

Cardiovascular Risk Factors and HIV Disease

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Abstract

An increased rate of coronary heart diseases is becoming an important cause of morbidity and mortality among HIV-infected patients. This emerging problem is due to the antiretroviral therapy success that allows HIV-positive patients to live longer. Increased coronary heart disease rates in the HIV population, as in the noninfected population, may be related to traditional risk factors, including advancing age, higher smoking rates, dyslipidemia, insulin resistance, and impaired glucose tolerance. Some nontraditional factors have to be considered too: these are due to the direct effects of the virus on the vasculature, as well as to direct effects of specific antiretroviral drugs, including inflammation, endothelial dysfunction, metabolic disorders, prothrombotic state, and changes in body composition with loss of subcutaneous fat and/or accumulation of visceral fat. The aim of this paper is to review traditional and emerging cardiovascular risk factors and consider their possible interactions in HIV-infected patients. (AIDS Rev. 2011;13:119-29)

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Key words

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Introduction

Recent reports suggest an increased rate of coronary heart disease (CHD) among HIV-infected patients¹, becoming an important cause of morbidity and mortality². This represents an emerging problem due to the antiretroviral therapy success: in fact, HIV-positive patients live longer with an increased estimated life quite comparable to an HIV-negative control. Increased CHD rates in the HIV population, as in the noninfected population, may be related to traditional risk factors, including advancing age, higher smoking rates, dyslipidemia, insulin resistance, and impaired glucose tolerance. Anyway, we must consider also

some nontraditional factors due to the direct effects of the virus on the vasculature, as well as to direct effects of specific antiretroviral drugs, including inflammation, endothelial dysfunction, metabolic disorders, prothrombotic state, and changes in body composition with loss of subcutaneous fat and/or accumulation of visceral fat³.

Cardiovascular disease and HIV-related disease, as well as its specific therapy, are overlapping and the published studies often reach contradictory conclusions. Data actually seem to be evidencing an increased cardiovascular risk in the HIV-positive population, but is this due to HIV infection or to its treatment? Or may it be the result of predisposing traditional risk factors, independently of HIV infection? The aims of our paper are:

- to review traditional and emerging cardiovascular risk factors;
- to consider their possible interactions in HIV-infected patients;
- to evaluate the points in favor or not of the role of HIV and antiretroviral therapy as hypothetical new links in the chain of cardiovascular pathophysiological events.

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Traditional cardiovascular risk factors

Before analyzing the cardiovascular risk factors, we think it is really important to define the meaning of “risk factor” and the role in the pathophysiological process. A risk factor is a variable associated with an increased risk of disease or infection. Risk factors are correlated and not necessarily causal, because correlation does not imply causation.

On the basis of the previous definition, different models, based on genetic susceptibility and phenotypic expression, try to explain the pathophysiology of cardiovascular disease (CVD). These models emerge from an “entwining” of knowledge arisen from several clinical trials. In 1991, a special report published by a panel of experts generated a hypothesis that portrayed CVD as a chain of events, initiated by a myriad of related and unrelated risk factors, and progressing through numerous physiological pathways and processes to the development of end-stage heart disease⁴. In the same paper, the authors hypothesized that intervention anywhere along the chain of events leading to CVD could disrupt the pathophysiological process and confer cardio-protection. Our understanding of the pathophysiology of CVD expanded considerably in the following years, so in 2006 a new special report was published. That paper, through a critical analysis of new pathophysiological mechanisms, new therapeutic agents, and the fulfillment of new landmark clinical trials, has confirmed the concept of a CVD continuum and reinforced the notion that intervention at any point along this chain can modify CVD progression. Well-established risk factors for CVD include lack of exercise, obesity, smoking, diabetes, hypertension, advanced age, dyslipidemia (high levels of total cholesterol and low-density lipoprotein [LDL] cholesterol and low levels of high-density lipoprotein [HDL] cholesterol), and insulin resistance^{5,6}. There is synergy among cardiovascular risk factors, so the co-occurrence of two or more risk factors (e.g. hypertension and dyslipidemia) may have greater than additive effects on overall cardiovascular risk⁷. Cardiovascular risk factors rarely occur in isolation, but rather tend to cluster, which confers high risk in individual persons. A well-known example of this phenomenon is the metabolic syndrome, which is characterized by a group of risk factors including central obesity, dyslipidemia, hypertension, and impaired glucose/insulin homeostasis. To better understand the cardiovascular continuum, in our paper we analyze the major risk factors involved in this chain of events.

