REVIEW

Clinical update

HIV and the heart: the impact of antiretroviral therapy: a global perspective

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From a global perspective, cardiovascular disease (CVD) in human immunodeficiency virus (HIV) may result from cardiac involvement upon presentation of opportunistic infections in the presence of advanced immunosuppression, be a consequence of HIV-induced immune activation or derive from antiretroviral therapy-associated dyslipidaemia and insulin resistance. Indeed, in developed countries with unlimited access to antiretroviral therapy CVD has become one of the major causes of death in HIV. Therefore, cardiovascular risk reduction and lifestyle modifications are essential and careful selection of the antiretroviral drugs according to underlying cardiovascular risk factors of great importance. In developing countries with delayed roll-out of antiretroviral therapy pericardial disease (often related to TB), HIV-associated cardiomyopathy, and HIV-associated pulmonary hypertension are the most common cardiac manifestations in HIV. In Africa, the epicentre of the HIV epidemic, dynamic socio-economic and lifestyle factors characteristic of epidemiological transition appear to have positioned the urban African community at the cross-roads between historically prevalent and 'new' forms of CVD, such as coronary artery disease. In this context, cardiovascular risk assessment of HIV-infected patients will become a critical element of care in developing countries similar to the developed world, and access to antiretroviral therapy with little or no impact on lipid and glucose metabolism of importance to reduce CVD in HIV.

Keywords Heart • HIV • Cardiovascular • Pericarditis • Cardiomyopathy • Antiretroviral therapy • ART • Protease inhibitors • Abacavir

Introduction

Combination antiretroviral therapy (cART) has dramatically improved survival of patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS).[1] When HIV infection is diagnosed early and cART is initiated in time, most patients experience acceptable immune recovery and can reach normal life expectancy.[2] With the decline of HIV-related morbidity and mortality and increased life expectancy, non-HIV-related conditions and comorbidities continue to rise in this cohort. Cardiovascular disease (CVD) is the leading comorbidity and cause of death in this population.[3] Some antiretroviral agents may also contribute to this increased rate of CVD in HIV and therefore require careful selection according to the underlying cardiovascular risk factors.[4] In general, antiretroviral agents causing dyslipidaemia or diabetes should be avoided in patients at risk. Nonetheless, in most parts of the world, including developed countries, HIV is often diagnosed at advanced stages of immunosuppression leading to severe opportunistic infections which can involve the heart and are associated with high mortality rates.[5–9] Also, immune recovery in those patients remains incomplete despite long-term successful viral suppression after initiating cART and patients remain at a higher risk of AIDS or death.[10] From a global perspective, CVD in HIV can be divided in two categories: CVD in regions with unlimited access to cART and regions where cART roll-out is delayed. In this review, we present an overview of both regions: HIV-associated CVD, CVD due to advanced immunosuppression, and the impact of cART on the heart.

Epidemiology of human immunodeficiency virus and cardiovascular disease

Human immunodeficiency virus /AIDS is a global pandemic affecting ~34 million people (*Figure 1*). Africa carries the highest burden with almost 70% of all HIV-infected individuals worldwide. Other regions

