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The Consequences of HIV Infection and Antiretroviral Therapy Use For Cardiovascular Disease Risk: *Shifting Paradigms*

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Abstract

Purpose of Review—To explore the mechanisms by which HIV infection and antiretroviral therapy (ART) may increase risk for atherosclerotic cardiovascular disease (CVD), with attention to the implications of earlier initiation of ART (i.e. at higher CD4 counts than currently recommended by guidelines).

Recent Findings—Compared to the general population, HIV-infected patients receiving ART have a greater burden of subclinical and clinical atherosclerotic disease. Findings from a recent international treatment interruption trial (SMART) has redirected attention from ART-related drug toxicity toward a better appreciation for the consequences of untreated HIV infection, which may increase CVD risk through inflammation, up-regulation of thrombotic pathways, and ultimately early vascular damage and dysfunction. In addition, CVD risk may increase with some ART, and this risk may be class- and/or drug-specific.

Summary—Compared to untreated HIV, ART may increase or decrease risk of CVD. Reliable data on the relative risk does not exist. A randomized trial of early ART will provide the best data for assessing the net risks and benefits of ART use on CVD.

Keywords

HIV infection; Antiretroviral therapy; Cardiovascular Disease; Endothelial Dysfunction; Inflammation; Dyslipidemia; Early Treatment

INTRODUCTION

With effective combination antiretroviral therapy (ART), HIV-infected persons are living longer, and premature cardiovascular disease (CVD) has become a major health challenge.¹ Atherosclerotic CVD is now a leading cause of death among persons with HIV infection.^{3–5} In addition, comparisons between HIV-infected and HIV-uninfected groups have demonstrated increased risk for CVD events.^{6–7} In the general population, mechanisms that promote atherogenesis involve inflammation, adverse lipid and metabolic changes, and vascular damage and dysfunction. These same factors are important mediators of CVD risk for individuals infected with HIV, whether related to HIV itself, ART use, or other factors.

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While treatment with ART may attenuate HIV-specific mechanisms, epidemiologic data suggest prolonged exposure to ART, and protease inhibitors (PI) specifically, increases risk for myocardial infarction.^{8 9} Furthermore, the prevalence of certain traditional risk factors, such as smoking, is also greater among persons with HIV infection, which remain important contributors to CVD risk in this context.¹⁰ For the purposes of this review, we will focus on understanding HIV- and ART-related CVD risk factors (figure 1), as these are the most relevant when considering the risks and benefits of HIV treatment at higher CD4 counts.

HIV-SPECIFIC FACTORS AND CARDIOVASCULAR RISK

Recent data suggesting HIV infection increases CVD risk have generally described mechanisms related to HIV-specific immune dysfunction, up-regulation of inflammation and thrombotic markers, vessel damage and dysfunction, and adverse changes in blood lipids and cholesterol metabolism. A summary of this research is presented here.

Immune Dysfunction

Epidemiologic data provided some of the initial evidence that HIV infection itself may contribute to CVD risk. Although CVD mortality has become important, several cohort studies have reported decreased CVD death rates since the advent of combination ART.^{4 11} Phillips et. al. has recently reviewed data on associations between CVD risk and latest CD4 count and HIV RNA level.¹² In four cohorts, there was a consistent, albeit modest, relationship between higher risk for fatal and non-fatal CVD events with lower CD4 counts.¹² In a report including patients from the HIV Outpatient Study (HOPS), baseline CD4 count <350 cells/mm³ on entry was associated with a higher incidence of CVD events.¹³ Carotid artery lesions and intima-media thickness (IMT) were assessed via ultrasound in HIV infected and uninfected men and woman from the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS).¹⁴ Compared to HIV negative persons in MACS/WIHS, HIV-infection was associated with subclinical atherosclerosis only among those with a nadir CD4 count <200 cells/mm³. The Strategies for Management of Anti-Retroviral Therapy (SMART) study was a randomized trial that demonstrated a strategy of CD4-guided intermittent ART use (DC arm), compared to continuous ART use (VS arm), increased risk for CVD and other end-organ disease events.⁹ In the SMART trial, the influence of both CD4 count and HIV RNA level on risk of CVD was examined, and higher HIV RNA levels were associated with an increased risk of CVD independent of CD4 count.¹² Thus, high levels of HIV replication and immune dysfunction, reflected in low CD4 counts, may both be important for CVD risk.

The pathogenesis underlying associations between immune status, or CD4 count, and CVD is not known. Specifically, a low CD4 count may not be directly permissive of vascular damage, but rather reflect immune dysregulation or a greater degree of inflammation—known to be important in the pathogenesis of atherosclerosis. A better understanding of these mechanisms may help guide potential use of adjunct treatments that reduce HIV-mediated CVD risk.

