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Cardiovascular Disease in HIV Infection

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Abstract

Purpose of Review—Highly active antiretroviral therapy (HAART) use has markedly reduced AIDS-related mortality and opportunistic illness. With improved survival, cardiovascular disease (CVD) has emerged as an important non-infectious chronic co-morbidity among antiretroviral (ARV)-treated HIV-infected persons.

Recent Findings—HIV infection can impact CVD and co-morbidiities known to increase CVD risk. Untreated HIV can cause proatherogenic elevations in serum lipids. Chronic HIV viremia results in increases in systemic inflammation, hypercoagulation, and reductions in endovascular reactivity, all of which are at least partially reversible with virally suppressive HAART. Chronic T cell activation can also result in adverse vascular effects. Use of some ARV drugs can impact CVD risk by causing pro-atherogenic serum lipid elevations, induction of insulin resistance, increases in visceral adiposity or subcutaneous fat loss. Abacavir use may increase myocardial infarction risk by reducing vascular reactivity and/or increasing platelet activation. Traditional risk factors such as advancing age, smoking, hyperlipidemia, and hypertension remain important predictors of CVD among HAART-treated HIV-infected persons.

Summary—HIV in the HAART era is a chronic manageable condition. CVD is an important cause of morbidity among HIV-infected persons. Untreated HIV can increase CVD risk in several ways and these effects are at least partially reversible with successful treatment. Use of specific ARV's can adversely impact CVD risk but the multiple long-term benefits of chronic HIV suppression and immune reconstitution achievable with potent HAART outweigh the adverse impact upon CVD risks that they may have. Standard CVD screening and risk-reducing interventions should be routinely undertaken for HIV-infected persons.

Key words/phrases

Cardiovascular disease in HIV infection; Inflammation; hypercoagulation; vascular functioning; Effects of antiretroviral drugs; Hyperlipidemia

Introduction

The use of highly active antiretroviral (ARV) therapy (HAART) has resulted in marked and sustained reductions in AIDS-related mortality and opportunistic diseases among treated persons (1). As a result, HIV infection has become a chronic and manageable condition. Non-infectious co-morbidities that are common among aging persons in the general population have emerged as important and their management has become central to the

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overall care of these patients. Likewise, among contemporary causes of death for HAART-treated HIV-infected persons, non-infectious causes predominate (2–4).

Prominent among these co-morbidities is cardiovascular disease (CVD). The prevention, screening for, timely diagnosis and treatment of CVD and its risk factors (such as hyperlipidemia and insulin resistance) have become priorities for HIV clinical care. Furthermore, ascertainment of interactions between HIV itself, ARV therapy, traditional CVD risk factors and host genetics in the etiology of CVD have occupied much of the recent research agenda.

Untreated HIV and CVD Risk

Existing data support associations between sustained plasma HIV viremia, CD4 lymphocyte depletion and the development of CVD. Multiple investigators have sought to establish links between elevation in markers of systemic inflammation and coagulation, immune activation, and their relationships to vascular endothelial disease and overall vascular functioning. Invariably these inquiries have necessitated the consideration of the presence of ART and its modifying impact upon HIV viremia, systemic inflammation, vascular health, and therefore CVD risk. While we will discuss the potential impact of specific ARV therapies upon CVD and its risks in the next section, it should be kept in mind that most investigative evaluations of CVD in HIV-infected persons (with some notable exceptions) have been undertaken among successfully ARV-treated individuals, and that therefore assigning proportional “attributabilities” regarding CVD risk to HIV itself, ARV therapies used, and other factors is difficult.

