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REVIEW

Novel therapeutic concepts

HIV infection and cardiovascular disease

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Aims With the success of antiretroviral therapy (ART), non-human immunodeficiency virus (HIV)-related comorbidities like cardiovascular diseases (CVDs) are of increasing concern. We describe important recent research developments on the epidemiology of CVD in HIV infection, ART-related metabolic changes, and cardioprotective anti-inflammatory mechanisms, and summarize management strategies for CVD risk reduction.

Methods and results We systematically identified and analysed systematic reviews and most cited literature published in the last 3 years and supplemented findings with selected evidence based on clinical expertise. Among HIV-infected individuals, the prevalence of CVD risk factors and the risk for CVD is higher compared with HIV negatives. Antiretroviral drugs may induce dyslipidaemia, reduce insulin sensitivity, and promote body fat redistribution that additionally contributes to CVD risk. Some antiretroviral drugs may increase risk for CVD events, but the absolute risk increase is moderate and has to be put into perspective with the massive HIV-related benefits. Sustained HIV suppression reduces systemic inflammatory markers and is associated with a moderate reduction in CVD events. Regular CVD risk assessment and counselling to stop smoking must be regularly done in all HIV-infected individuals. Statins are effective for the treatment of dyslipidaemia in HIV infection, but drug interactions with ART need to be considered.

Conclusion Human immunodeficiency virus-infected individuals are at increased risk for CVD. Timely initiation of ART with consequent viral suppression is likely to reduce CVD events and to offset potential side effects from ART-induced metabolic changes. Reduction in smoking in HIV-infected individuals is a public health priority.

Keywords Coronary heart disease • Cardiovascular disease • HIV infection • Antiretroviral therapy • Adverse events

Introduction

Antiretroviral therapy (ART) has led to a dramatic reduction in acquired immunodeficiency syndrome (AIDS)-related morbidity and mortality and human immunodeficiency virus (HIV) infection has become a chronic condition. With the introduction of more potent drugs, co-formulations and once daily to take drug regimens, patients with excellent adherence and immunological response may expect a life expectancy similar to non-HIV-infected individuals.[1] In parallel, a concomitant increase in morbidity and death not directly related to HIV was noted. Among the many comorbidity conditions, cardiovascular diseases (CVDs) have become of particular concern due to antiviral-drug-induced metabolic changes, the high prevalence of cardiovascular risk factors in HIV-infected individuals, and growing evidence on HIV-accelerated inflammatory processes that are known to promote atherosclerosis.

We give an umbrella review of up-to-date systematic reviews and other important publications on the complex association of HIV infection and CVD-related factors. We describe important recent developments and perspectives based on a systematic analysis of the most cited research in this field published in the last 3 years. Details on our approach are given in Supplementary material online.

Cardiovascular disease risk in human immunodeficiency virus-infected compared to human immunodeficiency virus-uninfected individuals

A meta-analysis found in HIV-infected untreated and treated individuals a significantly higher risk for CVD when compared with HIV-uninfected individuals (1.61; 95% CI 1.43–1.83 and RR 2.00; 95% CI 1.70–2.37).[2] Several studies included into this meta-analysis

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lacked data on traditional cardiovascular risk factors[3] and findings of increased CVD risk in HIV-infected individuals might partially be explained by residual confounding.[4] However, studies with appropriate adjustment for these risk factors still show a substantially increased CVD risk.[5–7]

Cardiovascular risk factors in human immunodeficiency virus-infected individuals

Substantial differences in cardiovascular risk profiles in HIV-infected compared with uninfected individuals were noted in a routinely collected data analysis from two large US hospitals between 1996 and 2004: among HIV-infected patients, a higher prevalence was found for smoking (38 vs. 18%), hypertension (21 vs. 16%), diabetes (12 vs. 7%), and dyslipidaemia (23 vs. 18%).[5] Similar rates were found in analyses from Kaiser Permanente in Northern California, however, rates of hypertension and diabetes were lower.[6]

The D:A:D study (Data Collection of Adverse events of Anti-HIV Drugs) is one of the largest databases on cardiovascular risk factors with 33 308 HIV-infected patients. During the 10-year observation period (1999 to 2008), 289 of 2482 deaths in D:A:D were related to CVD (rate = 1.60 deaths/1000 person-years (PY)).[8] The respective figures were 743 AIDS-related deaths (rate/1000 PY = 4.12), 341 liver-related deaths (rate/1000 PY = 1.89), and 286 non-AIDS malignancy deaths (rate/1000 PY = 1.59). At baseline, almost 75% of individuals were in age groups where risk of CVD is generally low (<45 years in men, <55 years in women), few had hypertension (8.5%), very few were obese (BMI > 30 kg/m^2; 3.5%) or had diabetes (2.5%), or previous myocardial infarction (MI) and/or stroke (1.4%). However, smoking rates were high (52%), 76% were male, 22% had a total cholesterol of ≥6.2 mmol/L, 34% had triglycerides of ≥2.3 mmol/L, and 26% had a HDL-cholesterol of ≤0.9 mmol/L.[9] In D:A:D, a substantial discrepancy between ART-treated and treatment-naïve patients with regard to raised triglyceride and total cholesterol levels was found, which was also observed in more recent analyses.[10] Although more HIV-infected patients are treated with lipid and blood pressure-lowering drugs, data from a large cohort study indicates that only modest decreases in lipid and blood pressure values were noted over time.[10,11]

Dyslipidaemia

Following HIV infection, a decrease in total cholesterol, HDL-cholesterol, and LDL-cholesterol but increase in triglycerides has been observed in untreated individuals.[12,13] After initiation of ART, marked increases in total cholesterol, LDL-cholesterol, and triglycerides are seen with HDL-cholesterol remaining low. The extent of lipid changes differs between antiretroviral drugs and drug classes (*Table 1*). First-generation compared with second-generation protease inhibitors (PIs; e.g. indinavir, lopinavir vs. atazanavir, and darunavir) lead to higher increase in total cholesterol, LDL-cholesterol, and triglycerides,[15] whereas non-nucleoside reverse transcriptase inhibitors (NNRTI; like efavirenz) lead to higher increase in total and LDL-cholesterol compared with newer PIs.[16] Typically, increases in triglycerides are the most prominent lipid changes in ART recipients. However, elevation of triglycerides carries only a spurious extra risk for CHD in analyses adjusting for all remaining lipid parameters and other CHD risk factors.[17] Antiretroviral therapy-induced lipid changes are in particular driven by a change in particle size with a preponderance of highly atherogenic small dense lipoproteins.[18] Small dense lipoproteins are increased in HIV-infected patients with a CHD event and may be associated with a small additional risk for a CHD event independent from other lipid parameters.[19]

In HIV-infected individuals, basal lipolysis and hepatic de novo lipogenesis are increased, ability of insulin to suppress lipolysis in adipocytes is reduced, and peripheral fatty acid trapping is impaired.[20] These mechanisms might be directly induced by HIV, in particular due to circulating inflammatory cytokines like interferon alfa.[20]

Lipodystrophy

Human immunodeficiency virus-infected patients may also experience important changes in body fat composition following exposure to ART. Patients may develop lipoatrophy in the face and limbs or lipohypertrophy with central visceral fat gain, increase in breasts or ectopic fat deposition in liver, muscles, or adipose tissue and develop, for example, a buffalo hump (*Figure 1*). Some patients may experience both lipohypo- and hypertrophy. Nearly half of the patients with long-term ART exposure develop changes in body composition.[21] The incidence in the Swiss HIV Cohort Study of any self- or clinically reported body fat composition is 13.2 changes per 100 patient-years.[22] An Italian study found incidence rates of lipoatrophy and fat accumulation of 8.2 and 4.8 per 100 PY, respectively.[23] Simple anthropomorphic measures like waist circumference are highly correlated with MRI-based anthropomorphic measure of fat distribution and should therefore be used for routine monitoring in ART recipients.[24]

