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Cardiovascular Disease and HIV Infection

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Abstract

The emergence of chronic disease complications in controlled HIV disease has changed the landscape of HIV clinical care. HIV infection confers an increased cardiovascular disease risk which is thought to be due to a complex interplay of mechanistic factors. While traditional cardiovascular risk factors likely play a role, recent evidence suggests that HIV-associated inflammation and immune activation are important mediators of cardiovascular risk. It is unclear whether established preventative interventions for the general population are applicable to HIV-infected patients, and the need to translate mechanistic knowledge into HIV-specific clinical interventions represents an important priority. Developing strategies to prevent cardiovascular disease in HIV-infected individuals calls for a multidisciplinary approach and represents an opportunity to exert a major public health impact in an at-risk population.

Introduction

As the HIV epidemic has evolved over time, the focus of clinical care has shifted in a way that seldom occurs for a specific disease. In the early stages of the epidemic, opportunistic infections and illnesses related to an immunocompromised state dominated, and a comprehensive body of research and clinical practice developed around these complications. HIV patients on suppressive antiretroviral therapy in the current treatment era confront a new set of complications. These chronic, non-infectious diseases – including cardiovascular disease (CVD) – merit management strategies which differ significantly from those for infectious complications. Moreover, optimal management of cardiovascular disease and other non-infectious complications for an HIV-infected patient may differ from that for an individual without HIV infection. The shifting focus of care for stably treated HIV-infected patients calls for new research into the epidemiology, pathophysiology, prevention, and treatment of chronic disease complications, and the translation of such research into guideline and policy development.

Our knowledge of the increased risk of cardiovascular disease in HIV infection has moved at a rapid pace in recent years, with extensive research on epidemiology and rapidly increasing understanding of mechanism. Considerably less is known about clinical management of CVD for HIV populations. Guidelines developed for the general population may not translate into optimal management in the setting of HIV. The critical next step in the field of HIV and cardiovascular disease will be to translate our understanding of epidemiology and mechanism to the development of HIV-specific clinical management strategies. This review will summarize the state of the field by 1) highlighting recent data on epidemiologic trends in HIV and CVD, focusing on expanded CVD outcomes and specific HIV patient subgroups; 2) describing recent insights into the pathophysiology and

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mechanism of HIV-related CVD, including the increasing emphasis on inflammation and immune dysfunction; and 3) discussing the implications of our current knowledge for cardiovascular disease prediction, prevention, and risk factor management for HIV-infected patients.

HIV-associated cardiovascular disease: Advances in epidemiology

HIV-infected patients confront an increased risk of cardiovascular disease. Multiple observational cohort studies[1–6] have demonstrated elevated rates of acute myocardial infarction (AMI) or coronary heart disease (CHD) in HIV-infected versus control patients, with an approximate 1.5 to 2-fold increased relative risk. Recent data have reinforced these findings. In a study of more than 27,000 HIV-infected predominantly male patients from the Veterans Aging Cohort Study Virtual Cohort, rates of adjudicated AMI were higher for HIV-infected patients in every age group compared to matched control patients.[7] In multivariate modeling controlling for potentially confounding sociodemographic and cardiovascular covariates, the hazard ratio for AMI associated with HIV status was 1.48, and a significant association between HIV and AMI persisted in an analysis restricted to virologically suppressed patients.[7] A recent meta-analysis that estimated the relative risk of cardiovascular disease among HIV-infected patients found HIV infection to confer a 61% increased risk of cardiovascular disease endpoints.[8] Moreover, when limited to HIV-infected patients on antiretroviral therapy (ART), the relative risk of CVD remained increased 2-fold compared to HIV-uninfected and 1.5-fold compared to treatment-naïve HIV-infected patients. Inadequate HIV-uninfected control groups in the original studies, unmeasured confounding, and competing risks represent limitations of this analysis.[9] Importantly, both the recent VA study and the meta-analysis found that cardiovascular risk persists even in patients on suppressive antiretroviral therapy, suggesting that CVD is likely to significantly impact the long-term health of this group.

