011) [28] and Garg *et al*. (2013) [36].

Table 4. Initial combination ART regimens for adult HIV-positive persons (one of the following to be selected), according to European AIDS Clinical Society (2016).

Regimen	Dosing	Cautions
2 NRTIs + INSTI		
ABC/3TC/DTG[I,II]	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd	Al/Ca/Mg-containing antacids or multivitamins should be taken well separated in time (minimum 2h after or 6h before). DTG 50 mg bid with rifampicin.
TAF/FTC[III] or TDF/FTC[IV,V] + DTG	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd	
TAF/FTC[III] or TDF/FTC[IV,V] + RAL	TAF/FTC/RPV 25/200/25 mg, 1 tablet qd or TDF/FTC/RPV 300/200/25 mg, 1 tablet qd	Co-administration of antacids containing Al or Mg not recommended. RAL 400 or 800 mg bid with rifampicin.
TAF/FTC/EVG/c[III] or TDF/FTC/EVG/c[IV,VI]	TAF/FTC/EVG/c 10/200/150/150 mg, 1 tablet qd or TDF/FTC/EVG/c 300/200/150/150 mg, 1 tablet qd	Al/Ca/Mg-containing antacids or multivitamins should be taken well separated in time (minimum 2h after or 6h before).
2 NRTIs + NNRTI		
TAF/FTC/RPV[III] or TDF/FTC/RPV[IV]	TAF/FTC/RPV 25/200/25 mg, 1 tablet qd or TDF/FTC/RPV 300/200/25 mg, 1 tablet qd	Only if CD4 count > 200 cells/μL and HIV-VL < 100,000 copies/mL. PPI contra-indicated. H2 antagonists to be taken 12h before or 4h after RPV.
2 NRTIs + PI/r or PI/c		
TAF/FTC[III] or TDF/FTC[IV,V] + DRV/c or + DRV/r	TAF/FTC 10/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd DRV/c 800/150 mg, 1 tablet qd or + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	Monitor in persons with a known sulfonamide allergy.

[I] ABC should be used with caution in persons with a high CVD risk (>20%).
[II] Use this combination only if HBsAg-negative.
[III] When available, combinations containing TDF can be replaced by the same combinations containing TAF, especially in elderly HIV-positive persons or in HIV-positive persons with or at increased risk of osteoporosis or renal impairment. Use TAF/FTC/EVG/c only if eGFR > 30mL/min. TAF may have a lower risk of tenofovir-related kidney and bone adverse effects but long-term experience is lacking.
[IV] Avoid TDF if osteoporosis.
[V] If TDF/FTC is not available, one alternative could be TDF+3TC, as separate entities.
[VI] TDF/FTC/EVG/c use only if eGFR ≥ 70 mL/min. It is recommended that TDF/FTC/EVG/c is not initiated in persons with eGFR < 90 mL/min, unless this is the preferred treatment.
3TC: Lamivudine; ABC: Abacavir; ART: Antiretroviral therapy; bid: Twice daily; CVD: Cardiovascular disease; DRV: Darunavir; DTG: Dolutegravir; eGFR: Estimated glomerular filtration rate; EVG: Elvitegravir; FTC: Emtricitabine; HIV: Human immunodeficiency virus; HIV-VL: Human immunodeficiency virus-viral load; INSTI: Integrase strand transfer inhibitor; NNRTI: Non-nucleoside reverse transcriptase inhibitors; NRTIs: Nucleos(t)ide reverse transcriptase inhibitors; PI: Protease inhibitors; PI/c: Protease inhibitors pharmacologically boosted with cobicistat; PI/r: Protease inhibitors pharmacologically boosted with ritonavir; PPI: Proton pump inhibitor; qd: Once daily; RAL: Raltegravir; RPV: Rilpivirine; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate.
Adapted from Battegay *et al.* (2016) [69].

HAART was introduced in the treatment of HIV infection with the goal of restoring CD4+ T-cell immunity by suppressing HIV replication [6, 22], which on its turn contributes to reduce immune activation and systemic inflammation elicited by the virus [17]. Although this goal is broadly achieved in the majority of the patients, the role of HAART in the development of CVD in HIV-infected individuals, particularly its contribution to the atherogenic process [4, 15, 21, 46, 73], is well documented. In a study by Islam *et al*. [3], a greater risk of CVD in people living with HIV infection was found to be associated with ART, particularly with PIs, and prolonged duration of treatment. This study presented a relative risk (RR) of 1.52 [95% confidence interval (CI) 1.35-1.70; p = 0.001] for CVD in HIV-infected individuals who were treated with ART, compared with treatment-naïve HIV-IP, and a RR for CVD of 2.00 (95% CI 1.70-2.37; p < 0.001) among HIV-IP on ART compared with HIV-uninfected people. Nevertheless, other studies are not in accordance with these findings and document a reduced risk of CVD in HIV-IP treated with ART [56, 62, 74], further highlighting the beneficial effects of this therapeutic regimen on suppressing HIV replication [62, 74], reducing immune activation [66, 74], systemic inflammation [5, 62, 74] and endothelial activation [56].

3.2.3.1. The Metabolic Effects of Antiretroviral Therapy

HIV-infected individuals receiving ART present a cluster of metabolic complications [36] namely dyslipidemia [5, 11, 73] with elevated triglycerides [19, 75] and low-density lipoprotein (LDL) cholesterol [11, 18], impaired glucose metabolism [5, 19, 25] and lipodystrophy [11, 13, 21, 25, 71].

