

Acute coronary syndromes in patients with HIV

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Highly active antiretroviral treatment (HAART) has considerably increased the life expectancy of patients infected with HIV. Coronary artery disease is a leading cause of mortality in patients infected with HIV. This is primarily attributed to their increased survival, HAART-induced metabolic derangements, and to HIV itself. The pathophysiology of atherosclerosis in HIV is both multifactorial and complex – involving direct endothelial injury and dysfunction, hypercoagulability, and a significant contribution from traditional cardiac risk factors. The advent of HAART has since heralded a remarkable improvement in outcomes, but at the expense of other unforeseen issues. It is thus of paramount importance to swiftly recognize and manage acute coronary syndromes in HIV-infected patients to attenuate adverse complications, which should translate into improved clinical outcomes. *Coron Artery Dis*

Introduction

Highly active antiretroviral treatment (HAART) has considerably increased the life expectancy of patients infected with HIV. Coronary artery disease (CAD) with associated acute coronary syndromes (ACS) is now a leading cause of death in patients with HIV. This is primarily attributed to their increased survival, HAART-induced metabolic derangements, and to HIV itself [1]. The pathophysiology of atherosclerosis in HIV is both multifactorial and complex – involving direct endothelial injury and dysfunction, hypercoagulability, and a significant contribution from traditional cardiac risk factors [2,3] (Fig. 1). The advent of HAART has since heralded a remarkable improvement in outcomes, but at the expense of other unforeseen issues. It is thus of paramount importance to swiftly recognize and manage ACS in HIV-infected patients to attenuate adverse complications, which should translate into improved clinical outcomes.

Epidemiology of acute coronary syndrome in HIV

The advent of HAART has significantly improved the survival of patients infected with HIV and this has resulted in more non-AIDS-related causes of death as opposed to AIDS-related causes of death [4]. Of the non-AIDS-related causes of death, Bedimo *et al.* [4] noted that

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28:166–172 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.

Coronary Artery Disease 2017, 28:166–172

Keywords: AIDS, acute coronary syndromes, coronary artery disease, HIV, highly active antiretroviral treatment

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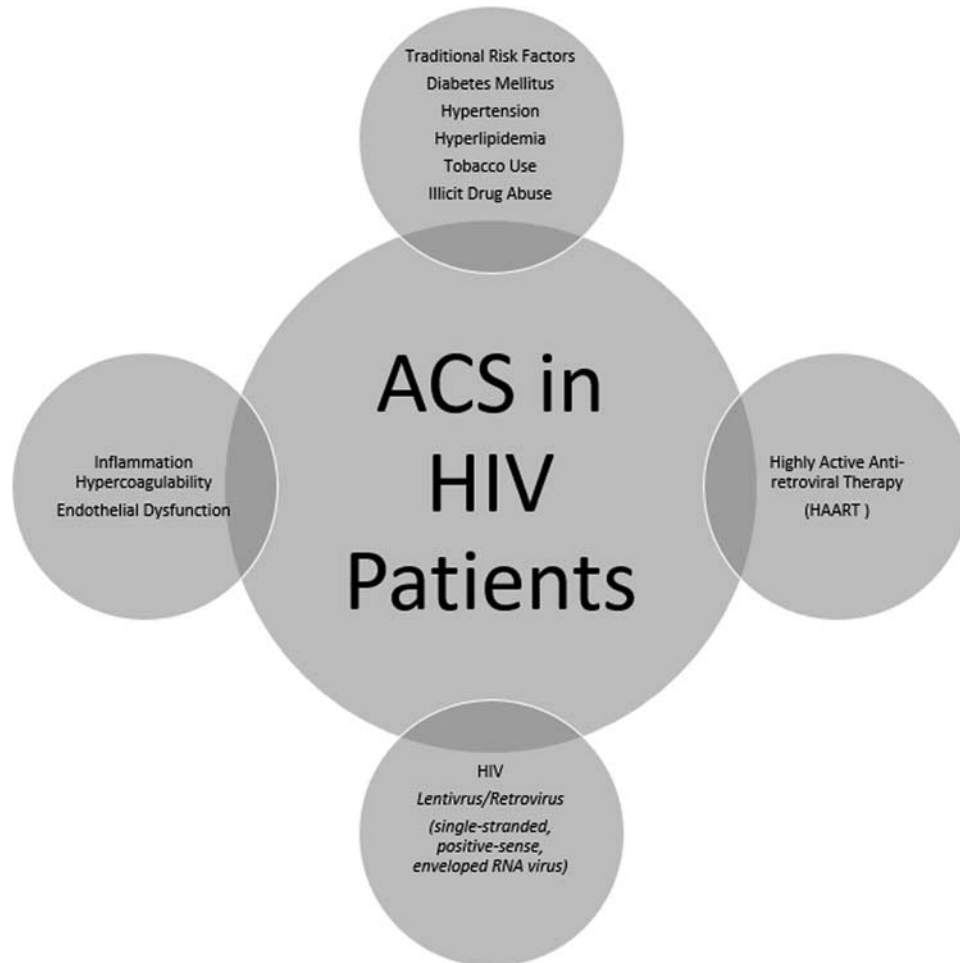
cardiovascular disease (CVD) accounts for 8–22% of deaths among HIV-infected patients and the percentage appears to be increasing in the aging HIV population. HIV infection portends an increased risk for CAD and ACS compared with the general population [5]. Durand *et al.* [5] found an incidence rate of 3.88 per 1000 patient-years in HIV-positive patients compared with 2.21 per 1000 patient-years in HIV-negative patients.