Lipohypertrophy and visceral fat deposits in individuals receiving ART is frequently associated with dyslipidaemia and hypertriglyceridemia, low-HDL-cholesterol, reduced insulin sensitivity, and diabetes.[25] These metabolic changes resemble those found in HIV-negative individuals with metabolic syndrome.[26] Mechanisms for lipohypertrophy are highly complex, different from those for lipoatrophy, and not known in detail, but include elevation of inflammatory cytokines, high levels of circulating triglycerides, and free fatty acids that are stored in the visceral fatty tissue and the liver.[27,28] Increased levels of high-sensitivity C-reactive protein, adiponectin, tumour necrosis factor-α, and Il-6 have been found in HIV-infected men with lipohypertrophy similar to those seen in obese non-HIV-infected men (*Figure 2*). Individuals with peripheral lipoatrophy and central lipohypertrophy have increased Framingham risk scores and higher coronary calcium scores and are thus at increased risk for CHD.[29,30] In a nested cohort study, lipoatrophy and lipohypertrophy were both associated with increased overall mortality.[31] Unfortunately, changes in body composition cannot be reverted to a clinically relevant extent in most patients and are typically seen in HIV-infected patients with long-time exposure, in particular, to first-generation antiretroviral drugs.[32,33]

Insulin resistance and diabetes

The incidence of type II diabetes in the D:A:D study was 4.2 per 1000 PY.[34] Low CD4 cell count (<200 cells/μL) and lipodystrophy have been reported as HIV-related factors associated with type II diabetes.[34–36] In analyses of D:A:D and a recent analysis from

Table 1 **Summary of the associations of metabolic complications and cardiovascular disease with exposure to antiretroviral drugs from different classes (Adapted from Table 13 in 'Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents'[14])**

Adverse effects	Nucleoside reverse transcriptase inhibitors	Non-nucleoside reverse transcriptase inhibitors	Protease inhibitors
Cardiovascular disease (CVD)	*Abacavir and didanosine*: Associated with an increased risk of myocardial infarction (MI) in some, but not all, cohort studies. Absolute risk greatest in patients with traditional CVD risk factors		*Protease inhibitors*: Associated with MI and stroke in some cohort studies. Data on newer PIs (Atazanavir, Darunavir, and Tipranavir) are limited. *Saquinavir + Ritonavir, Atazanavir + Ritonavir, and Lopinavir + Ritonavir:* PR interval prolongation. Risks include structural heart disease, conduction system abnormalities, cardiomyopathy, ischemic heart disease, and co-administration with drugs that prolong PR interval. *Saquinavir + Ritonavir*: QT interval prolongation in patients in a healthy volunteer study. Risks include underlying heart conditions, pre-existing prolonged QT or arrhythmia, or use with other QT-prolonging drugs. ECG is recommended before SQV initiation and should be considered during therapy.
Diabetes mellitus/insulin resistance	*Didanosine, Stavudine, Zidovudine*		Reported for *some protease inhibitors (Indinavir, Lopinavir + ritonavir)*, but not all protease inhibitors
Dyslipidemia	*Stavudine > Zidovudine > Abacavir:* ↑ LDL ↑ Triglycerides	*Efavirenz*: ↑ Triglycerides ↑ LDL ↑ HDL	*All Ritonavir -boosted protease inhibitors:* ↑ LDL, ↑ Triglycerides, ↑ HDL *Lopinavir + Ritonavir = Fosamprenavir + Ritonavir and Lopinavir + Ritonavir > Darunavir + Ritonavir and Atazanavir + Ritonavir:* ↑ Triglycerides

Order is alphabetical where not otherwise indicated; empty spaces in the table may mean no reported cases for the particular side effect or no data are available for the specific ARV drug class; for additional information please see Appendix B in 'Guidelines for the use of antiretroviral agents in HIV-1-Infected adults and adolescents'[14].

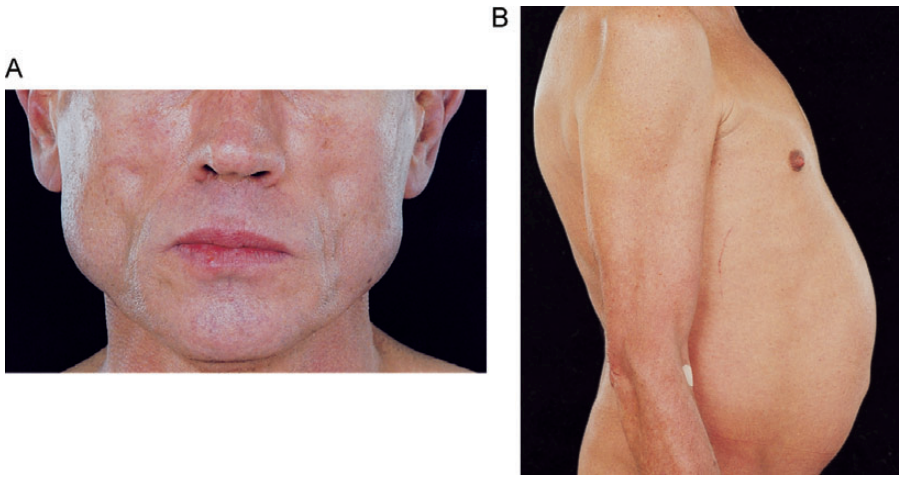

Figure 1 A, B: Lipodystrophy in a HIV-infected patient (From New England Journal of Medicine, Andrew Carr, David A. Cooper, Lipodysthrophy Associated with an HIV-Protease Inhibitor, 339, 18, 1, Copyright` (1998) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society)

Denmark, none of the newer antiretroviral drugs significantly contributed to the increased risk of diabetes (in contrast to previous observations with older drugs).[35,37] It appears that antiretroviral drug-induced risk of diabetes is associated with the use of PIs of the first-generation and with thymidine-containing analogues reverse transcriptase inhibitors that have known mitochondrial toxicity.[37] In non-resource-limited settings, these drugs have now been greatly replaced in HIV care. Mitochondrial toxicity may lead to impaired insulin sensitivity, and *in vitro* models indicate that first-generation PIs block glucose transporter GLUT4 and may also affect glucose-sensing β-cells, both causing impaired glucose sensitivity.[38,39] Other factors that may be associated with an increased risk of diabetes are high-sensitivity C-reactive protein and tumour necrosis factors 1 and 2.[40]

Chronic inflammation

A growing body of data indicate that HIV-related inflammatory and immunologic processes may contribute to additional risk for cardiovascular events in HIV-infected patients. Most convincing evidence for such a mechanism comes from the unanticipated findings from the SMART trial.[41] In SMART, HIV-infected were assigned to continuous use of ART (viral suppression group) or treatment interruption (drug conservation group) with deferral of therapy until a CD4+ count decrease <250 cells/μL. The trial rationale was to limit ART-related toxicity and cardiovascular side effects. The trial was stopped prematurely, because patients in the drug conservation arm experienced a higher hazard for AIDS or death. Intriguingly, patients in the drug conservation group compared with the viral suppression group also experienced more CVD events (1.3 vs. 0.8 events per 100 PY; HR 1.6; 95% CI 1.0–2.5).

Subsequent studies from SMART showed that ART interruption was associated with significant increases in blood levels of interleukin-6 (IL-6) and D-dimer. Interleukin-6 is a non-specific inflammatory biomarker (like high-sensitivity C-reactive protein) and D-dimer is a fibrin degradation product which primarily reflects increased activity in the thrombotic process and may be elevated in response to inflammatory stimuli and bacterial translocation. Chronic inflammatory processes in endothelial cells that promote atherosclerosis represent a very complex interplay of inflammatory cells with lymphocyte and macrophage activation, damage to the mucosal barrier, metabolic changes, and other factors directly or indirectly related to HIV replication.