Non-modifiable risk factors

Non-modifiable risk factors include age, sex, and family history of CVD. The risk for CVD increases with older age. At any given level of LDL cholesterol, risk for coronary artery disease (CAD) is higher in older than in younger people⁸. Age is a reflection of the progression of structural and hemodynamic changes in the cardiovascular system, of oxidative stress, and endothelial dysfunction, with the contribution of the cumulative exposure to atherogenic risk factors. On average, older people have more coronary atherosclerosis than do younger people.

The rise in absolute risk with aging becomes most clinically significant in men in their mid-forties and in women about the time of the menopause. The reasons for a gender difference in CVD risk are not fully understood. Part of the difference can be explained by the earlier onset of risk factors in men, e.g. elevations of LDL cholesterol and blood pressure, and lower HDL cholesterol; great importance has been given to hormonal protective effects in premenopausal women. However, the Framingham Heart Study has shown that the differences in absolute risk between the sexes cannot be explained entirely by standard risk factors.

A positive family history of CVD counts as a risk factor in both genders. Several prospective studies indicate that a family history of CHD is an independent risk factor even when other risk factors are taken into account. Relative risk for CHD in first-degree relatives has been reported to range from two- to as high as 12-times that of the general population^{9,10}. The clustering of CHD risk in families most closely resembles diseases of polygenic origin and does not follow a Mendelian recessive or dominant pattern that suggests a single gene locus¹¹. Among primary relatives, it appears that brothers and sisters have the highest relative risk, probably due to shared socio-cultural environment, exposures, and genetics. Many risk factors are under genetic control (e.g. blood pressure, lipids and lipoproteins, Lp[a], and obesity), but they account for only a portion of the aggregation of CHD seen in families^{12,13}. While family history is indisputable, a large number of modifiable risk factors are found in people with a history of CHD in a first-degree relative.

Modifiable risk factors

Dyslipidemia

Several studies showed a strict correlation between increased levels of plasmatic cholesterol and

cardiovascular event rates. Lowering of LDL cholesterol significantly reduces all-cause mortality and CHD morbidity and mortality. Oxidized LDL inactivates nitric oxide (NO), which results in increased oxidative stress and enhanced expression of cellular adhesion molecules¹⁴. Higher oxidized LDL content in the lipid core of atherosclerotic plaques may also promote plaque instability¹⁵. Small, dense LDL particles are highly atherogenic and are associated with increased triglyceride levels. The structure of small, dense LDL particles contributes to their atherogenicity, with increased susceptibility to oxidation, easier penetration into the arterial wall, and altered interactions with the LDL receptor. On the other hand, HDL cholesterol promotes cholesterol efflux from lipid-filled macrophages and it possesses several anti-inflammatory and antithrombotic properties that may protect against injury to endothelial surfaces¹⁶. In fact, HDL protects LDL from oxidation and decreases expression of adhesion molecules on endothelial cells (including E-selectin and soluble intercellular adhesion molecule-1)^{6,38}; it improves endothelial function through stimulation of nitric oxide synthase activity, enhances endothelium-dependent vasodilation, increases prostacyclin production by endothelial cells, and inhibits endothelial tissue factor expression, so downregulating thrombotic pathways^{16,17}.

Recent findings suggest that intensive LDL cholesterol-lowering regimens are significantly more effective than moderate treatments in reducing coronary events and atherosclerotic progression¹⁸⁻²⁰. As a result, consensus treatment panels have urged consideration of lower LDL cholesterol targets in patients at very high risk (LDL cholesterol < 70 mg/dl), including individuals with acute coronary syndrome and diabetes²¹. Much of the treatment of hyperlipidemia for primary and secondary prevention of CHD is based on reduction of elevated plasma total cholesterol and LDL cholesterol levels because of the established association between CHD and this lipoprotein²². Anyway, other vascular risk factors need to be considered, including elevated triglycerides and triglyceride-rich lipoproteins. The relation between elevated triglycerides and CHD has been less clear, and thus the role of elevated triglycerides as an independent CHD risk factor continues to be debated. In the Prospective Cardiovascular Münster (PROCAM) study, elevated triglycerides emerged as a significant ($p = 0.001$) and independent risk factor for major coronary events even after adjustment for LDL and HDL cholesterol levels, age, systolic blood pressure, cigarette smoking, diabetes mellitus, family history of myocardial