Pathogenesis and pathophysiology

Traditional risk factors

Overall, HIV-infected patients tend to be hospitalized more frequently with CAD, as well as present with ACS [5]. Expectedly, traditional cardiac risk factors are inextricably linked to ACS in these patients as they are for noninfected patients. There is generally a higher prevalence of diabetes mellitus (11.5 vs. 6.6%), hypertension (21.2 vs. 15.9%), and hyperlipidemia (23.3 vs. 17.6%) in HIV-infected patients compared with their uninfected counterparts. Impaired kidney function as reflected by an abnormal glomerular filtration rate of cystatin C also shows a robust association with increased cardiovascular events and mortality [6]. HIV-infected patients have a higher rate of illicit substance abuse, which portends worse cardiovascular outcomes [7–12], specifically more so in the younger, male patient subgroup. Severino *et al.* [7] also determined an increased risk of ACS in HIV-infected patient population, independent of the aforementioned conventional risk factors, suggesting additional mechanistic effects.

Fig. 1



The pathophysiology of ACS in HIV-infected patients is both multifactorial and complex. ACS, acute coronary syndrome.

Dyslipidemia

Several autopsy studies have shown evidence of premature CAD in HIV-infected patients, even before HAART initiation [8,9]. HIV-infected patients manifest a complex dyslipidemic pattern – reduced total cholesterol, HDL, and apolipoprotein B. In addition, LDL clearance is decreased, which in turn leads to increased serum levels [9]. Also, there is a direct correlation between hypertriglyceridemia and viremia. Atherosclerotic lesions in these patients show a mixed histologic pattern with features similar to both traditional CAD and transplant vasculopathy [10]. HDL and apolipoprotein A1 may increase following HAART initiation depending on the baseline level of inflammation, which suggests that activation of inflammatory pathways contribute toward HIV-associated changes in HDL [11]. Decreased HDL levels can independently identify HIV-infected patients at increased risk of CAD [13]. Generally, integrase inhibitors, fusion inhibitors, and C-C chemokine receptor type 5 antagonists have little impact on the lipid profile. Non-

nucleoside reverse-transcriptase inhibitors (NNRTIs) and nucleoside reverse-transcriptase inhibitors tend to have more variable effects on the lipid profile on the basis of the agent used (Table 1).