Individuals treated with older antiretroviral drugs like PIs [71] may develop lipoatrophy in the face and limbs as well as lipohypertrophy with central visceral fat gain [4, 11, 31, 65], fat deposition on the neck region ("buffalo hump") [4, 11] or ectopic fat deposition in the myocardium. In particular, ectopic fat deposition in cardiomyocytes might be one possible mechanism contributing to the high CVD burden observed in HIV-IP treated with HAART [76]. On the other hand, lipodystrophy in these patients is also a risk factor for pancreatic β-cell dysfunction [52] which might exacerbate insulin resistance [13] and thus leading to the development of diabetes [14].

It has been shown that PIs induce metabolic changes [75, 77, 78] like dyslipidemia [2, 28, 79] and insulin resistance [72], contributing to the formation of atherosclerotic lesions [22, 28, 46, 65].

Among other causes, the lipid metabolism impairment with PIs seems to be associated with the following aspects: (1) binding of PIs to the C-terminal region of Cytoplasmic Retinoic Acid Binding Protein Type 1 (CRABP1), promoting apoptosis and diminishing the proliferation of peripheral adipocytes; (2) PIs-mediated increase in the expression and secretion of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6, which contributes to decrease the levels of adiponectin and deregulate adipocyte functions; (3) suppression of proteasome-mediated degradation of Sterol Regulatory Element-Binding Proteins (SREBPs) in the liver and adipocytes, promoting an increase in the biosynthesis of triglycerides, and to a lesser extent, very-low density lipoprotein cholesterol [80, 81].

Besides their documented contribution to the development of lipid metabolism impairment and dyslipidemia, PIs also appear to be directly related to an increased risk of ACS, particularly, MI [14, 54] (Table **5**).

Similar to PIs, NRTIs older drugs (zidovudine [10], stavudine and didanosine [53]) induce dyslipidemia [53, 82] and insulin resistance. A relationship between older generation NRTIs and lipoatrophy has also been described [82]. However, according to Kelesidis & Currier [7], other drugs from this class, namely tenofovir, lamivudine and emtricitabine, seem to not be associated with lipid metabolism impairment, although other authors disagree with these findings (Table **6**).

Table 5. Summary of studies regarding the risk of MI among HIV-infected individuals treated with PIs.

Study	Findings	Reference
Case-control study 289 cases (patients with prospectively recorded first MI) 884 controls	Cumulative exposure to any protease inhibitor was associated with an increased risk of MI, except for saquinavir (OR per year: 1.15; 95% CI: 1.06-1.26; p = 0.002).	Lang *et al*. [84]
Multi-cohort study [Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study]	Cumulative exposure to indinavir or lopinavir/ritonavir was associated with an increased risk of MI (relative rate [RR] per year: 1.12; 95% CI: 1.07-1.18; p < 0.0001 and 1.13; 95% CI: 1.05-1.21; p = 0.001, respectively); No association for saquinavir or nelfinavir was found.	Worm *et al*. [85]
Meta-analysis 27 studies (8 studies included in formal meta-analysis)	Increased risk of MI for patients recently exposed (usually defined as within last 6 months) to PIs (RR: 2.13; 95% CI 1.06-4.28; p = 0.003).	Bavinger *et al*. [86]
Meta-analysis 11 studies	Incidence of MI in patients exposed to PIs showed an overall significant risk (OR: 2.68; 95% CI 1.89-3.89; p < 0.0001).	D'Ascenzo *et al*. [8]

HIV: Human immunodeficiency virus; MI: Myocardial infarction; OR: Odds ratio; PIs: Protease inhibitors; RR: Relative risk.

Globally, PIs and NRTIs are associated with a higher risk of CVD events. Tripathi *et al*. [32] report the RR of CVD associated with PIs and NRTIs to be 1.11 (95% CI 1.05-1.17; p = 0.002) and 1.05 (95% CI 1.01-1.10; p = 0.098) per year of exposure, respectively.

Among integrase inhibitors, raltegravir has shown no deleterious effects on the lipid metabolism [2] nor in the cardiovascular system [72, 74]. The same metabolic and neutral cardiovascular effect profile has been exhibited by some NNRTIs [36, 53, 83] and newer classes of ART drugs like CCR5 inhibitors [53, 74] (Table **6.A**).

Given the toxicity associated with some ART drugs, HIV-infected individuals should therefore be evaluated for serum concentration of lipids and fasting blood glucose levels before the initiation of HAART [48], at 3 to 6 months after initiation [18, 34], and once each year [28] in the absence of abnormalities [70] (Table **7**).

Table 6. Metabolic disorders associated with ART drugs: glucose and lipid metabolism impairment (A) and HIV-associated lipodystrophy syndrome (B).

A – Global impact of HAART drugs on glucose and lipid metabolism [81, 87].

Antiretroviral Class	Drugs	Effects on Glucose	Effects on Lipids			
			-	TG	LDL	HDL
Protease Inhibitors (PIs)	Amprenavir/ritonavir	Insulin resistance	↑↑↑ Dyslipidemia	Increase	Increase	Same/decrease
	Atazanavir/ritonavir	Insulin resistance	a)			
	Darunavir/ritonavir	Insulin resistance	↑ Dyslipidemia	Increase	Increase	Same/decrease
	Fosamprenavir/ritonavir	Insulin resistance	↑↑↑ Dyslipidemia	Increase	Increase	Same/decrease
	Indinavir	Insulin resistance	↑↑ Dyslipidemia			
	Lopinavir/ritonavir	Insulin resistance	↑↑↑ Dyslipidemia	Increase	Increase	Same/decrease
	Nelfinavir	Insulin resistance	↑↑ Dyslipidemia			
	Saquinavir	Insulin resistance	↑ Dyslipidemia			
	Tipranavir/ritonavir	Insulin resistance	↑↑↑ Dyslipidemia	Increase	Increase	Same/decrease
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Abacavir	No effect	↑ Dyslipidemia	Increase	Increase	Increase
	Didanosine	Insulin resistance	↑↑ Dyslipidemia			
	Tenofovir	No effect	↑ Dyslipidemia	Increase	Increase	Increase
	Emtricitabine	No effect	↑ Dyslipidemia	Increase	Increase	Increase
	Lamivudine	No effect	↑ Dyslipidemia			
	Stavudine	Insulin resistance	↑↑ Dyslipidemia	Increase	Increase	Increase
	Zidovudine	Insulin resistance	↑↑ Dyslipidemia	Increase	Increase	Increase
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Efavirenz	No effect	↑ Dyslipidemia	Increase	Increase	Increase
	Etravirine	No effect	Neutral effect			
	Nevirapine		↑Dyslipidemia	Increase	Increase	Increase
	Rilpivirine		Neutral effect			
Integrase inhibitors	Dolutegravir	No effect	Neutral effect			
	Elvitegravir	No effect	Neutral effect	Increase	Increase	Increase
	Raltegravir	No effect	Neutral effect			
Entry and fusion inhibitors	Maraviroc	No effect	Neutral effect			
	Enfuvirtide	No effect	Neutral effect			

