Published in final edited form as:

J Nucl Cardiol. 2018 June ; 25(3): 872–883. doi:10.1007/s12350-016-0689-7.

Differences by HIV serostatus in coronary artery disease severity and likelihood of percutaneous coronary intervention following stress testing

Matthew J. Feinstein, MD^{a,b}, Brian Poole, MD^c, Pedro Engel Gonzalez, MD^d, Anna E. Pawlowski, MBA^e, Daniel Schneider, MS^e, Tim S. Provias, MD^f, Frank J. Palella, MD^g, Chad J. Achenbach, MD, MPH^g, and Donald M. Lloyd-Jones, MD, ScM^b

^aDivision of Cardiovascular Diseases, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

^bDepartment of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

^cDepartment of Medicine, Beth Israel Deaconess Medical Center, Boston, MA

^dDepartment of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

^eNorthwestern Medicine Enterprise Data Warehouse, Chicago, IL

^fDivision of Cardiovascular Diseases, Northwestern University Feinberg School of Medicine, Chicago, IL

^gDivision of Infectious Diseases, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

Abstract

Background—HIV-infected persons develop coronary artery disease (CAD) more commonly and earlier than uninfected persons; however, the role of non-invasive testing to stratify CAD risk in HIV is not well defined.

Methods and results—Patients were selected from a single-center electronic cohort of HIV-infected patients and uninfected controls matched 1:2 on age, sex, race, and type of cardiovascular testing performed. Patients with abnormal echocardiographic or nuclear stress testing who subsequently underwent coronary angiography were included. Logistic regressions were used to assess differences by HIV serostatus in two co-primary endpoints: (1) severe CAD (≥70% stenosis of at least one coronary artery) and (2) performance of percutaneous coronary intervention (PCI). HIV-infected patients (N = 189) were significantly more likely to undergo PCI following abnormal stress test when compared with uninfected persons (N = 319) after adjustment for demographics, CAD risk factors, previous coronary intervention, and stress test type (OR 1.85, 95% CI 1.12–3.04,

Reprint requests: Matthew J. Feinstein MD, Division of Cardiovascular Diseases, Department of Medicine, Northwestern University Feinberg School of Medicine, 676 N. St. Clair, Suite 600, Chicago, IL 60611; matthewjfeinstein@northwestern.edu.

Electronic supplementary material: The online version of this article (doi:10.1007/s12350-016-0689-7) contains supplementary material, which is available to authorized users.

Disclosure: The authors have no conflicts of interest to declare.

$P = 0.003$). No associations between HIV serostatus and CAD were statistically significant, although there was a non-significant trend toward greater CAD for HIV-infected patients.

Conclusions—HIV-infected patients with abnormal cardiovascular stress testing who underwent subsequent coronary angiography did not have a significantly greater CAD burden than uninfected controls, but were significantly more likely to receive PCI.

Keywords

HIV; chronic complications of HIV; chronic co-morbid illnesses in HIV infection; non-invasive cardiovascular testing; cardiovascular disease; coronary artery disease

Introduction

The increasing and aging human immunodeficiency virus (HIV)-infected population is at substantially elevated risk for cardiovascular disease (CVD), which includes coronary artery disease (CAD), myocardial infarction (MI), cardiac arrhythmias, and sudden death.^{1–8} Despite this risk, there are no HIV-specific CAD risk stratification schemes in routine clinical use. The degree to which existing risk prediction tools are valid among HIV-infected persons is unclear because the few studies evaluating them in HIV-infected populations have involved relatively few individuals, used inadequate assessment of endpoints, or used relatively homogenous cohorts.^{9–12}

The ability of practitioners to understand CAD and MI risks for their HIV-infected patients is further hampered by a dearth of studies evaluating the yield of clinically indicated non-invasive CAD testing in this patient group. Several studies have demonstrated that HIV-infected persons have greater carotid intima-media thickness (C-IMT) and are more likely to have non-calcified coronary plaque and inflammatory arterial plaque when compared with uninfected controls.^{13–18} Of note, these studies were performed for research purposes and not for clinical indications. Although a potential advantage of this approach is generalizability for CVD screening of asymptomatic patients, these results may not be as applicable to patients undergoing clinically indicated CVD prompted by symptoms or other high-risk features.

Non-invasive functional testing, or cardiovascular stress testing, is commonly used to risk stratify patients with symptoms suggestive of CAD and/or persons at higher CAD risk levels, but has rarely been studied in the setting of HIV. The only report, to our knowledge, that evaluated stress testing in the setting of HIV infection found that stress echocardiography can effectively stratify CAD risk in the setting of HIV infection; this study lacked coronary angiography data and an uninfected control group, the latter of which made comparisons by HIV serostatus impossible.¹⁹ In light of their elevated burdens of inflammatory plaque and myocardial infarction even after adjustment for CVD risk factors, HIV-infected persons may conceivably have a particularly high likelihood of “true positive” stress tests—in other words, abnormal stress tests that reflect actual coronary stenosis/ischemia as confirmed by further testing. In order to evaluate the potential yield of stress testing in the setting of HIV infection, we used a novel electronic health record (EHR)-based cohort to compare CAD burden and need for percutaneous coronary intervention (PCI)

among HIV-infected persons versus matched HIV-uninfected controls who had abnormal stress tests who underwent subsequent coronary angiography. We anticipated that HIV-infected persons referred for stress testing would have greater likelihoods of obstructive CAD necessitating PCI, given the known HIV-associated elevated risks for MI and soft, potentially unstable coronary plaque. Thus, the central hypothesis of this study was that HIV-infected persons with abnormal stress tests would have more CAD on coronary angiography and a greater likelihood of undergoing PCI when compared with uninfected matched controls.