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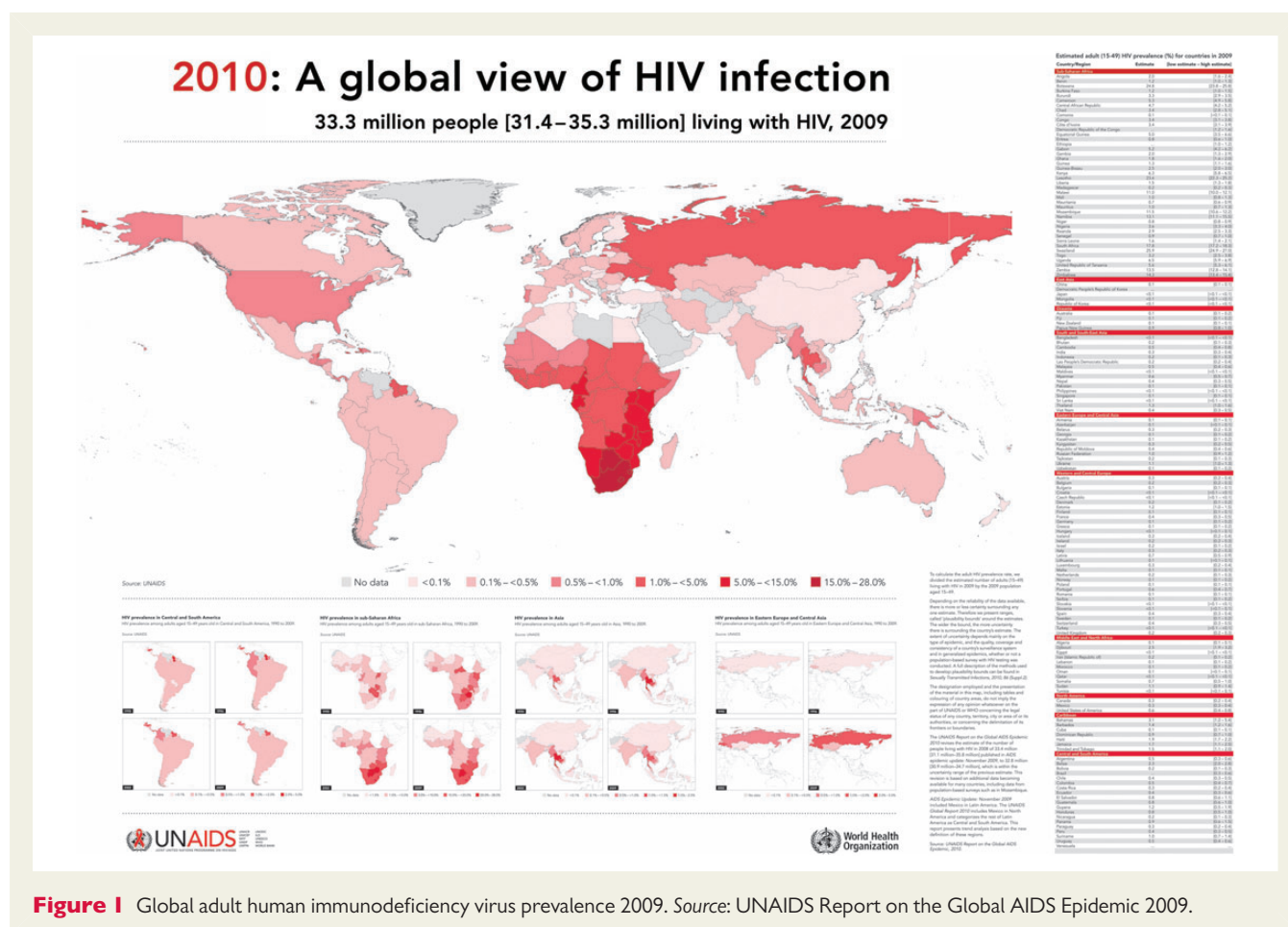
Figure 1 Global adult human immunodeficiency virus prevalence 2009. *Source*: UNAIDS Report on the Global AIDS Epidemic 2009.

with high HIV/AIDS prevalence rates are South-East Asia and countries of the former Soviet Republic.[11] It has been recognized that the incidence of opportunistic infections involving the heart has increased since the advent of the epidemic, but systematic data remain scarce. The most commonly reported cardiac manifestations in HIV/AIDS are pericardial disease (often related to tuberculosis), cardiomyopathy, and pulmonary hypertension (PH) (*Figure 2*).[5–9] We previously reported in this journal on the contribution of HIV/AIDS to heart disease in a large cohort of 5328 patients presenting with *de novo* heart diseases in Africa.[9] Five hundred and eighteen (9.7%) were identified HIV positive (*Figure 3*). More than half (54%) of the patients were on cART at the time of presentation.

Cardiac manifestations of human immunodeficiency virus infection

Human immunodeficiency virus pericarditis

Worldwide, pericarditis is one of the most common cardiac disorders in HIV.[5,7,8,12] Presentations can vary from small and asymptomatic pericardial effusion to cardiac tamponade.[7–9,12–18] Causes of pericardial effusion can be manifold ranging from opportunistic infections with mycobacteria, bacteria, viruses and fungi to AIDS-related

malignancies (*Table 1*);[12,19] aetiology is thus largely dependent on the degree of immunosuppression and exposure to infection. The incidence of pericardial effusion in patients with advanced HIV has been described at 11% per annum (*Table 2*).[12] The diagnostic yield of pericardial fluid cultures and biopsies lies between 24 and 37%, suggesting that HIV itself may be a the primary contributor.[12,20–22] An independent association between pericardial effusion and survival could be found.[12] Survival of AIDS patients with pericardial effusion on echocardiography was significantly shorter compared with AIDS patients without pericardial effusion.[12,20–22] The epidemiology of pericardial effusion seems to change dramatically in patients on cART. Within the HIV-HEART study 802 HIV-positive outpatients underwent echocardiography screening of which 85% were receiving cART at the time.[23] Pericardial effusion was only present in 0.25% of patients.

Human immunodeficiency virus pericarditis in the context of a high tuberculosis burden