Early in the HIV epidemic, it was clear that HIV infection caused increases in systemic biomarkers of inflammation such as tumor necrosis factor as well as pro-atherogenic changes in serum lipids (decreases in serum total serum cholesterol and HDL, and increases in serum triglycerides and LDL) (5–8)*.The severity of these changes appeared to be associated with the extent and duration of plasma HIV viremia. A report from the Multicenter AIDS Cohort Study (MACS) profiled longitudinal changes in serum lipids in a group of male HIV seroconverters compared to HIV seronegative controls. (9)* In this report, HIV infection was associated with reductions in total cholesterol, HDL and LDL but the subsequent introduction of HAART resulted in increases in total cholesterol and HDL (but not LDL) to levels that, after adjustment for age, were similar to pre HIV-infection levels for these men. These findings raised the question of whether the lipid changes observed changes observed in association with HAART use (and presumably HIV suppression) may have represented a “return to health” in lipid levels with resumption of a more normal age-related trajectory in serum lipids.

Data was emergent from the general population testifying to associations between systemic inflammation and increased risk for CVD (10–12) in which the roles of C-reactive protein (CRP) and IL-6 were particularly prominent. Another report from the MACS (13) described positive associations between plasma CRP levels and the risk for HIV disease progression among HIV-infected men. Though it was clear that HIV plasma viremia was a major determinant of levels of systemic inflammation, independent associations between CD4 cell counts (both in terms of lower nadir CD4 and absolute CD4 counts) and CVD events, were apparent in a few HIV infected patient cohorts (14, 15). In these cohorts the extent to which CD4 depletion was for the most part a marker for more prolonged HIV viremia. which in turn itself comprised a significant CVD risk, is unclear. While specific pathophysiologic mechanisms by which the immune system influences risk for CVD among HIV-infected persons remain unclear, we do know that CD4 T-lymphocytes exist in vascular atheromatous lesions. As such, these lesions produce inflammation-inducing cytokines that in turn promote further acceleration of atherosclerotic process (16). Data from other groups

have documented decreases in vascular distensibility associated with untreated HIV infection, including increases in aortic stiffness (17) and impairments of arterial flow-mediated dilation (FMD).

Data from the SMART, a study of approximately 6000 asymptomatic HIV infected persons with CD4 counts >350 cells who were randomized either to interrupt or to remain on ARV(18), provided dramatic evidence that overall mortality and CVD events in particular, were higher among ARV-treated versus untreated persons (19)*. Furthermore, this study demonstrated positive correlation between risks for death or CVD events with systemic levels of pro-inflammatory cytokines and endovascular thrombotic risk (20). These findings were clinically corroborative of earlier work that described cytokine dysregulation and pro-coagulation effects associated with HIV infection, HIV's interaction with vascular endothelium, and the role of inflammation in AIDS vasculopathy (21–25). Findings demonstrating that HAART use resulted in reductions in markers of endothelial and coagulation activation (26) and improvements in vascular endothelial functioning (27)* supported the notion that CVD pathophysiology among HIV-infected persons is related to hypercoagulability and alterations in endovascular reactivity and that these changes are at least partially reversible with viral suppression.

A report from the large observational FRAM cohort cross-sectionally evaluated pre-clinical atherosclerosis by measuring carotid intima media thickness (cIMT) using ultrasound (US) among nearly 5500 HIV uninfected persons and compared these findings to those seen in over 400 HIV-infected persons (28). After adjusting for demographics and CVD risk factors, HIV infection was significantly associated with greater amounts of atherosclerosis than HIV uninfected controls. In multivariable analysis of factors associated with greater cIMT thickness HIV infection comprised an independent risk for atherosclerosis that was similar in magnitude to traditional CVD risk factors such as smoking and advancing age (per decade of life). Combined cIMT data from the Womens Interagency HIV Study (WIHS) and the MACS (15) found that the adjusted prevalence ratio for the presence of carotid lesions among HIV-infected women and men with CD4 cell counts <200 compared to HIV-uninfected controls was 2.0 and 1.74, respectively. In the MACS, coronary artery calcium (CAC) measurements (29)* among HIV-infected and uninfected men revealed that CAC prevalence and extent was most strongly associated with advancing age. In this study, although HIV infection and long-term HAART use modestly increased the likelihood for the presence of any CAC, among persons with CAC its extent was lower among HAART users and, after excluding persons taking lipid-lowering therapy, long-term HAART use (≥8 years) was associated with markedly reduced CAC scores.