Methods

Study population: HIV electronic comprehensive cohort of complications of CVD

We created an EHR-based cohort of HIV-infected persons and uninfected matched controls who underwent CVD testing in the course of routine clinical care at our institution between 2000 and 2015 using the Northwestern Medicine Enterprise Data Warehouse (NMEDW). The NMEDW serves as the primary vehicle for data integration and transfer for both research and clinical operations at Northwestern Medicine (NM), storing over 80 billion observations on approximately 4.5 million patients. We selected HIV-infected patients for inclusion in our cohort, the HIV Electronic Comprehensive Cohort of Complications of CVD (HIVE-4CVD), if they had undergone cardiac magnetic resonance imaging (cMR), cardiac computed tomography (CT), cardiac catheterization, cardiac stress testing, or echocardiography during the course of routine clinical care at Northwestern Medicine since 2000. In order to optimize power for sub-analyses, we frequency-matched HIV-infected patients with uninfected controls on age, sex, race, and CVD test modality in the ratio of 1:2. We captured relevant clinical covariates and followed patients included in the EHR prospectively for MI, heart failure, stroke, and death.

Study sample

Figure 1 displays the selection process of this study's participants from the HIVE-4CVD cohort. In order to evaluate CAD burden as evident on angiography following abnormal stress testing, we first excluded patients in HIVE-4CVD who did not undergo cardiovascular stress testing and subsequent coronary angiography on the same date or a later date. We then excluded patients who underwent stress testing other than echocardiography or nuclear stress testing because this represented a small (<10%) and heterogeneous portion of the sample with limited clinical applicability. This left 265 HIV-infected patients and 426 uninfected controls who underwent echocardiographic or nuclear perfusion stress testing and subsequent coronary angiography at NM. We then excluded patients who underwent coronary angiography following normal stress tests because normal stress tests should reclassify CAD risk downward and generally not prompt coronary angiography; thus, we were concerned that this group would not be representative of standard clinical care. Finally, we excluded patients with stress test results designated as equivocal, given the potential heterogeneity and subjectivity associated with equivocal stress testing. This left 189 HIV-infected patients and 319 controls with abnormal stress tests who subsequently underwent coronary angiography, representing 79.1% of the 239 HIV-infected patients with abnormal stress tests and 92.2% of the 346 uninfected controls with abnormal stress tests.

Exposure variables

We evaluated the following exposure variables: age, race, sex, cardiovascular risk factors (hypertension, diabetes, total cholesterol, high-density lipoprotein cholesterol (HDL-c), triglycerides, antihypertensive use, and statin use), previous PCI or coronary artery bypass grafting (CABG), and type of stress test performed. We assessed hypertension using international classification of diseases codes (ICD-9-CM 401-405; ICD-10-CM I10-I15) rather than blood pressure readings, given the variability in settings of blood pressure measurement in our cohort, which captures both inpatient and outpatient encounters. Diabetes was determined based on the presence of any of the following: ICD-9-CM codes 249-250, ICD-10-CM codes E08-E11 and E13, any measured hemoglobin A1c >6.4%, or use of any antidiabetic medication. Values for total cholesterol, HDL-c, and triglycerides were based on the earliest measurements taken for each participant prior to undergoing stress testing. We used these lipid measurements although we were unable to differentiate between fasting and non-fasting lipid panels, given the substantial recent evidence suggesting little meaningful difference between fasting and non-fasting lipid panels.²⁰ Of note, we did not have reliable data related to smoking status and pre-test clinical presentation (e.g., acute coronary syndromes, stable angina, or other) for our analyses; thus, these were not included as covariates.

Stress testing

Stress testing included echocardiographic stress imaging (with dobutamine or exercise as the stressor) or nuclear perfusion imaging (with vasodilator or exercise as the stressor). Stress test reports were individually reviewed and designated as normal, abnormal, or equivocal based on standardized, software-generated reporting language used at NM for each stress test modality (Table 1). This categorical approach to determining normality (or lack thereof) of stress tests is widely accepted clinically and has been used commonly in studies evaluating characteristics of cardiovascular stress tests.²¹⁻²³ For patients with multiple stress tests and/or coronary angiograms, we designated the first angiogram with a preceding stress test as the index angiogram and then designated the most recent stress test prior to the index angiogram as the index stress test. We chose the chronologically earliest tests because the purpose of this study was to evaluate stress tests for CAD screening, ideally among persons for whom CAD burden was not yet known at the time of stress testing. Furthermore, this approach minimized angiographic referral bias, which has been shown to negatively affect the test characteristics of stress testing in several studies.^{24,25}

Coronary angiography

For coronary angiography, we obtained finalized reports for each study, which use standardized, software-generated reporting language used at NM. We then reviewed these reports blinded to HIV serostatus in order to determine the maximal percent stenosis of each coronary artery [left main, left anterior descending (LAD), left circumflex (LCx), or right coronary artery (RCA)] and whether or not a percutaneous coronary intervention (PCI, including balloon or stent) was performed.