a) Atazanavir is an exception to all ritonavir boosted PIs, since it has fewer effects on the lipid metabolism.
ART: Antiretroviral therapy; HAART: Highly active antiretroviral therapy; HDL: High-density lipoprotein; HIV: Human immunodeficiency virus; LDL: Low-density lipoprotein; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NRTIs: Nucleoside reverse transcriptase inhibitors; PIs: Protease inhibitors; TG: Triglycerides.

B – Prevention and management of lipodistrophy, according to European AIDS Clinical Society (2016) [69].

-	Lipoatrophy	Lipohipertrophy
Clinical findings [81]	Sunken eyes and/or cheeks, prominent zygomatic arch, prominent veins, skinny or muscular appearance, loose skin folds	Increased abdominal girth with visceral fat accumulation, dorsocervical or supraclavicular fat pad
Prevention	• Avoid use of stavudine and zidovudine • Avoid excessive weight loss due to diet and exercise	• Avoid inhaled fluticasone (and potentially other inhaled corticosteroids) with ritonavir or cobicistat-boosted PIs as it may cause Cushing syndrome or adrenal insufficiency
Management	• Modification of ART — Switch stavudine or zidovudine to abacavir or tenofovir (only ART modification proven to partially restore subcutaneous fat: increase in total limb fat ~ 400-500 g/year) — Switch to regimen not including NRTIs (increase in total limb fat ~ 400-500 g/year) • Surgical intervention — For cosmetic relief of facial lipoatrophy	• Diet and exercise may reduce visceral adiposity — Although there is limited data regarding this matter, there is a possible reduction in visceral adipose tissue and improvement in insulin sensitivity and blood lipids — May worsen subcutaneous lipoatrophy • Pharmacological interventions to treat lipohypertrophy have not been proven to provide long-term effects • Growth hormone (not approved for this indication in Europe) — Decreases visceral adipose tissue — May worsen subcutaneous lipoatrophy and insulin resistance • Metformin (not approved for this indication in Europe) — Decreases visceral adipose tissue in insulin resistant people — May worsen subcutaneous lipoatrophy • Surgical therapy can be considered for localised lipomas/"buffalo humps"

AIDS: Acquired immunodeficiency syndrome; ART: Antiretroviral therapy; NRTIs: Nucleoside reverse transcriptase inhibitors; PIs: Protease inhibitors.
Adapted from da Cunha *et al*. (2015) [81], Battegay *et al.* (2016) [69] and Seecheran *et al*. (2017) [87].

Table 7. Assessment of cardiovascular risk factors for ART-naïve HIV-infected individuals, according to European AIDS Clinical Society (2016).

-	At HIV Diagnosis	Before Starting ART	Follow-up Frequency
Body composition Body-mass index	+	+	Annual
Cardiovascular disease risk Framingham score	+	+	2 years
ECG	+	+/-	As indicated for each case
Hypertension Blood pressure	+	+	Annual
Lipids TC, HDL-c, LDL-c, TG	+	+	Annual
Glucose Serum glucose	+	+	Annual

ART: Antiretroviral therapy; ECG: Electrocardiogram; HDL-c: High-density lipoprotein cholesterol; HIV: Human immunodeficiency virus; LDL-c: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglycerides.
Adapted from Battegay *et al*. (2016) [69].

Taken together, in spite of the CVD risk that has been proven to be associated with ART, the beneficial effects of this therapeutic regimen (by reducing CVD-related morbidity and mortality in HIV-IP [11, 88]) appear to outpass the risks [4, 14, 15, 17, 30, 41, 51]. Furthermore, the Strategies for Management of Antiretroviral Therapy (SMART) trial showed that ART interruption in patients with chronic HIV infection whose CD4 cell count reached greater than 350 cells/mm^3, was associated with a higher rate of major cardiovascular events when compared to HIV-IP receiving continuous treatment [hazard ratio (HR) 1.6; 95% CI 1.0–2.5; p = 0.03] [89].

Nevertheless, health care providers should be aware of the multiple pharmacological interactions between ART components and other class drugs (Table **8**), that may aggravate HAART-associated cardiovascular complications, abolish or reduce the therapeutic effect of other concomitant treatment regimens and/or lead to the development of adverse reactions [69].

Table 8. Drug-drug interactions between antiretroviral drugs and non-antiretroviral cardiovascular drugs, according to European AIDS clinical society (2016).