infarction, and angina pectoris²³. Different data suggest that the combination of high triglyceride and low HDL cholesterol levels is a powerful risk factor for cardiac events or CHD death, even when LDL cholesterol levels are normal. It is not known if the observed relation between triglycerides and CHD is primarily direct or indirect. This failure results from the large number of inter-correlated variables associated with elevated triglycerides. Lipoprotein metabolism is integrally linked, and elevations of serum triglycerides can be confounded by significant correlations with total, LDL, and HDL cholesterol levels. Non-lipid risk factors of obesity, hypertension, diabetes, and cigarette smoking are also interrelated with triglycerides^{24,25} as are several emerging risk factors (insulin resistance, glucose intolerance, and prothrombotic state). Thus, many people with elevated triglycerides are at increased risk for CHD, even when this greater risk cannot be independently explained by triglycerides. Hypertriglyceridemia may contribute to the etiology of CHD through a direct atherogenic effect of triglyceride-rich lipoproteins (particularly, very low-density lipoprotein [VLDL])²⁶. Alternatively, hypertriglyceridemia may be associated with other atherogenic lipoprotein profiles such as low HDL cholesterol or the presence of small, dense LDL particles, or of large apolipoprotein-E-enriched VLDL particles. In addition, hypertriglyceridemia may enhance thrombogenesis through abnormal alterations in coagulation and fibrinolytic mechanisms²⁷. The triad of elevated triglycerides, low HDL cholesterol, and a preponderance of small, dense LDL particles is termed mixed or atherogenic dyslipidemia. However, it is not entirely clear whether increased cardiovascular risk associated with elevated triglycerides is due to increased levels of triglyceride-rich lipoproteins, such as β -VLDL and remnant particles, or to secondary changes in lipoprotein profiles, including decreases in HDL cholesterol and/or increases in small, dense LDL particles, which more readily penetrate the wall of the endothelium and are more readily oxidized²⁸.

Hypertension

Hypertension is a risk factor for CHD, heart failure, cerebrovascular disease, renal failure, and peripheral vascular disease. Data obtained from the Framingham Heart Study indicated that blood pressure in the 130-139/85-89 mmHg range is associated with a > 2-fold increase in relative risk from CVD compared with those with blood pressure levels < 120/80 mmHg. Elevated blood pressure promotes the development of

atherosclerotic plaques and increases the risk of CVD complications. Endothelial dysfunction in chronic hypertension is associated with decreased endothelium-dependent relaxation. In hypertensive vessels, increased expression of matrix proteins, matrix proteinases, and growth factors leads to structural changes such as decreased lumen diameter, increased extracellular matrix, and thickened media²⁷. In addition, hypertension is associated with increased production of free radicals and oxidative stress that may promote an inflammatory state and enhance the atherosclerotic process²⁸. Blood pressure severity and its treatment are established based on the level of blood pressure and the concomitant presence of risk factors, coexisting CVD, or evidence of target-organ damage.

Diabetes

Diabetes mellitus is considered a “cardiovascular risk equivalent” that confers on diabetic persons a risk of future CVD events equivalent to that of persons who have survived a prior myocardial infarction. Approximately 50-75% of all deaths among patients with diabetes mellitus are CVD-related, and type 2 diabetes mellitus increases the risk of death from CHD by 2- to 4-fold²⁹. In patients with diabetes, other cardiovascular risk factors coexist beyond hyperglycemia, including hypertension and dyslipidemia.

Owing to the high risk associated with diabetes, the aggressive control of all risk factors is especially important and includes both lifestyle changes and pharmacological intervention. Clinical trials in diabetes mellitus have examined cardiovascular risk reduction in patients with existing disease and the prevention of new-onset diabetes mellitus in patients with no evidence of diabetes at baseline²⁰⁻³¹.

Metabolic syndrome

Metabolic syndrome is associated with increased CVD risk. The metabolic syndrome comprises a group of lipid and non-lipid risk factors such as insulin resistance and its associated hyperinsulinemia, atherogenic dyslipidemia, central obesity, and hypertension³². Clinical studies have noted a high correlation between abdominal obesity and the characteristic risk factors of the metabolic syndrome. For example, closely associated with abdominal obesity is an elevation of serum triglycerides. A higher triglyceride level is usually accompanied by lower HDL cholesterol concentrations^{33,34}. The excess adipose tissue characteristic of the metabolic

syndrome secretes prothrombotic factors and proinflammatory cytokines, which may contribute to vascular disease. Insulin resistance and subsequent hyperinsulinemia contribute to endothelial dysfunction and impaired NO responses. Furthermore, the chronic exposure of vascular smooth muscle to hyperinsulinemia may promote intimal hyperplasia^{35,36}.

