International Journal of Cardiology 241 (2017) 50–56

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Cardiovascular disease in women with HIV-1 infection

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ARTICLE INFO

Article history:
Received 3 December 2016
Received in revised form 30 January 2017
Accepted 24 February 2017
Available online 27 February 2017

Keywords:
Cardiovascular disease
HIV
Risk factors
Women
Cardiovascular prevention

ABSTRACT

Cardiovascular disease is a leading cause of death in women, nevertheless it is often underestimated in female patients without overt risk factors. The chronic infection by Human Immunodeficiency Virus (HIV) is clearly associated, along with the use of certain antiretroviral drugs and traditional risk factors, with an increased risk of cardiovascular diseases. The aim of this manuscript is to review the epidemiology, risk factors, pathogenesis, diagnostic approach, primary and secondary prevention strategies of cardiovascular disease in HIV-negative and HIV-positive female subjects. The ultimate goal is to promote knowledge and development of specific and appropriate clinical interventions and guidelines in this group of high-risk patients, mostly in view of the expected growth of ageing females with HIV.

1. Introduction

Cardiovascular disease (CVD) accounts for >17 million deaths globally each year, which represent approximately 30% of all deaths. Of note 80% of CVD occurs in low- and middle-income countries [1]. CVD is also the leading cause of death in women and it is often underestimated owing to a general misperception that females are less susceptible and have a lower CV risk. Notably it is estimated that 50% of American women will die of coronary heart disease (CHD) or stroke, compared to 1 in 25 of breast cancer [2]. Females have lower risk for CVD and specifically acute myocardial infarction (AMI), compared to males (−22% after adjusting for several risk factors) [3]. Sex-related features, such as smaller body size and weight, slower drug metabolism and decreased renal function, as well as co morbidities and concomitant drug therapy, may specifically influence incidence and outcomes of CVD. Among co-morbidities, which may heavily affect CV risk in women, much attention has been recently developed with regards to human immunodeficiency virus (HIV) and antiretroviral therapy in HIV.

In fact, HIV-positive patients have a higher risk of CV disorders because of several HIV- and non-HIV-related features. With the increased life expectancy associated with highly active antiretroviral therapy (HAART) non-acquired immunodeficiency syndrome (AIDS) CV complications are therefore now recognized as a leading cause of death in this population [4]. In particular, several studies have analysed large clinical databases and cohorts worldwide to compare the incidence of CVD in patients with and without HIV infection. These studies consistently report a 1.5-fold increase in the rate of CV events in HIV-infected individuals compared to controls [5,6]. The incidence of CHD in the years 1994–2000 was low overall, but higher in those infected with HIV compared with the uninfected, even in the younger strata [7]. Although most of the studies in HIV-positive patients have been conducted in male subjects, HIV infection has been associated with a significant risk of CVD in females [8,9]. In two studies, the age-adjusted relative risk of AMI was found to be higher in female than male subjects as compared to HIV-negative patients; risk ratios were 2.98 (USA) and 2.7 (France) for females and 1.40 (USA and France) for males [10,11]. In a recent study conducted in United States female veterans incident CVD/1000 person-years was significantly higher among HIV-positive than HIV-negative women with a hazard ratio of 2.8 after adjusting for CV risk factors [12].

In view of the commonly less aggressive clinical approach (including prevention and stringent diagnostic screening) adopted in women, the

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http://dx.doi.org/10.1016/j.ijcard.2017.02.117

increased risk of CVD as compared to HIV-negative individuals, may represent a clinically emerging issue in the ageing HIV population.

2. HIV and increased risk of CVD

Despite HIV-positive patients have been recognized at significant higher risk of CVD, there is still uncertainty on the relative role that has to be attributed to HIV, to antiretroviral treatment or to concurrent major CV risk factors [13]. Early studies reported a higher prevalence of hypertension (21.2% vs.15.9%), diabetes (11.5% vs. 6.6%) and dyslipidaemia (23.3% vs. 17.6%) in HIV-infected patients compared to the non-HIV subjects ($p < 0.0001$ for each comparison) [14–15]. Smoking habit, illicit drug use and heavy alcohol consumption have been reported to be more common in HIV-positive subjects and these bad habits may influence CVD presentation and treatment [16–17]. Chronic renal disease is not uncommon in HIV-positive treated subjects due to the effect of the virus and to the nephrotoxic consequences of several antiretrovirals [18].