Inflammation and Thrombosis

The importance of inflammation in CVD pathogenesis is well established.¹⁵ Elevated C-reactive protein (CRP) levels, an acute phase reactant, and IL-6 levels, a cytokine released by monocytes that stimulates release of CRP from hepatocytes, are both independent predictors of CVD events in the general population.^{16 17} Within MACS, CRP levels were elevated in patients with HIV infection, were increased over time, were associated with progression to AIDS, and were correlated inversely with CD4 count and directly with HIV RNA levels.¹⁸ The mechanisms underlying inflammation and release of cytokines with HIV infection are complex and beyond the scope of this review, but may be a result of HIV replication, activation

and dysregulation of leukocytes (and antigen-presenting cells) and/or damage to the mucosal barrier with increased bacterial translocation.^{19 20}

Increased thrombosis provides one mechanism by which inflammation may increase CVD risk. IL-6 up-regulates thrombosis and fibrinolysis activity, in part, by increasing tissue factor and fibrinogen production and enhancing endothelial cell and platelet activation.²¹ In the general population, higher D-dimer levels are associated with CVD event risk.²² In SMART, increases in HIV RNA levels 1 month after stopping ART use were correlated with increases in IL-6 and D-dimer levels.²³ In addition, IL-6 and D-dimer levels at baseline in SMART were strongly associated with increased risk for all-cause mortality, leading authors to speculate that inflammatory mediated endothelial injury up-regulates thrombotic pathways.²³ Additional studies have reported elevations in D-dimer, von-Willebrand factor (vWf) and other pro-thrombotic markers in persons with HIV infection, compared to HIV negative controls, and a review of these data has been published.^{24–26}

Endothelial Injury and Early Vascular Disease

Injury to endothelial cells perpetuates a local inflammatory response that promotes thrombosis, impairs vessel responsiveness, and is a permissive factor in arterial plaque formation.^{27 28} HIV replication may activate endothelial surfaces directly or via up-regulation of pro-inflammatory cytokines.^{29–31} Endothelial cell adhesion molecules (intercellular and vascular cell adhesion molecules; ICAM and VCAM respectively) are expressed by endothelial cells in response to leukocytes and cytokines, and are elevated in persons with HIV infection, when compared to HIV negative controls.³² Endothelial cell activation, though a normal physiologic response to inflammation, can lead to vessel damage and dysfunction with chronic stimulation.²⁸ Studies using a murine AIDS model have demonstrated that vascular dysfunction was correlated to oxidative stress and endothelial activation.³³

Clinical studies also suggest untreated HIV infection contributes to early vascular disease. Brachial artery flow mediated dilation (FMD), a functional vessel assessment of NO, was impaired among 75 HIV infected participants when compared to an historic cohort of 223 HIV negative controls.³⁴ In this study, impaired FMD was associated with a detectable HIV RNA level, though only 16 participants were not receiving ART.³⁴ Impaired arterial stiffness, or elasticity, is a marker of early CVD, is associated with traditional risk factors and risk for clinical events, and provides information about both functional and structural vascular changes.³⁵ A recent study demonstrated impaired aortic stiffness among 39 untreated HIV infected persons compared to 78 HIV negative controls.³⁶ More such research is needed using reproducible markers of vascular damage, within both large and small vessels, to study HIV- and ART-related CVD risk including assessments of adjunct treatments.

Changes in Lipid Levels and Cholesterol Metabolism

HIV infection has a substantial impact on blood lipids.^{37–40} Among men in MACS, total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) decrease following HIV seroconversion.⁴⁰ Decreases in LDL with HIV infection are associated with an increased predominance of small LDL particles, a subclass of LDL with pro-atherogenic properties.^{39 41} Triglyceride levels (TG) are also elevated with HIV infection, when compared to HIV-negative cohorts, and TG have pro-thrombotic properties in-vitro.^{37 40 42} In SMART, despite lower TC levels with interruption of ART, the TC/HDL ratio increased when compared to participants on continuous ART.⁴³ TC/HDL ratio remains one of the best lipoprotein indices in terms of predicting CVD event risk in the general population.⁴⁴

HDL may reduce CVD risk in part through reverse cholesterol transport (RCT), a process that directs cholesterol from peripheral cells to the liver for processing and excretion. ATP-binding cassette transporter A1 (ABCA1) facilitates uptake of cholesterol from cells by HDL. A recent study showed that HIV impairs ABCA1-dependent cholesterol efflux in vitro, resulting in the accumulation of lipids in macrophages similar to foam cells.⁴⁵ In this same study, HIV-positive foam cells were identified in atherosclerotic plaques from HIV-infected persons. In the later stages of RCT, cholesteryl ester transfer protein (CETP) facilitates the delivery of cholesterol by HDL to atherogenic LDL and very low-density lipoprotein (VLDL) particles, versus delivery to hepatocytes. CETP is up-regulated in persons with untreated HIV infection when compared to HIV negative controls.⁴⁶ In addition, a recent report by Feingold demonstrated that hepatic LDL receptor expression was decreased with inflammation, thereby reducing liver uptake of LDL particles from serum.⁴⁷ Thus, lipid disorders and alterations in cholesterol metabolism associated with HIV infection are pro-atherogenic.