Smoking

Cigarette smoking has been established as a powerful contributor to risk for coronary artery disease and other forms of CVD. The relationship between smoking and CVD risk is dose dependent and observed both in men and women. Consequences of smoking on the cardiovascular system are due to the effects on platelets, function of endothelial progenitor cells, vascular endothelial function, and heart rate variability. These effects both increase the likelihood of an acute event as well as contribute to long-term development of CAD. Observational data suggest that smoking cessation reduces the risk for CVD events and that the decline in risk begins within months after quitting. The risk of myocardial infarction falls by half within a year of cessation³⁷.

Emerging risk factors

Different biomarkers have been identifying as emerging risk factors that could improve global risk assessment. The clinical usefulness of an individual biomarker depends on its ability to satisfy many criteria, including whether the marker identifies or predicts patients at risk, how easily and accurately it can be measured in the clinical setting, and whether therapeutic modification of the marker has a beneficial impact on cardiovascular risk.

C-reactive protein (CRP) appears to be the most reliable inflammatory marker available at present. Numerous studies have demonstrated that elevated CRP levels independently add predictive risk information above and beyond traditional approaches. Obesity and the metabolic syndrome are commonly accompanied by increases in CRP, suggesting a close link between metabolic abnormalities and inflammation³⁸. However, some gaps in the evidence remain. Interventions that reduce CRP (weight loss, exercise, smoking cessation, statins, and fibrates) are already known to reduce the risk for coronary events. A primary prevention trial of rosuvastatin 20 mg versus placebo in 17,802 patients with a CRP level > 2 mg/l and a LDL

cholesterol level < 3.36 mmol/l (< 130 mg/dl) was terminated early because of “overwhelming benefit”. The investigators did not provide the number of participants who could be classified as low- or intermediate-risk on the basis of their Framingham risk score, so the applicability of this trial to intermediate-risk persons is not clear³⁹. Debate continues on the importance of CRP’s contribution to atherosclerosis: is CRP a marker of inflammation that predicts the atherosclerotic process or is it a consequence of this? A recent study⁴⁰ defined CRP as a useful biomarker, but not causally associated with CAD.

The link between homocysteine and CHD is not well understood, although elevations of serum homocysteine are positively correlated with risk for CHD. In any case, the strength of association between homocysteine and CHD is not as great as that for the major risk factors. Moreover, an elevation of homocysteine is not so common. Some investigators maintain that it could be a direct target of therapy. The available intervention for elevated homocysteine is dietary folic acid, perhaps combined with other B vitamins (B_6 and B_{12})^{41,42}. Several clinical trials are underway to test whether homocysteine lowering will reduce CHD risk²¹. A recent study⁴³ showed that active treatment does not significantly decrease the risk of death from cardiovascular causes, myocardial infarction, and stroke.

Beyond biomarkers, a number of surrogate markers of target-organ damage have been investigated to determine their usefulness in risk stratification. Structural surrogate markers reflect abnormalities in the arteries or the heart that result from the CVD process. Some examples include left ventricular hypertrophy, carotid intima-media thickness (IMT), and ankle-brachial index.

Several studies suggest that reversal of left ventricular hypertrophy as measured by electrocardiography or echocardiography may be useful as a surrogate endpoint for treatment of hypertension. A high baseline left ventricular mass value in initially normotensive patients predicts subsequent increases in blood pressure and the development of hypertension, independent of other risk factors. Moreover, elevated left ventricular mass is a strong predictor of CVD morbidity and mortality, regardless of blood pressure values or the presence of other CVD risk factors⁴⁴⁻⁴⁷.

In different randomized trials, carotid IMT, as measured by carotid ultrasonography, has been used widely as a measure of the progression of atherosclerotic disease. The extent of carotid atherosclerosis correlates positively with the severity of coronary atherosclerosis. Furthermore, different studies showed that

severity of IMT independently correlates with risk of major coronary events⁴⁸. Anyway, differences in measurement of carotid IMT, extensive overlap with other risk factors for coronary events, inadequate measurement and adjustment of these risk factors, and different definitions of endpoints contributed to the wide variation in risk ratios⁴⁹. So its usefulness in cardiac risk assessment needs to be validated in prospective, population-based cohort studies, using appropriate measurement methods to determine whether interventions that affect IMT translate in a reduction of clinical events.