Even though the most common cause of pericarditis in HIV in developed countries is idiopathic, tuberculosis probably remains the most common cause of pericarditis in HIV worldwide.[5,7,12] In some regions Africa up to 80% of patients with tuberculosis are also infected with
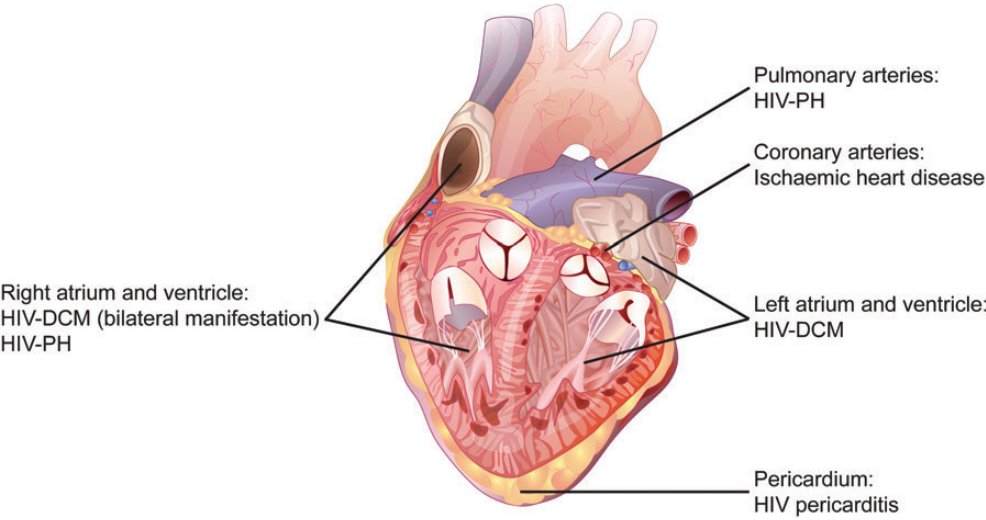
Figure 2 Cardiac manifestations of human immunodeficiency virus infection. HIV-PH, HIV-associated pulmonary hypertension, HIV-DCM, HIV-associated dilated cardiomyopathy.
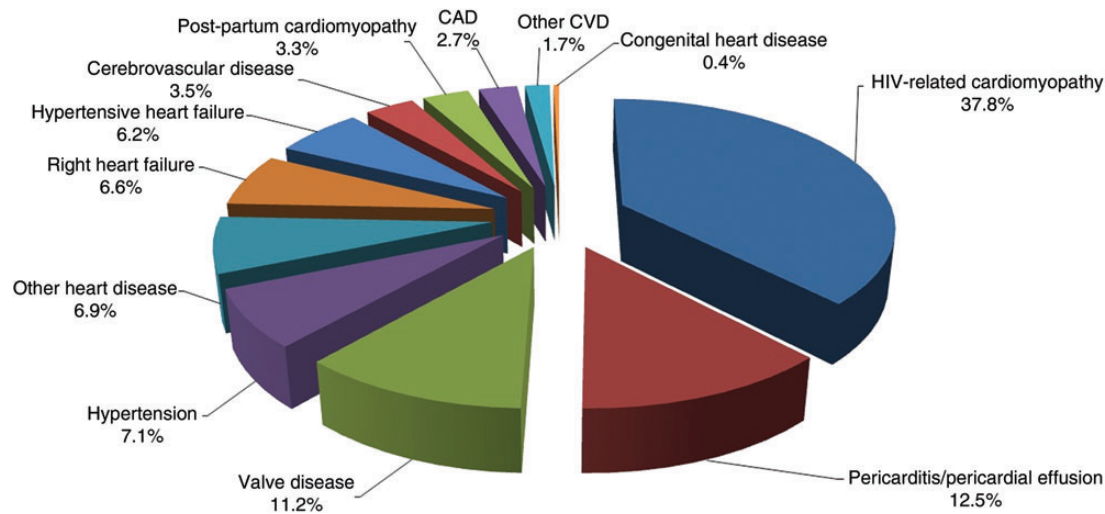

Figure 3 Primary cardiovascular diagnosis of all human immunodeficiency virus patients (%) presenting with *de novo* heart disease at a tertiary cardiac service in South Africa (*n* = 518). CAD, coronary artery disease; CVD, cardiovascular disease. *Source*: Sliwa *et al.*[9]

HIV. In this epicentre of two epidemics, *Mycobacterium tuberculosis* is the cause of pericardial disease in 86–100% of HIV-positive patients.[5,13,24–26]

Human immunodeficiency virus-associated cardiomyopathy

In autopsy studies, myocarditis has been reported in up to 52% of HIV patients with biventricular involvement in 10% of cases.[27] An opportunistic pathogen other than HIV could only be detected in 19–26%

(*Table 2*).[27,28] In countries with high tuberculosis/HIV-coinfection rates, HIV-associated tuberculosis pericarditis has been associated with the development of concomitant myopericarditis.[29] However, in ~80% of cases the aetiology remains uncertain and direct infection of myocytes and autoimmune processes triggered by HIV have been implicated.[28]

The estimated incidence of HIV-associated dilated cardiomyopathy (HIV-DCM) pre-cART is 15.9/1000 per annum (*Table 2*).[28] Human immunodeficiency virus-associated dilated cardiomyopathy is considered WHO Clinical Stage IV (AIDS)[30] and is associated

Table 1 Cause of pericardial disease in human immunodeficiency virus with risk stratification by CD4 count

Type	Infectious and non-infectious cause	CD4 count[a] (cells/μL)
Bacteria	Staphylococcus aureus Streptococcus pneumoniae Proteus sp. Nocardia sp. Pseudomonas aeruginosa Klebsiella sp. Enterococcus sp. Listeria monocytogenes	Any CD4 count
Mycobacteria	Mycobacterium tuberculosis Atypical mycobacteria	<500 <50
Viruses	HIV Herpes simplex virus I/II Cytomegalovirus	Any CD4 count <300 <50
Fungi	Histoplasma capsulatum Cryptococcus neoformans Candida sp.	<50 <50 <300
Protozoa	Toxoplasma gondii	<100
Malignancies	Kaposi's sarcoma Non-Hodgkin's lymphoma	Any CD4 count <200
Other	Immune reconstitution inflammatory syndrome Left ventricular dysfunction (ejection fraction $<50\%$)	<50 Any CD4 count