Higher levels of IL-6, high-sensitivity C-reactive protein, and D-dimer were associated with increased all-cause mortality[42] and predicted CVD independent of other risk factors[43] (*Table 2*). However, the model improvement for risk prediction when added to the Framingham risk score was modest. For each marker, the increase in risk from the lowest to highest quartile, i.e. the risk difference between someone with blood levels <75% of the population compared with someone with blood levels >75% of the population, corresponds to two additional cardiovascular events per 100 patient-years.[43] The association of high-sensitivity C-reactive protein, IL-6, and D-dimer with all-cause mortality was also seen in nested case–control studies, one including individuals with very advanced immunosuppression and high rate or previous AIDS.[47] There is further evidence that HIV-infected individuals with advanced immunosuppression (<200 CD4 cells/μL) and not fully suppressed viral load (>500 copies/mL) have a higher prevalence of elevated Il-6, D-dimer, and soluble CD14 than HIV-uninfected individuals of similar CVD risk.[45]

Soluble CD14 is a marker for monocyte and macrophage activation and was in an additional nested case–control study of SMART associated with increased odds for death but not CVD[50] (*Table 2*). Human immunodeficiency virus may lead to a compromised mucosal barrier resulting in subsequent translocation of microbial products, such as lipopolysaccharide that bind to soluble CD14 and may lead to systemic immune activation.

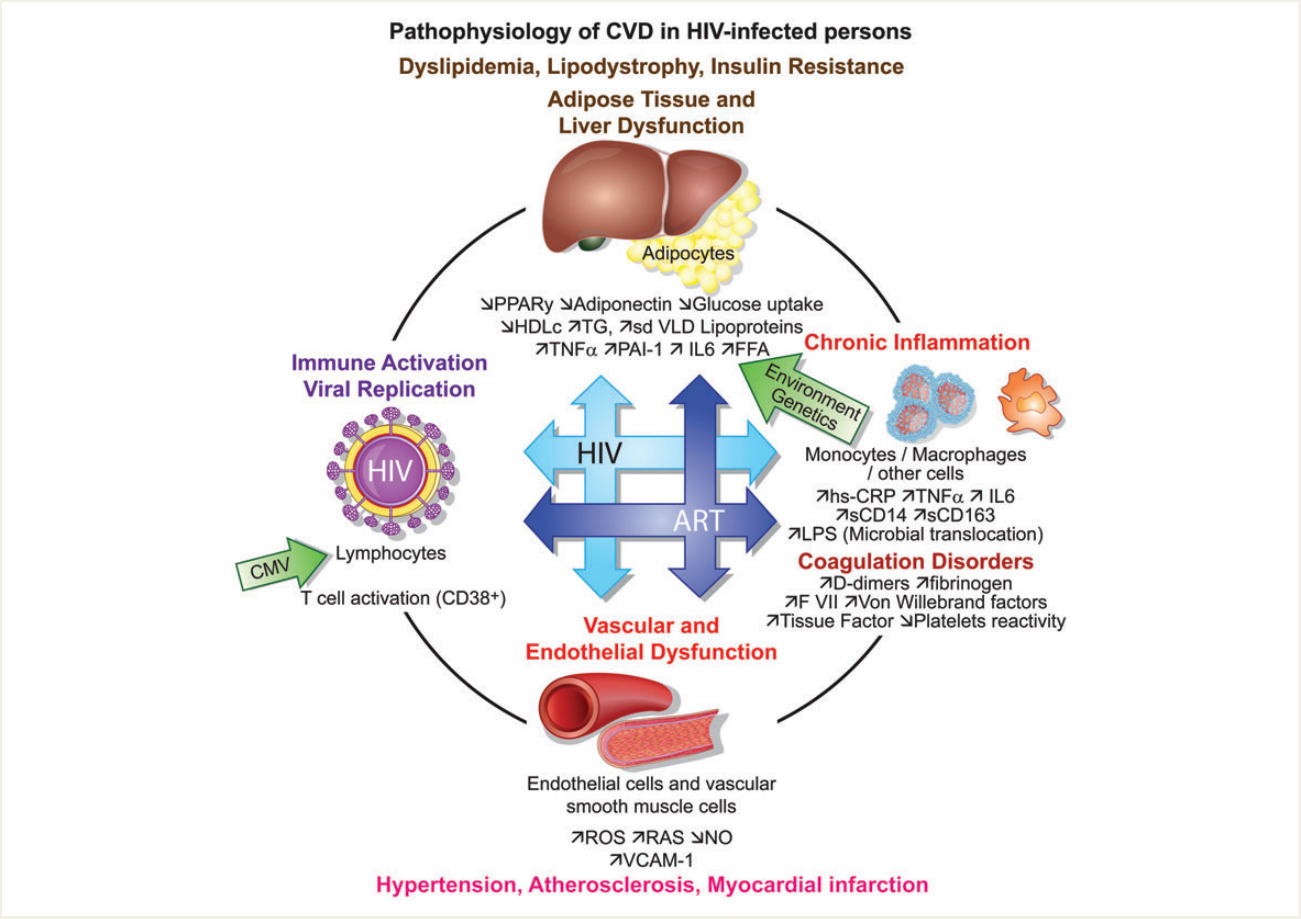

Figure 2 HIV and antiretroviral treatment (ART) might affect cardiovascular disease (CVD) through various pathophysiological pathways (together with environmental and genetic factors). There is a very complex interaction of various related factors. HIV and ART have direct effects on adipose tissue and liver function with subsequent dyslipidemia, lipodystrophy and insulin resistance. Other direct impact includes effects on endothelial cells and vascular smooth muscle cells leading to vascular and endothelial dysfunction with subsequent hypertension, atherosclerosis and myocardial infarction. Continuous immune activation and viral replication might lead to a permanent T cell activation which might also be affected by a reactivation of other viruses, e.g. Cytomegalovirus (CMV). ART and HIV might also stimulate a chronic status of inflammation and have a complex interaction with coagulation factors. These pathways itself are more or less interrelated and mediate indirect effects of HIV and ART on CVD. ART: Antiretroviral therapy; hs-CRP: high-sensitivity C-reactive protein; F VII: Factor VII; FFA: Free fatty acids; HDLc: High-density lipoprotein cholesterol; IL6: Interleukin 6; LPS: lipopolysaccharide; NO: Nitrogen oxide; PAI-1: Plasminogen activator inhibitor type 1; PPARγ: peroxisome proliferator-activated receptors; RAS: Renin angiotensin system; ROS: Reactive oxygen species; sCD14: Soluble CD14; sCD163: Soluble CD163. Hypothetical model for the pathogenesis of cardiovascular disease in HIV-infected persons taking antiretroviral therapy (based on a figure from Boccara et al.: J Am Coll Cardiol, Franck Boccara, Sylvie Lang, Catherine Meuleman, Stephane Ederhy, Murielle Mary-Krause, Dominique Costagliola, Jacqueline Capeau, Ariel Cohen, HIV and Coronary Heart Disease: Time for a Better Understanding, 61, 5, 511-523, Copyright (2013) Elsevier. Re-used with permission from Elsevier)

Soluble CD163 is expressed by macrophages in atherosclerotic plaques, correlates well with arterial inflammation as measured with fluorine-2-deoxy-D-glucose positron emission, and may be a more promising marker for endothelial inflammation in HIV infection.[53] In a study of ART-treated patients with well-suppressed viral load, arterial inflammation in the aorta was higher than in HIV-negative healthy controls and of similar magnitude as in HIV-negative patients with established atherosclerosis.[51] Findings from this study are particularly intriguing because all HIV-infected patients had been well treated for years and this may indicate that endothelial inflammation in HIV infection may persist independently from ART.