The ankle-brachial index is an indicator of peripheral atherosclerotic disease that involves the large arteries of the lower extremity. The ankle-brachial index is determined by measuring systolic blood pressure at the ankle, based on palpation or ultrasonographic measurement of the *dorsalis pedis* pulse, and dividing this by the systolic blood pressure measured in the arm. An ankle-brachial index < 0.9 is the cutoff point commonly used to indicate possible significant compromise of lower-extremity arterial blood flow. In the Framingham cohort, the principal risk factors for CHD events (hyperlipidemia, hypertension, and smoking) were found to be equally good as predictors of incident peripheral artery disease. Peripheral arterial disease is classified as a coronary equivalent and the Adult Treatment Panel III recommends patient management similarly to the ones at high risk according to the Framingham system. However, the evidence is still insufficient to establish the value of ankle-brachial index for cardiac risk assessment in asymptomatic intermediate-risk persons^{21,50}.

Cardiovascular risk factors in HIV patients

The prevalence rates of these factors in HIV patients are high and may predate acquisition of HIV infection. For example, smoking prevalence in the HIV population is higher than in controls in several studies. HIV-infected patients have diets high in saturated fat compared with community control groups. Analysis of data from two large patient cohorts showed that patients with HIV infection have a higher total:HDL cholesterol and LDL cholesterol:HDL cholesterol ratios and serum triglyceride levels than uninfected subjects, thus placing these HIV-infected patients at even greater risk for CVD⁵¹⁻⁵⁸.

The relative contribution of each cardiovascular risk factor is similar in HIV-infected and uninfected populations, which suggests that these factors contribute to

cardiovascular risk in a comparable way irrespective of HIV status. That being so, analyses that compare the observed incidence of CHD in HIV-infected populations with that predicted in the general population have reported reasonably similar outcomes⁵⁹. In addition, the accumulated evidence indicates that the events leading to disease progression overlap and intertwine and do not always occur as a sequence of discrete, tandem incidents.

Effects of HIV infection

The increased incidence of cardiovascular events during interruption of antiretroviral treatment suggests that HIV infection itself may increase cardiovascular risk.

Uncontrolled HIV replication has been demonstrated to be a significant independent risk factor for lipid changes, including hypercholesterolemia, elevated levels of VLDL cholesterol and triglycerides, and lowered HDL cholesterol levels. High-density lipoprotein cholesterol levels decrease early in HIV infection, with predominant small, dense LDL particles. Subsequently, triglycerides and VLDL cholesterol increase, often at the time when signs and symptoms of AIDS occur and especially during therapy with protease inhibitors^{60,61}. So the increased atherogenic profile of these patients before and during antiretroviral therapy (ART) consists of greater circulating amounts of small, dense lipoprotein particles, greater LDL triglyceride content, and smaller mean LDL particle size⁶². The pathogenesis of lipid abnormalities caused by HIV infection is not well understood. Possible mechanisms may include increased hepatic lipogenesis, impaired clearance of lipids from the blood, and effects of immunologic status⁶³. Lower levels of HDL cholesterol may be a consequence of HIV infection and/or thrombotic activity, a mediator of endothelial injury and thrombogenesis, or both. In HIV populations, lower levels of HDL cholesterol are inversely correlated with markers of endothelial activation and thrombotic activity, and HIV seroconversion leads to decreases in HDL cholesterol levels that do not completely revert with ART initiation^{17,64}.

HIV may interfere with adipose tissue homeostasis regardless of antiretroviral drug-induced lipodystrophy. These lipid changes have been found to be statistically associated with lower CD4⁺ T-cell counts and higher viral RNA levels⁶⁵. In addition, a higher viral load is correlated with endothelial dysfunction, which is also related to an increased risk of cardiovascular

events⁶⁶. The mechanism of HIV-related endothelial dysfunction is not clear, but may include lipid disorders associated with HIV infection, viral protein-related endothelial activation, effects of systemic inflammatory cytokine or chemokine dysregulation, or direct HIV infection of the endothelium⁶⁷ and vascular smooth muscle cells.

Different HIV components may have a direct action in the modulation of inflammation regardless of CD4 cell counts. HIV may directly induce monocyte/macrophage, endothelial, and adipocyte activation. These cells may upregulate the secretion of inflammatory molecules and downregulate anti-inflammatory factors. This altered status may further contribute to endothelial activation and atherosclerosis development. Injured endothelial cells release the adhesion molecule, soluble vascular cell adhesion molecule 1 (sVCAM-1), in the vessel lumen, which should be considered as a marker of endothelial activation⁶⁸. Virus proteins, such as Tat and Nef, may influence monocyte actions (i.e. cytokine and chemokine production)^{69,70}. So, HIV replication may lead to a dysregulated interaction among leukocytes, endothelial cells, and adipose tissue, modifying the serum levels of cardiovascular endothelial and inflammatory markers and favoring atherosclerosis.

