HHS Public Access

Author manuscript

Curr Opin HIV AIDS. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Curr Opin HIV AIDS. 2017 November ; 12(6): 540–547. doi:10.1097/COH.0000000000000410.

Epidemiology of Ischemic Heart Disease in HIV

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Abstract

Purpose of review—The purpose of this review is to summarize and synthesize recent data on the risk of ischemic heart disease (IHD) in HIV-infected individuals.

Recent findings—Recent studies in the field demonstrate an increasing impact of cardiovascular disease (CVD) on morbidity and mortality in HIV relative to AIDS-related diagnoses. Studies continue to support an approximately 1.5 to 2-fold increased risk of IHD conferred by HIV, with specific risk varying by gender and virologic/immunologic status. Risk factors include both traditional CVD risk factors and novel, HIV-specific factors including inflammation and immune activation. Specific antiretroviral therapy (ART) drugs may increase CVD risk, yet the net effect of ART with viral suppression is beneficial with regards to CVD risk. Management of cardiovascular risk and prevention of CVD is complex, because current general population strategies target traditional CVD risk factors only. Extensive investigation is being directed at developing tailored CVD risk prediction algorithms and interventions to reduce CVD risk to HIV.

Summary—Increased IHD risk is a significant clinical and public health challenge in HIV. The development and application of HIV-specific interventions to manage CVD risk factors and reduce CVD risk will improve the long-term health of this aging population.

Keywords

HIV; cardiovascular disease; ischemic heart disease; risk factor; epidemiology

Introduction

HIV infection confers an increased risk of ischemic heart disease (IHD) that impacts the population's long-term health. Mechanistic factors are thought to include both traditional and novel risk factors related to inflammation and immune activation. Multiple studies have investigated the pathophysiology of this association, and recent studies have sought to elucidate the relative roles of traditional and novel risk factors. An extensive literature is

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Conflicts of interest

The remaining author has no conflicts of interest.

emerging regarding optimal management of cardiovascular disease (CVD) risk factors and prevention of IHD in HIV, focusing on both the appropriateness of current interventions for traditional risk factors and the development of new interventions that target novel risk factors specific to HIV. The development and implementation of CVD risk reduction strategies tailored to HIV will be increasingly relevant as this population ages.

The impact of HIV on ischemic heart disease

The widespread use of antiretroviral therapy (ART) has altered the course of HIV disease, increasing life expectancy and transforming HIV to a chronic disease. With the remarkable gains of ART come a new set of clinical challenges: noncommunicable chronic diseases (NCDs), including CVD, occur in HIV-infected individuals at elevated rates and now surpass infections in frequency.[1–11] Both mortality[9] and hospital admissions[3] attributable to CVD are increasing relative to AIDS-associated diagnoses. A recent study found CVD to be one of the most frequent causes of death among HIV-infected individuals surviving more than 10 years after starting ART.[12] The proportionate mortality from CVD has also significantly increased in HIV over time; from 1999 to 2013, overall mortality increased but CVD mortality increased.[13] Yet recent data suggest that absolute rates of myocardial infarction (MI) among HIV-infected individuals are decreasing over time,[14] an advance thought to reflect improvement in recognition and management of CVD risk factors.

Multiple studies over time and across diverse clinical settings demonstrate HIV to confer a 1.5 to 2-fold increased risk of IHD.[15–22] This risk is relatively greater among patients with lower CD4 counts[21, 23, 24] and detectable HIV RNA[21, 25] and among women,[17, 19] due to potential increased indices of immune activation.[26] Recent data continue to support this increased risk. A two-fold increased risk of MI was demonstrated, comparing an HIV cohort to the general population in Italy (standardized incidence ratio [SIR] 2.02).[27] As demonstrated previously and highlighting the unique impact of HIV on CVD risk among women, the relative risk comparing HIV-infected to control individuals was greater among women (SIR 2.91 for women versus 1.89 for men).[27] In a recent study through 2014 comparing incidence rates of type 1 MIs in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) versus Atherosclerosis Risk in Communities (ARIC) cohort, MI incidence rates were significantly higher in the HIV versus comparator control cohort (adjusted incidence rate ratio 1.30).[28] Analyses among HIV-infected individuals showed increased risk of MI with decreasing CD4 count and detectable HIV RNA, when CD4 was excluded.[28] Recent data suggest that the difference in IHD rates between HIV-infected and control groups is converging over time,[29] likely reflecting initiation of ART at higher CD4 cell counts as well as increased awareness of CVD risk among HIV providers.