Statistical analyses

We first compared demographics, cardiovascular risk factors (hypertension, diabetes, total cholesterol, high-density lipoprotein cholesterol (HDL-c), triglycerides, and statin use), previous PCI or coronary artery bypass grafting (CABG), and type of stress test performed for HIV-infected patients and uninfected controls using t tests for continuous variables (or the non-parametric equivalent where appropriate) and Chi square tests for categorical variables. We then used non-conditional logistic regression to determine odds ratios for each of our two co-primary endpoints for HIV-infected versus uninfected persons:¹ 70% stenosis of at least one coronary artery on angiography, and² whether PCI was performed. We also evaluated secondary endpoints (50% stenosis of at least one coronary artery on angiography; 50% stenosis of the left main artery or of 3 arteries) in a similar fashion. Three models were used for logistic regression analyses evaluating associations between HIV serostatus and these endpoints using the following models: an initial unadjusted model; a second model adjusted for age, sex, and race; and a third model adjusted for age, sex, race, hypertension, diabetes, total cholesterol, HDL cholesterol, statin use, previous PCI or coronary artery bypass grafting, and stress modality (echocardiography or nuclear perfusion).

For exploratory analyses, we then repeated analyses of the two co-primary endpoints (70% stenosis of at least one coronary artery on angiography and whether PCI was performed) and one secondary endpoint (50% stenosis of at least one coronary artery on angiography) separately for patients who underwent stress echocardiography and those who underwent nuclear perfusion stress tests. Specific to the HIV-infected cohort, we also performed multivariable logistic regressions to determine associations of HIV-specific covariates [nadir CD4+ T lymphocyte cell count/mm³ (CD4 count) and log of peak HIV RNA] and lipid parameters [peak total cholesterol, peak triglycerides, and nadir high-density lipoprotein (HDL) cholesterol] with the primary and secondary endpoints; patients with missing covariates were excluded from these analyses, as were uninfected controls. A $P < 0.05$ was considered statistically significant. All analyses were performed using STATA statistical software version 14 (StataCorp, 2015: College Station, TX). For primary and secondary analyses, our sample size of 508 provided a power of 0.92 to detect an odds ratio of 1.5 at an alpha of 0.05, assuming at least 100 persons with the outcome of interest.

Results

Demographics and test characteristics

HIV-infected patients (N = 189, median time between stress test and angiography = 9 days) who underwent stress testing and subsequent coronary angiography had similar overall demographics as uninfected controls (N = 319, median time between stress test and angiography = 10 days) (Table 2). HIV-infected patients in our cohort had lower HDL-c and higher triglycerides, which was unsurprising given the well-described lipid abnormalities (particularly low HDL-c and high triglycerides) among HIV-infected persons on ART (Table 2).²⁶ There were no significant differences between HIV-infected and uninfected persons in prevalence of hypertension, diabetes, statin use, antihypertensive use, stress test modality performed, or history of PCI or CABG (Table 2).

Likelihood of coronary artery disease and percutaneous coronary intervention following abnormal stress testing: HIV+ versus uninfected patients

There was a non-significant trend toward higher frequency of moderate or severe CAD (50% or 70% stenosis, respectively, of at least one coronary artery on angiography) and triple vessel or left main coronary artery disease (50% stenosis of the left main artery or of 3 coronary arteries) for HIV-infected patients when compared with uninfected controls (Table 3). HIV-infected patients were significantly more likely than uninfected controls to undergo PCI following abnormal stress tests in unadjusted models (OR 1.75, 95% CI 1.12-2.72, $P=0.01$), age/sex/race-adjusted models (OR 1.86, 95% CI 1.19-2.93, $P=0.007$), and models adjusted for age, sex, race, hypertension, diabetes, total cholesterol, HDL cholesterol, antihypertensive use, statin use, previous PCI or CABG, and stress test modality (OR 1.85, 95% CI 1.12-3.04, $P=0.02$).

Exploratory analyses

When we stratified by stress imaging modality, similar associations persisted, although the statistical significance was attenuated for patients who underwent stress echocardiography (total $N=127$; Table 4). Among persons with abnormal nuclear stress test results (total $N=381$; Table 5), HIV-infected patients were significantly more likely than uninfected controls to undergo PCI in fully adjusted models (OR 1.86, 95% CI 1.03-3.36, $P=0.04$). All associations between HIV serostatus and CAD severity remained statistically nonsignificant.

For exploratory analyses evaluating associations of HIV-specific and lipid parameters with the co-primary endpoints among the HIV-infected cohort, several patterns were apparent (Supplementary Table 1). Lower nadir HDL cholesterol was associated with a significantly greater likelihood of severe CAD ($P=0.01$) and a near significantly greater likelihood of undergoing PCI ($P=0.08$); total cholesterol and triglycerides were not significantly associated with severe CAD or PCI. Regarding HIV-specific parameters, lower nadir CD4 count was associated with a significantly greater likelihood of PCI ($P=0.04$) and a borderline significantly greater likelihood of severe CAD ($P=0.06$). However, peak HIV RNA level (which was log-transformed for analytic purposes) was not associated with a significantly greater likelihood of PCI ($P=0.32$) or CAD ($P=0.46$).