A *post hoc* analysis of the STACCATO trial, comprising a subgroup of participants who had no prior ART exposure, investigated plasma levels of soluble mediators associated with cardiovascular risk. The biomarkers analyzed are involved in endothelial activation (sVCAM-1 and P-selectin), systemic inflammation (chemokine ligand CCL2, CCL3, GM-CSF, CRP, IL-6 and IL-10), platelet (P-selectin) and coagulation cascade (D-dimer), adipose tissue activation (adiponectin and leptin). These markers were measured before initiation of combined ART, during combined ART when plasma HIV RNA was undetectable, and then in the randomized phase of the trial when patients either continued or suspended combined ART. The aim was to test whether and how the values of the different cardiovascular markers correlated with HIV replication. In this study, HIV RNA replication was showed to be associated with increased levels of sVCAM-1 and CCL2 and decreased levels of adiponectin and IL-10. This association persisted after adjustment for known cardiovascular risk factors. There was no significant correlation for the other biomarkers between patients treated and those who stopped combined ART at week 12 of the trial. These soluble markers (sVCAM-1, CCL2, adiponectin, and IL-10) may have an active

role in the increased cardiovascular risk provoked by HIV infection⁷¹.

Effects of antiretroviral therapy on cardiovascular risk

Treatment with potent ART has transformed HIV infection from a rapidly fatal disease into a chronic illness. However, shortly after ART was introduced there were several reports of acute myocardial infarction and premature atherosclerotic vascular disease among young patients receiving such treatment^{72,74}. Several studies demonstrated that the type, duration, and current use or nonuse of antiretroviral therapy is strongly associated with the severity of metabolic disorders, including hyperlipidemia, insulin resistance, and lipodystrophy^{73,76-78}.

In the ongoing Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, the relative risk of myocardial infarction associated with the use of protease inhibitors (PI), adjusted for exposure to the other drug class and established cardiovascular risk factors (e.g. hypertension and diabetes), was 1.16 per year of exposure (95% CI: 1.10-1.23), whereas treatment with a nonnucleoside reverse transcriptase inhibitor (NNRTI) did not increase the risk of myocardial infarction appreciably (relative risk, 1.05/year of exposure; 95% CI: 0.98-1.13)⁹³.

Although the D:A:D Study Group found that the relative risk of CVD increased as the duration of ART increased, the absolute risk of cardiovascular disease will remain low for most patients, except those with multiple other cardiovascular risk factors⁹⁰.

The realization that HIV infection, particularly uncontrolled viremia, and the presence of risk factors shared with the general population, are important causes of CVD among patients with HIV infection has significant implications for therapeutic intervention in patients with both conditions^{75,79}.

Most importantly, it suggests that stopping or interrupting ART may be of relatively little benefit in decreasing cardiovascular risk. Results from a cardiovascular substudy of The Strategies for Management of AntiRetroviral Therapy (SMART) trial indicated that patients in the CD4-guided intermittent treatment group were at increased risk for evidence of myocardial damage compared with patients who received treatment aimed at early and continuous viral suppression.

The SMART trial demonstrated a 60% increased relative risk for CVD events with a strategy of CD4⁺ cell count-guided interruption of ART, and adverse changes in HDL cholesterol after stopping ART may explain

some of the excess CVD risk⁸¹. Further analyses of SMART demonstrated markers of inflammation (IL-6) and thrombotic activity (D-dimer) at baseline were strongly associated with CVD and mortality risk. Furthermore, IL-6 and D-dimer levels increased after discontinuation of ART, and this increase was associated with increases in HIV RNA levels⁸².

There is still confusion about the relationship between ART and cardiovascular risk. However, a growing body of evidence suggests that HIV-positive patients, regardless of HAART regimen, generally have traditional risk factors for CVD that may complicate determination of risk associated with specific antiretroviral agents. Recent data suggest that ART may improve factors (e.g. endothelial dysfunction) associated with increased cardiovascular risk⁸³⁻⁸⁷.