-			ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	EVG/c	TAF	TDF
ANTIHYPERTENSIVES	Angiotensin antagonists	Candesartan												
		Irbesartan	↓		↓	↓	↑	↑				↓		
		Losartan	↓[a]		↓[a]	↓[a]	↑[b]	↑[b]				↓[a]		
		Olmesartan												
		Telmisartan												
		Valsartan												
	β blockers	Atenolol	↔[c]			↔[c]								
		Bisoprolol	↑[c]	↑	↑	↑[c]	↓	↓	↓			↑		
		Carvedilol	↑↓[c]	↑	↑↓	↑↓[c]	↑↓	↑↓				↑		
		Metoprolol	↑[c]	↑	↑	↑[c]						↑		
		Propranolol	↑[c]	↑	↑	↑[c]						↑		
	Calcium channel blockers	Amlodipine	↑[d]	↑	↑	↑[e]	↓	↓	↓			↑		
		Diltiazem	↑[d]	↑	↑	↑[e]	↓	↓	↓			↑		
		Felidipine	↑[d]	↑	↑	↑[e]	↓	↓	↓			↑		
		Lacidipine	↑[d]	↑	↑	↑[e]	↓	↓	↓			↑		
		Lercanidipine					↓	↓	↓					
		Nicardipine	↑[d]	↑	↑	↑[e]	↓	↓	↓			↑		
		Nifedipine	↑[d]	↑	↑	↑[e]	↓	↓	↓			↑		
		Nisoldipine	↑[d]	↑	↑	↑[e]	↓	↓	↓			↑		
		Verapamil	↑[d]	↑	↑	↑[e]	↓	↓	↓			↑		
	Diuretics	Amiloride												
		Chlortalidone												
		Furosemide												
		Indapamide	↑	↑	↑	↑	↓	↓	↓			↑		
		Torasemide	↓		↓	↓	↑	↑				↓		
	Others	Doxazosin	↑	↑	↑	↑	↓	↓	↓			↑		
		Spironolactone												
ANTICOAGULANTS	Acenocoumarol		↓		↓	↓	↓	↑	↓			↓		
	Apixaban						↓	↓	↓			↑		
	Dabigatran		↑	↑	↑	↑?				↑?		↑		
	Dalteparin													
	Edoxaban		↑	↑	↑	↑						↑		
	Enoxaparin													
	Fondaparinux													
	Heparin													
	Rivaroxaban						↓	↓	↓			↑		
	Warfarin		↑or↓[f]	↑	↓	↓	↑or↓	↑	↑or↓			↓		
ANTIPLATELET AGENTS	Aspirin													[g]
	Clopidogrel		↓[h]	↓[h]	↓[h]	↓[h]	↑[i]	↓[h]	↑[i]			↓[h]		
	Dipyridamole		↓[j]		↓	↓	↓	↓						
	Prasugrel											[k]		
	Ticagrelor						↓	↓	↓			↑		

↑ potential elevated exposure of the non-ARV drug; ↓ potential decreased exposure of the non-ARV drug; ↔ no significant effect when used simultaneously; a) [parent drug] decreased, but [active metabolite] increased; b) [parent drug] increased, but [active metabolite] decreased; c) risk of PR interval prolongation; d) ECG monitoring recommended; e) use with caution as both LPV and calcium channel blockers prolong the PR interval; f) unboosted ATV predicted to increase the anticoagulant, monitor INR; g) potential risk of nephrotoxicity, monitor renal function; h) an alternative to clopidogrel should be considered, since there is decreased conversion to the active metabolite; i) the amount of active metabolite increases via induction of CYP3A4 and CYP2B6; j) unboosted ATV predicted to increase dipyridamole exposure due to UGT1A1 inhibition; k) reduced active metabolite, but without a significant reduction in prasugrel activity.

☐ No clinically significant interaction expected; ▢ These drugs should not be co-administered; ▩ Potential interaction, which may require a dosage adjustment or close monitoring; ■ Potential interaction predicted to be of weak intensity (< 2 fold ↑AUC or < 50% ↓AUC); a dosage adjustment is *a priori* not recommended.

Note: Angiotensin-converting-enzyme inhibitors present no significant pharmacological interactions with any of the ART drugs depicted above. DTG, RAL, ABC, FTC, 3TC and ZDV, which are not included in the table, present no significant drug-drug interactions with antiplatelet agents, anticoagulants nor antihypertensive drugs.

3TC: Lamivudine; ABC: Abacavir; ACE; ARV: Antiretroviral; ATV/r: Atazanavir pharmacologically boosted with ritonavir; AUC: Area under the curve; DRV/c: Darunavir pharmacologically boosted with cobicistat; DRV/r: Darunavir pharmacologically boosted with ritonavir; DTG: Dolutegravir; ECG: Electrocardiogram; EFV: Efavirenz; ETV: Etravirine; EVG/c: Elvitegravir pharmacologically boosted with cobicistat; FTC: Emtricitabine; LPV: Lopinavir; Lopinavir/r: Lopinavir pharmacologically boosted with ritonavir; MVC: Maraviroc; NVP: Nevirapine; RAL: Raltegravir; RPV: Rilpivirine; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate; UGT1A1: UDP glucuronosyltransferase family 1 member A1; ZDV: Zidovudine. (Adapted from Battegay *et al.* (2016) [69]).

3.3. Atherosclerosis and HIV Infection: The Host, the Virus and the Therapeutic Perspective

The development of atherosclerosis in HIV-IP is a complex and multifactorial process in which the effects of the virus *per se* [14, 90], higher exposure to traditional CVD risk factors [14, 50], long-term ART treatment [14, 90-92] and genetic predisposition intervene simultaneously [50].

The stimulation of proatherogenic mechanisms in HIV infection is intimately related to the ability of the virus and particularly some viral proteins to elicit endothelial activation, increase endothelial permeability and promote apoptosis [66]. Thus, endothelial dysfunction is perceived as an impaired ability of the vascular lining to maintain normal homeostasis and occurs in the early stages of atherogenesis [49, 72].