Discussion

In this study, we used a novel EHR-based cohort of HIV-infected persons and uninfected controls who underwent cardiac stress testing and subsequent coronary angiography to evaluate differences in severity of CAD and likelihood of PCI. This is the first study to our knowledge comparing CAD severity and likelihood of PCI following stress testing among HIV-infected persons and matched uninfected persons. An additional strength of the study was our ability to evaluate coronary angiography results for each patient who had an abnormal stress test.

Our primary findings were as follows: (1) while there was a trend toward more CAD in HIV-infected patients, we did not find a statistically significant greater CAD burden in HIV-infected patients than uninfected controls in this study; and (2) despite the lack of apparent

substantial differences by HIV serostatus in CAD following abnormal stress testing, HIV-infected persons were nearly twice as likely as uninfected controls to undergo PCI. The lack of a statistically significant association between HIV serostatus and CAD burden in this study may simply reflect inadequate power, although the weak effect estimates for moderate CAD (OR 1.14, 95% CI 0.73-1.80) and severe CAD (OR 1.02, 95% CI 0.65-1.80) by HIV status were more likely responsible for this lack of a statistically significant association. We had sufficient power to detect a 50% greater (or lesser) likelihood of CAD after abnormal stress testing for HIV-infected versus uninfected persons, but were underpowered to detect <30% between-group differences in the presence of CAD. Taken together, these findings are consistent with prior research showing a greater burden of atherosclerosis and MI among HIV-infected persons.^{4,6,7,13-18} Although none of these previous studies evaluated cardiac stress testing among HIV-infected persons, a logical corollary is that if HIV-infected persons are more likely to have atherosclerosis/CAD than uninfected persons, their pretest probabilities of CAD prior to stress testing would be elevated. As a result, their post-test probabilities of CAD following abnormal stress testing (suggestive of ischemia due to significant CAD) would also be greater.

It is possible that differences between HIV-infected and uninfected persons in CAD burden are minimized in analyses such as this that only include persons who underwent clinically indicated stress testing. A recent analysis of the Multicenter AIDS Cohort Study (MACS) demonstrated significantly greater amounts of subclinical coronary plaque, especially soft plaque, among asymptomatic HIV-infected men compared with a control group of asymptomatic uninfected men.¹⁷ Conversely, our cohort for this study represents a higher-risk group with a relatively high burden of risk factors that underwent relatively advanced screening for CAD; one could reasonably argue that as more of these traditional CAD risk factors accumulate with advancing age, HIV-related contributions to CAD may become relatively less influential on CAD progression. However, recent findings from the Veterans Aging Cohort Study (VACS) that MI risks are greater for HIV-infected persons across CAD risk factor strata counter this theory.⁶

It is interesting and somewhat surprising that while HIV-infected persons did not have evidence of substantially greater CAD burden than uninfected controls after abnormal stress tests, they were nearly twice as likely to undergo PCI. Previous studies evaluating PCI among HIV-infected persons suggest that, while HIV-infected persons with acute coronary syndromes may be somewhat more likely to require PCI,²⁷ PCI is on the whole performed with similar frequency and safety as in the general population.²⁸⁻³⁰ The observational nature of our study precludes us from fully ascertaining reasons for this discrepancy, although several explanations are possible. A central question is whether factors other than diameter of coronary stenosis seen on angiography (e.g., 70% stenosis) that affect decisions to proceed with PCI might systematically differ for HIV-infected persons and uninfected controls. One potential factor is the functional, or flow-limiting, nature of such coronary lesions; while one 70% stenosis may cause ischemia due to impaired pressure and flow distal to the lesion, another 70% stenosis may not cause ischemia. This may be particularly meaningful given the prognostic significance of ischemic burden.³¹ Although we were able to distinguish between abnormal/ischemic and normal/non-ischemic stress tests in this study, we were unable to evaluate the extent of ischemic burden in this analysis. Coronary

collateral and microvascular flow can decrease the likelihood of a given stenosis to cause ischemia by providing supplemental blood and oxygen delivery to the area distal to the stenosis. In theory, if these supplemental sources of perfusion were impaired in the setting of HIV—a plausible explanation in light of known HIV-associated vascular endothelial dysfunction^{16,32,33}—then HIV-infected persons might be more likely to experience ischemia distal to a given stenosis when compared with uninfected persons. If this were the case and HIV-infected persons had greater ischemic burdens than uninfected persons with comparable levels of coronary stenosis, interventional cardiologists might be more likely to perform PCI in the presence of a given diameter of coronary stenosis for HIV-infected persons. No studies to our knowledge have yet examined coronary microvascular function among HIV-infected persons; therefore, this theoretical explanation certainly requires further validation. Future studies using quantitative methods, such as fractional flow reserve or coronary flow reserve, respectively, to evaluate coronary ischemia and microvascular disease in the setting of HIV would be of great interest.

It is also possible that HIV-infected persons were more likely to have other unmeasured factors, such as worse anginal symptoms, that may have influenced decisions to perform PCI; however, a previous study evaluating clinical characteristics of acute coronary syndromes in the setting of HIV found that HIV-infected persons with acute coronary syndromes tend to present with fewer symptoms than uninfected persons.³⁴ An alternative potential explanation relates to selection bias and delayed stress testing. If providers have a higher threshold to order stress tests for HIV-infected patients due to concerns regarding competing co-morbidities and increasing polypharmacy, they may tend to refer patients more likely to truly require PCI. This could, in turn, increase PCI rates for HIV-infected patients relative to uninfected controls.