Endothelial cells that are altered by injury or inflammation express chemokines and vascular cell adhesion molecule-1 (VCAM-1) which have a prominent role for attracting monocytes and promoting inflammatory cell entry. Soluble VCAM-1 is increased in HIV infection[49] and evidence from randomized controlled trials (RCTs) indicates that ART reduces this endothelial activation marker.[46,48]

Similar core mechanisms of inflammation have been described in the adipose tissue and adipocytes leading to the release of inflammatory mediators or the migration of inflammatory cells into adipose tissue and the exertion of systemic inflammatory responses.[54] These similarities are of particular interest in HIV infection because

Table 2 Overview of reported effects of HIV infection and antiretroviral therapy on selected biomarkers and association with clinical outcomes

	Effect of HIV-infection	Effect of ART	Association with clinical outcomes in HIV
Inflammation			
IL-6	Blood levels increased (62–152%)[44] Higher prevalence of elevated levels[45]	Decrease after initiation[46] Increase after stopping[38]	All-cause mortality.[38,47] CVD[43]
High-sensitivity C-reactive protein	Blood levels increased (50–55%)[44]	Heterogeneous effects of initiation or stopping[46,48]	All-cause mortality.[38,47] CVD[43] (Not seen in[19])
Thrombotic activity			
D-Dimer	Blood levels increased (94%)[44] Higher prevalence of elevated levels[45]	Decrease after initiation[48,49] Increased or no effect after stopping[38,48]	All-cause mortality[38,47] CVD[43] (Not seen in[19])
Monocyte and macrophage activation			
sCD14	Blood levels increased (unmatched data)[50] Higher prevalence of elevated levels[45]		All-cause mortality[47,50]
sCD163	Increased blood levels[51]		
Endothelial activation			
sICAM-1/sVCAM-1	Increased blood levels[49]	Decrease after initiation[46,48,49] Increase after stopping[48]	
Highly atherogenic lipoproteins			
VLDL	No clear change of blood levels[12,18]	Elevated with ART[18]	CVD[19] (Not seen in[52])

HIV and certain antiretroviral drugs can induce important metabolic and body fat mass changes (*Table 1*). A model of the likely pathophysiological mechanisms of atherosclerosis in HIV infection is provided in *Figure 2*.

Overall, there is a rapidly growing literature on inflammatory biomarkers and CVD or surrogate markers of CVD (such as carotid intima media thickness or coronary calcium score) in HIV infection.[55] It needs to be emphasized that most of these studies use cross-sectional or case–control designs and are explorative by nature. The use of these biomarkers by clinicians as measures for comorbidity for better risk prediction and/or targeted interventions will have to be determined in clinical intervention trials, ultimately in RCTs.

Effects of antiretroviral drugs on clinical cardiovascular disease endpoints

A number of observational and experimental studies have examined the effect of ART and risk for CVD. Two recently published systematic reviews collected, analysed, and synthesized the available literature.[2,56] The more recent observational data meta-analysis by Bavinger *et al.* showed an increased risk of MI associated with recent exposure (e.g. within the last 6 months) to abacavir, a reverse transcriptase inhibitor (RR 1.91; 95% CI 1.50–2.42) and PIs (RR 2.13, 95% CI 1.05–1.17). Alternative analyses for cumulative ART exposure suggest an increased risk for MI with each additional year of treatment with the first-generation PIs indinavir (RR 1.11, 95% CI 1.05–1.17) and lopinavir (RR 1.22, 95% CI 1.01–1.47). Studies included into these meta-analyses were of mixed quality, estimates between studies were heterogeneous and the summary findings, therefore, have to be interpreted with caution. Following the first publication of an increased risk of MI with abacavir exposure by the D:A:D study investigators[57] Cruciani *et al.* re-analysed in a meta-analysis all RCTs comparing abacavir with control reverse transcriptase inhibitors that were provided by the manufacturer of abacavir and a second analysis was conducted by the Federal Drug Administration (FDA).[58,59] It should be stressed that cardiovascular events were only safety endpoints in all these trials and the statistical power of these meta-analyses is limited. In both analyses, no increased risk of MI with abacavir exposure was found with an RR of 0.73 (95% CI 0.39–1.35), based on 18 RCTs and 7054 patients[58] and an OR (Odds ratio) of 1.02 (95% CI 0.56–1.84), based on 26 trials and 9868 patients.[59] Myocardial infarction was a rare event in these analyses (3 events per 1000 patient-years of follow-up in Cruciani *et al.*, 46 events among 9868 patients in the FDA analysis) and of similar frequency like in the D:A:D study.[60] The D:A:D investigators also reported an increased CVD risk associated with the older NRTI didanosine and Bavinger *et al.* also describe a harmful association in a meta-analysis based on D:A:D and another, smaller, observational study.[56,57] Evidence from a few small studies indicates that in HIV-infected individuals MI with ST elevation (STEMI) appear to be slightly more frequent than non-STEMI MI.[61]

The excess risk for current use of didanosine and abacavir compared with other reverse transcriptase inhibitors was in the range

of 1 and 3 MIs per 1000 PY follow-up.[57] Overall, based on the available evidence, it is unclear whether there is an increased risk for MI associated with current abacavir use. A potentially existing absolute risk increase with abacavir use would be moderate and needs to be put into perspective with the massive benefit from ART and possible side effects from other reverse transcriptase inhibitors.

Managing human immunodeficiency virus and risk factors for cardiovascular disease

Antiretroviral therapy

Growing evidence suggests that HIV suppression and improved immune function is associated with reductions in systemic inflammatory markers and risk for a CVD event. Thus, treatment of HIV by sustained and lifelong viral suppression has the first priority. For these reasons, guidelines favour the initiation of antiretroviral treatment irrespective of CD4 cell counts in patients aged >50 years due to the increased risk of serious non-AIDS events including CVD events.[14] The benefit of early ART in patients not fulfilling the traditional CD4-cell and viral-load-based criteria for ART initiation must be balanced against the potential long-term side effects from ART, which for many drugs are insufficiently known. The choice of the regimen must therefore reflect the risk for CVD and other co-morbidity, psychosocial conditions as well as patients' preferences and understanding to adhere to lifelong drug intake.

Cardiovascular disease risk prediction

Human immunodeficiency virus-infected patients are at increased risk for CVD and therefore assessment of cardiovascular risk should be routinely and regularly done in all patients and particular in those receiving ART. A cardiovascular risk-assessment model has been developed based on data from the D:A:D study with a risk score calculator (http://www.cphiv.dk/TOOLS/Framingham/tabid/302/Default.aspx) that besides established risk factors for CVD includes exposure to antiretroviral drugs with known increased risk of coronary heart disease (CHD) and/or CVD.[62] Although the validation of this tool had some limitations,[63] this instrument has been shown to predict the individual CVD risk marginally better than the established Framingham risk functions.[62] The Framingham risk score tended to overpredict CHD in the general HIV population but to underpredict CHD risk in the subgroups of females, former smokers and diabetic patients. This tool seems to be currently the best way to assess the individual cardiovascular risk in HIV-infected patients but does not yet include inflammatory or immunologic markers.

Modification of risk factors

Given the high prevalence of traditional risk factors for CVD in HIV-infected individuals, management of dyslipidaemia, hypertension and counselling for behaviour changes is the first priority. Management of such risk factors for CVD can, with few exceptions (see below), be done according to guidelines established for non-HIV-infected individuals.