Recent studies have delineated specific types of MIs and angiographic characteristics among HIV populations. In a large study from the Centers for AIDS Research Network of Integrated Clinical Systems Cohort (CNICS), MI events were divided evenly between type 1 (atherosclerotic plaque instability/rupture) and type 2 (oxygen supply/demand mismatch), with type 2 MIs more common among patients <40 years, with lower CD4 counts, and with lower traditional CVD risk.[30] Earlier data demonstrated HIV-infected individuals with acute

coronary syndromes (ACS) more likely to have single-vessel disease and high restenosis rates.[31] A recent study found HIV-infected individuals presenting with ACS to have a lower overall burden of coronary plaque compared with matched control patients,[32] but another found no difference in rates of severe coronary artery disease in HIV-infected versus matched control patients undergoing coronary angiography.[33]

Risk factors for ischemic heart disease in HIV

Traditional CVD risk factors

Traditional CVD risk factors such as smoking, dyslipidemia, diabetes, and hypertension occur at increased rates in HIV-infected individuals compared with control patients.[34–42] These risk factors will be discussed in separate accompanying review articles. Rates of cocaine use have also been shown to be higher in HIV-infected individuals and may impact ischemic heart disease risk, but cocaine abuse/dependence has not been shown to change the significant association between HIV and MI.[21]

Antiretroviral therapy

Several specific antiretroviral drugs may contribute to excess CVD risk. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) group demonstrated an initial association between cumulative use of protease inhibitors (PIs) and increased MI risk,[43] with subsequent analyses showing indinavir and lopinavir-ritonavir to be associated with increased risk.[44] More recent data have focused on potential cardio-protective effects of the PI atazanavir. One study showed slower carotid intima-media thickness (cIMT) progression with atazanavir- versus non-atazanavir-containing regimens as well as a significant correlation between total bilirubin, which is elevated with atazanavir use and has known antioxidant effects, and reduced cIMT progression.[45] Another study demonstrated atazanavir-based therapy to be associated with lower levels of oxidative stress biomarkers.[46] Results from a systematic review of ten studies found that atazanavir use was associated with improved cIMT and no increased risk of cardiovascular events.[47]

Within the nucleoside reverse transcriptase inhibitors (NRTI) class, recent exposure to abacavir was initially associated with increased MI risk in the D:A:D cohort.[48] Multiple analyses were subsequently conducted to investigate this association and yielded conflicting results.[20, 49–58] Most recently, a study from Kaiser evaluated patients initiating regimens with and without abacavir and found abacavir users to have a more than two-fold increased risk of CVD, after accounting for traditional CVD risk factors including renal dysfunction.[59] Updated data from the D:A:D cohort through early 2013 continued to show a nearly two-fold increased risk of MI with abacavir, with no difference in the relative risk comparing time periods before and after the initial abacavir publication.[60]

Novel CVD risk factors in HIV

Elevated CVD risk in HIV persists after adjusting for traditional CVD risk factors and use of ART drugs, suggesting the presence of unaccounted-for mechanistic factors. Extensive data points to inflammation and immune activation as key factors that further increase CVD risk in HIV. Increased CVD rates have been specifically demonstrated following ART

interruption[61] and in association with decreased CD4 counts,[23, 24, 62, 63] increased HIV RNA,[64, 65] and immune activation.[66] Understanding the role of inflammation and immune activation in conferring CVD risk is critical to guide risk stratification, prevention, and management strategies.

The potential association between HIV-specific inflammation and atherosclerosis was initially demonstrated in the Strategies for Management of Antiretroviral Therapy Study (SMART) study,[61] in which increased CVD event rates were observed in the drug conservation (episodic treatment) compared with the viral suppression (continuous treatment) group (HR=1.57, P=0.05), concomitant with increasing viremia and inflammatory markers interleukin-6 (IL-6) and d-dimer.[61, 67, 68]

Since the SMART study, multiple investigations have linked systemic inflammation and immune activation with CVD surrogate markers and outcomes. Recent data have shown increased mortality with increasing levels of IL-6, soluble CD14 (sCD14), and d-dimer,[69] increased risk of serious non-AIDS conditions or death with increased IL-6 and d-dimer,[70] greater cIMT and higher mortality with higher IL-6,[71] increased risk of non-AIDS events with higher d-dimer,[72] increased microvascular dysfunction with elevated markers of inflammation, coagulation, and T-cell activation,[73] and greater prevalence of severe coronary stenosis and coronary artery calcification score with increased tumor necrosis factor α (TNFα).[74] Inflammation also impacts outcomes following CVD events. In a study of HIV-infected patients undergoing percutaneous coronary intervention (PCI), CD8 T-cell level and persistent C-reactive protein (CRP) elevation at 6-months were significantly associated with angiographic restenosis.[75]