Interestingly, we found a notable difference in the proportions of HIV-infected and uninfected persons with abnormal stress tests who subsequently underwent coronary angiography (189/239 (79%) versus 319/346 (92%), respectively, $P < 0.01$). This finding may have impacted our results in either direction. On the one hand, this could suggest that providers selectively referred only the highest risk HIV-infected patients for angiography after abnormal stress tests, thus potentially making the pool of HIV-infected patients who actually underwent angiography particularly likely to have true CAD/ischemia. On the other hand, it is possible that providers were less likely to refer HIV-infected patients with abnormal stress tests for angiography due to concerns regarding comorbidities and adverse effects, which could have removed some of the sickest HIV-infected patients from the pool of those with abnormal stress tests who underwent angiography. While the former possibility would likely have biased our findings away from the null, the latter possibility would have likely biased our findings toward the null.

In our exploratory analyses of HIV-specific parameters, we found that lower nadir CD4+ T cell count—but not peak HIV RNA—was associated with a significantly greater likelihood of PCI and a borderline significantly greater likelihood of severe CAD following abnormal stress testing. It is somewhat surprising that only CD4+ T cell count was associated with greater likelihood of PCI and severe CAD in light of large prospective cohort data finding significant independent associations of both CD4+ T cell count and HIV RNA with incident

MI.⁴ Nevertheless, our findings provide further support for the theory that chronic immune dysfunction—as proxy-measured in this study by lower nadir CD4+ T cell count—is a dominant prognostic factor for non-communicable disease (including CVD) morbidity and mortality in the setting of HIV. Over the past decade, data from large cohort studies and randomized trials of ART strategies have clearly demonstrated that HIV-infected persons whose CD4+ T cell counts remain >500 cells/mm³ experience substantially less morbidity and mortality—at levels potentially on par with the general population—than persons with CD4+ T cell counts <500 cells/mm³.^{35,36} Nadir CD4+ T cell count is a useful proxy-indicator of immune dysfunction, as persons with CD4+ T cell counts <200 cells/mm³ are unlikely to fully reconstitute and achieve CD4+ T cell counts >500 cells/mm³.^{37,38} Chronic immune dysfunction and senescence—marked by loss of CD4+ T cells—leads to persistent systemic and vascular inflammation,^{16,32,39,40} which may decrease neovascularization in ischemic myocardial territories and make the myocardium particularly vulnerable to ischemia and infarction in the setting of HIV.^{41–43} Thus, HIV-infected persons with lower v T cell counts may be particularly likely to experience ischemia (and related angina) in the setting of obstructive CAD, which could thus make them particularly likely to undergo clinically indicated, symptom-driven PCI. Further research is needed to better characterize myocardial ischemia and related outcomes across strata of CD4+ T cell counts for HIV-infected persons.

This study should be interpreted in the context of its limitations. This study was retrospective and had a relatively small study population. As with any observational study of retrospectively collected data, selection bias can limit the overall validity of findings. If there were systematic differences in referral patterns for, or physician interpretation of, cardiac stress testing for HIV-infected versus uninfected persons in this cohort, this would potentially affect the yield of the stress tests as well as the likelihood of patients to ultimately undergo PCI. This is certainly possible, although we did not find any striking differences between HIV-infected patients and uninfected controls with regard to demographics, CAD risk factors, or known previous PCI or CABG. Furthermore, we sought to minimize such potential differences and optimize similarities between comparison groups by limiting our analyses exclusively to persons with abnormal stress tests who then underwent coronary angiography.

Another potential limitation was our inability to objectively assess coronary lesions with quantitative coronary angiography (QCA) or fractional flow reserve (FFR); instead, coronary lesion severity was assessed visually by clinicians who were not blinded to HIV serostatus. Since maximum diameter stenosis derives from visual assessment of angiography and the decision for PCI also derives from this visual assessment instead of more thorough assessment of hemodynamic significance of the lesion (for instance, by FFR), it is possible that operators were more likely to consider PCI in HIV-infected patients than non-infected patients. It is also possible that the operators were more likely to overestimate the stenoses in these patients. Therefore, an ideal future analysis would include a blinded QCA of the angiograms.

Our ability to measure relevant covariates was somewhat limited. We did not have information on smoking status and thus were unable to calculate cardiovascular risk scores.

Additionally, we were unable to assess medication adherence, which theoretically may have affected presenting symptoms and decisions for PCI and thus could have affected the results if systematically different between HIV-infected and uninfected patients. Another limitation of this study is its combination of patients who underwent two different stress test modalities (echocardiography and nuclear imaging) into unified groups. This fact might have impacted our findings if, for instance, a far greater proportion of HIV-infected persons referred for stress testing underwent nuclear stress testing rather than echocardiography and if the yield of nuclear stress testing differed dramatically from that of echocardiographic stress testing. However, the proportions of HIV-infected and uninfected persons in this study who underwent each type of stress testing were similar, thus minimizing this concern.