Specific factors that may expose HIV-positive patients to higher CVD susceptibility might also be linked to immune-depression and HAART treatment. The evidence for a potential role of CD4 lymphocyte depletion and immune activation in the development of CVD among individuals with HIV infection is still debated [19,20]. Changes in body fat distribution (lipodystrophy including both lipoatrophy and lipohypertrophy) are not uncommon in HIV-infected subjects: this abnormal fat redistribution has clear clinical implications, such as modifications of body reshaping and self-perception (thus affecting compliance and self-commitment, medication adherence and mood), ectopic fat distribution (mostly in heart, liver and muscle tissues) and, eventually, increased CV risk [21].

"Old" nucleoside reverse transcriptase inhibitors (NRTIs, such as zidovudine, didanosine and stavudine) and protease inhibitors (PI, such as indinavir and lopinavir/ritonavir) are associated with increased total and low density lipoprotein (LDL)-cholesterol and lipodistrophy thus increasing CV risk. Additional drug-associated effects include reduced insulin sensitivity, endothelial dysfunction and cardiac remodelling [22]. An increased CV risk has been observed with indinavir and lopinavir/ritonavir in a large cohort study [23]. Abacavir, a widely used NRTI, has been associated to a higher risk of CVD although data appear controversial: independent cohort studies confirmed such potential association of recent abacavir use with CVD, but the underlying biological mechanisms are still uncertain [24,25].

The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study has recently updated the prediction model for CVD using data from 32,663 HIV-positive individuals [26]. The full D:A:D CVD prediction model includes exposure to antiretroviral drugs (cumulative protease inhibitor and NRTI exposure, current abacavir use) and markers of immunodeficiency (CD4 lymphocyte count), in addition to modifiable and non modifiable CV risk factors [age, gender, family history of CVD, systolic blood pressure (SBP) and smoking status, total and high density lipoprotein (HDL) cholesterol, diabetes]. The performance of the models was superior to that of a recalibrated Framingham CVD prediction model in this population. In a large cohort of 11,338 HIV-positive patients several risk scores [Framingham, Adult Treatment Panel-3 (ATP-3), Atherosclerotic Cardiovascular Disease (ASCVD) and D:A:D] were compared as for their ability to predict incident type 1 (spontaneous from atherosclerotic plaque instability) and type 2 (secondary to oxygen demand/supply mismatch) AMI. ASCVD displayed a significantly better area under the curve (AUC) than other scores for all AMIs and for type 2 AMIs, and was not inferior to the other AUCs for type 1 AMIs [27].

3. CVD risk in HIV-positive women

HIV-positive women present CV risk factor profiles substantially comparable to those discussed of HIV-positive male individuals. Gender differences such as lower body weight, slower drug metabolism and hormonal control of intranuclear receptors may explain differences in drug exposure as well as a higher prevalence of antiretroviral-associated toxicities [28]. Furthermore the use of CVD-related therapeutic interventions (with the exclusion of anti-hypertensive drugs) is lower in HIV-positive female as compared to male subjects with similar risk profiles [29]. The prevalence of early and premature (<40 years of age) menopause was deemed to be variable, but higher than usually reported in HIV-negative subjects (20–27% versus 5% early and 2–5% versus <1% premature menopause). Several demographic, nutritional, lifestyle and clinical factors (including HCV co-infection and severe immune-depression) have been associated with early menopause in HIV-positive patients [30,31].

The potential relationship between specific CV risk factors and development of tailored interventions has been poorly explored in HIV-positive females: studies assessing the role of early menopause as well as of hormonal therapies are needed in order to evaluate possible improvements in womens' care.

4. Pathogenetic considerations

The relative contribution of various pathogenic processes leading to AMI differs markedly between genders. Patients with evidence of AMI and non-obstructive atherosclerotic disease of the coronary arteries are more likely to be women and non-white [32]. Other mechanisms may play a role in women, such as abnormal coronary vasomotion, non-atherosclerotic coronary artery dissection, impaired coronary microcirculation and thrombophilia.

On the other hand, HIV-positive patients have an increased risk of subclinical atherosclerosis [33]. A recent meta-analysis reported that HIV-infected patients present higher rates of non-calcified plaques (NCP) compared to similar cohorts of HIV-negative subjects and that NCP prevalence and degree were positively associated with worse immune-virological parameters, suggesting that the disease stage contributes to development of coronary plaque instability [34,35]. NCPs represent an early stage of atherosclerosis, resulting to be more prone to rupture and thrombus formation compared to calcified lesions, potentially predisposing to AMI, as observed in several case series of HIV-positive patients.