An impaired endothelium facilitates the entrance of plasma lipids like LDL into the subendothelial space, where, due to the excessive concentration of free radicals [25], the particles are oxidized [16]. Oxidized low-density lipoproteins then penetrate the intima of the arterial wall, triggering the exposure of Monocyte Chemoattractant Protein-1 (MCP-1) [93], which promotes the recruitment of circulating leukocytes (namely monocytes) [66]. The so recruited leukocytes up-take oxidized low-density lipoproteins forming "foam cells" [22, 94] that release inflammatory cytokines such as TNF-α, Interferon-γ (IFN-γ) [25], Interleukin-1 (IL-1), IL-6 and interleukin-8 (IL-8) [28, 95], as well as Vascular Cell Adhesion Molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin [56, 95] and von Willebrand Factor (vWF) [28, 95]. In the particular setting of HIV infection, the synthesis of inflammatory cytokines by macrophages and the expression of adhesion molecules appear to be closely related to the action of HIV trans-activator of transcription (Tat) [66] and envelope protein Gp120, leading to endothelial activation and increased endothelial permeability [95].

Besides being the hallmark of the atherogenic process, endothelial dysfunction also contributes to a hypercoagulability state [25]. Platelets interact with exposed subendothelial structures when the endothelium is injured through adhesive receptors on both platelets and endothelial cells, thus initiating the aggregation process. Platelet activation in the presence of endothelial dysfunction might also be explained by the loss of platelet-inhibiting mediators namely Nitric Oxide (NO) and prostacyclin (PGI2) [95]. On the other hand, viral replication itself may partially promote coagulation by up-regulating tissue-factor pathways [73].

Although the atherosclerotic process may be similar in both HIV-infected and non-infected populations, the accelerated atherogenic process that occurs in the course of the infection [6, 25, 96, 97] is characterized by an increased formation of non-calcified [25, 50, 98, 99] atypical plaques [31], that due to their thin fibroatheroma caps are prone to erosion [46] or rupture [19, 31, 99], thus conditioning a higher risk of CVD-related events [31, 74, 100]. Furthermore, endothelial dysfunction is more prevalent in untreated HIV-IP when comparing with age and gender-matched controls [56], and the macrophage activation that occurs in HIV infection and actively contributes to subclinical atherosclerosis [11] is independent of traditional CVD risk factors [64].

Another possible explanation for the ongoing development of chronic inflammatory conditions in HIV-infected individuals, such as atherosclerosis, is the activity of negative regulatory factor (Nef) protein. This protein, encoded by lentoviruses like HIV-1, is transferred from circulating monocytes and T-cells infected by the virus into endothelial cells, conditioning activation of the endothelium. On another hand, this activation process, particularly in the pro-inflammatory state that characterizes HIV infection, leads to increased chemokine expression, thus promoting T-cell and monocyte adherence to endothelial cells [49]. Furthermore, Nef protein mediates down-regulation of ATP binding cassette transporter 1 (ABCA1) which ultimately reduces cholesterol removal from macrophages [64, 101].

3.4. Coronary Heart Disease and Acute Coronary Syndrome

As successful HAART decreased severe immunosuppression-related complications, HIV-IP are currently facing new challenges such as CHD [14, 15, 90]. Although there are some discordant data regarding this matter, current evidence suggests that ACS is more frequent in HIV-infected individuals when comparing to the uninfected counterparts [22] and it is the main clinical presentation of CHD in the setting of infection [14, 70]. In a prospective study of more than 27,000 HIV-IP from the Veterans Aging Cohort Study (VACS) Virtual Cohort, Acute Myocardial Infarction (AMI) risk among HIV-positive veterans with no major CVD risk factors was 2-fold greater than among those who were HIV-negative with the same no major CVD risk factor profile [37].

In HIV-infected individuals, the first manifestation of ACS tends to occur at a younger age [24, 33, 41] (around 50 years old) in current smoking men previously exposed to PIs or NRTIs [41, 45]. In a meta-analysis conducted by D'Ascenzo *et al*. [8], the most common ACS presentation at admission was ST-segment Elevation Myocardial Infarction (STEMI), with a prevalence of 57.19% (95% CI 47.64-66.75), which is in accordance with the results presented by Boccara *et al*. [45] and Lang *et al*. [14]. Other less common forms of ACS in the HIV-infected population are unstable angina and non-ST-segment elevation MI [22], with a global prevalence of 46.08% (95% CI 38.13-54.02) among HIV-IP admitted with a clinical presentation of ACS [8]. The increased risk of CAD in the HIV-infected population [10, 25, 42] is intimately related to the progression of the premature atherogenic process in the intima of arterial coronary vessels [46, 66]. When atherosclerotic plaques become unstable and rupture, partial or total thrombotic occlusion is elicited [19, 99] and acute ischemic events might occur [6].

Furthermore, the immunologic state and viremia appear to be related to ACS in the setting of HIV infection. D'Ascenzo *et al*. [92] found a significant association between a CD4+ cell count less than 200 cells/mm^3 and the risk of AMI. Lang *et al*. [54] corroborate these findings reporting that low CD4+ T-cell nadir and HIV-RNA levels >50 copies/mL increase the risk of MI [Odds Ratio (OR) 1.51; 95% CI 1.09-2.10; p = 0.01] in HIV-infected individuals.

Taken together, HIV and ART, by eliciting lipid abnormalities, insulin resistance and lipodystrophy [33, 70] may contribute to the development of CAD [3]. A large observational study from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study group demonstrated that prolonged exposure to combined ART increases the incidence of MI, showing an RR of MI per year of PIs exposure of 1.16 (95% CI 1.10-1.23; $p < 0.0001$) [102].