Antiretroviral therapy, Lipodystrophy and Cardiovascular disease

Early in the HAART era it was recognized that use of specific ARV drugs can be associated with changes in serum lipid profiles in patterns that are known to pose increased risk for the development of CVD. Use of ritonavir alone or in combination with certain other protease inhibitors (PI's, as a pharmaco-enhancer) such as indinavir or lopinavir has been associated with elevations in serum total cholesterol, low-density lipoproteins (LDL) and triglycerides (30). In addition, use of these drugs has been associated with central obesity, prominently including visceral abdominal lipoaccumulation (31), which is itself a known risk for the development of CVD (32)** including myocardial infarctions (MI's)(33) among HIV-infected persons receiving ARV. Likewise, use of some, but not all, of these agents has been linked to increases in insulin resistance (34, 35). Mechanisms by which PI's adversely impact risk for CVD have also been shown to include impairment of endothelial function and the promotion of atherogenic plaque formation (36–38), pathogenic mechanisms that have been ascribed to untreated HIV itself.

Use of thymidine analogue reverse transcriptase inhibitors (tNRTI's), particularly stavudine, has been shown to give rise to increases in serum triglycerides, promote of insulin resistance, and lead to the development of subcutaneous lipoatrophy (which in turn itself has been linked to insulin resistance (39)). Mechanistically, stavudine use-associated abnormalities have been tied to reductions in cellular oxidative metabolism as evidenced by decreases in mitochondrial mass (40). Use of non-nucleoside reverse transcriptase inhibitors (NNRTI), particularly efavirenz, also been demonstrated give rise to pro-atherogenic serumlipid profiles (41).

Analyses of data from multiple observational cohorts have sought to identify relationships between ARV use and clinical CVD events such as MI's. While reports from a few HIV-infected cohorts have not indicated an association between specific ARV agent use and CVD risk or even an excess risk of CVD associated with HIV infection overall (42) multiple reports from diverse longitudinally studied patient group indicate links between PI use in general or specific PI drug use and increased risk for MI (43–49). Among the specific PI's which have been identified as associated with increases in risk for MI are ritonavir, indinavir, and the fixed dose combination of lopinavor/ritonavir.

Use of the NRTI abacavir was shown in the very large observational multicohort D:A:D study to comprise an independent risk for the development of MI's among HIV infected persons with pre-existing risks for CVD as evidenced by moderate to high Framingham equation-derived MI risk scores (48, 50*, 51*). Subsequent analysis of data from the SMART study corroborated these findings (52). Analyses of long term clinical outcomes from other observational cohorts have variably confirmed or failed to support associations between abacavir use and MI occurrence (53–56). A very recent report describing a meta analysis undertaken by the U.S. FDA to evaluate clinical outcomes using combined data from 26 prospective interventional HIV treatment studies failed to reveal an association between abacavir use and the occurrence of MI (57).

Considerable investigative effort has been exerted to evaluate possible pathophysiologic mechanisms by which abacavir use could impact MI risk. While findings from the SMART suggested that abacavir use was associated with increases in systemic inflammation, longitudinal biomarker data from other cohorts, including the MACS (58) and participants in the HEAT study (59) demonstrated HAART-associated declines in systemic pro-inflammatory cytokines with no differences seen between abacavir and non-abacavir recipients. In the SCOPE cohort, abacavir use was associated with reduced endothelial function among patients receiving ARV who were virally suppressed (60). In this report, after adjustment for age, gender, traditional CVD risk factors, CD4 cell counts and baseline brachial artery diameter, current abacavir use was independently associated with lower brachial artery flow-mediated dilation (FMD). At least one report (61) has demonstrated increases in platelet activation induced by effects of the abacavir metabolite carbovir triphosphate.