HIV infection leads to disarray of immune system and persistent systemic immune hyper activation in spite of full HIV viremia suppression by antiretroviral treatment. In particular, soluble CD14 (sCD14) and soluble CD163 (sCD163), both known markers of monocyte/macrophage activation, have been identified as reliable predictors of increased atherosclerotic disease as detected by coronary computed tomography (CT). Moreover, CD14 has been associated with an increased risk of death in HIV-positive patients and a history of heart disease [36]. Furthermore, higher levels of inflammatory markers, (high-sensitivity c reactive protein, interleukin 6) and coagulation markers such as D-dimer, have been reported in HIV-infected patients and are associated with fatal and non-fatal CV events and all-cause mortality in HIV-positive patients [37].

Interestingly, microbial translocation has been proposed as a main mechanism behind immune hyperactivation during HIV infection [38]. Most recently, microbiota-derived metabolites of phosphatidilcoline, more specifically trimethylamine and oxidized-TMA were associated with coronary plaque burden at CT in HIV-positive patients, thus suggesting that diet and intestinal microbiota may significantly impact accelerated atherosclerosis in HIV-infected patients.

Limited data are available so far about pathogenetic determinants of atherosclerosis in HIV-positive women. In young and asymptomatic HIV-positive women with many risk factors (cigarette smoking, diabetes, obesity and illicit drug abuse) significantly higher percentages of segments with NCP (74% vs. 23%) were found, compared to HIV-negative controls. CT scan also showed more segments with NCP (0.92 vs. 0.40). Immune activation parameters, including sCD163, CXCL10 and CD14+, CD16+ monocytes were higher in HIV-infected than

HIV-negative subjects; sCD163 levels were higher in HIV-infected women with NCP compared to those with calcified plaques, thus supporting the inflammatory nature of NCPs [39].

Several gaps exist in our knowledge of CVD pathogenesis in HIV-infected women: longitudinal studies assessing the formation and features of plaques, the role of antiretroviral treatment and levels of immune activation and accelerated senescence are needed in order to design specific primary and secondary interventions.

5. Diagnostic approach

For the diagnosis of CHD in female subjects, the use of imaging tests is recommended because of the relatively low predictive value of the exercise tolerance test (ETT), widely used and more reliable in man [40].

Indeed, HIV-positive patients, having a high pre-test probability of CHD, may further benefit from imaging techniques with the screening program. On the other hand, women are generally less likely to receive cardiac imaging than men to diagnose or rule out ischemic heart disease. The reasons behind this gender difference are unclear [40], though they might be related to a persistent misperception of the risk of CHD in women still today.

Myocardial perfusion scintigraphy has been used to assess the prevalence of perfusion defects in HIV-positive and matched negative subjects without known CV risk factors: HIV patients demonstrated higher prevalence of perfusion defects than controls (18% vs. 0%; $p < 0.001$) [41]. Using cardiac magnetic resonance imaging (MRI), HIV-infected adults showed reduced myocardial function as compared to controls in the absence of known CVD. This is associated with evidence abnormal myocardial tissue composition, characterized by increased lipid component and diffuse myocardial fibrosis and raised inflammatory markers [42].

The risk–benefit ratio between using a test that requires ionizing radiation (i.e. CT), which has shown to be effective in rule out CHD and predict CV prognosis in both sexes, compared to one that does not require radiation, remains unclear in women [43].

Recent evidence is also shifting the focus of imaging from an anatomy-based CHD diagnosis to a more functionally-based test. This is because women are more likely than men to suffer from microvascular cardiac disease, specifically at the level of the precapillary coronary arterioles [40].

Today, because of the lack of evidence, the exact diagnostic approach for subclinical atherosclerotic disease in HIV-positive women remains uncertain: whereas coronary CT scan might be reserved to selected high-risk cases, the ultrasound evaluation of carotid plaques might be useful in the attempt to correctly classify patients with intermediate CV risk. The widest experience derives from the use of carotid ultrasound in HIV-positive patients: the prevalence of plaques is higher in HIV-positive patients and the progression is more rapid [44].