Smoking

Because the prevalence of smoking in HIV-infected individuals is so high, the reduction of smoking would lead to the highest absolute reduction in CVD. However, this goal is the most difficult to achieve. Human immunodeficiency virus-infected individuals who succeed in quitting experience marked reductions in CVD and CHD.[64] Epidemiological data indicate that the number of patients receiving blood pressure and lipid-lowering drugs has increased over time but management of dyslipidaemia and hypertension in HIV infection in particular among individuals at high risk remains insufficient.[10,11]

Dyslipidaemia

Treatment of dyslipidaemia in HIV-infected individuals receiving ART poses some particularities in relation to possible drug interactions with antiretroviral drugs. There is no evidence from RCTs investigating the efficacy of antilipidaemic (and antihypertensive) drugs for patient-relevant endpoints in HIV-infected individuals and it is unlikely that such trials will be ever conducted. Many RCTs comparing different antiretroviral drugs for antiretroviral efficacy, however, have investigated the alteration of lipids in relation to different antiretroviral drug combinations. This trial data indicate that newer PIs (atazanavir and darunavir), NNRTIs (intelence), or integrase inhibitors (raltegravir) induce less lipid changes. Substitution of antiretroviral drug to less atherogenic drugs may be thus an option but can lead to drug failure if previous drug failures, presence of drug resistance, and issues of drug intake convenience are not carefully considered. Therefore, the modification of a successful antiretroviral drug combination should be made by the specialist.

Few RCTs have investigated statins in HIV-infected individuals and found similar reductions of LDL-cholesterol compared with HIV negatives.[65–67] Fibrates, niacin, and fish-oil have all been shown to effectively reduce ART-related increases in triglycerides in HIV-infected patients.[68,69] However, the use of these compounds cannot be generally recommended given evidence based on patient-important outcomes in HIV-negative individuals. Meta-analyses of randomized trials with fibrates indicate a moderate reduction in CHD events that is offset by an increase in non-CHD-related mortality.[70] Meta-analyses and clinical trials found no reduction in CHD mortality when niacin was compared with placebo or added to a statin.[71,72] Large clinical trials of fish oil in patients at risk for CHD indicate no benefit.[73,74] Achievement of LDL-cholesterol treatment goals with dietary intervention and use of statins therefore remains the first priority in the management of dyslipidaemia in HIV-infected individuals at moderate to high risk for CHD.

Simvastatin, lovastatin, and atorvastatin are all metabolized in the liver via the cytochrome P450 3A4 isoenzyme system and are susceptible to drug interactions with PIs and the NNRTI efavirenz.[75] Fluvastatin and, to a much smaller extent, rosuvastatin are primarily metabolized via CYP 2C9 and are vulnerable to interactions with PIs as well. Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore a preferred statin in HIV-infected individuals. The use of simvastatin and lovastatin in combination with all PIs and efavirenz is not recommended (*Table 3*). Atorvastatin, fluvastatin, and rosuvastatin when co-administered with PIs should be initiated at the lowest dose and patients must be carefully monitored because of the increased risk for potential drug interactions. Drug interactions with antiretroviral drugs are best checked in the

Table 3 Drug interactions between lipid-lowering and antiretroviral drugs (reproduced with kind permission of the Liverpool HIV Pharmacology Group, University of Liverpool)

www.hiv-druginteractions.org

UNIVERSITY OF LIVERPOOL

Lipid-Lowering Treatment Selector

Charts revised August 2013. Full information available at www.hiv-druginteractions.org and www.hiv-druginteractionslite.org

		ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	EVG/c	RAL	ABC	FTC	3TC	TDF	ZDV
Statins	Atorvastatin	↑	↑	↑153%	↑	↑490%	↑	↓43%	↓37%	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	Fluvastatin	↔	↔	↔	↑	↔	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Lovastatin	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	Pravastatin	↔	↑81%	↔	↑	↔	↓50%	↓44%	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Rosuvastatin	↑213%	↑48%	↑8%	↑	↑107%	↑	↔	↑	↔	↔	↔	↑ 48%	↔	↔	↔	↔	↔	↔
	Simvastatin	↑	↑	↑	↑	↑	↑	↓68%	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
Fibrates	Bezafibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Clofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑⇑	↔
	Fenofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Gemfibrozil	↓	↓	↓	↓	↓41%	↓	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔
	Ezetimibe	↑[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Colour Legend

- No clinically significant interaction expected
- These drugs should not be coadministered.
- 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). No *a priori* dosage adjustment is recommended.

Text Legend

↑ Potential increased exposure of the lipid-lowering drug
↓ Potential decreased exposure of the lipid-lowering drug
↔ No significant effect

⇑ Potential increased exposure of HIV drug
⇓ Potential decreased exposure of HIV drug

a Unboosted atazanavir

Numbers refer to increased or decreased AUC of the lipid-lowering drug as observed in drug-drug interaction studies.

HIV–drug interaction database of the University of Liverpool (www.hiv-druginteractions.org) and/or by checking interaction tables provided in treatment guidelines.[14] The University of Liverpool interaction database offers excellent and easy-to-use online tools with apps and downloadable interactions charts for lipid and blood pressure-lowering drugs (*Table 3*).

Hypertension

Human immunodeficiency virus-infected patients with elevated and not well-controlled blood pressure are at increased risk of a CDV event.[11] HIV-infected patients are also at increased risk for developing end-stage renal failure. Reported risk factors for the development of chronic kidney disease include ethnicity (Afro-Americans), HIV-related factors (such as transmission risk), concomitant diabetes and exposure to tenofovir, a nucleotide reverse transcriptase inhibitors that is eliminated by the kidney and very commonly used.[76,77] Blood pressure management recommendations for HIV-infected patients are similar to that for HIV negatives but most importantly potential drug interactions with antiretroviral drugs have to be kept in mind[14,78,79]: concomitant use of diltiazem and atazanavir is problematic and all PIs may increase levels of dihydropiridine calcium-channel-blockers (see reference[14] for details).

Alternative therapies

Sustained viral suppression reduces inflammatory markers and CVD events. However, there is a growing evidence of continuing endothelial inflammation activation in the presence of active ART.[44] The JUPITER trial has shown that rosuvastatin in patients with normal LDL-cholesterol reduces high-sensitivity C-reactive protein and cardiovascular events.[80] Several ongoing trials are investigating whether rosuvastatin or aspirin in HIV-infected patients with successfully established ART may reduce systemic and endothelial inflammation

markers, slow cIMT progression, or reduce prothrombotic markers.[81–83] Whether alternative anti-inflammatory drugs like methotrexate or canakinumab may be safely used and offer additional benefit in HIV-infected individuals with high-sensitivity C-reactive protein and CVD risk needs to be carefully explored once results from currently on-going large trials in HIV negatives are available.[84,85]

Conclusions

Human immunodeficiency virus-infected patients are at increased risk for developing CVD due to the high prevalence of CVD risk factors, ART-related metabolic changes, and systemic immune activation that promotes endothelial inflammation and atherosclerosis.

Timely initiating of ART with the goal of long-term sustained virological suppression of HIV for optimal immune reconstitution and survival benefit is the first priority. Sustained virological response is in addition associated with reduced levels of the inflammation markers high-sensitivity C-reactive protein and IL-6 and a moderated reduction in risk for CVD events. These benefits have to be balanced against ART-induced metabolic changes.

The routine assessment of CVD risk based on the D:A:D risk scores and consequent treatment of dyslipidaemia and hypertension is paramount to reduce CVD risk in particular in individuals at moderate to high risk and the second priority. Statins can effectively improve ART-induced dyslipidaemia, but potential drug interactions must be considered. Counselling for smoking cessation is of outmost importance and referring motivated patients to stop smoking clinics might have the highest impact on CVD risk reduction.

Antiretroviral drugs may induce increases in cholesterol, triglycerides, and LDL-cholesterol. Two first-generation PIs (indinavir and lopinavir) seem to be associated with an increased CVD risk, the data are less clear for the NRTI abacavir. However, such a risk increase is moderate and has to be put into perspective with the massive HIV-related benefits of these drugs. Therefore, the choice of the optimal antiretroviral drug combination must be individualized and reflect the patient's ability to adhere to therapy, and his or her risk for CVD and other comorbidity.