Angiographic presentation, management, and outcomes following an acute cardiovascular event may differ for HIV-infected patients. Several studies have documented clinical and angiographic differences in acute coronary syndrome (ACS) presentation based on HIV status, including higher rates of restenosis,[10] fewer complex lesions,[11] and more frequent presentation with ST-elevation MI versus non-ST-elevation MI or unstable angina[12] in HIV-infected patients versus controls. Studies have differed regarding extent of vessel involvement, with HIV patients having higher rates of single-vessel disease in one study[10] but similar rates of multivessel disease in another.[11] Cardiovascular intervention and procedures have also been shown to differ by HIV status, with lower rates of thrombolysis and anticoagulation, left cardiac catheterization, and coronary artery bypass graft surgery among HIV-infected patients.[13] Finally, HIV infection appears to impact mortality and cardiovascular outcomes following ACS, with one study showing higher in-hospital mortality following AMI in adjusted analyses[13] and another showing similar in-hospital and 1-year mortality but more subsequent hospitalizations for heart failure among HIV-infected patients.[14] A recent meta-analysis of 11 studies of HIV-infected patients with ACS found higher-than-anticipated rates of in-hospital cardiovascular mortality (8%) and recurrent AMI (9%), although control groups were unavailable for comparison.[15]

Although most recent investigation has focused on ischemic heart disease, the effect of HIV on broader cardiovascular outcomes is being increasingly delineated. While early reports of cardiovascular disease in HIV groups focused on cardiomyopathy and cardiovascular manifestations of infections – notably TB pericarditis – patients treated for HIV disease today confront an array of complications spanning the vasculature. HIV-infected patients have been shown to have an increased risk of stroke and cerebrovascular endpoints in comparison to control cohorts,[16, 17] and an increasing number of U.S. stroke

hospitalizations were found to be in the setting of HIV disease between 1997 and 2006.[18] Recently, a study of HIV-infected patients at San Francisco clinic demonstrated a 4.5-fold increase in rates of sudden cardiac death in the HIV group compared to the expected city-wide rate.[19] Whether this is related to ischemic CVD versus predisposition to arrhythmias remains unclear. Additional data support a role for HIV in conferring risk for peripheral arterial disease[20] and congestive heart failure,[21] and for more advanced HIV disease to increase risk of incident atrial fibrillation.[22]

Cardiovascular risk may vary within HIV-infected subgroups based on demographic or clinical factors. In several analyses, HIV-infected women appear to be at disproportionately increased CVD risk, with approximately double the relative risk for AMI in HIV-infected women versus men.[4, 6] While absolute CVD rates remain lower for women, HIV infection appears to increase this baseline risk more for women than for men. Although the mechanisms explaining this striking difference have yet to be clearly delineated, differing levels of immune activation by gender at a constant HIV RNA is one potential explanation for the disproportionate impact of HIV on the development of CVD among women.[23]

Co-infections might further modulate CVD risk in HIV disease by altering the degree or nature of the HIV immune response. Hepatitis C virus (HCV) co-infection has been demonstrated to increase risk of CVD beyond the risk conferred by HIV alone in several studies of CVD outcomes[24, 25] yet a study of AMI rates comparing HCV/HIV co-infected to HIV mono-infected patients did not find a significant difference between the two groups.[26] Several studies focusing on measures of subclinical atherosclerosis have implicated CMV as playing a role in disease progression,[27, 28] and a recent study demonstrated HSV-2 seropositivity to be associated with a four-fold increased risk of coronary atherosclerosis as measured by coronary artery calcium (CAC).[29] Additional clinical factors which have been recently shown to confer CVD risk among HIV-infected patients include impaired renal function,[30] vitamin D deficiency,[31] and low serum albumin.[32]

HIV-related immunologic and virologic parameters and disease characteristics have also been demonstrated to predict CVD risk in this population, with associations between 1) low recent CD4 cell count and CVD outcome events in three studies[7, 33, 34]; 2) low nadir CD4 cell count and AMI events[35]; 3) nadir CD4 cell count less than 350 and impaired endothelial function as measured by flow-mediated dilation (FMD) [36]; 4) low CD4 cell count and non-calcified coronary artery plaque[37]; 5) poorer immunologic recovery after ART initiation and increased cardiovascular event rates[38]; and 6) CD4 decline on ART and increased cardiovascular event rates.[39] Increased or detectable HIV RNA has been shown to be significantly associated with several CVD-related endpoints, including AMI,[7, 35] CVD,[40, 41] stroke[17] and non-AIDS event rates.[42] These data suggest that untreated HIV disease or more advanced disease at treatment initiation increases cardiovascular risk, reinforcing the hypothesized role of inflammation and immune activation in mediating risk and further supporting earlier antiretroviral treatment initiation.