Non-HIV-specific CVD risk factors known to be operative in CVD risk for the general population clearly remain important among ARV-treated HIV-infected persons. These include ethnicity, age, and chronic comorbidities such as hypertension, diabetes mellitus, tobacco use, and chronic hepatitis C virus infection. In ARV-treated HIV-infected persons, as in HIV-uninfected persons, metabolic diseases like diabetes mellitus increase in prevalence with age and are more common in ethnic minorities than whites (40, 62). Likewise there appear to be age-related increased incidences of lipid abnormalities associated with ARV use (30, 49, 63, 64). The presence of pro-atherogenic hyperlipidemia has been demonstrated to be a significant independent predictor of MI occurrence in the D:A:D study (65). In this report 580 MI's occurred among over 30,000 HIV-infected

persons. Using time-updated serum triglyceride (TG) levels, doubling of serum TG level was associated with an 11% increased risk for MI in analytic models adjusted for other CVD risks,.

Conclusion

In an era during which the beneficial effects of potent combination ARV therapy have markedly extended survival among treated persons with HIV infection, effectively transforming HIV into a chronic manageable condition, cardiovascular disease has emerged as an important non-infectious chronic co-morbidity and cause of mortality for these patients. While the extent to which actual cardiovascular events occur more frequently or at an earlier age among HIV infected persons compared to otherwise similar HIV-uninfected persons is not yet entirely clear, treatable CVD risks known to be important in the general population, such as smoking, hyperlipidemia, and insulin resistance, appear to be more prevalent in this group. Furthermore, chronic HIV infection itself results in conditions that are known to adversely impact atherogenesis risk; these include increased systemic inflammation, hypercoagulation, and decreased vascular reactivity. These effects are direct consequences of both chronic viremia and of persistent immune activation, with existing data suggesting that duration of viremia and extent of immune depletion/activation are important determinants themselves of CVD risk

Though some the combination antiretroviral drug therapies used to treat HIV infection can increase the risk for co-morbidities known to enhance vascular atherogenesis and overall CVD risk, such as hyperlipidemia and insulin resistance, the net effect of ARV use upon CVD risk is a salutary one, largely (but not necessarily completely) mitigating the adverse effects of HIV upon vascular health and CVD risk by making possible profound and durable suppression of HIV replication. This is likely to be even more the case with currently used ARV drugs that are more potent, less toxic, and appear to have less adverse impact upon traditional CVD risks.

It is also clear that chronic treatable co-morbidities known to adversely impact CVD risk in the general population also do so among HIV infected persons, even after accounting for HIV-specific factors. While “hard” clinical CVD outcome data among HIV-infected populations is emerging, this knowledge implies that interventions known to reduce CVD in the general population, including lipid-lowering therapy, glycemic control, smoking cessation, and weight reduction, are likely to exert similar beneficial risk-reducing effects among HIV-infected persons.

Thus far, it is unclear whether the risks for CVD commence at earlier ages for HIV-infected persons than HIV-uninfected persons; hence, whether CVD screening and preventive measures are warranted at earlier ages for persons with HIV infection is yet to be determined. It is clear, however, that timely intervention with HAART and routine CVD screening and prevention measures should be part of routine care for all HIV-infected persons.

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Key Points

1. During the HAART era HIV, CVD has emerged as an important cause of morbidity among HIV-infected persons.
2. Untreated HIV infection can increase CVD risk in several ways. These include: a) increases in systemic inflammation; b) increases in systemic hypercoagulability; c) decreases in vascular reactivity. These effects are at least partially reversible with successful ARV treatment.
3. While the use of specific ARV drugs can adversely impact CVD risk, the long-term benefits of chronic HIV suppression and immune reconstitution achievable with HAART far outweigh any adverse adverse CVD impact.
4. Treatable CVD risks such as smoking, hyperlipidemia, and insulin resistance, remain important predictors of CVD among HIV-infected persons. Hence, standard CVD screening and risk-reducing interventions should be routinely undertaken for HIV-infected persons.