Inflammation

Inflammation is associated with endothelial dysfunction in HIV-infected patients. CAD can appear throughout the spectrum of HIV infection, ranging from clinical quiescence to advanced AIDS with opportunistic diseases. A study by Hsue *et al.* [12] reported increased carotid intima-media thickness and C-reactive protein levels despite HAART and degree of viremia, implying that chronic inflammation may play a pivotal role in premature CAD within this population. Another study with HIV-infected patients showed that elevated interleukin-6 and D-dimer levels are associated with both a higher risk of fatal CVD and death after a nonfatal CVD event [6] (odds ratio 2.8, $P=0.03$). The results from these studies suggest that these circulating molecules may in

Table 1 Lipid abnormalities that tend to be observed in HIV-infected patients on selected antiretroviral drugs

Antiretroviral drug class	Selected drugs from ART drug classes	TG	LDL	HDL	Total cholesterol
PIs	All Ritonavir-boosted PIs ^{a,b}	Increase	Increase	Same/decrease	Increase
NNRTIs	Efavirenz	Increase	Increase	Increase	Increase
NRTIs	Stavudine + Zidovudine + Abacavir	Increase	Increase	Increase	Increase
INSTIs	Elvitegravir + Cobicistat + Tenofovir + Emtricitabine	Increase	Increase	Increase	Increase

ART, antiretroviral therapy; INSTI, integrase inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; TG, triglyceride.

^aCobicistat-boosted regimens will have similar effects as Ritonavir-boosted regimens as Cobicistat is a CYP3A4 inhibitor.

^bAtazanavir is an exception; it has fewer effects on the lipid profile.

part explain this increased risk by contributing to both a pro-inflammatory and prothrombotic milieu. This inherent risk is almost equivalent to that of insulin-resistant obesity with the attendant sequelae of the accelerated diabetogenesis and elevated cardiac risk, even in treated HIV infection [14]. In addition, a virtual histology-intravascular ultrasound analysis [7] showed a high prevalence of unstable plaque morphology rich in necrotic tissue. These plaques are in contrast to traditional CAD plaques as they tend to be less calcific, more necrotic, and with a thicker fibrous cap.

Hypercoagulability

HIV-associated thrombogenicity arises from both the plasmatic and the cellular coagulation pathways. HIV replication in itself can lead to a prothrombotic state, chiefly attributed to the upregulation of the extrinsic tissue factor coagulation pathway. There are also changes in serum factor VIII and antithrombin levels that suggest underlying hepatocyte dysfunction [15]. Moreover, a high incidence of thromboembolic events and intraluminal demonstration of fresh thrombus has been reported, probably related to a highly thrombophilic state [16]. A positive correlation has been found between thrombocytopenia and advancing HIV disease with sequelae of opportunistic diseases [17,18]. There is increased platelet reactivity in HIV-infected patients that may increase the risk for thrombosis; however, the contribution of platelets in HIV-related procoagulant activity requires further study [19,20]. With respect to HAART, interrupting therapy increases the risk of thrombocytopenia, but reinitiation typically reverses it.

Highly active antiretroviral treatment therapy and vascular disease

The literature is replete with conflicting studies suggesting a possible link between ACS and HAART. Several studies confirmed a statistically significant association [21], whereas others refuted this relationship [4,22]. These studies have considerable heterogeneity with respect to the study design, population, and endpoint definitions [23]. A pivotal study, Data Collection on Adverse Events of Anti-HIV Drugs study [23,24], indicated that the relative risk of myocardial infarction per year of protease inhibitor (PI) exposure was 1.16 (95% confidence interval: 1.10–1.23) adjusting for several