ART with viral suppression consistently decreases inflammation and immune activation, yet they are persistently elevated even in patients who have achieved viral suppression,[76] and this residual inflammation may increase long-term CVD risk and severity.[77, 78] Consistent with these data, a recent study suggested initiation of ART was insufficient to decrease arterial inflammation.[79] A study from the Veterans Aging Cohort Study (VACS) found patients who were either virally suppressed or immune reconstituted (CD4 ≥ 200) to have a persistently elevated MI risk of approximately 40%.[21] Even in the setting of viral suppression, inflammation levels are variable. In a study of virally-suppressed men from the MACS cohort, lower ART adherence (<100%) was associated with higher levels of several inflammatory markers; these findings suggest that targeting residual viremia may impact chronic disease outcomes.[80]

Decreased CD4 counts have been linked to increased CVD risk,[23, 24, 62, 63] supporting the role of immune activation in imparting risk. Recent studies have demonstrated a lower or inverted CD4/CD8 ratio, a surrogate marker of immune senescence, to independently predict increased CVD risk[81] and cIMT progression.[82] Yet results from the Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection (START) study, which evaluated immediate (CD4 cell count >500) versus deferred (CD4 cell count <350) ART initiation, did not show a clear CVD benefit with earlier ART.[83] Immediate ART initiation provided a net benefit with regards to both AIDS-related (72% reduction) and non-AIDS-related (39% reduction) events, yet there was no difference observed between study arms for

CVD events (hazard ratio 0.84, p=0.65 for immediate initiation compared with deferred initiation).[83] While these data may indicate a true lack of effect of immediate ART initiation on CVD outcomes, the finding may also be attributed to the low age of participants or inadequate power due to lower-than-anticipated non-AIDS-related event rates and early termination of the deferred therapy arm.[83] A START substudy that evaluated markers of vascular function also found no difference comparing the immediate versus deferred therapy arms.[84]

Management and prevention of ischemic heart disease in HIV

Predicting and preventing CVD in HIV-infected individuals is challenging because recommended practices do not reflect current pathophysiologic understanding. While both traditional and novel CVD risk factors mediate risk, clinical risk prediction and prevention strategies incorporate only traditional risk factors. It is therefore unclear whether established guidelines to prevent and manage CVD that were developed for the general population are accurate in the setting of HIV. Moreover there is not consistent evidence of compliance with guidelines. Multiple studies have demonstrated underuse of lipid-lowering therapy or statins,[85–88] anti-hypertensives[85, 88] and aspirin[87, 89] in HIV populations. In contrast, a study from the Women's Interagency HIV Study (WIHS) cohort showed HIV-infected women to have better controlled hypertension and diabetes compared with HIV-uninfected women.[90]

Disparities also exist with regards to management and outcomes of MI events. In a study assessing MI management, HIV-infected patients with MI were less likely than controls to receive invasive management or undergo coronary artery bypass grafting (CABG); patients with HIV also had higher in-hospital mortality rates.[91] Disparities by gender were apparent in another study that showed rates of CVD interventions, including Invasive cardiovascular procedures, lipid-lowering drugs, and anti-hypertensives, to be lower in women than in men.[92] In contrast, a study assessing patients undergoing coronary angiography found HIV-infected patients to be more likely to receive PCI compared with matched controls.[33]

CVD risk prediction

The Framingham Risk Score (FRS) and the 2013 American College of Cardiology/American Heart Association (ACC/AHA) risk score are used to risk stratify individuals and guide prevention strategies, yet these algorithms developed for the general population may not be accurate in patients with HIV because they do not include novel risk factors specific to HIV. The FRS has been shown to underestimate risk of AMI[93] and stroke.[94] More recently, the FRS was shown to have moderate discrimination (ability to distinguish patients with and without outcome) and good calibration (agreement between observed and predicted risk) and the ACC/AHA to have good discrimination but poor calibration in HIV.[95] A recent large study from CNICS found that the ACC/AHA risk score underestimated risk and had reasonable discrimination but moderate calibration,[96] and that the incorporation of HIV-specific variables did not improve its performance.[96]

The D:A:D group has generated a CVD risk prediction tool incorporating HIV-specific variables[97] and recently updated the model to include both traditional CVD risk factors, CD4 count, cumulative PI and NRTI exposure, and abacavir use.[98] Together, these studies

suggest that CVD risk prediction models developed for the general population may fail to accurately identify high-risk patients for the consideration of CVD reduction strategies.