Risk assessment

Several screening strategies are available to assess global cardiovascular risk. The prevalence rate of traditional cardiovascular risk factors in HIV patients is high and their relative contribution is similar to that of the uninfected population. So, with existing insufficient evidence about a different screening approach in HIV patients, the recommended screening strategies are the same as for the non-HIV population. Several multivariate models are available for calculating global CHD risk⁹⁷. The most commonly used model to define the 10-year CHD risk is the Framingham Risk Score, which incorporates age, sex, blood pressure, LDL cholesterol, HDL cholesterol, diabetes, and smoking. Low, intermediate, and high risks are defined as 10-year risk of CHD of 10, 10-20, and 20%, respectively. However, according to different data the Framingham model appears to underestimate CHD events in HIV patients who also smoke⁹⁸.

Several emerging risk factors and surrogate markers for atherosclerosis have been demonstrated to monitor the inflammatory process and lipid metabolism. On the basis of the available evidence, the CDC/AHA suggests that measurement of CRP, an acute-phase protein, is indicated in patients with moderate risk (10-20% risk of CVD over 10 years). C-reactive protein is elevated in HIV-infected patients and associated with more rapid disease progression to AIDS. However, for patients with HIV, the role of CRP in clinical practice is less clear because results could be confounded by comorbid conditions. Other inflammatory biomarkers include proinflammatory cytokines, chemokines, products of hepatic circulation, homocysteine, and immunoglobulin

molecules. Higher intrahepatic levels of the proinflammatory cytokines, tumor necrosis factor- α (TNF- α) and interferon gamma, are found in treatment-naive patients with HIV/HCV coinfection, and elevated serum levels of TNF- α receptor in patients with HIV-associated lipodystrophy are correlated with severe insulin resistance⁸⁸⁻⁹⁴.

Lipid biomarkers include the traditional lipid profile, adiponectin, other lipoproteins, LDL fractions, and HDL subfractions. Carotid IMT, flow-mediated vasodilation of the brachial artery, and coronary calcium score represent new surrogate markers that predict cardiovascular outcomes, but there are few data that suggest their clinical utility in the evaluation of cardiovascular risk among HIV-infected patients⁹⁵⁻⁹⁸. An increased carotid IMT has been correlated to endothelial dysfunction, increased plasma levels of thrombophilia factor VIII activity and VLDL cholesterol, and decreased clearance of apolipoprotein particles. In patients with HIV infection, carotid IMT is also associated with increased CD4⁺ and CD8⁺ T-cell activation and CD4⁺ count \leq 200 cells/mm³ at nadir⁹⁹⁻¹⁰². However, the correlation of these pro-atherogenic surrogate markers with increased cardiovascular risk and long-term outcomes in HIV-infected patients remains to be validated in larger studies. Identifying the presence of predisposing risk factors, we seek to define the pretest likelihood of disease.

There are no specific data about the sensitivity and specificity of diagnostic tests for CAD in the HIV population, so recommendations do not differ from the uninfected population. According to the US Preventive Services Task Force¹⁰³, patients with a low pretest probability and a low global CHD risk score (e.g. < 10%) should not be referred for further testing, whereas those with a high pretest probability (> 20%) have a high false-positive rate on noninvasive tests, such as exercise ECG, and should be considered for invasive arteriography. Patients at intermediate risk are most suitable for noninvasive testing. The use of graded levels of stress is most commonly employed to detect myocardial ischemia. Stress may be physiological (e.g. exercise) or pharmacological (e.g. dipyridamole) and may be assessed with ECG, echocardiography, or nuclear imaging. If stress tests are not significant and doubts remain, a more sophisticated imaging technique, like coronary computed tomography, is indicated. Important questions and priorities for future research were identified, including the need to determine the optimal screening strategy and risk stratification algorithm, to define the sensitivity and specificity of

diagnostic tests for CHD, and to determine the clinical utility of inflammatory and surrogate markers of CHD in HIV-infected patients.

Conclusion

HIV infection could be seen as a new link in the chain of events leading to CAD in this peculiar population. But how could this "new" link interact with CVD continuum? HIV and ART can contribute to increase CVD risk in three main ways: (i) HIV may be a marker to identify a subgroup of the general population with a higher prevalence of traditional cardiovascular risk factors, regardless of HIV or ART (e.g. HIV-infected patients are often smokers and have an unhealthy diet); (ii) HIV or ART may influence the risk of developing traditional cardiovascular risk factors (e.g. HIV or ART may worsen dyslipidemia); and (iii) HIV or ART may contribute to the pathogenesis of CVD (e.g. through effects on inflammation or endothelial function). Different evidences suggest that all three mechanisms can be involved in the development of CVD in HIV patients¹⁰⁴.