Pathophysiology: A shift in understanding

Expanding knowledge regarding the mechanism of HIV-related CVD has fueled a shift in understanding, with many earlier investigations focusing on the role of traditional CVD risk factors and antiretroviral medications, and more recent inquiry directed towards understanding the roles of immune activation and association inflammation. The true underlying mechanism is likely to reflect a complex interplay of factors partially explained by established mechanistic pathways of cardiovascular disease and partially explained by novel effects related to immunologic sequelae of HIV infection.

Traditional CVD risk factors, including dyslipidemia, diabetes, smoking and hypertension, have been shown from early in the epidemic to be heightened in HIV groups and have been reviewed previously in detail.[43] Genetic factors have also been explored within HIV-infected patients, in whom an unfavorable genetic risk score based on 23 CHD-associated single-nucleotide polymorphisms (SNPs) conferred a risk similar to that of traditional risk factors.[44] As metabolic abnormalities were observed in association with ART use, investigation turned to possible risk of cardiovascular events related to antiretroviral drugs. Several studies have demonstrated increased CVD risk associated with ART classes[45] or individual medications which are not currently recommended as first-line treatment in the U.S.[46, 47] Newer drugs such as atazanavir do not appear to be implicated in this increased risk,[48] although some newer drugs have yet to be evaluated. While a recent meta-analysis confirmed several of the observed effects from observational studies,[49] other meta-analyses which included data from randomized trials have failed to show associations of individual antiretroviral drugs – abacavir in particular – with AMI.[50, 51]

While plausible that increased CVD risk could be explained by the combined effects of traditional CVD risk factors and cumulative exposure to antiretroviral drugs, the Strategies for Management of Antiretroviral Therapy (SMART) study results prompted a shift in thinking.[52] Although event rates were low, the finding of increased CVD event rates in HIV-infected patients with treatment interruption instigated reconsideration of the balance between toxicity of ART exposure versus that of uncontrolled viremia. These data represent some of the earliest and most robust evidence suggesting a prominent role for the virus and its associated anti-inflammatory effects in mediating CVD risk beyond ART or traditional risk factors.

Recent investigation has consequently focused increasingly on the potential roles of immune activation and inflammation as drivers of cardiovascular disease in HIV, and several recent reviews have been dedicated to understanding this immunopathogenesis.[53–56] Among HIV-infected patients, generalized circulating inflammatory markers have been shown to be associated with ongoing HIV replication,[57] markers of subclinical atherosclerosis,[58] CVD events,[59, 60] and mortality.[61] In a recent analysis of SMART study data, IL-6, hsCRP and D-dimer were shown to be associated with an increased risk of cardiovascular events independent of other CVD risk factors.[62] Studies evaluating predictors of subclinical atherosclerosis as measured by carotid intima-media thickness (cIMT) have differed in terms of the predominant risk factors. While two studies have shown T cell activation to be associated with carotid artery lesions or cIMT,[63, 64] another showed cIMT to be associated with traditional CVD risk factors but not with inflammatory markers or HIV viremia.[65] A recent study moved beyond circulating inflammatory markers and assessed arterial inflammation in the coronary vasculature directly. HIV-infected patients were shown to have significantly increased levels of arterial inflammation as assessed by target-to-background ratio in FDG-PET compared to Framingham Risk Score-matched controls patients, and levels similar to those of non-HIV-infected patients with known atherosclerotic disease.[66] Furthermore, HIV-infected patients have been shown to have higher prevalence of vulnerability features of coronary plaque.[67]

Inflammation is heightened in uncontrolled HIV infection, yet evidence suggests that chronic inflammation persists in treated and virologically suppressed HIV-infected patients and may explain elevated CVD rates despite virologic suppression. Multiple studies indicate that levels of inflammatory markers and indicators of immune activation do not fully normalize in the setting of virologic suppression and immune reconstitution with ART.[68, 69] Moreover, several studies focusing on HIV elite controllers – a group that lacks the potential confounding effects of ART – indicate that this persistent inflammation does in fact confer increased CVD risk. A study comparing HIV elite controllers to seronegative

control patients found increased levels of preclinical atherosclerosis in the elite controllers even after accounting for traditional CVD risk factors.[70] In a recent study utilizing CT angiography, prevalence of atherosclerotic lesions was significantly increased in HIV elite controllers compared with HIV-negative controls.[71]

Most recently, specific pathways of immune activation have been investigated. Monocyte activation has been shown to play a potentially important role in several studies. Notably, a study of activation phenotypes of monocyte subpopulations showed profiles in patients with uncontrolled HIV infection to be similar to those with acute coronary syndrome.[72] Studies linking monocyte activation to CVD outcome measures have largely supported this potential causal pathway. A specific marker of monocyte activation, sCD163, was the only factor significantly associated with vulnerable coronary plaque among HIV-infected patients[67] and was associated with direct arterial inflammation while general inflammatory markers were not.[66] In contrast to these data, a recent study of cIMT found no marker of monocyte activation – including sCD163 and sCD14 – to be associated with the outcome.[64]