In conclusion, we found that HIV-infected patients with abnormal cardiac stress testing who underwent subsequent coronary angiography were significantly more likely than uninfected controls to receive PCI. Whether this is due to HIV-related factors driving myocardial ischemia or simply reflects differential provider referral patterns for cardiac stress testing by HIV serostatus remains unknown. Interestingly, while there was a trend toward more CAD in HIV-infected patients with abnormal stress tests who underwent coronary angiography, we did not find a statistically significant greater CAD burden in HIV-infected patients than uninfected controls in this study. Future studies should evaluate coronary microvascular function and collateral circulation by HIV serostatus in order to better understand potential mechanisms that could increase the ischemic burden associated with coronary lesions for HIV-infected persons. Furthermore, the role of non-invasive cardiovascular risk stratification for HIV-infected persons requires further study in future well-powered prospective analyses. These analyses should be multicenter in order to account for differential referral biases and should be designed to ascertain differential test characteristics (e.g., sensitivity and specificity) of cardiovascular stress tests by HIV serostatus.

New Knowledge Gained

Following abnormal cardiovascular stress testing, HIV-infected patients may be more likely than to have significant coronary artery disease on angiography and are significantly more likely to undergo percutaneous coronary intervention. This may reflect an elevated burden of “true” ischemia for HIV-infected persons undergoing stress testing when compared with uninfected persons undergoing stress testing who have similar clinical characteristics and CVD risk factors. Further study is needed to confirm these findings, evaluate differences in coronary ischemia on quantitative coronary angiography by HIV serostatus, and refine cardiovascular risk assessment tools for HIV-infected persons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

American Heart Association 16FTF31200010 (PI: Feinstein); National Institutes of Health P30AI117943 [PI: D'Aquila (Center for AIDS Research Pilot Grant); Investigators: Feinstein, Achenbach, Lloyd-Jones].

References

1. Butt AA, Chang CC, Kuller L, Goetz MB, Leaf D, Rimland D, et al. Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease. *Arch Intern Med.* 2011; 171:737–43. [PubMed: 21518940]
2. Chow FC, Regan S, Feske S, Meigs JB, Grinspoon SK, Triant VA. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. *J Acquir Immune Defic Syndr.* 2012; 60:351–8. [PubMed: 22580566]
3. Currier JS, Lundgren JD, Carr A, Klein D, Sabin CA, Sax PE, et al. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. *Circulation.* 2008; 118:e29–35. [PubMed: 18566319]
4. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med.* 2013; 173:614–22. [PubMed: 23459863]
5. Hsue PY, Deeks SG, Hunt PW. Immunologic basis of cardiovascular disease in HIV-infected adults. *J Infect Dis.* 2012; 205:S375–82. [PubMed: 22577211]
6. Paisible AL, Chang CC, So-Armah KA, Butt AA, Leaf DA, Budoff M, et al. HIV infection, cardiovascular disease risk factor profile, and risk for acute myocardial infarction. *J Acquir Immune Defic Syndr.* 2015; 68:209–16. [PubMed: 25588033]
7. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab.* 2007; 92:2506–12. [PubMed: 17456578]
8. Tseng ZH, Secemsky EA, Dowdy D, Vittinghoff E, Moyers B, Wong JK, et al. Sudden cardiac death in patients with human immunodeficiency virus infection. *J Am Coll Cardiol.* 2012; 59:1891–6. [PubMed: 22595409]
9. Aboud M, Elgalib A, Pomeroy L, Panayiotakopoulos G, Skopelitis E, Kulasegaram R, et al. Cardiovascular risk evaluation and antiretroviral therapy effects in an HIV cohort: implications for clinical management: the CREATE 1 study. *Int J Clin Pract.* 2010; 64:1252–9. [PubMed: 20653801]
10. Edwards-Jackson N, Kerr S, Tieu H, Ananworanich J, Hammer S, Ruxrungtham K, et al. Cardiovascular risk assessment in persons with HIV infection in the developing world: comparing three risk equations in a cohort of HIV-infected Thais. *HIV Med.* 2011; 12:510–5. [PubMed: 21375686]
11. Friis-Moller N, Thiebaut R, Reiss P, Weber R, Monforte AD, De Wit S, et al. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. *Eur J Cardiovasc Prev Rehabil.* 2010; 17:491–501. [PubMed: 20543702]
12. Moreira Guimaraes M, Bartolomeu Greco D, Ingles Garces AH, de Oliveira AR Jr, Bastos Foscolo R, de Campos Machado LJ. Coronary heart disease risk assessment in HIV-infected patients: a comparison of Framingham, PROCAM and SCORE risk assessment functions. *Int J Clin Pract.* 2010; 64:739–45. [PubMed: 20518949]
13. Currier JS, Kendall MA, Henry WK, Alston-Smith B, Torriani FJ, Tebas P, et al. Progression of carotid artery intima-media thickening in HIV-infected and uninfected adults. *AIDS.* 2007; 21:1137–45. [PubMed: 17502724]
14. Grunfeld C, Delaney JA, Wanke C, Currier JS, Scherzer R, Biggs ML, et al. Preclinical atherosclerosis due to HIV infection: carotid intima-medial thickness measurements from the FRAM study. *AIDS.* 2009; 23:1841–9. [PubMed: 19455012]
15. Hsue PY, Lo JC, Franklin A, Bolger AF, Martin JN, Deeks SG, et al. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. *Circulation.* 2004; 109:1603–8. [PubMed: 15023877]
16. Burdo TH, Lo J, Abbara S, Wei J, DeLelys ME, Preffer F, et al. Soluble CD163, a novel marker of activated macrophages is elevated and associated with noncalcified coronary plaque in HIV-infected patients. *J Infect Dis.* 2011; 204(8):1227–36. [PubMed: 21917896]
17. Post WS, Budoff M, Kingsley L, Palella FJ Jr, Witt MD, Li X, et al. Associations between HIV infection and subclinical coronary atherosclerosis. *Ann Intern Med.* 2014; 160:458–67. [PubMed: 24687069]