3.4.1. Managing Acute Coronary Syndrome in HIV-IP

The management of ACS in HIV-infected individuals presents no difference when compared to the approach conducted in the general population, namely, what concerns the use of antithrombotic drugs such as aspirin, clopidogrel, ticagrelor, unfractioned heparin and low-molecular-weight heparin. Nevertheless, antithrombotic medications must be prescribed with caution, since HIV-IP often present coagulation disorders and thrombocytopenia, thus increasing the risk of severe bleeding events. Another concern regarding the use of anti-ischemic medications are the pharmacological interactions with other drugs, specifically the ones included in HAART regimens (Table **8**), due to the existence of common pathways of metabolism [87].

Regarding Percutaneous Coronary Intervention (PCI) and coronary artery bypass graft surgery in the set of HIV infection, Pham & Torres [103] report no difference in the short-term or long-term mortality, when comparing to HIV-uninfected individuals. Boccara *et al*. [45] further state that PCI can be safely performed during the acute phase of ACS in HIV-infected patients, with no difference in the rate of clinical restenosis or stent thrombosis after 12 months of a first episode of ACS, comparing to a age and sex-matched uninfected group. However, in the prospective multicentre study conducted by the authors, HIV-IP were more likely to present recurrent ACS (HR 6.5; 95% CI 1.7-23.9; $p = 0.005$) and to undergo urgent PCI at 1-year follow-up (OR 3.29; 95% CI 0.94-11.53; $p = 0.04$) than HIV-uninfected patients.

3.5. HIV Infection and Cardiovascular Risk Assessment

As HIV-infected population ages and rates of CVD-related events increase [103], appropriate cardiovascular assessment in these patients is needed to guide risk factor management and ART regimen choice, particularly in individuals at higher risk [104].

The currently available cardiovascular risk scores include Framingham risk score (FRS), Systematic Coronary Risk Evaluation (SCORE), DAD risk equation, Prospective Cardiovascular Münster Study (PROCAM) score, Reynolds, VACS and Pooled cohort equations [105] (Table **9**).

FRS, which was developed in the general population, is based on age, gender, systolic blood pressure, total and HDL cholesterol levels and smoking status. DAD risk equation, that was specifically developed to estimate cardiovascular risk in HIV-IP [88], adds to the FRS variables like family history of CVD, as well as duration and current use of antiretroviral drugs namely indinavir, lopinavir and abacavir [103, 106]. On the other hand, PROCAM, that differs from FRS by including variables such as triglyceride levels and family history of CHD, does not take into account the exposure to ART drugs [106].

Risk assessment models developed in the general population, namely FRS, may underestimate the true CVD-related events risk in HIV-infected individuals [25, 103, 107]. Results from previous studies suggest that the DAD equation is the most accurate predictor of subclinical atherosclerosis [104, 108] and CVD risk in HIV-IP [108].

Serrano-Villar *et al*. [104] found that FRS, SCORE and PROCAM equations underestimate the risk of subclinical atherosclerosis and therefore CVD risk in nearly 20% of the cases, proposing that non-invasive tools such as carotid ultrasound assessing Carotid Intima-media Thickness (CIMT) might be useful in the recognition of subclinical atherosclerosis in HIV-positive patients. Furthermore, the early detection of atherosclerotic plaques in subjects with HIV infection and with low measurable CVD risk factors might provide an important insight into the hazard of developing end-organ vascular damage [109]. This early detection might also be achieved in asymptomatic HIV-IP with carotid vessel wall imaging using cardiovascular magnetic resonance (CMR) [68]. Additionally, coronary computed tomography (CT) allows physicians to assess coronary artery calcification (CAC).

CAC is a marker of atherosclerosis with a high predictive profile for coronary events [16]. Nonetheless, since there is evidence of differing plaque morphology in patients with HIV [34, 99], some authors suggest that, on the contrary, CAC scanning may not adequately assess high-risk patients [50, 98]. In this regard, CT angiography scanning is thus presented as a valuable research tool to assess non-calcified coronary artery plaque burden and composition [50, 110]. Another non-invasive imaging tool used to evaluate arterial inflammation is ^{18}F-fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG-PET) [2, 31, 50, 100]. ^{18}F-fluorodeoxyglucose is taken up into metabolic pathways, hence allowing imaging of metabolically active cells in vulnerable plaque [31].

Mooney *et al*. [67] and Serrano-Villar *et al*. [104] suggest that standard risk assessment CVD scores like the DAD equation might also be further calibrated by incorporating markers of immune status, vascular damage [67, 104] and inflammation [108]. Supporting this hypothesis, previous findings from Miller *et al*. [111] show that higher levels of IL-6 and D-dimer, reflecting an activation of inflammatory [112] and coagulation pathways [22, 113, 114], are significant global predictors of mortality and non-AIDS complications, such as cardiovascular disease, in HIV-IP [HR 1.5; 95% CI 1.4-1.7; $p < 0.001$ (IL-6) and HR 1.4; 95% CI 1.3-1.6; $p < 0.001$ (D-dimer)] [111].

Collectively, the imaging modalities and biomarkers previously presented have elucidated new pathways for investigating the pathophysiology of arterial disease and increased CVD risk in patients with HIV infection [50] and thus may improve the prediction of CVD endpoints already achieved with established assessment risk scores such as FRS [25]. In this regard, the more recent Reynolds and VACS scores (Table **9**), by including HIV-infection related variables such as high-sensitivity C-reactive protein (hs-CRP) levels and CD4 count, respectively [105], may provide a more accurate evaluation of CVD risk in HIV-IP.

Table 9. Risk scores and algorithms to assess CVD risk in the general population and among patients with HIV infection.