6. Primary prevention

Recent guidelines have approached the most appropriate primary prevention strategy in HIV-negative female patients [45]. In HIV-positive patients, recommendations for the prevention of CVD have been included in the European AIDS Clinical Society (EACS) guidelines as well as in the Italian guidelines for the use of antiretroviral agents and the diagnostic-clinical management of HIV-1 infected persons [46,47]. So far, no specific recommendations have been issued for HIV-positive women. Annual estimation of patients' CV risk in those aged above 40 (male) or above 50 (female) years using either the Framingham equation or American College of Cardiology/American Heart Association (ACC/AHA) ASCVD risk calculator or the previously mentioned D:A:D risk calculator, which include data about lopinavir and abacavir assumption, are currently recommended. ACC/AHA ASCVD risk calculator, which gives an estimation of major CV events in the lifetime, seems to be more reliable in HIV patients [48].

Based on the EACS guidelines and considering the recommendation from the Italian Ministry of Health for the management of HIV female patients, Fig. 1 proposes an algorithm for the screening of CV risk in HIV- positive women.

Actually, in this regard, the possibility that the risk score for ASCVD from ACC/AHA might underestimate the risk of AMI in specific groups of subjects has been recently challenged by Feinstein et coll. (49) Indeed, it is unknown how well the ACC/AHA pooled cohort equations—based on risk factors of sex, race/ethnicity, total cholesterol, HDL-cholesterol, smoking, diabetes, SBP, and antihypertensive treatment—predict ASCVD risk in black men and women and in white women. To better address this issue, especially in women, Feinstein et coll. Proposed two HIV-specific MI risk estimation models including variables from the ASCVD risk score plus statin use and HIV-specific variables, such as HIV viral load, CD4 lymphocyte count, antiretroviral therapy, and protease-inhibitor use. Actually, in contrast with proponents' expectations, in a large, multicenter HIV positive cohort, the two new risk-estimation models did not discriminate MI risk any better than the ACC/AHA pooled cohort equation [49].

Proposed interventions in HIV positive female subjects focus on 4 key modifiable risk factors beside lifestyle changes: smoking cessation, control of BP, reduction of glucose levels (if diabetics) with the target of HbA1C <6.5–7%, control of lipid abnormalities with drug therapies (if 10-year CVD risk ≥ 10% or diabetics) with standard and optimal target for total cholesterol (190 and 155 mg/dL) and LDL-cholesterol (115 and 80 mg/dL, respectively). The guidelines also suggest low-dose aspirin in patients above 50 years of age with 10-year estimated CVD risk > 20%. In the setting of HIV infection low dose aspirin is underused, though it may hold potential advantages that need to be investigated in larger prospective trials [50].

Moreover, besides suggesting firm lifestyle interventions in all patients, it has been proposed to consider HAART changes if 10-year calculated CVD risk exceeds 20%. Although several treatments, thoroughly discussed in the Italian guidelines, have been associated with better lipid profile, reduced platelet hyper-reactivity and increased insulin sensitivity, the impact of switching to such drugs on the prevention of CV events is unclear [51]. Furthermore several clinically relevant drug-to-drug interactions must be considered when co-administering CV drugs and HAART (Table 1) [52].

Primary prevention will be a key feature of integrated care of people living and ageing with HIV: evidence-based interventions considering both pharmacological and non-pharmacological interventions must be prospectively assessed and cost–benefit established.

To further investigate the role of statins in decreasing CVD risk in HIV–infected individuals, a clinical trial funded by the National Institutes of Health (REPRIEVE) began in 2015 [53].

7. Secondary prevention

Although much research on gender difference has been performed during the acute phase of CHD, little is still known about sex disparity in the secondary prevention setting.

It has been previously reported that women after an ACS are less likely to achieve LDL-C target levels, BP control and fasting glucose normal values [54]. This is apparently the consequence of under usage of preventive strategies in female subjects. In particular, there is a reduced use of lipid-lowering therapy between men and women with CHD, since they tent to receive insufficient doses of statins and combination lipid-lowering therapy and are less likely than men to achieve their optimal LDL and HDL cholesterol goals [55]. On the contrary, clinical studies indicate that both genders, when appropriately treated, have similar improvements in CV risk factor [56].