CVD prevention

Statins have been shown to have a number of beneficial effects in HIV and are considered to be a promising intervention for this population due to their lipid-lowering and anti-inflammatory properties. Statins have been shown to effectively reduce LDL in HIV, with specific effects shown for rosuvastatin[99] and pitavastatin, which was superior to pravastatin in the HIV-infected Patients and Treatment with Pitavastatin vs Pravastatin for Dyslipidemia (INTREPID) study.[100] In this study, pitavastatin also significantly decreased key indices of inflammation and immune activation, sCD14, oxidized LDL (oxLDL), and lipoprotein-associated phospholipase 2 (Lp-PLA2) to a greater extent that pravastatin.[101] In a multisite, randomized trial of lipid reduction strategies, rosuvastatin more effectively reduced total and LDL cholesterol when compared with switching off a PI.[102] Statins have also been demonstrated to decrease oxLDL levels in HIV.[103, 104]

The immunomodulatory properties of statins have been consistently demonstrated in a number of recent studies in HIV which have shown significant reductions in markers of inflammation and immune activation (including monocyte activation).[101, 104–106] In contrast, rosuvastatin did not influence immune activation markers but did increase the CD4/CD8 ratio in another study.[107] With regards to outcomes in HIV populations, statins appear to slow progression of cIMT and reduce non-calcified coronary plaque in treated patients[99, 108] and have been associated with reductions in mortality in virally suppressed patients.[109]

Despite our vastly expanding knowledge of statins in HIV, no study has answered the question of whether statins effectively reduce cardiovascular events in this population. Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE)[110] will answer this question. As the first large-scale randomized clinical trial of CVD prevention in HIV, REPRIEVE will address the hypothesis that statins prevent CVD in HIV-infected individuals, particularly those who do not meet current guidelines for statin use based on traditional risk factor profile.

There are less data on the optimal use of aspirin in HIV populations. A pilot study showed that one week of aspirin decreased markers of T-cell activation and monocyte activation in treated HIV-infected individuals,[111] yet a follow-up study of aspirin treatment for 12 weeks failed to show an impact on markers of inflammation or monocyte activation, or on endothelial function.[112] As in the general population, in which indications for aspirin use for primary prevention continue to evolve, particularly for women, decisions regarding aspirin use in HIV should be guided by established guidelines with individualized discussions of potential risks and benefits.

Studies assessing modification of traditional CVD risk factors in HIV continue to expand and underscore the importance of addressing traditional risk factors while investigation of novel risk reduction modalities is underway. Smoking cessation is a priority in HIV.[113] It may be necessary to tailor current approaches to HIV-infected populations who have been shown to have unique barriers to contemplating cessation or quitting smoking, including

alcohol use,[114] having a detectable HIV RNA,[115] lower nicotine dependency level,[116] and older age.[116] In a randomized study of 12 weeks of varenicline alone versus in combination with text messaging and a cell phone-delivered adherence intervention, smoking abstinence was higher in the intervention group.[117] A recent randomized pilot trial showed a multidisciplinary lifestyle intervention in HIV-infected individuals with high CVD risk scores to be effective in increasing smoking cessation at 36 months but not in lipid-lowering or prevention of cIMT progression.[118]

Extensive investigation is being directed at developing immunomodulatory approaches to further decrease residual inflammation and immune activation in suppressed HIV disease. Findings from a recent trial of pentoxifylline to reduce endothelial function in patients initiating ART showed that pentoxifylline failed to improve endothelial dysfunction and attenuated decreases in inflammatory markers following ART initiation.[119] Additionally, low-dose methotrexate is currently being investigated for its effect in inflammatory markers and endothelial dysfunction.[120]

Conclusion

Our understanding of the epidemiology of ischemic heart disease in HIV has advanced considerably in recent years, with enhanced recognition of the increased CVD risk conferred by HIV and of specific mediators of risk and at-risk sub-populations, including women and individuals with detectable viremia. In parallel with these advances in epidemiology has been a progressive delineation of mechanistic factors driving CVD risk in HIV, which will in turn impact the development of targeted risk reduction strategies. Future challenges include translating knowledge of pathophysiology into feasible, evidence-based clinical interventions to accurately estimate CVD risk and prevent CVD and to incorporate this guidance into existing HIV care frameworks.

Acknowledgments

Financial support and sponsorship

This work was supported by NIH 1U01HL123336 to SKG and R01HL132786 to VAT.

Dr. Grinspoon has received grants from KOWA Pharmaceutical and Navidea and has consulted for Theratechnologies and Navidea.

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Key points

- The risk of cardiovascular disease is increased in HIV approximately 1.5 to 2-fold above baseline risk.
- This increased risk persists, although is attenuated, in patients who are virally suppressed on antiretroviral therapy.
- Novel, HIV-related risk factors contribute to increased cardiovascular risk in HIV in addition to traditional risk factors.
- Current cardiovascular management and prevention approaches do not account for novel risk factors related to HIV.
- There is extensive research underway to identify interventions to target and decrease residual inflammation thought to drive cardiovascular risk in HIV.