[a]Risk of HIV-associated pericardial disease increases in incidence as CD4 count declines.

with a poor prognosis with an adjusted mortality hazard ratio of 4.0 when compared with HIV-negative controls with idiopathic DCM;[31] the median survival of HIV-DCM is 101 days compared with 472 days in HIV-positive control without DCM.[32] Data from Africa revealed a HIV-DCM prevalence of 18−32%.[33,34] A study in China found HIV-infection to be independently associated with cardiac diastolic dysfunction;[35] 42.8% of HIV patients had diastolic dysfunction, with similar results found in India.[36] These studies were performed before cART became available in 1996, in cART-naive patients at advanced stage of disease, or in regions where cART is not widely available (Table 2). In the latter, malnutrition has been described as contributor to the frequent occurrence of HIV-DCM within the African context.[33,37] With the introduction of cART, the prevalence of HIV-DCM dropped by ~30% in developed countries,[38] but in developing countries where cART roll-out is delayed and penetration of cART, especially in rural areas is scanty, HIV-DCM remains common with possibly a multifactorial pattern.

Human immunodeficiency virus-associated pulmonary hypertension

On a global scale, the prevalence of PH in HIV-infected individuals varies between 0.5 and 5.0% with HIV being recognized as an independent risk factor for the development of PH.[8,39−42] The prevalence of HIV-associated pulmonary hypertension (HIV-PH) in developed countries with access to cART is 0.5%, while 5.5% of patients with no symptoms of PH may be at risk for PH; 1000-fold higher than in the general population.[42−44] Studies conducted in Africa found evidence of PH by echocardiographic measurements in 0.6− 5% of HIV patients in Nigeria, Burkina Faso, and Zimbabwe.[8,45] Estimated survival rates in developed countries in the

Table 2 Epidemiology of cardiovascular disease in human immunodeficiency virus and the impact of combination antiretroviral therapy

Cardiovascular disease	cART-naive patients, pre-cART era, or countries with limited access to cART	Patients on cART, cART era, or countries with unlimited access to cART

Pericardial disease	Incidence of 11% per annum in advanced HIV
	  In one-third a cause other than
	  HIV can be established
	  Tuberculosis is most common cause of pericardial disease
	  Pericardial effusion predictor of mortality
		Pericardial disease is rare
		  Prevalence $<1\%$ in patients on cART

Dilated cardiomyopathy (DCM)	Incidence of 1.6−5.0% per annum
	  Risk factors: low CD4 count, high HIV viral load, advanced HIV
	  In one-fifth a cause other than HIV can be established
	  Cardiotrophic viruses, Epstein-Barr virus, toxoplasmosis,
	  Cryptococcus neoformans, or malnutrition can cause myocarditis
	  Tuberculosis can cause perimyocarditis
	  Poor prognosis
		Prevalence of HIV-DCM dropped by 30% in countries with unlimited access to cART

Pulmonary hypertension (PH)	Prevalence of HIV-PH 0.6−5.0%
	  No association between HIV-PH and CD4 count, HIV viral load, or stage of disease
		Prevalence of HIV-PH 0.5%
		  No change in incidence of HIV-PH since the advent of cART

Coronary artery disease (CAD)	HIV-infection amplifies risk for CAD, but data inconclusive	Exposure to specific antiretroviral drugs may also increase risk for CAD

cART, combination antiretroviral therapy.

pre-cART era were ~70% at 1 year and 50% at 3 years compared with ~90% at 1 year and 70% at 3 years after the advent of cART. Even though these data seem convincing a direct benefit of cART on the incidence and survival of HIV-PH could not be demonstrated.[40,46,47] Combination antiretroviral therapy alone without specific treatment for PH does not result in an improved cardiac function.[46] Also, no association between HIV-PH and CD4 count, viral load, or stage of disease could be identified.[39,48]

Coronary artery disease

Over the past decade, the association between HIV infection and coronary artery disease (CAD) and the effects of cART on the risk of CAD have been discussed with great controversy (see next paragraph). In fact, little is known about the impact of HIV infection itself on coronary arteries, but HIV infection does amplify the risk for CAD before exposure to cART.[49] Chronic immune activation in HIV may lead to a chronic inflammatory state, endothelial dysfunction, coagulopathy and thombophilia, and/or lipid disturbance and therefore promote arteriosclerosis.[49–53] In Africa, CAD is uncommon, but dynamic socio-economic and lifestyle factors characteristic of epidemiological transition appear to have positioned the urban African community at the cross-roads between historically prevalent and 'new' forms of heart disease, such as CAD.[54,55] Data from South America also demonstrated a high prevalence of risk factors for CAD.[56] This increasing or underlying prevalence of modifiable cardiovascular risk factors such as hypertension and obesity in less developed countries may lead to this predicted epidemiological transition of the aetiology of heart diseases.[57,58] Indeed, under consideration of the increasing proportion of patients on cART and the earlier initiation of HIV therapy in these regions altogether an increase in the proportion of ageing patients and eventually rise in CVD associated morbidity and mortality can be expected. Therefore, it is extremely important to learn from regions with extensive cART experience which cardiovascular risks are associated with prolonged cART exposure to be able to prevent the extent of CVD in HIV patients now being observed in the developed world.