Cardiovascular risk factors play an important role and are known to be necessary but not sufficient in the pathophysiological continuum. A lot of uncertainties, on the contrary, exist about the effective role of inflammation in the pathogenesis of CAD. HIV increases lipid disorders and provokes an inflammatory burden, favoring an atherogenic milieu. Antiretroviral therapy, through the control of HIV replication, reduces systemic inflammation but it is associated to metabolic disorders, including hyperlipidemia, insulin resistance, and lipodystrophy. Finally, what is the net effect obtained by the correlation of all these factors? (Fig. 1). We may distinguish two categories of patients. First, patients with traditional cardiovascular risk factors and concomitant atherosclerosis who contract HIV infection: the atherogenic milieu by itself is a source of inflammation and the overlapping HIV may contribute to increase the inflammatory burden and endothelial dysfunction. On the other hand, we may have patients without any traditional cardiovascular risk factors in which HIV is the *primum movens* of the inflammatory cascade and continuously sustains it; moreover, the virus, and then the antiretroviral therapy, favor metabolic disorders that contribute to developing an atherogenic milieu. Because of the different pathogenetic mechanism, we could hazard a guess: is the atherogenic plaque composition different in these two groups of patients?

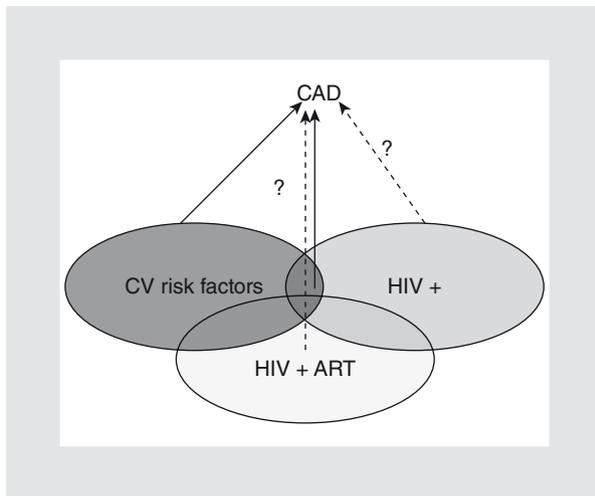


Figure 1. Different studies show an overlapping among traditional cardiovascular (CV) risk factors, HIV infection and antiretroviral therapy (ART) in the pathogenesis of cardiovascular disease. May HIV infection by itself or with the contribution of ART lead to coronary artery disease (CAD) in patients without traditional cardiovascular risk factors?

To get an answer we need the design of adequate prospective studies, with a long-term follow-up and based on the collaboration between cardiologist and infectologist, that follow and compare the evolution of CVD in well-defined categories of patients:

- uninfected patients with traditional cardiovascular risk factors;
- naive HIV-infected patients without cardiovascular risk factors and organ damage;
- HIV-infected patients, without cardiovascular risk factors and organ damage, treated with different combinations of ART.

In this way it will be possible to outline the contribution of each factor and their overlapping in acceleration of the atherogenic process. What to do in the meantime? Collectively, the data linking viremia, endothelial dysfunction and inflammation, the increased risk of cardiovascular events with treatment interruption, and the association between CVD and CD4 cell depletion, suggest that early control of HIV replication with ART can be used as a strategy to reduce CVD risk¹⁰⁵. The initial choice of ART regimen and subsequent ART modifications may be considered in planning CVD prevention strategies, because the risks of inadequately treated HIV infection outweigh any increase in CVD risk that may be associated with ART¹⁰⁶. Efforts to prevent CVD in patients with HIV should focus also on improving modifiable risk factors such as cigarette smoking, hypertension, dyslipidemia, and disordered glucose metabolism. They should be treated in a manner similar

to the general population: through lifestyle modifications and specific drugs, including statins, fibrates, antihypertensive therapies, etc. However, the application of the famous risk charts to the HIV-infected population could underestimate the global cardiovascular risk in these specific patients. A better detection of cardiovascular risk and organ damage in HIV-infected people is needed, through more sophisticated methods and identifying specific biomarkers as surrogate endpoints for CVD. In the absence of HIV-specific long-term studies, recommendations for both the screening and diagnosis of coronary artery disease in HIV-infected patients do not differ generally from the strategies that have been proven effective in uninfected populations.

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