Descriptor	Population	Age, y	Years Risk Prediction	Variables	Guidelines Using Score
Framingham Risk Score	General population from Framingham, MA, USA	30-74	10-y risk of CHD events; 30-y risk of CHD and stroke	Sex, age, total-C, HDL-C, smoking status, systolic blood pressure (treated or not treated)	NCEP ATP III, Canadian Cardiovascular Society, International Atherosclerosis Society, National Lipid Association Recommendations
SCORE	European	19-80	10-y risk of CVD fatality	Sex, age, total-C or total-C/HDL-C, systolic blood pressure, smoking status	European (ESC/EAS)
D:A:D	D:A:D cohort of HIV-1 infected men in Europe, Argentina, Australia and USA	16-85	5-y risk of CVD	Number of years on indinavir, lopinavir (and/or currently on indinavir, lopinavir, abacavir), sex, age, current cigarette smoker, previous cigarette smoker, family history of CVD, systolic blood pressure, total-C, HDL-C	None
PROCAM	European men	35-65	10-y fatal or nonfatal MI or sudden cardiac death	Age, LDL-C, HDL-C, TG, smoking status, family history of MI, systolic blood pressure	None
REYNOLDS	Men and women from USA	Men: 57-80; Women: ≥45	10-y risk for CVD	Sex, age, smoking status, total-C, HDL-C, hs-CRP, parental history of MI, glycated hemoglobin (if diabetic)	None
VACS	HIV-1 infected USA veterans, men	≥18	5-y mortality	Age, CD4 count, HIV-1 RNA (viral load), hemoglobin, FIB-4, eGFR, hepatitis C infection status	None
Pooled cohort equations	Population-based cohort studies funded by NHLBI	Varied	10-y risk of ASCVD	Sex, age, race (white or black), total-C, HDL-C, systolic blood pressure, treatment for high blood pressure (if systolic >120 mm Hg), smoking status	2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, National Lipid Association Recommendations

ACC/AHA: American College of Cardiology/American Heart Association; ART: Antiretroviral therapy; ASCVD: Atherosclerotic cardiovascular disease; CHD: Coronary heart disease; CVD: Cardiovascular disease; D:A:D: Data Collection on Adverse Events of Anti-HIV Drugs; eGFR: Estimated glomerular filtration rate; ESC/EAS: European Society of Cardiology/European Atherosclerosis Society; FIB-4: (years of age x aspartate transaminase)/(platelets x alanine transaminase); HDL-C: High-density lipoprotein cholesterol; HIV-1: Human immunodeficiency virus-1; hs-CRP: High-sensitivity C-reactive protein; LDL-C: Low-density lipoprotein cholesterol; MI: Myocardial infarction; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; NHLBI: National Heart, Lung, and Blood Institute of the National Institutes of Health; PROCAM: Prospective Cardiovascular Münster Study; RNA: Ribonucleic acid; SCORE: Systematic Coronary Risk Estimation; Total-C: Total cholesterol; VACS: Veterans Aging Cohort Study.
Adapted from Jacobson *et al*. (2015) [105].

3.6. Management of CVD Risk Factors in HIV Infection

As far as the control of CVD risk in HIV-IP is concerned, guidelines developed for the general population may not reflect an optimal disease management [2, 51]. Nevertheless, to assess the risk of CVD in a 10-year span, the use of the Framingham equation is also recommended [69].

In the absence of specific randomized trials in HIV-infected individuals, general strategies to minimize CVD risk in this population include [30]: reducing the burden of traditional risk factors [21, 42], by promoting smoking cessation [2, 11, 15, 24, 90], control of blood pressure [30] and possible coagulation disorders [69], management of insulin resistance and dyslipidemia [2, 30, 31, 82], as well as nutritional counselling [11, 15, 28] and exercise [11, 15, 16, 30]. Regarding the control of blood pressure, antihypertensive treatment is particularly indicated when the 10-year CVD risk is superior by 20% [69]. Furthermore, although there is still limited data regarding the role of acetylsalicylic acid in primary prevention of CVD [30], the 2016 EACS recommendations support its use when HIV-IP aged 50 years or more present high risk of CHD events. Concerning the management of glucose metabolism impairment in HIV-IP, it is recommended to initiate pharmacologic treatment as soon as the diagnosis of diabetes is confirmed, being 6.5%-7.0% the proposed maximum target levels of hemoglobin A1c protein (HbA1c) for these patients [69].

The contribution of the virus itself for the development of CVD might be reduced by early initiation of ART [2, 31, 74] in primary HIV infection, thus allowing to decrease the long-

Table 10. Statins: simplified management of dyslipidemia in HIV patients and drug-drug interactions with ART.

-	Statins					
	Pravastatin 20-80 mg qd	**Fluvastatin 20-80 mg qd**	**Rosuvastatin 5-40 mg qd**	**Atorvastatin 10-80 mg qd**	**Simvastatin 10-40 mg qd**	**Lovastatin**
Side effects	Gastrointestinal symptoms, headache, insomnia, toxic hepatitis, myalgias/myositis (frequent) and rhabdomyolysis (rare)					
Use with PIs	Usual dosing regimen	Usual dosing regimen	Use lower dose and monitor	Use lower dose and monitor	Contraindicated	Contraindicated
Use with NNRTIs (except delavirdine)	Usual dosing regimen	Usual dosing regimen	Use lower dose and monitor	Use lower dose and monitor	Usual dosing regimen	Usual dosing regimen
Observations	Not metabolized by CYP3A4 and first choice	Metabolized by CYP2C9 and second choice	Contraindicated with boosted lopinavir and atazanavir regimens	-	Higher risk of rhabdomyolysis and myopathy with PIs	Higher risk of rhabdomyolysis and myopathy with PIs