Cardiovascular disease in the context of combination antiretroviral therapy

Large HIV cohort studies have convincingly demonstrated an excess cardiovascular risk in HIV-infected individuals compared with the general population in developing countries.[59–61] Based on the 10-year cardiovascular risk estimation, a disproportionate increase in cardiac events has to be expected in ageing HIV patients in the next decades ($\geq$45/$\leq$45 years 16.4 vs. 4.2%, $P < 0.01$).[60] The pathophysiology of this increased risk is complex and multifactorial. On the one hand traditional risk factors including smoking (which is overrepresented in HIV cohorts) may contribute to increased cardiovascular risk.[62] On the other hand cART (either directly or via associated dyslipidaemia and insulin resistance), as well as HIV-induced immune activation, may both further aggravate the risk of CVD.[63]

Cardiovascular risk and protease inhibitors

To address some of these concerns, the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study was initiated in 1999. In their first analyses, the D:A:D Study Group found that cART was independently associated with a 26% relative increase in the rate of myocardial infarction per year of exposure during the first 4 to 6 years of cART.[4] Four years later, the same group demonstrated that in particular cumulative exposure to protease inhibitors (PIs) contributed to an increased rate of myocardial infarction in HIV patients, which could partially but not fully be explained by dyslipidaemia associated with these drugs.[64] Increased risk of myocardial infarction in HIV patients on a PI-based cART was also reported by other cohorts.[65,66] With increasing person years of treatment for the various boosted and unboosted PIs available for HIV therapy a more distinct picture emerged of a significantly increased cardiovascular risk with the use of indinavir and ritonavir-boosted PIs lopinavir, amprenavir, and fosamprenavir.[66] More recently, no increased risk was found for boosted atazanavir.[67] Data on the more recently introduced PI darunavir are still lacking.

Cardiovascular risk and nucleos(t)ide reverse transcriptase inhibitors

Further studies then aimed at evaluating the potential contribution of nucleos(t)ide reverse transcriptase inhibitors (NRTI) 'backbones' on the increased cardiovascular risk in HIV patients on cART. Within the D:A:D study an increased risk for myocardial infarction in patients being treated with abacavir or exposed to this drug within the preceding 6 months was reported for the first time.[68] These findings were confirmed by several studies, but not all. Indeed, studies are difficult to compare as patient characteristics and patient numbers vary considerably. Of note, a more recent FDA initiated meta-analysis found no association with abacavir use and increased cardiovascular risk.[69] However, this was done mostly in antiretroviral treatment studies which included patients with no or only small risk for cardiovascular events thereby potentially limiting the findings to patients with low cardiovascular risk when starting abacavir-based cART. Within the French Hospital database short-term/recent exposure to abacavir was associated with an increased risk of myocardial infarction in the overall cohort [odds ratio (OR) 2.01; 95% confidence interval (CI), 1.11–3.64] but not in the subset of matched cases and controls who did not use cocaine or intravenous drugs (OR: 1.27; CI: 0.64–2.49).[66] This has raised the question as to how far cohort studies can adjust for all potential confounding factors which may contribute to cardiovascular risk and which may have been over-represented in the abacavir-treated patients.

With regard to other NRTIs no increased risk has been found with the exception of a potentially increased risk associated with didanosin. However, this is of primarily historic interest as this particular NRTI is no longer recommended in general for HIV therapy due to its extensive toxicity profile. *Table 3* summarizes the main classes of antiretroviral drugs, their effects on lipid and glucose metabolism, and the potential for contributing to the risk of CVD.

Azidothymidine, a NRTI and component of first line cART, has been described to cause cardiac dysfunction induced by

Table 3 Main classes of antiretroviral drugs and their impact on lipid and glucose metabolism and coronary artery disease