parameters. In contrast, a recent study reported that HIV-infected patients who presented with an ACS had significantly lower viral loads and a higher cluster of differentiation 4 counts [22–24] than patients with HIV/AIDS-related cardiomyopathy, suggesting that HIV infection is not principally implicated in CAD. The Strategies for Management of Antiretroviral Therapy trial showed that the rate of major cardiovascular events was higher if HAART was interrupted, compared with continuous treatment, with a hazard ratio of 1.57 (95% confidence interval: 1.0–2.46, $P = 0.05$) [25]. This association between treatment interruption and coronary events does not appear to be related to the level of viremia [13,25]. Moreover, treatment interruption may increase the risk of mortality, evidenced by increased inflammatory markers of interleukin-6 and D-dimer [26]. Interruption does not favorably impact a patient's lipid panel, with little or no effect on the total/HDL cholesterol ratio, LDL, and HDL. Lowering of lipid parameters after HAART interruption was not associated with a class of ART and may be linked to increased viral replication, inflammation, and coagulation [27].

HIV and vascular disease

As mentioned above, several studies suggest that HIV-infected patients are exposed to an increased risk of premature CAD, whereas others suggest differently. A recent meta-analysis [28] of 11 studies including more than 2000 HIV-infected patients presenting with ACS showed that the most common presentation was ST-segment elevation myocardial infarction [29]. Coronary anatomy seems to be variable, with some studies showing a higher prevalence of single-vessel disease and others showing a higher prevalence of two-vessel and three-vessel disease than noninfected control participants. Traditional factors are the predominant determinants of risk. Higher levels of N-terminal prohormone of brain natriuretic peptide are associated with an increased risk of CVD in HIV-infected patients even after considering established CAD risk factors [30]. ECG evidence of asymptomatic ischemic heart disease (IHD) was common and more so than a history of symptomatic IHD. No clear association was noted between HAART type or duration and asymptomatic IHD [31]. It is unknown whether HIV-infected patients have a higher frequency of atypical presentations such as silent ischemia that can be seen in

Table 2 Characteristics of commonly used antithrombotic agents in acute coronary syndrome

Antithrombotic agent	Mechanism of action	Route of administration	Metabolism	Excretion
Aspirin	COX inhibitor	Per oral, per rectal, less commonly intravenous, intramuscular	Hepatic	Renal
Clopidogrel	P2Y12 inhibitor	Per oral	Hepatic	Renal and fecal
Prasugrel	P2Y12 inhibitor	Per oral	Primarily CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19	Renal and fecal
Ticagrelor	P2Y12 inhibitor	Per oral	CYP3A4	Hepatic, fecal, and renal
Cangrelor	P2Y12 inhibitor	Intravenous	Peripheral circulation	Renal and fecal
Abciximab	Glycoprotein 2B/3A inhibitor	Intravenous	RES	Renal
Eptifibatid	Glycoprotein 2B/3A inhibitor	Intravenous	Negligible	Renal
Tirofiban	Glycoprotein 2B/3A inhibitor	Intravenous	Negligible	Renal and fecal
Unfractionated heparin	AT3-dependent inhibitor of factor Xa and thrombin	Intravenous, subcutaneous	Hepatic and RES	RES and renal
Low-molecular-weight heparin	AT3-dependent inhibitor of factor Xa and thrombin	Intravenous, subcutaneous	Hepatic and RES	RES and renal
Fondaparinux	AT3-dependent inhibitor of factor Xa	Subcutaneous	Negligible	Renal
Bivalirudin	Direct thrombin inhibitor	Intravenous	Proteolytic cleavage	Proteolytic cleavage and renal
Rivaroxaban	Direct factor Xa inhibitor	Per oral	Both CYP3A4, CYP2J2 and CYP-independent mechanisms	Renal and fecal
Vorapaxar	Thrombin receptor (PAR-1) antagonist	Per oral	CYP3A4 and CYP2J2	Fecal and renal

COX, cyclooxygenase; CYP, cytochrome P450; PAR-1, protease-activated receptor 1; RES, reticuloendothelial system.

other chronic diseases, for example, diabetes mellitus and chronic kidney disease.