Clinical strategies: Moving towards HIV-specific interventions

While our understanding of epidemiology and pathophysiology is accelerating at a rapid pace, data on CVD management tailored to HIV-infected patients are more limited. Recommendations for management of CVD in the setting of HIV are largely reliant on guidelines and data from the general population.[73, 74] Yet dependence on general population guidelines may not be appropriate for this group of patients, whose risk profile for CVD likely differs from that of the general population. Cardiovascular risk prediction specific to HIV disease has been summarized in detail previously.[75] Although standard CVD risk prediction tools have been applied and compared within HIV cohorts, they have not been formally validated for use in this group of patients. The D:A:D group has developed a risk prediction tool for AMI tailored to HIV-infected patients that incorporates specific antiretroviral medications in addition to common CVD risk factors.[76]

Use of cardiovascular interventions proven beneficial for the general population has been shown to vary, and in many cases be lower than expected, for HIV-infected groups. Patients from the HOPS cohort were assessed in terms of physician compliance to published guidelines for the general population.[77] While the majority was treated pharmacologically for elevated LDL (81–87%), this was not the case for other parameters (2–11% treated for low HDL, 56–91% for hypertriglyceridemia, 46–69% for hypertension). Moreover, patients in higher cardiovascular risk group were less likely to meet treatment goals. A second recent study showed overall lipid treatment rate to be lower (LDL appropriately treated in 30% of those at high CVD risk and 50% of those at moderate risk).[78] Studies of aspirin use have found HIV-infected patients to be prescribed the drug at significantly lower rates than expected.[79, 80] Only about half of HIV-infected patients are treated for diabetes[78] or hypertension.[77, 78] Whether these data reflect suboptimal awareness of CVD preventative measures or the lack of interventions specific for HIV-infected patients is unclear, but recommendations are to treat CVD risk factors at least as aggressively in HIV-infected patients as in the general population.

Smoking is a well-established and intervenable risk factor for cardiovascular disease, with consistently documented heightened rates among HIV-infected patients. In a striking recent study, HIV-infected patients who smoked lost more life years to smoking than to HIV.[81] Within HIV populations, smoking has been linked to an increased cardiovascular event risk, with a population attributable risk for CVD of 25%.[82] Smoking cessation has been shown to confer cardiovascular benefit for HIV-infected patients, with a reduction in hazard of CVD event risk with longer time since quitting.[83] In recent years smoking cessation has

increasingly become a recognized priority for HIV-infected patients,[84, 85] and several trials have demonstrated promise in designing smoking cessation interventions tailored to HIV-infected patients. A randomized cell phone smoking cessation intervention for HIV patients was shown to be effective, with more than four times increased 7-day abstinence rates.[86] Recently, a large institution-wide smoking cessation training program was developed for HIV clinicians. Compared with other institutions affiliated with an established HIV cohort, patients at the intervention site were more likely to quit smoking and had fewer relapses.[87] Further data will help to inform providers whether cessation methods for the general population can be transferred to HIV groups.

HMG co-A reductase inhibitors (statins) are likely to benefit the HIV population, in light of their anti-inflammatory properties as well as their lipid-lowering capacity, with appropriate consideration of drug interactions. Indeed, statins have been shown to decrease markers of immune activation among HIV-infected patients not on ART[88] and inflammatory markers in treated HIV-infected patients.[89] Data on the effect of statins on clinical outcomes (apart from lipid-lowering effects) among HIV-infected patients are scarce, and no study has specifically investigated the association of statin use with cardiovascular event rates. All-cause mortality was decreased by 67% with statin use in patients from the Johns Hopkins HIV clinical cohort who achieved virologic suppression after ART initiation.[90] In contrast, a recent study from the Danish nationwide HIV cohort assessed the impact of statin use on all-cause mortality before and after a diagnosis of CVD, CKD, or DM and found a significant association only after the diagnosis of one of the co-morbidities.[91] In a study of a surrogate marker of atherosclerotic disease, treatment with rosuvastatin for 24 months significantly reduced mean cIMT.[92] Ultimately the question of the presence and extent of clinical benefit conferred by statins for HIV populations will best be answered through a clinical trial.