ANTIRETROVIRAL THERAPY USE AND CARDIOVASCULAR RISK

Research linking CVD risk with ART use has accumulated since the advent of combination therapy. A brief summary of these data is presented here, with an emphasis on ART-mediated factors related to adverse blood lipid and metabolic changes, inflammation, and the influence of ART initiation on vessel damage and dysfunction.

Clinical and Subclinical Vascular Disease in Patients Receiving ART

Early clinical observations implicated ART, and PI use in particular, as a possible determinant of CVD risk.⁴⁸ Subsequently, the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study, a prospective study of 23,468 HIV-infected patients from 11 cohorts on three continents, reported that combination ART use was associated with a 26% relative increase in rate of myocardial infarction (MI) per year of exposure to ART.³ With longer follow-up and more events, these data now suggest that the risk of MI is increased with use of PIs but not non-nucleoside reverse transcriptase inhibitors (NNRTIs).⁸ These data are consistent with findings from HOPS and the French Hospital Database, but the Veterans Affairs (VA) study, a large retrospective cohort study, did not find an increased risk of CVD with PI or other ART use.^{49–52} Findings from these and other epidemiologic studies have been recently reviewed.⁵³

Subclinical atherosclerosis can be estimated using ultrasound measures of carotid IMT or computed tomography estimations of coronary artery calcification (CAC). Findings from studies comparing IMT in HIV-infected and HIV negative populations have been mixed. Some have reported increased IMT among HIV-infected patients,^{54–56} while others find no differences after adjusting for traditional risk factors.^{57–58} CAC was recently assessed in MACS, including participants that were HIV-negative and HIV-infected and receiving longstanding (≥ 8 years) ART.⁵⁹ The prevalence of CAC was increased among those receiving longstanding ART compared to HIV-negative participants, though the extent of CAC, or degree based on CAC score, among HIV-infected persons with identified lesions was significantly reduced with longstanding ART exposure when compared to those ART-naïve.⁵⁹ This distinction highlights the unique complex pathophysiology of CVD among HIV-infected persons, and suggests that initiating ART may include both positive and negative influences on the progression of atherosclerotic disease. Ultimately non-randomized studies of HIV-infected patients are unable to determine the net influence of treatment with ART on CVD risk, versus the risks related to untreated HIV infection.

Lipid and Metabolic Changes

ART-related lipid and metabolic alterations, including proposed mechanisms for CVD risk, have been previously discussed and is beyond the scope of this review.⁶⁰ The typical pattern of these changes includes hypertriglyceridemia, hypercholesterolemia, lipodystrophy and alterations of glucose metabolism. Specifically, ART initiation among HIV-infected patients in MACS led to increases in TC and LDL, while HDL remained approximately 10mg/dl below pre-infection levels.⁴⁰ Further analysis of lipoprotein subclasses in MACS demonstrated ART-associated increases in pro-atherogenic small LDL particles and VLDL.⁶¹ PI-treated patients showed greater increases in VLDL, but not small LDL particles, when compared to NNRTI-treated patients in MACS.⁶¹ Insulin resistance and changes in body composition may be less likely with newer agents.^{60 62–64} In addition, regimens including the relatively lipid neutral integrase inhibitors and CCR5 receptor antagonists may lead to more favorable lipid and metabolic changes.^{65 66}

Inflammation in Patients Receiving ART

Whether related to drug toxicity, persistent low level viral replication, or other factors, inflammatory markers remain up-regulated in HIV-infected patients receiving ART. Fibrinogen (men and women) and CRP (men only) levels were elevated in 1131 HIV-infected patients from the Study of Fat Redistribution and Metabolic Change in HIV infection (FRAM), when compared to 281 general population controls from the Coronary Artery Risk Development In Young Adults (CARDIA) study.^{67 68} In FRAM, fibrinogen levels were also 11% higher among those taking a PI- versus an NNRTI-based regimen.⁶⁷ The lipid and metabolic effects of PI therapy offer potential explanations for higher levels of inflammatory markers, and IL-6, CRP and fibrinogen levels are elevated among persons in the general population with metabolic syndrome.⁶⁹ A recent study reporting higher CRP levels in 129 HIV-infected participants receiving ART, compared with 42 ART-naïve participants, supports the importance of lipid and metabolic changes as mediators of ART associated inflammation.⁷⁰ In this study, CRP levels were positively correlated with intra-abdominal fat thickness, total cholesterol, fasting glucose and post-parandial insulin and glucose levels.⁷⁰ Among participants in FRAM (HIV-infected) and CARDIA (general population), CRP levels positively correlated with greater visceral and subcutaneous fat.⁶⁸