Management

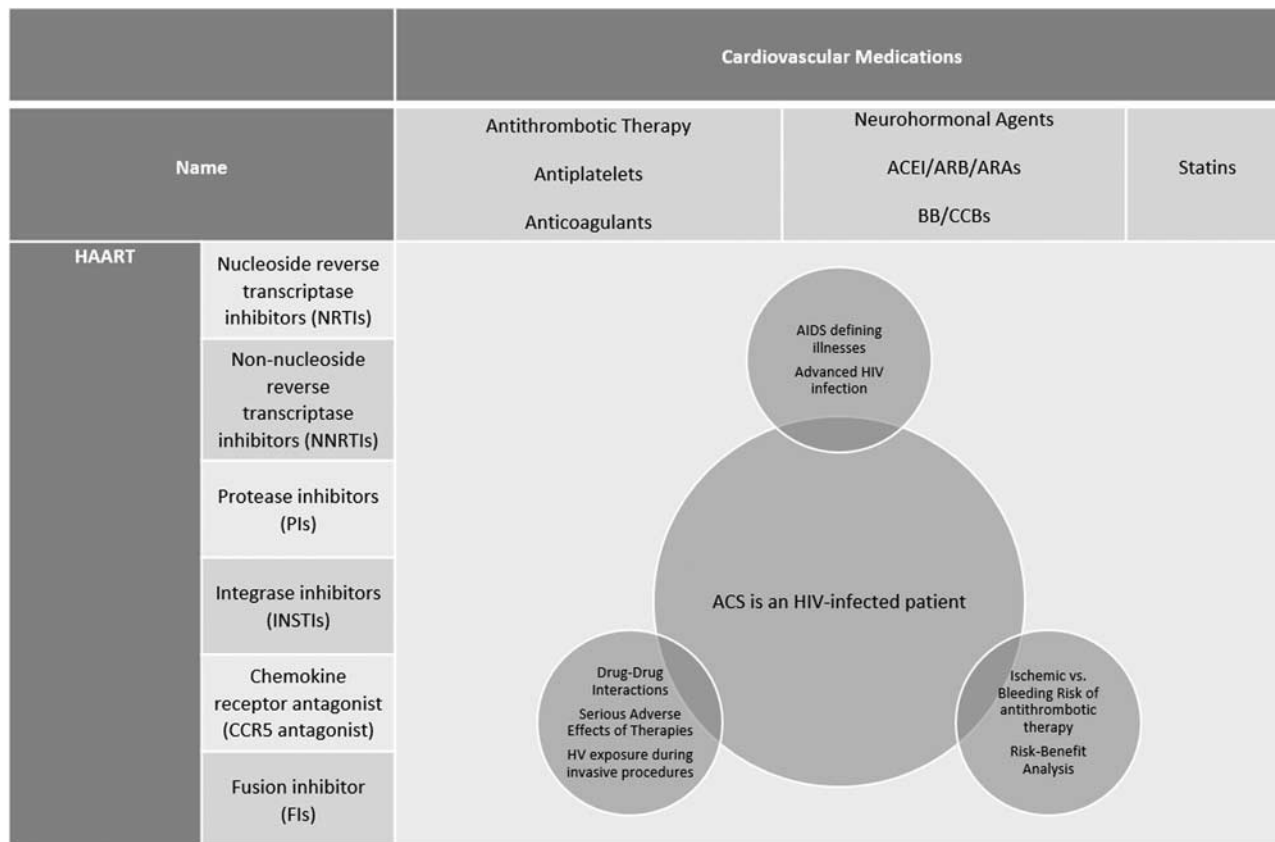
Coronary artery disease and acute coronary syndromes