Drug class	Antiretroviral	Effects on lipids[a]	Effects on glucose[a]	Impact on coronary artery disease
Nucleos(t)ide reverse transcriptase inhibitors	Abacavir	TC⇑ LDL⇑	No effect	Recent exposure associated with increased risk for MI (controversial)
	Azidothymidine	TC⇑ LDL⇑	Insulin resistance+	No association with increased risk for MI
	Emtricitabine	Neutral effect	No effect	No association with increased risk for MI
	Lamivudine	Neutral effect	No effect	No association with increased risk for MI
	Stavudine	Dyslipidaemia+	Insulin resistance+	No association with increased risk for MI
	Tenofovir	TC⇓ LDL⇓	No effect	No association with increased risk for MI
Non-nucleoside reverse transcriptase inhibitors	Efavirenz	TC⇑ LDL⇑	No effect	No association with increased risk for MI
	Etravirine	Neutral effect		No data available (not enough patients exposed)
	Nevirapine	HDL⇑		No association with increased risk for MI
	Rilpivirine	Neutral effect		No data available (not enough patients exposed)
Protease inhibitors	Amprenavir + Ritonavir	Dyslipidaemia++	Insulin resistance+	Cumulative exposure independently increased risk for MI
	Atazanavir + Ritonavir	Dyslipidaemia+	Insulin resistance+	No association with risk for MI
	Darunavir + Ritonavir	Dyslipidaemia+	Insulin resistance+	No data available (not enough patients exposed)
	Indinavir	Dyslipidaemia+	Insulin resistance+++	Controversial results
	Lopinavir + Ritonavir	Dyslipidaemia+++	Insulin resistance+++	Cumulative exposure independently increased risk for MI
	Nelfinavir	Dyslipidaemia+	Insulin resistance+	No association with risk for MI
	Saquinavir	Dyslipidaemia+	Insulin resistance+	No association with risk for MI
	Tipranavir + Ritonavir	Dyslipidaemia+	Insulin resistance+	No data available (not enough patients exposed)
Integrase inhibitors	Elvitegravir/cobicistat Raltegravir	Neutral effect	No effect	No data available (not enough patients exposed)
Entry inhibitors	Maraviroc	Neutral effect	No effect	No data available (not enough patients exposed)

[a]Dyslipidaemia defined as increased total cholesterol (TC), low-density lipoprotein cholesterol (LDL), triglycerides and decreased high-density lipoprotein cholesterol (HDL); +, weak effect; ++, moderate effect; +++, important effect; ⇑, increase; ⇓, decrease. MI, myocardial infarction.

mitochondrial toxicity.[70,71] In these two reports on adults, seven patients on azidothymidine developed cardiac dysfunction, and in four patients this improved after discontinuation of azidothymidine. However, three larger studies could not confirm an association between exposure to azidothymidine and myocardial dysfunction.[72–74]

Impact of diabetes on cardiovascular disease in human immunodeficiency virus

Diabetes mellitus is a global major public health problem and CVD is the leading cause of morbidity and mortality in diabetic patients.[75] The association of HIV infection and diabetes is poorly understood and complicated by different risk profiles of HIV-positive and negative persons for the development of diabetes such as co-infection with *M. tuberculosis* and Hepatitis C.[76,77] Age, obesity, and race independently remain the major risk factors for diabetes in HIV patients.[78] Several studies could not demonstrate that HIV infection itself (in cART-naive patients) is independently associated with diabetes suggesting no increased risk of diabetes in HIV;[76,79] but increased rates of insulin resistance have been observed in antiretroviral-naïve HIV patients.[79] The risk of diabetes in HIV is enhanced once patients

start cART.[78–80] Protease inhibitors reversibly increase insulin resistance, the risk of diabetes and subsequently the risk for CVD through the inhibition of glucose translocation through GLUT4.[81] Also the NRTIs azidothymidine, didanosin, and stavudine have been identified to have direct effect on glucose metabolism through mitochondrial toxicity.[82,83] Interestingly, a recent publication demonstrated that the increased long-term risk for heart failure in HIV-infected compared with HIV-negative patients was independently associated with HIV and diabetes at 12-month follow-up.[84] Therefore, careful glucose monitoring is warranted in patients on cART, especially in patients on PIs and older NRTIs.

Electrocardiographic abnormalities in human immunodeficiency virus

More than half of all HIV patients may have abnormalities on electrocardiography (ECG).[85] QT interval prolongation has been described in HIV and is associated with sudden death.[86–89] Ritonavir-boosted PIs may prolong the QT interval on ECG.[90] Boosted saquinavir has been described to prolong the QT interval more than other boosted PIs and should therefore be used with caution in patient
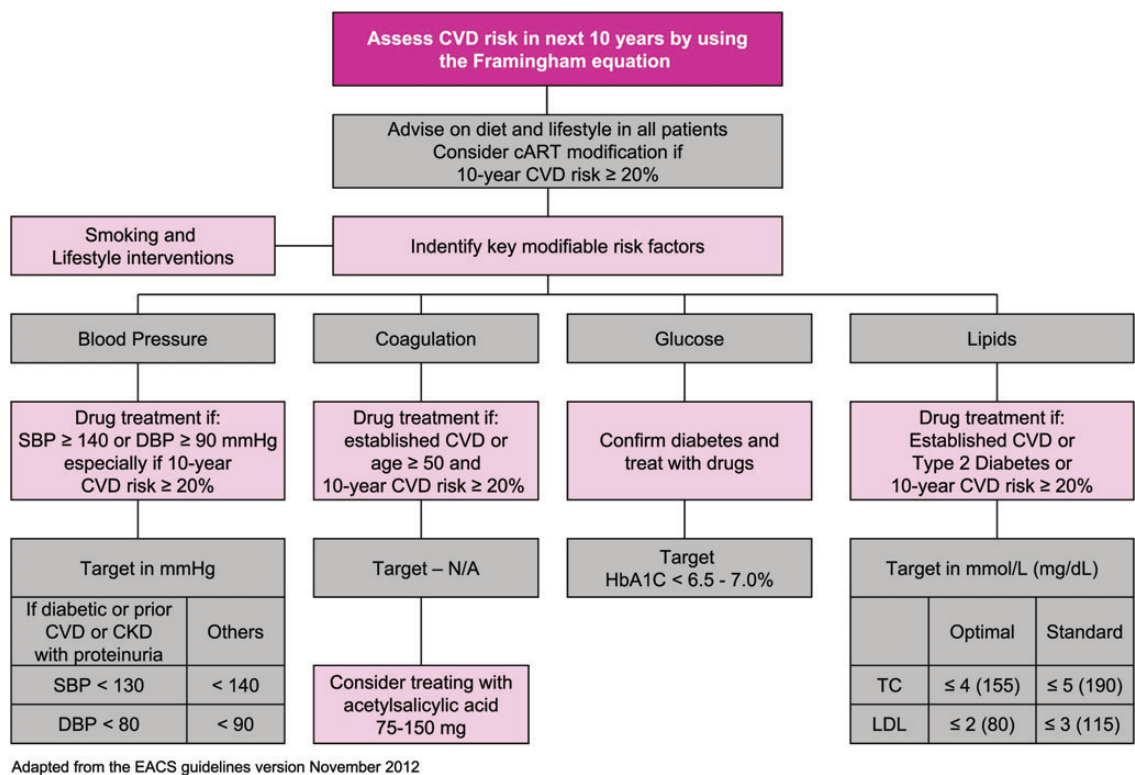
Figure 4 Algorithm for the prevention of cardiovascular diseases. CVD, cardiovascular disease; cART, combination antiretroviral therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidneys disease; TC, total cholesterol; LDL, low-density lipoprotein. *Source*: European AIDS Clinical Society.