18. Subramanian S, Tawakol A, Burdo TH, Abbata S, Wei J, Vijayakumar J, et al. Arterial inflammation in patients with HIV. *JAMA*. 2012; 308:379–86. [PubMed: 22820791]
19. Wever Pinzon O, Silva Enciso J, Romero J, Makani H, Fefer J, Gandhi V, et al. Risk stratification and prognosis of human immunodeficiency virus-infected patients with known or suspected coronary artery disease referred for stress echocardiography. *Circ Cardiovasc Imaging*. 2011; 4:363–70. [PubMed: 21750273]
20. Mora S. Nonfasting for routine lipid testing: from evidence to action. *JAMA Intern Med*. 2016; 176:1005–6. [PubMed: 27119719]
21. Bangalore S, Gopinath D, Yao SS, Chaudhry FA, et al. Risk stratification using stress echocardiography: incremental prognostic value over historic, clinical, and stress electrocardiographic variables across a wide spectrum of bayesian pretest probabilities for coronary artery disease. *J Am Soc Echocardiogr*. 2007; 20:244–52. [PubMed: 17336749]
22. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE, et al. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. *J Am Coll Cardiol*. 2007; 49:227–37. [PubMed: 17222734]
23. Navare SM, Mather JF, Shaw LJ, Fowler MS, Heller GV, et al. Comparison of risk stratification with pharmacologic and exercise stress myocardial perfusion imaging: a meta-analysis. *J Nucl Cardiol*. 2004; 11:551–61. [PubMed: 15472640]
24. Ladapo JA, Blecker S, Elashoff MR, Federspiel JJ, Vieira DL, Sharma G, et al. Clinical implications of referral bias in the diagnostic performance of exercise testing for coronary artery disease. *J Am Heart Assoc*. 2013; 2:e000505. [PubMed: 24334965]
25. Miller TD, Hodge DO, Christian TF, Milavetz JJ, Bailey KR, Gibbons RJ. Effects of adjustment for referral bias on the sensitivity and specificity of single photon emission computed tomography for the diagnosis of coronary artery disease. *Am J Med*. 2002; 112:290–7. [PubMed: 11893368]
26. Lo J. Dyslipidemia and lipid management in HIV-infected patients. *Curr Opin Endocrinol Diabetes Obes*. 2011; 18:144–7. [PubMed: 21297466]
27. D'Ascenzo F, Cerrato E, Biondi-Zoccai G, Moretti C, Omede P, Sciuto F, et al. Acute coronary syndromes in human immunodeficiency virus patients: a meta-analysis investigating adverse event rates and the role of antiretroviral therapy. *Eur Heart J*. 2012; 33:875–80. [PubMed: 22187508]
28. Boccara F, Mary-Krause M, Teiger E, Lang S, Lim P, Wahbi K, et al. Acute coronary syndrome in human immunodeficiency virus-infected patients: characteristics and 1 year prognosis. *Eur Heart J*. 2011; 32:41–50. [PubMed: 20965887]
29. Boccara F, Teiger E, Cohen A, Ederhy S, Janower S, Odi G, et al. Percutaneous coronary intervention in HIV infected patients: immediate results and long term prognosis. *Heart*. 2006; 92:543–4. [PubMed: 16537777]
30. Ren X, Triletskaya M, Kwan DM, Nguyen K, Shaw RE, Hui PY. Comparison of outcomes using bare metal versus drug-eluting stents in coronary artery disease patients with and without human immunodeficiency virus infection. *Am J Cardiol*. 2009; 104:216–22. [PubMed: 19576350]
31. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003; 107:2900–7. [PubMed: 12771008]
32. Kuller LH, Tracy R, Bellosso W, De Wit S, Drummond F, Lane HC, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med*. 2008; 5:e203. [PubMed: 18942885]
33. Parikh RV, Scherzer R, Grunfeld C, Nitta EM, Leone A, Martin JN, et al. Elevated levels of asymmetric dimethylarginine are associated with lower CD4+ count and higher viral load in HIV-infected individuals. *Atherosclerosis*. 2013; 229:246–52. [PubMed: 23711612]
34. Perello R, Calvo M, Miro O, Castaneda M, Saubi N, Camon S, et al. Clinical presentation of acute coronary syndrome in HIV infected adults: a retrospective analysis of a prospectively collected cohort. *Eur J Intern Med*. 2011; 22:485–8. [PubMed: 21925057]
35. Lewden C, Chene G, Morlat P, Raffi F, Dupon M, Dellamonica P, et al. HIV-infected adults with a CD4 cell count greater than 500 cells/mm³ on long-term combination antiretroviral therapy reach