Inflammation and increased risk of CVD associated with ART may not be limited to PIs. Among patients in the DAD study, recent exposure to abacavir and didanosine was associated with an increased risk of myocardial infarction but not stroke.⁷¹ This association was also noted in SMART, where current use of abacavir was associated with a 40–90% increased risk for CVD event, a 27% increase in CRP levels, and 16% increase in IL-6 levels, when compared with those receiving other nucleoside reverse transcriptase inhibitors (NRTIs).⁷² Future studies will need to consider differential effects of specific ART drugs on markers of inflammation and thrombosis, given the potential influence on CVD risk.

Impact of ART use on Endothelial Dysfunction

ART initiation is associated with short-term improvement in HIV-mediated endothelial damage and dysfunction. In a longitudinal study, markers of endothelial activation (ICAM, VCAM and vWf) decreased within HIV-infected participants receiving ART.²⁶ In a study of 82 patients starting ART, FMD improved after 4 weeks of either PI or NNRTI-based therapy, and improvements after 24 weeks were associated with HIV RNA levels.⁷³ However, a prior study of 37 HIV-infected patients receiving ART for an average of 5+ years demonstrated impaired FMD among those receiving PIs, but not among those treated with NNRTIs.⁷⁴ In this same study, alterations in lipoproteins (elevated VLDL and chylomicron levels) and glucose explained most of the effect of PIs on FMD.⁷⁴ The mechanisms of PI-related endothelial dysfunction are complex, and may include lipoprotein changes, insulin resistance,

inhibition of NO, and increased oxidative stress.^{75 76} In addition, PI-associated endothelial damage may vary by PI, as studies of HIV-negative persons demonstrate endothelial dysfunction after indinavir but not with atazanavir or lopinavir/ritonavir use.^{77 78}

CONCLUSION: THE RISKS/BENEFITS OF EARLY TREATMENT FOR HIV INFECTION MUST BE DETERMINED

While it has been appreciated for some time that HIV treatment with combination ART is associated with an increased risk of CVD, it has been recently recognized that the consequences of untreated HIV infection may be worse. Many of the same mechanisms for CVD risk described in the context of HIV infection may also explain increases in CVD noted with other viral infections (e.g. influenza) and auto-immune diseases (rheumatoid arthritis and systemic lupus).^{79–81} Increased inflammation associated with viral infections and auto-immune diseases suggests adjunctive treatments that lower inflammatory markers, in addition to those that target thrombotic activity, may prove useful in this context. Thus, expanding our understanding of HIV-mediated CVD risk, and the influence of ART, will be relevant to disease states beyond HIV infection.

The findings of SMART have greatly changed our understanding of ART use and CVD risk in persons with HIV infection.^{9 23 82 83} Although SMART was a treatment interruption trial, the protocol modification allowed characterization of change in CVD risk associated with resuming continuous ART among those previously using ART episodically. In SMART, the risk for CVD events was 60% higher in DC versus VS arm pre-modification; subsequently, when participants in the DC arm re-initiated continuous ART, CVD risk was substantially reduced.⁸² Despite limitations, these findings and the cohort data linking levels of CD4 count and HIV RNA level to CVD risk begin to suggest that treating HIV infection with ART may reduce the incidence of CVD in HIV-infected individuals.

Future use of ART agents with lower CVD risk potential, and improved management of risk factors by HIV care providers, may also improve ART-related CVD risk.⁸⁴ Nevertheless, initiating early treatment for HIV-infected patients, or at higher CD4 counts, will commit them to prolonged ART exposure.⁸⁵ In addition, an aging HIV population may lead to greater increases in chronic diseases such as CVD, and the annual cost of ART in the U.S. and Western Europe generally exceeds \$12,000 (USD) annually. Thus, it remains important that the risk for CVD related to untreated HIV infection, compared to prolonged ART use, be quantified more precisely so that accurate cost-benefit discussions can be had. The international Strategic Timing of AntiRetroviral Therapy (START) study will provide randomized trial data to address this question, and the results could have important public health implications for future management of HIV infected patients.

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Figure 1.

Multiple factors contribute to CVD risk among patients with HIV infection, including traditional risk factors as well as mechanisms related to viral replication and ART. While ART use may decrease HIV-mediated CVD risk via suppression of viral replication, it is also associated with drug toxicity that itself is known to confer CVD risk. There may also be other HIV- and ART-specific CVD risk factors not discussed here (dotted lines). Thus, the net influence of ART on CVD risk, in the setting of HIV infection, remains to be defined.