The early detection and treatment of comorbidities and modifiable risk factors through lifestyle changes such as smoking cessation, dietary changes, and exercise is likely to have a significant impact on cardiovascular risk in this population. Because HIV infection by itself and HAART likely increase the risk of plaque rupture and atherothrombosis [2,32], routine primary and secondary prevention should be considered in HIV-infected patients. However, as reported in some studies [2], LDL goals are less frequently achieved in HIV-infected patients during follow-up. Within the current armamentarium of cardiovascular medications and HAART, there are other important issues to consider when treating ACS in an HIV-infected patient (Fig. 2). The management of ACS in HIV patients is similar to its management in non-HIV patients (Table 2). This suggests that the coronary risk of HIV-infected patients is not fully addressed by conventional secondary prevention measures and that more aggressive preventive measures and/or specifically targeted treatments may be required to attenuate this risk [2]. In attaining anti-ischemic effects, potent antithrombotic therapies can have devastating and catastrophic bleeding events in patients with advanced HIV/AIDS and opportunistic infections. These patients often have coagulopathies and thrombocytopenia amidst other intracranial and gastrointestinal pathology that make them susceptible to severe bleeding. Serious adverse events with drug–drug interactions must also be considered as many of these pharmacotherapies share a common pathway of metabolism (Table 2).

Percutaneous coronary intervention and coronary artery bypass grafting

Percutaneous coronary intervention (PCI) in HIV-infected patients has been associated with a high incidence of nonfatal reinfarction, restenosis, and in-stent thrombosis [34]. PCI with and without stenting as well as coronary artery bypass grafting seems to be a safe, effective, and feasible option in HIV patients, but it is associated with a higher incidence of repeat revascularization in the long term [2,29,35]. Recurrent ACS and urgent PCI were more frequent in HIV-infected patients, with no difference in the rates of major adverse cardiovascular and cerebral events and clinical restenosis at the 1-year follow-up. Another major concern is occupational exposure to HIV during invasive procedures such as PCI and coronary artery bypass grafting and immediate availability of postexposure prophylaxis (PEP). In the event that an exposure occurs, there should be prompt reporting and management according to institutional protocols. This would involve administration of antiretroviral therapy, three or more drugs, ideally within hours of exposure. PEP becomes less effective more than

Fig. 2



Clinical implications of treating ACS in an HIV-infected patient. ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARA, aldosterone receptor antagonist; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; HAART, highly active antiretroviral treatment.

Table 3 Use of statins in patients on antiretroviral therapy [33]

Statin	PI	NNRTI (except delavirdine)	Comments
Pravastatin	Use lower dose and monitor	Usual dosing regimen	Not metabolized by CYP3A4 and first choice
Fluvastatin	Use lower dose and monitor	Usual dosing regimen	Metabolized by CYP2C9 and second choice
Rosuvastatin	Use lower dose and monitor	Use lower dose with some NNRTIs	Contraindicated with boosted lopinavir and atazanavir regimens
Atorvastatin	Use lower dose and monitor	Use lower dose with some NNRTIs	–
Simvastatin	Contraindicated	Usual dosing regimen	High risk of rhabdomyolysis and myopathy with PIs
Lovastatin	Contraindicated	Usual dosing regimen	High risk of rhabdomyolysis and myopathy with PIs

Delavirdine has interactions similar to PIs.

CYP, cytochrome P450; NNRTI, non-nucleoside reverse-transcriptase inhibitors; PI, protease inhibitor.

72 h after exposure. Regimens that are well tolerated and have the least side effects are used and healthcare workers should be counseled on adherence. PEP should be administered for 4 weeks and healthcare workers should have HIV testing performed at baseline, 6, 12 weeks, and 6 months. Testing can be concluded at 4 months if the fourth-generation HIV assay is performed. Counseling should also be a part of PEP treatment protocols [36].

Noninvasive testing

Noninvasive stress testing should be preceded by a prerequisite history, physical examination, 12-lead ECG, and an assessment of pretest probability of CAD [37].