Specific guidelines for secondary prevention in HIV-positive male and female subjects have not been produced. In view of the higher risk of subsequent CV events in patients who already suffered from AMI or revascularization, it seems reasonable at this time to apply the

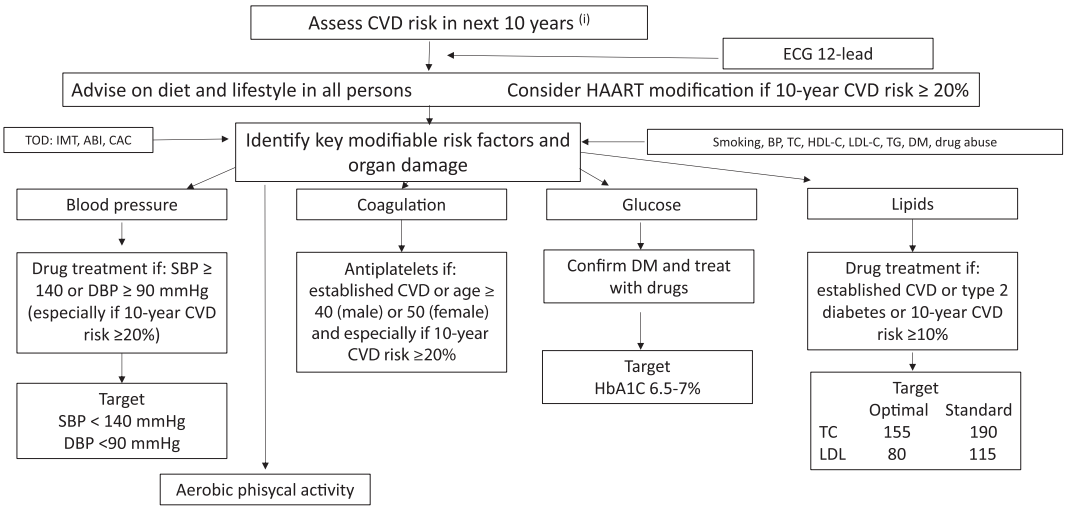

Fig. 1. Suggested clinical approach for periodical CV risk estimation and management. (i) ACC/AHA ASCVD risk calculator should be preferred (http://tools.cardiosource.org/ASCVD-Risk-Estimator/). This assessment and the associated considerations outlined in this figure should be repeated annually in all persons under care to ensure that the various interventions are initiated in a timely way.CAC: coronary artery calcium; IMT: intima-media thickness; ABI: ankle brachial index; SBP: sistolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL- C: low density lipoprotein cholesterol; TG: triglycerides; DM: diabetes mellitus; CVD: cardiovascular disease; HAART: highly active antiretroviral therapy; TOD: target organ damage.Figure modified from reference [45,46].

same interventions to women as those suggested in the guidelines issued for the general population [57].

Some specific issues, however, need to be considered. The spectrum of CHD in HIV-infected patients is similar to that in non–HIV-infected patients and the extension of coronary involvement is generally low, being more frequent the report of single-vessel disease [58]. The short-term outcomes of both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) seem to be similar in HIV-positive and HIV-negative patients. However, in HIV-infected patients a higher rate of recurrent ischemic events was reported [59]. In the PACS (Prognosis of Acute Coronary Syndrome in HIV-Infected Patients) study, recurrent ACS was more frequent in HIV-infected compared to uninfected patients [16]. A meta-analysis of studies conducted on PCI showed that HIV-infected patients with ACS had a significantly higher long-term risk for recurrent coronary revascularization and MI and it has been suggested that drug- eluting stents might be a better option in HIV-positive patients [60,61]. Another multicenter study suggests that HIV-positive patients may undergo less-invasive strategies and are discharged less frequently on dual antiplatelet therapy (53% versus 88%, in HIV negative) and statins (64% versus 89%) [62]. Furthermore, occurrence of sudden cardiac death in HIV-positive patients was found 4.5-fold higher than expected (2.6 per 1000 person-years, 95%CI 1.8–3.8). This could be related to myocardial ischemia, arrhythmias or other abnormalities in these patients [63]. The underutilization of aspirin in HIV-positive subjects has also been reported in secondary prevention strategies, probably reflecting a concern of major bleeding in these “fragile” subjects. Recent data suggest a lower response to aspirin in HIV-positive subjects [64]. Simultaneously the underutilization of dual antiplatelet therapy and high-dose statins may be accounted for by a reasonable concern of significant drug/drug interactions (DDIs). Indeed, cohort studies reported that CV and antiretroviral drugs are the most common compounds to generating clinically relevant DDIs. Specific reviews and updated websites (http://www.hiv-druginteractions.org) may help to get a better appraisal for the optimization and safer management of complex pharmacological regimens in HIV patients [65].