Optimally coordinated care between cardiovascular disease and HIV specialists is paramount for the chronic disease management of HIV and to further improve prognosis of patients living with HIV.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord, Lewden C, Bouteloup V, De Wit S, Sabin C, Mocroft A, Wasmuth JC, van Sighem A, Kirk O, Obel N, Panos G, Ghosn J, Dabis F, Mary-Krause M, Leport C, Perez-Hoyos S, Sobrino-Vegas P, Stephan C, Castagna A, Antinori A, d'Arminio Monforte A, Torti C, Mussini C, Isern V, Calmy A, Teira R, Egger M, Grarup J, Chene G. All-cause mortality in treated HIV-infected adults with CD4 $\geq$500/mm^3 compared with the general population: evidence from a large European observational cohort collaboration. *Int J Epidemiol* 2012;**41**:433–445.
2. Islam FM, Wu J, Jansson J, Wilson DP. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. *HIV Med* 2012;**13**:453–468.
3. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;**97**:1837–1847.
4. Althoff KN, Gange SJ. A critical epidemiological review of cardiovascular disease risk in HIV-infected adults: the importance of the HIV-uninfected comparison group, confounding, and competing risks. *HIV Med* 2013;**14**:191–192.
5. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab* 2007;**92**:2506–2512.
6. Klein D, Hurley LB, Quesenberry CP Jr, Sidney S. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? *J Acquir Immune Defic Syndr* 2002;**30**:471–477.
7. Durand M, Sheehy O, Baril JG, Lelorier J, Tremblay CL. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Quebec's public health insurance database. *J Acquir Immune Defic Syndr* 2011;**57**:245–253.
8. Data Collection on Adverse Events of Anti H. I. V. drugs Study Group, Smith C, Sabin CA, Lundgren JD, Thiebaut R, Weber R, Law M, Monforte A, Kirk O, Friis-Moller N, Phillips A, Reiss P, El Sadr W, Pradier C, Worm SW. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D study. *AIDS* 2010;**24**:1537–1548.
9. Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio Monforte A, Pradier C, Morfeldt L, Mateu S, Law M, El-Sadr W, De Wit S, Sabin CA, Phillips AN, Lundgren JD, D. A. D. study group. Cardiovascular disease risk factors in HIV patients—association with antiretroviral therapy. Results from the DAD study. *AIDS* 2003;**17**:1179–1193.
10. Glass TR, Ungsedhapand C, Wolbers M, Weber R, Vernazza PL, Rickenbach M, Furrer H, Bernasconi E, Cavassini M, Hirschel B, Battegay M, Bucher HC, Swiss H. I. V. Cohort Study. Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: the Swiss HIV Cohort Study. *HIV Med* 2006;**7**:404–410.
11. Nuesch R, Wang Q, Elzi L, Bernasconi E, Weber R, Cavassini M, Vernazza P, Thurnheer MC, Calmy A, Battegay M, Bucher HC, the Swiss HIVCS. Risk of cardiovascular events and blood pressure control in hypertensive HIV-infected patients: Swiss HIV Cohort Study (SHCS). *J Acquir Immune Defic Syndr* 2013;**62**:396–404.
12. Riddler SA, Smit E, Cole SR, Li R, Chmiel JS, Dobs A, Palella F, Visscher B, Evans R, Kingsley LA. Impact of HIV infection and HAART on serum lipids in men. *JAMA* 2003;**289**:2978–2982.
13. Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab* 1992;**74**:1045–1052.
14. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. **http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf** Accessed 27 May 2013.
15. Molina JM, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N, Moyle G, Mancini M, Percival L, Yang R, Wirtz V, Lataillade M, Absalon J, McGrath D, Castle Study Team. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr* 2010;**53**:323–332.
16. Daar ES, Tierney C, Fischl MA, Sax PE, Mollan K, Budhathoki C, Godfrey C, Jahed NC, Myers L, Katzenstein D, Farajallah A, Rooney JF, Pappa KA, Woodward WC, Patterson K, Bolivar H, Benson CA, Collier AC, Aids Clinical Trials Group Study A Team. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med* 2011;**154**:445–456.
17. Worm SW, Kamara DA, Reiss P, Kirk O, El-Sadr W, Fux C, Fontas E, Phillips A, D'Arminio Monforte A, De Wit S, Petoumenos K, Friis-Mller N, Mercie P, Lundgren JD, Sabin C. Elevated triglycerides and risk of myocardial infarction in HIV-positive persons. *AIDS* 2011;**25**:1497–1504.
18. Riddler SA, Li X, Otvos J, Post W, Palella F, Kingsley L, Visscher B, Jacobson LP, Sharrett AR, Multicenter Aids Cohort Study. Antiretroviral therapy is associated with an atherogenic lipoprotein phenotype among HIV-1-infected men in the multicenter AIDS cohort study. *J Acquir Immune Defic Syndr* 2008;**48**:281–288.