with underlying heart disease or cardiac arrhythmia.[91] QT interval prolongation have also been described for efavirenz and rilpivirine.[92]

The right combination antiretroviral therapy for the heart

Considering the higher prevalence of CVD in HIV, screening for CVD is essential and should occur in every HIV patient. In the European AIDS Clinical Society (EACS) guidelines an initial CVD risk assessment, including Framingham score determination, recording of an ECG and performing of a blood pressure measurement is recommended at the baseline visit after HIV diagnosis as well as prior to starting cART (see www.europeanaidsclinicalsociety.org and *Figure 4*). After cART initiation annual follow-up is suggested. As outlined above, HIV replication *per se* may aggravate CVD which is one of the main reasons why in patients with a high risk for CVD (>20% estimated 10-year risk) or a history of CVD the EACS guidelines recommend considering early ART initiation, even in patients with a CD4 count >500 cells/μL. In this context, however, it is important to select a cART which at best not itself contributes to cardiovascular risk (*Table 3*). Moreover, interventions for risk factor modification such as smoking cessation therapy need to be considered. Interestingly, the contribution of smoking to CAD in HIV-positive adults was generally greater than the contributions of diabetes and hypertension, and was almost twice as high as that in HIV-negative

adults.[93] Therefore, development of effective smoking cessation strategies should be prioritized.

Prevention of cardiovascular disease and lifestyle modification

Cardiovascular risk in HIV patients needs to be evaluated before starting and during treatment with cART. The most frequently used tool for cardiovascular risk assessment is the Framingham equation. A risk equation developed from HIV populations has also been developed (see www.cphiv.dk/tools.aspx), but so far is not widely used. *Figure 4* is adapted from the EACS guidelines and represents a possible algorithm for risk assessment and subsequent risk factor-driven treatment intervention which should be repeated annually. In general, interventions for cardiovascular risk reduction follow those of the general population. It is important to highlight the treatment of atherogenic dyslipidaemia frequently found in HIV patients taking antiretroviral therapy particularly in the context of PI-based therapy. Serum concentrations of lipids should be evaluated in fasting patients before cART is started, at 3−6 months after initiation, and then yearly in the absence of abnormalities. The currently recommended lipid level targets are depicted in *Figure 4*. Target levels are to be used as guidance not as definitive values. If low-density lipoprotein cholesterol (LDL-C) cannot be calculated because of high triglyceride (TG) levels (not uncommon in PI-based therapy), the non-high-density lipoprotein cholesterol (non-HDL-C; calculated

Table 4 Drug–drug interactions between antiretroviral and cardiovascular drugs

		Atazanavir	Darunavir	Lopinavir	Ritonavir[a]	Efavirenz	Etravirine	Rilpivirine	Navirapine	Maraviroc	Raltegravir	ELV/c
CARDIOVASCULAR DRUGS	atorvastatin	↑	↑	↑	↑	↓	↓	↔	↓*	↔	↔	↑*
	fluvastatin	↔*	↔*	↔*	↔*		↑*	↔		↔*	↔*	↔*
	pravastatin	↔*	↑	↔	↔	↓	↓*	↔	↔*	↔	↔	↔*
	rosuvastatin	↑	↑*	↑	↑	↔	↑*	↔	↔	↔	↔	↑*
	simvastatin	↑	↑	↑	↑	↓	↓*	↔	↓*	↔	↔	↑*
	amlodipine	↑*(3)	↑*	↑*	↑*	↓*	↓*	↔	↓*	↔*	↔	↑*
	diltiazem	↑(3)	↑*	↑	↑	↓	↓*	E*	↓	E*	↔	↑*
	metoprolol	↑*	↑*	↑*	↑*	↔*	↔*	↔	↔*	↔*	↔*	↑*
	verapamil	↑*(3)	↑*	↑*	↑*	↓*	↓*	↔	↓*	E*	↔*	↑*
	warfarin	↑ or ↓*	↓	↓	↓	↑ or ↓*	↑*	↔	↑ or ↓*	↔*	↔*	↓*

[a]Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent.