8. Other HIV-CV related diseases

Individuals with HIV are exposed to many pathologic modifications and the final clinical expression of CVDs is highly variable and depends on a number of factors, such as the stage of the HIV infection and subsequent degree of immunodeficiency, combination with HAART, associated opportunistic infections, drug interactions and toxicities.

The high risk of secondary CV events and associated mortality supports the need for immediate, aggressive and collaborative efforts (including infectious disease specialists, cardiologists and nutritionists) aiming at a significant reduction of risk. The appropriate interventions are yet to be defined in both HIV-positive male and female subjects.

Among these, HIV-related cardiomyopathy may present as 1) focal myocarditis; 2) subclinical left ventricular (LV) or right ventricular dysfunction and 3) symptomatic dilated cardiomyopathy with reduced ejection fraction [66]. The reported prevalence rates for HIV associated cardiomyopathy vary widely due to nonuniform definitions, different approach to diagnosis, and studies in different populations. Moreover, it is often subclinical, therefore it may go undetected [67]. An Italian prospective echocardiographic study in 114 HIV-positive patients found that the prevalence of cardiomyopathy in AIDS patients was 16.6% [68]. A recent meta-analysis of studies evaluating cardiac dysfunction during HIV infection in the context of HAART therapy identified LV systolic dysfunction in 8% and diastolic dysfunction in as many as 43% of HIV-infected adults [69].

Several mechanisms for the pathogenesis of HIV associated cardiomyopathy have been proposed from the direct HIV cardiac myocyte invasion to the promotion of abnormal detrimental inflammatory response in situ leading to abnormal myocardial tissue composition characterized by increased lipid components and diffuse myocardial fibrosis [42,70]. Despite the lack of data that HAART can reverse HIV-associated cardiomyopathy, HAART should be instituted in all patients, as restoration of immune status and suppression of the virus may ameliorate cardiac dysfunction [71].

HIV infected patients have a greater incidence of pulmonary artery hypertension (PAH) compared to general population [72]. It was estimated to occur in 0.5% of HIV-positive patients in the pre-HAART age, and, interestingly, its prevalence has not changed, despite the introduction of HAART [73]. Indeed, since HAART has substantially improved the survival rates of patients with HIV, chronic cardiac conditions, such as PAH, are significantly increasing [74]. Reports about HIV positive subjects in African showed that there is no difference between the prevalence in male (6–19%) and in female people (around 10%) [75]. On the other hand, a study including >800 people from the urban population in one of the largest industrial areas in the middle of Europe showed

Table 1
Drug–drug interactions with compounds used for treating cardiovascular disorders.

	Drug or drug class	NRTIs	NNRTIs				bPIs			INSTI			CCR5I
		NRTIs	EFV	NVP	ETV	RPV	LPV	ATV	DRV	RAL	bEVG	DGV	MVC
Anti-hypertensive drugs	ACE inhibitors	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
	Sartans	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
	Beta-blockers	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
	Calcium-antagonists	OK	Titer dose	Titer dose	Titer dose	Titer dose	Titer dose	Titer dose	Titer dose	OK	Titer dose	OK	OK
	Furosemide	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
	Thiazide diuretics	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
Anti-coagulants and anti-platelets drugs	Warfarin	OK	Titer dose	Titer dose	Titer dose	Titer dose	Titer dose	Titer dose	Titer dose	OK	Titer dose	OK	OK
	Clopidogrel	OK	Caution–alt?	Caution–alt?	Caution–alt?	Caution–alt?	Caution–alt?	Caution–alt?	Caution–alt?	OK	Caution–alt?	OK	OK
	Apixaban	OK	Caution–alt?	Caution–alt?	Caution–alt?	Caution–alt?	No	No	No	OK	No	OK	OK
	Rivaroxaban	OK	Caution–alt?	Caution–alt?	Caution–alt?	Caution–alt?	No	No	No	OK	No	OK	OK
	Dabigatran	OK	OK	OK	OK	OK	? Caution	? Caution	? Caution	OK	? Caution	OK	OK
	Aspirin	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
	Heparins	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
Anti-arrhytmics and dopamine	Amiodarone	OK	OK	OK	OK	OK	No	No	No	OK	No	OK	OK
	Flecainide	OK	OK	OK	?	OK	No	No	No	OK	No	OK	OK
	Lidocaina	OK	?	?	?	OK	No	No	No	OK	No	OK	OK
	Propaphenon	OK	?	?	?	OK	No	No	No	OK	No	OK	OK
	Dopamine	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
Cardiac failure, pulmonary hypertension	Digoxin	OK	OK	OK	OK	OK	Titer dose	Titer dose	Titer dose	OK	Titer dose	OK	OK
	Doxazosin	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
	Nitrates	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
	Bosentan	OK	OK	OK	OK	OK	Titer dose	Titer dose	Titer dose	OK	Titer dose	OK	MVC dose
	Sildenafil	OK	OK	OK	OK	OK	Titer dose	Titer dose	Titer dose	OK	Titer dose	OK	OK
Lipid-lowering	Atorvastatin	OK	OK	OK	OK	OK	Titer dose	Titer dose	Titer dose	OK	Titer dose	OK	OK
	Fluvastatin	OK	Titer dose	OK	Titer dose	OK	OK	OK	OK	OK	OK	OK	OK
	Pravastatin	OK	Titer dose	OK	OK	OK	OK	OK	No	OK	OK	OK	OK
	Rosuvastatin	OK	OK	OK	OK	OK	Titer dose	Titer dose	Titer dose	OK	OK	OK	OK
	Simvastatin	OK	OK	OK	OK	OK	No	No	No	OK	No	OK	OK
	Fibrates	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
	Ezetimibe	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK

NRTI, Nucleoside reverse transcriptase inhibitors; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitors; PIs, Protease inhibitors; INSTI, integrase strand transfer inhibitor; CCR5I, C-C chemokine receptor type 5 Inhibitor; EFV, Efavirenz; NVP, Nevirapine; RVP, Aspartyl Protease; LPV, Lopinavir; ATV, Atazanavir; DRV, Darunavir; RAL, Raltegravir; bEVG, Elvitegravir; DGV, Dolutegravir; MVC, Maraviroc; ACE, angiotensin converting enzyme.
Filled with data from http://www.hiv-druginteractions.org. (Last accessed February 15th, 2016).

that women are more often affected than previously reported, with a marked female predominance in symptomatic HIV–PAH [74]. The presence of PAH is of crucial importance since about two-thirds of the deaths in patients with HIV-related PAH are due to its consequences, such as right heart failure, cardiogenic shock and sudden death [76].

The pathophysiology of HIV-PAH is still questioned. The absence of viral particles in vascular pulmonary lesions suggests an indirect action of the virus, with abnormal inflammation process acting as a trigger in predisposed individuals [77]. The effect of HAART on patients with HIV-PAH is controversial [74] and it is also important to be aware of potential drug interactions in patients with HIV-PAH as some specific HAARTs might modify metabolism and side effects of PAH therapies [78].

9. Conclusions

HIV-infected women have increased rates and risk of incident CVD events, as compared to uninfected women, after adjustment for demographic characteristics, risk factors, other comorbidities, and substance use and abuse with additional burden also linked to the use of antiretroviral drugs. Future studies should focus on the identification of risk factors contributing to this excess of CV risk among HIV-infected women and on the development of strategies based on appropriate flowcharts to prevent CVD in this high-risk population. The implementation of the current clinical approach in women (improved diagnosis and appropriate interventions in primary and secondary prevention) represents a growing important issue in the prespective of progressively ageing HIV population. This may result in an improvement in prevention of future CVD, in the quality of life of the patients and in a potential reduction of the mounting healthcare costs related to the clinical and social management.

Conflict of interest disclosure

Rita Bellagamba has received consultancy and/or speakers' fee from BMS, GILEAD SCIENCES, Janssen-Cilag, MSD, VIIV. **Teresa Bini** has received research funding and/or honoraria from Merck Sharp & Dohme, Bristol-Myers Squibb, and Janssen-Cilag. **Antonella Castagna** report no conflicts of interest in this work. **Giulia Marchetti** has received research funding and/or honoraria from Abbvie, Janssen-Cilag, Merck Sharp and Dohme, Gilead, ViiV. **Cristina Mussini** has been involved in advisory boards or educational courses supported by Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, now ViiV Healthcare, Merck Sharp & Dohme, and Janssen-Cilag. **Daniela Mancusi, Roberta Termini, Alessia Uglietti** are employees of Janssen-Cilag SpA, Italy. **Massimo Volpe** has no conflict of interest to disclose related to this work.

Acknowledgments

The authors wish to thank Caterina Santolamazza, MD and Allegra Battistoni, MD for the help in the preparation of this manuscript.

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