Routine evaluation of CAD in patients infected with HIV/AIDS should be guided by the established clinical practice guidelines and appropriateness criteria for test selection used in patients without HIV/AIDS [37,38]. These recommendations are largely based on conventional populations and there is a paucity of data with respect to HIV-specific populations that call the performance of these noninvasive testing modalities into question.

Dyslipidemia

Specific guidelines for the evaluation and management of HAART-related HLD have been developed by the

Infectious Disease Society of America, Adult AIDS Clinical Trials Group [39], and the European AIDS Clinical Society. These guidelines recommend estimation of Framingham-predicted 10-year cardiovascular risk [40]. Currently, there is no difference in HLD goal treatment between HIV-infected and non-HIV-infected patients. In the choice of specific lipid-lowering therapy, it is critical to consider drug–drug interactions. In general, all PIs and delavirdine, an NNRTI, inhibit CYP3A4. Nevirapine and Efavirenz result in the induction of the enzyme. Therefore, the first-choice agents for lowering LDL are Pravastatin (not metabolized by CYP3A4), with Fluvastatin (metabolized CYP2C9) as the second choice. Rosuvastatin concentrations appear to be increased when used in combination with some NNRTIs; thus, in that setting, 10 mg should be considered the maximum safe dose [41,42]. Similarly, Atorvastatin should be used at lower doses in HIV patients. Finally, during PI therapy, Simvastatin and Lovastatin are not recommended because of the high risk of rhabdomyolysis [42,43]. Nucleoside reverse-transcriptase inhibitors, integrase inhibitors, and entry inhibitors do not have drug–drug interactions with statins. PIs and NNRTIs can have significant drug–drug interactions with statins and these need to be reviewed before prescribing statins for patients on these regimens [44]. Cobicistat-boosted regimens will have similar effects as ritonavir-boosted regimens as cobicistat is a CYP3A4 inhibitor. Lack of data limits the precise estimation of benefits related to anti-inflammatory properties of statins. Clinicians can consider switching HAART in cases of dyslipidemia because of adverse drug effects (Table 3).

Controversial issues and future research

Our understanding of CAD in HIV continues to evolve; however, there are still knowledge gaps and controversial issues that are yet to be resolved. These include non-invasive modalities and their application and performance in patients infected with HIV, clinical utility of novel biomarkers, comparing the clinical presentations of angina and silent ischemia, and determining long-term outcomes to enhance screening and management strategies. These will be addressed in several ongoing studies that will provide valuable information with respect to the interplay of these two disease processes. Firstly, there is a German HIV/HEART study, which will assess the incidence, prevalence, and clinical course of CVD in HIV-infected patients over a 10-year period. A French study comparing the rate of major adverse cardiovascular events in both HIV-positive and HIV-negative patients after an index ACS event over 3-year period is currently underway. There is also a Danish study evaluating the effect of omega-3-acid ethyl esters on lipid parameters and on function and stiffness on vasculature in HIV-infected patients on HAART. Finally, there are two American studies, one of which is utilizing cardiac computed tomography angiography to evaluate CAD in patients on

long-term HAART whereas the other is comparing moderate-dose statin therapy with high-dose statin therapy in HIV-infected patients taking HAART who have CAD.

Conclusion

ACS represents a leading cause of mortality in patients infected with HIV. Despite treatment regimens involving novel and contemporary HAART, this remains a challenging issue. In addition, evolving procedural techniques and pharmacology may prove useful in attenuating many of the adverse complications that commonly arise in this population.

Acknowledgements

The authors thank David J. Schneider, MD, FACC of The University of Vermont Medical Center (UVMMC), Burlington, Vermont, USA, and The Cardiovascular Research Institute of Vermont (CVRI-VT), Burlington, Vermont, USA, for his valuable contribution in reviewing the manuscript.

Conflicts of interest

There are no conflicts of interest.

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