ART: Antiretroviral therapy; CYP: Cytochrome P450; HIV: Human immunodeficency virus; NNRTIs: Non-nucleos(t)ide reverse transcriptase inhibitors; PIs: Protease inhibitors; qd: Once a day.
Adapted from Kellick *et al.* (2014) [115], Battegay *et al.* (2016) [69] and Seecheran *et al*. (2017) [87].

term cardiovascular system impairment. Upcoming results from ongoing trials, such as the Strategic Timing of Antiretroviral Treatment (START) – an international multicentre trial that includes participants from nearly 30 countries –, will add important insight on how to improve the timing of HAART introduction in HIV-IP, by determining whether immediate initiation of antiretroviral treatment is superior to deferral of ART until the CD4+ count reaches less than 350 cells/mm^3, in terms of associated morbidity and mortality [107]. Regarding the choice of the ideal ART regimen for each patient, is not only important to perform a proper initial evaluation of CVD risk, but also to preferably chose ART drugs with the least metabolic toxicity profile [31] and to identify the possible drug-drug interactions between HAART regimen drugs and other medications used in primary and secondary prevention of CVD (Table **8**).

As predicted by Vos *et al*. [29], the median age of patients receiving ART treatment will be 56.6 years by 2030 and 54% of these individuals will be taking at least one more long-term drug aside from ART regimen drugs, namely statins (Table **10**).

Statin therapy has been proposed when lifestyle modifications and adjustment of ART therapy are not enough [16, 90] to maintain total cholesterol ≤ 190mg/dL or LDL-cholesterol ≤ 115mg/dL [18], particularly in patients with a 10-year CVD risk superior to 10% and/or diagnosed with type 2 diabetes [69]. Statins have not only lipid-lowering effects but also anti-inflammatory properties, thus contributing to reduce the risk of CVD [2]. However, some statins present pharmacological interactions with ART drugs [41]. Simvastatin and lovastatin, which are metabolized by the cytochrome P450 CYP3A, are contraindicated to use in co-administration with PIs [35, 46], since the latter are potent inhibitors of the P450 cytochrome isoenzyme.

CONCLUSION

As till now, HIV infection will remain a challenging disease in the future [29]. HIV-infected individuals are living longer and the risk of non-AIDS morbidity and mortality is raising, thus conditioning an increased need to improve patient and health care provider education. In order to detect and properly manage early signs of CVD, routine cardiovascular assessment should be performed in these patients, allowing to guide risk factor management and ART regimen choice, particularly among individuals at higher risk [104]. Finally, as risk assessment models developed in the general population may underestimate the CVD risk in HIV-infected individuals [25, 103, 107], recent imaging available tools such as ^{18}F-FDG-PET [100] and biomarkers might play an important role in improving the prediction of CVD related-events [25].

LIST OF ABBREVIATIONS

ABCA1	=	ATP Binding Cassette Transporter 1
ACS	=	Acute Coronary Syndrome
AIDS	=	Acquired Immunodeficiency Syndrome
AMI	=	Acute Myocardial Infarction
ART	=	Antiretroviral Therapy
CAC	=	Coronary Artery Calcification
CAD	=	Coronary Artery Disease
CCR5	=	C-C Chemokine Receptor 5
CHD	=	Coronary Heart Disease
CI	=	Confidence Interval
CIMT	=	Carotid Intima-Media Thickness
CMR	=	Cardiovascular Magnetic Resonance
CRABP1	=	Cytoplasmic Retinoic Acid Binding Protein Type 1
CT	=	Computed Tomography
CVD	=	Cardiovascular Disease

DAD	=	Data Collection on Adverse Events of Anti-HIV Drugs
ER	=	Endoplasmic Reticulum
^{18}F-FDG-PET	=	^{18}F-fluorodeoxyglucose Positron Emission Tomography
FRS	=	Framingham Risk Score
HAART	=	Highly Active Antiretroviral Therapy
HbA1c	=	Hemoglobin A1c Protein
HDL	=	High-density Lipoprotein
HIV	=	Human Immunodeficiency Virus
HIV-IP	=	Human Immunodeficiency Virus-Infected Patients
HIV-RNA	=	Human Immunodeficiency Virus-Ribonucleic Acid
HR	=	Hazard Ratio
hs-CRP	=	High-sensitivity C-reactive Protein
ICAM-1	=	Intercellular Adhesion Molecule-1
IFN-γ	=	Interferon-γ
IL-1	=	Interleukin-1
IL-1β	=	Interleukin-1β
IL-6	=	Interleukin-6
IL-8	=	Interleukin-8
LDL	=	Low-density Lipoprotein
MCP-1	=	Monocyte Chemoattractant Protein-1
MI	=	Myocardial Infarction
Nef	=	Negative Regulatory Factor
NNRTIs	=	Non-nucleoside Reverse Transcriptase Inhibitors
NO	=	Nitric Oxide
NRTIs	=	Nucleoside Reverse Transcriptase Inhibitors
OR	=	Odds Ratio
PCI	=	Percutaneous Coronary Intervention
PGI2	=	Prostacyclin
PIs	=	Protease Inhibitors
PR	=	Prevalence Ratio
PROCAM	=	Prospective Cardiovascular Münster Study
QTc	=	Corrected QT
RR	=	Relative Risk
SCORE	=	Systematic Coronary Risk Evaluation
SMART	=	Strategies for Management of Antiretroviral Therapy
SREBPs	=	Sterol Regulatory Element-binding Proteins
START	=	Strategic Timing of Antiretroviral Treatment
STEMI	=	ST-segment Elevation Myocardial Infarction
Tat	=	Trans-activator of Transcription
TNF	=	Tumor Necrosis Factor
TNF-α	=	Tumor Necrosis Factor-α
VACS	=	Veterans Aging Cohort Study
VCAM-1	=	Vascular Cell Adhesion Molecule-1
vWF	=	von Willebrand Factor

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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