19. Bucher HC, Richter W, Glass TR, Magenta L, Wang Q, Cavassini M, Vernazza P, Hirschel B, Weber R, Furrer H, Battegay M, Bernasconi E. Small dense lipoproteins, apolipoprotein B, and risk of coronary events in HIV-infected patients on antiretroviral therapy: the Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr* 2012;**60**: 135–142.
20. Stanley TL, Grinspoon SK. Body composition and metabolic changes in HIV-infected patients. *J Infect Dis* 2012;**205**(Suppl 3):S383–S390.
21. Grunfeld C, Saag M, Cofrancesco J Jr, Lewis CE, Kronmal R, Heymsfield S, Tien PC, Bacchetti P, Shlipak M, Scherzer R, Study of Fat Redistribution Metabolic Change in H. I. V. Infection. Regional adipose tissue measured by MRI over 5 years in HIV-infected and control participants indicates persistence of HIV-associated lipoatrophy. *AIDS* 2010;**24**:1717–1726.
22. Young J, Weber R, Rickenbach M, Furrer H, Bernasconi E, Hirschel B, Tarr PE, Vernazza P, Battegay M, Bucher HC. Lipid profiles for antiretroviral-naive patients starting PI- and NNRTI-based therapy in the Swiss HIV cohort study. *Antivir Ther* 2005;**10**:585–591.
23. De Luca A, Nasi M, Di Giambenedetto S, Cozzi-Lepri A, Pinti M, Marzocchetti A, Mussini C, Fabbiani M, Bracciale L, Cauda R, Cossarizza A. Mitochondrial DNA haplogroups and incidence of lipodystrophy in HIV-infected patients on long-term antiretroviral therapy. *J Acquir Immune Defic Syndr* 2012;**59**:113–120.
24. Scherzer R, Shen W, Bacchetti P, Kotler D, Lewis CE, Shlipak MG, Heymsfield SB, Grunfeld C, Study of Fat Redistribution Metabolic Change in H. I. V. Infection. Simple anthropometric measures correlate with metabolic risk indicators as strongly as magnetic resonance imaging-measured adipose tissue depots in both HIV-infected and control subjects. *Am J Clin Nutr* 2008;**87**:1809–1817.
25. Grunfeld C, Rimland D, Gibert CL, Powderly WG, Sidney S, Shlipak MG, Bacchetti P, Scherzer R, Haffner S, Heymsfield SB. Association of upper trunk and visceral adipose tissue volume with insulin resistance in control and HIV-infected subjects in the FRAM study. *J Acquir Immune Defic Syndr* 2007;**46**:283–290.
26. Wohl D, Scherzer R, Heymsfield S, Simberkoff M, Sidney S, Bacchetti P, Grunfeld C, Fram Study Investigators. The associations of regional adipose tissue with lipid and lipoprotein levels in HIV-infected men. *J Acquir Immune Defic Syndr* 2008;**48**:44–52.
27. Huang-Doran I, Sleigh A, Rochford JJ, O'Rahilly S, Savage DB. Lipodystrophy: metabolic insights from a rare disorder. *J Endocrinol* 2010;**207**:245–255.
28. Johnson JA, Albu JB, Engelson ES, Fried SK, Inada Y, Ionescu G, Kotler DP. Increased systemic and adipose tissue cytokines in patients with HIV-associated lipodystrophy. *Am J Physiol Endocrinol Metab* 2004;**286**:E261–E271.
29. Lake JE, Wohl D, Scherzer R, Grunfeld C, Tien PC, Sidney S, Currier JS. Regional fat deposition and cardiovascular risk in HIV infection: the FRAM study. *AIDS Care* 2011; **23**:929–938.
30. Guaraldi G, Stentarelli C, Zona S, Orlando G, Carli F, Ligabue G, Lattanzi A, Zaccherini G, Rossi R, Modena MG, Alexopoulos N, Palella F, Raggi P. Lipodystrophy and anti-retroviral therapy as predictors of sub-clinical atherosclerosis in human immunodeficiency virus infected subjects. *Atherosclerosis* 2010;**208**:222–227.
31. Scherzer R, Heymsfield SB, Lee D, Powderly WG, Tien PC, Bacchetti P, Shlipak MG, Grunfeld C, Study of Fat Redistribution Metabolic Change in H. I. V. Infection. Decreased limb muscle and increased central adiposity are associated with 5-year all-cause mortality in HIV infection. *AIDS* 2011;**25**:1405–1414.
32. Lo J, You SM, Canavan B, Liebau J, Beltrani G, Koutkia P, Hemphill L, Lee H, Grinspoon S. Low-dose physiological growth hormone in patients with HIV and abdominal fat accumulation: a randomized controlled trial. *JAMA* 2008;**300**:509–519.
33. Hadigan C, Corcoran C, Basgoz N, Davis B, Sax P, Grinspoon S. Metformin in the treatment of HIV lipodystrophy syndrome: a randomized controlled trial. *JAMA* 2000;**284**:472–477.
34. Petoumenos K, Worm SW, Fontas E, Weber R, De Wit S, Bruyand M, Reiss P, El-Sadr W, Monforte AD, Friis-Moller N, Lundgren JD, Law MG, D. A. D. Study Group. Predicting the short-term risk of diabetes in HIV-positive patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *J Int AIDS Soc* 2012;**15**:17426.
35. Rasmussen LD, Mathiesen ER, Kronborg G, Pedersen C, Gerstoft J, Obel N. Risk of diabetes mellitus in persons with and without HIV: a Danish nationwide population-based cohort study. *PLoS One* 2012;**7**:e44575.
36. Capeau J, Bouteloup V, Katlama C, Bastard JP, Guiyedi V, Salmon-Ceron D, Protopopescu C, Leport C, Raffi F, Chene G, Anrs Co Aproco-Copilote Cohort Study Group. Ten-year diabetes incidence in 1046 HIV-infected patients started on a combination antiretroviral treatment. *AIDS* 2012;**26**:303–314.
37. De Wit S, Sabin CA, Weber R, Worm SW, Reiss P, Cazanave C, El-Sadr W, Monforte A, Fontas E, Law MG, Friis-Moller N, Phillips A, Data Collection on Adverse Events of Anti H. I. V. Drugs study. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Diabetes Care* 2008;**31**:1224–1229.
38. Murata H, Hruz PW, Mueckler M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem* 2000;**275**:20251–4.
39. Koster JC, Remedi MS, Qiu H, Nichols CG, Hruz PW. HIV protease inhibitors acutely impair glucose-stimulated insulin release. *Diabetes* 2003;**52**:1695–1700.
40. Brown TT, Tassiopoulos K, Bosch RJ, Shikuma C, McComsey GA. Association between systemic inflammation and incident diabetes in HIV-infected patients after initiation of antiretroviral therapy. *Diabetes Care* 2010;**33**:2244–2249.
41. Strategies for Management of Antiretroviral Therapy Study Group, El-Sadr WM, Lundgren J, Neaton JD, Gordin F, Abrams D, Arduino RC, Babiker A, Burman W, Clumeck N, Cohen CJ, Cohn D, Cooper D, Darbyshire J, Emery S, Fatkenheuer G, Gazzard B, Grund B, Hoy J, Klingman K, Losso M, Markowitz N, Neuhaus J, Phillips A, Rappoport C. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006;**355**:2283–2296.
42. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, Ledergerber B, Lundgren J, Neuhaus J, Nixon D, Paton NI, Neaton JD, Insight Smart Study Group. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med* 2008;**5**:e203.
43. Duprez DA, Neuhaus J, Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, Ledergerber B, Lundgren J, Nixon D, Paton NI, Prineas RJ, Neaton JD, Insight Smart Study Group. Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. *PLoS One* 2012;**7**:e44454.
44. Neuhaus J, Jacobs DR Jr, Baker JV, Calmy A, Duprez D, La Rosa A, Kuller LH, Pett SL, Ristola M, Ross MJ, Shlipak MG, Tracy R, Neaton JD. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. *J Infect Dis* 2010; **201**:1788–1795.
45. Armah KA, McGinnis K, Baker J, Gibert C, Butt AA, Bryant KJ, Goetz M, Tracy R, Oursler KK, Rimland D, Crothers K, Rodriguez-Barradas M, Crystal S, Gordon A, Kraemer K, Brown S, Gerschenson M, Leaf DA, Deeks SG, Rinaldo C, Kuller LH, Justice A, Freiberg M. HIV status, burden of comorbid disease, and biomarkers of inflammation, altered coagulation, and monocyte activation. *Clin Infect Dis* 2012;**55**: 126–136.
46. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Melbourne K, Ha B, Brown TT, Bloom A, Fedarko N, Sax PE. Inflammation markers after randomization to abacavir/lamivudine or tenofovir/emtricitabine with efavirenz or atazanavir/ritonavir. *AIDS* 2012;**26**:1371–1385.
47. Hunt PW, Sinclair E, Rodriguez B, Shive C, Clagett B, Funderburg N, Epling L, Van Natta M, Medvik K, Huang Y, Deeks SG, Martin JN, Meinert C, Lederman MM. Gut epithelial barrier dysfunction, inflammation, and coagulation predict higher mortality during treated HIV/AIDS. *CROI* 2012.
48. Calmy A, Gayet-Ageron A, Montecucco F, Nguyen A, Mach F, Burger F, Ubolyam S, Carr A, Ruxungtham K, Hirschel B, Ananworanich J, Staccato Study Group. HIV increases markers of cardiovascular risk: results from a randomized, treatment interruption trial. *AIDS* 2009;**23**:929–939.
49. Wolf K, Tsakiris DA, Weber R, Erb P, Battegay M, Swiss HIVCS. Antiretroviral therapy reduces markers of endothelial and coagulation activation in patients infected with human immunodeficiency virus type 1. *J Infect Dis* 2002;**185**:456–462.
50. Sandler NG, Wand H, Roque A, Law M, Nason MC, Nixon DE, Pedersen C, Ruxrungtham K, Lewin SR, Emery S, Neaton JD, Brenchley JM, Deeks SG, Sereti I, Douek DC, Insight Smart Study Group. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis* 2011;**203**:780–790.
51. Subramanian S, Tawakol A, Burdo TH, Abbara S, Wei J, Vijayakumar J, Corsini E, Abdelbaky A, Zanni MV, Hoffmann U, Williams KC, Lo J, Grinspoon SK. Arterial inflammation in patients with HIV. *JAMA* 2012;**308**:379–386.
52. Duprez DA, Kuller LH, Tracy R, Otvos J, Cooper DA, Hoy J, Neuhaus J, Paton NI, Friis-Moller N, Lampe F, Liappis AP, Neaton JD, Group ISS. Lipoprotein particle subclasses, cardiovascular disease and HIV infection. *Atherosclerosis* 2009;**207**:524–529.
53. Aristoteli LP, Moller HJ, Bailey B, Moestrup SK, Kritharides L. The monocytic lineage specific soluble CD163 is a plasma marker of coronary atherosclerosis. *Atherosclerosis* 2006;**184**:342–347.
54. Lo J, Plutzky J. The biology of atherosclerosis: general paradigms and distinct pathogenic mechanisms among HIV-infected patients. *J Infect Dis* 2012;**205**(Suppl 3): S368–S374.
55. Hsue PY, Ordovas K, Lee T, Reddy G, Gotway M, Schnell A, Ho JE, Selby V, Madden E, Martin JN, Deeks SG, Ganz P, Waters DD. Carotid intima-media thickness among human immunodeficiency virus-infected patients without coronary calcium. *Am J Cardiol* 2012;**109**:742–747.
56. Bavinger C, Bendavid E, Niehaus K, Olshen RA, Olkin I, Sundaram V, Wein N, Holodniy M, Hou N, Owens DK, Desai M. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. *PLoS One* 2013;**8**:e59551.
57. D. A. D. Study Group, Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, De Wit S, Law M, D'Arminio Monforte A, Friis-Moller N, Kirk O, Pradier C, Weller I, Phillips AN, Lundgren JD. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multicohort collaboration. *Lancet* 2008;**371**:1417–1426.
58. Cruciani M, Zanichelli V, Serpelloni G, Bosco O, Malena M, Mazzi R, Mengoli C, Parisi SG, Moyle G. Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data. *AIDS* 2011;**25**:1993–2004.