Whether aspirin is effective for all HIV-infected patients or for specific subgroups is an important question that remains as yet unanswered. Aspirin has been shown to be effective in the primary and secondary prevention of AMI in the general population, but no trial has assessed its efficacy for HIV-infected patients. Aspirin's recently demonstrated role in attenuation of platelet activation as well as immune activation in treated HIV disease suggests that it might be an effective preventative measure,[93] yet comparative data on interventions specific to HIV immune dysregulation are lacking. At this time, available guidelines and consensus suggest prescribing aspirin based on the same criteria as those used for the general population.

Novel interventions targeted at inflammation and immune activation are likely to be important components of CVD preventative care among HIV-infected patients, although few have shown clear benefit to date. Hydroxychloroquine failed to reduce T cell activation among HIV-infected patients and unexpectedly resulted in increases in T cell decline and viral replication.[94] Raltegravir intensification, aimed at further reducing viral replication and associated inflammation, did not improve cardiovascular risk as measured by endothelial function,[95] yet the anti-inflammatory agent pentoxyfylline was shown to reduce circulating markers of endothelial activation.[96] Several conventional treatments have been assessed in novel ways. ACE-inhibitor treatment was shown to reduce inflammatory indices in an HIV group.[97] Vitamin D supplementation, shown to be related to CVD outcomes in HIV-infected patients, was assessed in relation to endothelial function and failed to improve FMD.[98] Finally, low-dose methotrexate, which has been shown to improve inflammatory indices and reduce CVD risk among non-HIV-infected patients, is being investigated in a trial of patients without HIV infection but with a history of CVD and persistent inflammation[99] but has not specifically been studied for HIV-infected groups with respect to cardiovascular prevention.

An effective potential intervention to prevent HIV-associated CVD is ART itself. Synthesis of epidemiologic data which shows low CD4 and detectable viral load to predict AMI events and mechanistic data invoking inflammation and immune activation in CVD pathogenesis suggests that treating HIV may prevent cardiovascular disease. While individual antiretroviral agents may pose increased risk, the immunologic benefits conferred by ART appear to outweigh this risk. Based on a mathematical model developed to optimize timing of ART initiation with respect to variables including CVD risk – and assuming that ART doubles CVD risk – immediate ART treatment initiation yielded the greatest life expectancy for young patients.[100] Further insight into this critical question will be added by the Strategic Timing of Antiretroviral Treatment (START) trial, designed to assess the risks and benefits, including the role of non-infectious complications, related to the timing of ART initiation.

Future directions and priorities

Salient gaps exist in our understanding of HIV and cardiovascular disease. While our knowledge has vastly increased compared to a decade ago, critical questions remain unanswered. First, what are the effects of HIV on the heart and vasculature in certain HIV subgroups, including women, children/adolescents and patients in resource-limited settings (RLS)? While summary of data on RLS was beyond the scope of this review, the association of HIV and CVD in this setting remains a research priority, and quantification of specific chronic disease outcome rates will inform clinical care and prevention strategies. Second, what are the long-term consequences of chronic inflammation, and how do these effects interplay with traditional CVD risk factors in the setting of an aging HIV population? Perhaps the relative effects of traditional versus non-traditional risk factors will differ according to age or cumulative viremia/immunosuppression, and interventions will need to be modified accordingly. Third, how does our expanding knowledge on mechanism translate into clinical practice? HIV providers lack evidence-based guidance on how to accurately predict CVD risk and intervene to reduce risk. The development of HIV-specific cardiovascular prevention strategies will vastly improve the care we provide to this at-risk population.

Conclusion

HIV clinical care is undergoing a significant transition, and our understanding of the intersection between HIV and cardiovascular disease suggests that CVD will disproportionately impact this population's long-term well being. In further expanding and enhancing our knowledge, there are a number of overarching challenges: 1) identifying demographic and clinical HIV subgroups at heightened risk; 2) further delineating CVD mechanism, including interplay of traditional risk factors, ART, and effects of chronic inflammation and immune activation; 3) ensuring aggressive modification of traditional CVD risk factors; 4) translating knowledge of the mediators of CVD to clinically relevant HIV-specific interventions; 5) ascertaining the extent to which vast knowledge of CVD in the general population is relevant to HIV; 6) moving these processed forward in a truly multidisciplinary and coordinated approach, with collaboration between the fields of HIV, cardiology, immunology, epidemiology, and metabolism. Responding to these challenges represents a tremendous opportunity to shape the long term trajectory of clinical care and public health interventions for patients with HIV disease.

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