[b]ECG monitoring recommended; *, prediction based on metabolic profiles of drugs only, no clinical data from interaction study; absence of * indicates that clinical data are available; ↑, elevated exposure of cardiovascular drug; ↓, decreased exposure of cardiovascular drug; ↔, no significant effect; E, elevated exposure of antiretroviral drug; D, decreased exposure of antiretroviral drug; ELV/c, Elvitegravir/cobicistat (cobicistat is used as pharmacokinetic enhancer without anti-HIV activity). Adopted from European AIDS Clinical Society (EACS).

as total cholesterol minus HDL-C) target should be used which is 0.8 mmol/L (30 mg/dL) higher than the corresponding LDL-C target. Target levels for TG are not listed because an independent contribution from TG to cardiovascular risk is uncertain and, hence, it remains uncertain whether this condition should be treated. Lipid-lowering therapy is also recommended for patients with established CVD or Type 2 diabetes or 10-year CVD risk ≥20% (*Figure 4*). Drug–drug interactions between statins, fibrates and HIV drugs need to be checked (see next paragraph and *Table 4*).

In addition to lipids, control of blood pressure and glucose metabolism is warranted (*Figure 4*). Of the modifiable risk factors outlined, drug treatment is reserved for certain subgroups where benefits are considered to outweigh potential harm. Of note, there is a combined benefit of various interventions in target groups identified. Per 10 mmHg reduction in systolic blood pressure, per 1 mmol/L (39 mg/dL) reduction in total cholesterol (TC) and with the use of acetylsalicylic acid, each reduces risk of ischaemic heart disease by 20–25%; the effect is additive. With regard to the use of acetylsalicylic acid, the EACS guidelines state that evidence for benefit when used in persons without a history of CVD (including diabetics) is less compelling. A recent pilot trial of low-dose acetylsalicylic acid in HIV patients demonstrated that heightened platelet activation and immune activation in treated HIV disease are attenuated after 1 week of acetylsalicylic acid therapy.[94] Therefore, acetylsalicylic acid should be further studied in treated HIV disease.

Modification of antiretroviral therapy

In HIV patients on cART who have newly developed a cardiovascular event or developed a substantial increase in cardiovascular risk cART modification may represent a good option to discontinue antiretroviral drugs with a risk of enhancing cardiovascular risk or may help to improve the dyslipidaemia observed mostly with ritonavir-boosted PI-based therapy. Treatment modifications would include replacement of PI with non-nucleoside reverse transcriptase inhibitors (NNRTI), raltegravir or by another PI with less metabolic disturbances (*Table 3*). A further modification could be to consider replacing stavudine, azidothymidine, or abacavir with tenofovir or use a NRTI sparing regimen.

Drug–drug interactions

Most of the antiretroviral drugs, in particular the PIs and NNRTIs, are metabolized via the cytochrome P450 (CYP) 3A4 pathway. Protease inhibitors and also low-dose ritonavir (which is dosed as a pharmacokinetic enhancer, 'boosting') mainly inhibit CYP and can increase the toxicity of concomitant drugs such as some statins (*Table 4*). Non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz) on the other hand are inducers of CYP and can potentially reduce drug levels. *Table 4* summarizes the drug–drug interactions between antiretroviral drugs and some commonly prescribed cardiovascular co-medications. This table is not exhaustive; for additional information refer to www.hiv-druginteractions.org.

Conclusion

In the natural course of HIV, particularly with the outbreak of AIDS, involvement of the heart within various opportunistic infections and HIV-associated malignancies is common. Therefore, HIV infection needs to be included into differential diagnosis considerations particularly in the setting of tuberculosis-associated pericarditis. Besides cardiac involvement in various AIDS manifestations, HIV

itself induced immune activation is considered to independently contribute to CVD and may partially explain the higher cardiovascular mortality in this patient group. Moreover, cART via associated dyslipidaemia or insulin resistance may further enhance cardiovascular risk. Therefore, careful selection of antiretroviral drugs as well as cardiovascular risk management is necessary to counter balance the increased cardiovascular morbidity in this patient population and close attention towards multiple complex drug–drug interactions between HIV therapy and commonly used cardiovascular drugs is mandated. With regard to developing countries, dynamic socio-economic, and lifestyle factors characteristic of an epidemiological transition appear to have positioned the urban community also at risk for traditional CVD. In this context, cardiovascular risk assessment of HIV patients needs to become a critical element of care similar to developed countries. Also, access to first and second line cART with little or no impact on lipid and glucose metabolism will become of importance to reduce CVD in HIV in the future.

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