59. Ding X, Andraca-Carrera E, Cooper C, Miele P, Kornegay C, Soukup M, Marcus KA. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. *J Acquir Immune Defic Syndr* 2012;**61**:441–447.
60. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, De Wit S, Law M, Monforte AD, Friis-Moller N, Kirk O, Fontas E, Weller I, Phillips A, Lundgren J. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis* 2010;**201**:318–330.
61. Boccara F, Lang S, Meuleman C, Ederhy S, Mary-Krause M, Costagliola D, Capeau J, Cohen A. HIV and coronary heart disease: time for a better understanding. *J Am Coll Cardiol* 2013;**61**:511–523.
62. Friis-Moller N, Thiebaut R, Reiss P, Weber R, Monforte AD, De Wit S, El-Sadr W, Fontas E, Worm S, Kirk O, Phillips A, Sabin CA, Lundgren JD, Law MG, D. A. D. study group. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. *Eur J Cardiovasc Prev Rehabil* 2010;**17**:491–501.
63. D'Agostino RB Sr. Cardiovascular risk estimation in 2012: lessons learned and applicability to the HIV population. *J Infect Dis* 2012;**205**(Suppl 3):S362–S367.
64. Petoumenos K, Worm S, Reiss P, de Wit S, d'Arminio Monforte A, Sabin C, Friis-Moller N, Weber R, Mercie P, Pradier C, El-Sadr W, Kirk O, Lundgren J, Law M, D. A. D. Study Group. Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D study(*). *HIV Med* 2011;**12**:412–421.
65. Moyle GJ, Lloyd M, Reynolds B, Baldwin C, Mandalia S, Gazzard BG. Dietary advice with or without pravastatin for the management of hypercholesterolaemia associated with protease inhibitor therapy. *AIDS* 2001;**15**:1503–1508.
66. Bonnet F, Aurillac-Lavignolle V, Breilh D, Thiebaut R, Peuchant E, Bernard N, Lacoste D, Dabis F, Beylot J, Chene G, Morlat P, GESCA. Pravastatin in HIV-infected patients treated with protease inhibitors: a placebo-controlled randomized study. *HIV Clin Trials* 2007;**8**:53–60.
67. Calza L, Manfredi R, Colangeli V, Tampellini L, Sebastiani T, Pocaterra D, Chiodo F. Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidaemia. *AIDS* 2005;**19**:1051–1058.
68. Gerber JG, Kitch DW, Fichtenbaum CJ, Zackin RA, Charles S, Hogg E, Acosta EP, Connick E, Wohl D, Kojic EM, Benson CA, Aberg JA. Fish oil and fenofibrate for the treatment of hypertriglyceridemia in HIV-infected subjects on antiretroviral therapy: results of ACTG A5186. *J Acquir Immune Defic Syndr* 2008;**47**:459–466.
69. Balasubramanyam A, Coraza I, Smith EO, Scott LW, Patel P, Iyer D, Taylor AA, Giordano TP, Sekhar RV, Clark P, Cuevas-Sanchez E, Kamble S, Ballantyne CM, Pownall HJ. Combination of niacin and fenofibrate with lifestyle changes improves dyslipidemia and hypoadiponectinemia in HIV patients on antiretroviral therapy: results of 'heart positive,' a randomized, controlled trial. *J Clin Endocrinol Metab* 2011;**96**:2236–2247.
70. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, Grobbee DE, Cass A, Chalmers J, Perkovic V. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 2010;**375**:1875–1884.
71. Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. Effect of different antilipidemic agents and diets on mortality: a systematic review. *Arch Intern Med* 2005;**165**:725–730.
72. Investigators A-H, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;**365**:2255–2267.
73. Origin Trial Investigators, Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, Jung H, Maggiono AP, Probstfield J, Ramachandran A, Riddle MC, Ryden LE, Yusuf S. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med* 2012;**367**:309–318.
74. Risk Prevention Study Collaborative Group, Roncaglioni MC, Tombesi M, Avanzini F, Barlera S, Caimi V, Longoni P, Marzona I, Milani V, Silletta MG, Tognoni G, Marchioli R. n-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med* 2013;**368**:1800–1808.
75. Smith MEB, Lee NJ, Haney E, Carson S. Drug Class Review: HMG-CoA Reductase Inhibitors (Statins) and Fixed-dose Combination Products Containing a Statin: Final Report Update 5 [Internet]. Portland (OR): Oregon Health & Science University; 2009 Nov. Available from:. http://www.ncbi.nlm.nih.gov/books/NBK47273/. Accessed 27 May 2013.
76. Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, Ross M, Fux CA, Morlat P, Moranne O, Smith C, Lundgren JD, D. A. D. Study Group. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *J Infect Dis* 2013;**207**:1359–1369.
77. Jotwani V, Li Y, Grunfeld C, Choi AI, Shlipak MG. Risk factors for ESRD in HIV-infected individuals: traditional and HIV-related factors. *Am J Kidney Dis* 2012;**59**:628–635.
78. (EACS) EACS. EACS Guidelines Version 6.1, November 2012. **http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/EacsGuidelines-v6.1–2edition.pdf**. Accessed 30 May 2013.
79. Balt CA. Hypertension and HIV infection. *J Assoc Nurses AIDS Care* 2013;**24**(Suppl): S127–S134.
80. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, Jupiter Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;**359**:2195–2207.
81. ClinicalTrials.gov. Effect of rosuvastatin on endothelial function. **http://clinicaltrials.gov/show/NCT00986999**. Accessed 30 May 2013.
82. ClinicalTrials.gov. Use of rosuvastatin in HIV-infected subjects to modulate cardiovascular risks. **http://clinicaltrials.gov/show/NCT01218802**. Accessed 30 May 2013.
83. ClinicalTrials.gov. Aspirin and Antiretroviral Therapy in HIV Infected Patients. **http://clinicaltrials.gov/show/NCT00783614**. Accessed 30 May 2013.
84. Ridker PM. Testing the inflammatory hypothesis of atherothrombosis: scientific rationale for the cardiovascular inflammation reduction trial (CIRT). *J Thromb Haemost* 2009;**7**(Suppl 1):332–339.
85. Ridker PM, Howard CP, Walter V, Everett B, Libby P, Hensen J, Thuren T, Cantos Pilot Investigative Group. Effects of interleukin-1beta inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. *Circulation* 2012;**126**:2739–2748.