- same mortality rates as the general population. *J Acquir Immune Defic Syndr*. 2007; 46:72–7. [PubMed: 17621240]
36. Rodger AJ, Lodwick R, Schechter M, Deeks S, Amin J, Gilson R, et al. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. *AIDS*. 2013; 27:973–9. [PubMed: 23698063]
37. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. 2007; 44:441–6. [PubMed: 17205456]
38. Nash D, Katyal M, Brinkhof MW, Keiser O, May M, Hughes R, et al. Long-term immunologic response to antiretroviral therapy in low-income countries: a collaborative analysis of prospective studies. *AIDS*. 2008; 22:2291–302. [PubMed: 18981768]
39. Ho JE, Scherzer R, Hecht FM, Maka K, Selby V, Martin JN, et al. The association of CD4+ T-cell counts and cardiovascular risk in treated HIV disease. *AIDS*. 2012; 26:1115–20. [PubMed: 22382147]
40. Paiardini M, Muller-Trutwin M. HIV-associated chronic immune activation. *Immunol Rev*. 2013; 254:78–101. [PubMed: 23772616]
41. Hofmann U, Frantz S. Role of lymphocytes in myocardial injury, healing, and remodeling after myocardial infarction. *Circ Res*. 2015; 116:354–67. [PubMed: 25593279]
42. Meng X, Yang J, Dong M, Zhang K, Tu E, Gao Q, et al. Regulatory T cells in cardiovascular diseases. *Nat Rev Cardiol*. 2016; 13:167–79. [PubMed: 26525543]
43. Tang TT, Yuan J, Zhu ZF, Zhang WC, Xiao H, Xia N, et al. Regulatory T cells ameliorate cardiac remodeling after myocardial infarction. *Basic Res Cardiol*. 2012; 107:232. [PubMed: 22189560]

Abbreviations

ART	Antiretroviral therapy
CAD	Coronary artery disease
CVD	Cardiovascular disease
HER	Electronic health records
HIV	Human immunodeficiency virus
LAD	Left anterior descending artery
LCx	Left circumflex artery
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
RCA	Right coronary artery

Figure 1.
Cohort creation and matching.

Table 1
Determination of normal stress test by standard reporting language

Stress test type	Normal test result	Equivocal test result	Abnormal test result
Stress echocardiography	"No clinical, echocardiographic, or electrocardiographic evidence of myocardial ischemia at heart rates achieved"	Language describing any portion of the testing as follows:	Language describing any portion of the testing as follows:
		Equivocal	Abnormal
		Possibly abnormal	Consistent with ischemia
		May be abnormal	Concerning for ischemia
Nuclear perfusion stress	"Myocardial perfusion testing is within normal limits"	Same as above	Same as above

Table 2
Study sample: demographics and stress test modalities

	HIV-infected (N = 189)	Uninfected (N = 319)	P value
Mean age at index stress test (years)	52.9	53.5	0.49
Race			0.15
Black, N (%)	91 (48.2%)	135 (42.3%)	
White, N (%)	79 (41.8%)	134 (42.0%)	
Other/declined/unknown, N (%)	19 (10.0%)	50 (15.7%)	
Sex			0.70
Male, N (%)	152 (80.4%)	252 (79.0%)	
Female, N (%)	37 (19.6%)	67 (21.0%)	
Cardiovascular risk factors & medications			
Hypertension, N (%)	171 (90.5%)	280 (87.8%)	0.35
Diabetes, N (%)	73 (38.6%)	122 (38.2%)	0.93
Total cholesterol (mg/dL)	189.5 ± 47.9	180.6 ± 56.1	0.08
HDL cholesterol (mg/dL)	38.4 ± 14.7	41.9 ± 15.2	0.01
Triglycerides (mg/dL)	225.2 ± 227.0	162.7 ± 383.4	0.05
Statin use, N (%)	150 (79.4%)	242 (75.9%)	0.36
Antihypertensive use, N (%)	174 (92.1%)	286 (89.7%)	0.37
Previous PCI or CABG, N (%)	27 (14.2%)	62 (19.3%)	0.14
HIV-related factors			
Nadir CD4 T cell count (cells/mm ³)	324.2 (279.6–368.9)	–	
Peak HIV viral load (copies/mL)	21078 (1729–40426)	–	
Taking antiretroviral therapy, N (%)	138 (73.0%)		
Taking protease inhibitor, N (%)	91 (48.1%)		
Time from stress test to angiogram (days)			0.69
Median (interquartile range)	9 (2–49)	10 (2–39)	
Stress test modality			0.27
Echo	41 (22.1%)	83 (26.0%)	
Nuclear	148 (77.9%)	236 (74.0%)	

P > 0.05 for all comparisons

Table 3
Odds ratios for coronary artery disease and percutaneous coronary intervention following abnormal stress testing (all modalities): HIV-infected vs. uninfected patients

	HIV + (N = 189)	Uninfected (N = 319)	Model 1*			Model 2**			Model 3***		
			Odds ratio (95% CI)	P value		Odds ratio (95% CI)	P value		Odds ratio (95% CI)	P value	
Moderate CAD: 50% stenosis (%)	99 (52.4%)	160 (50.2%)	1.09 (0.76-1.57)	0.63		1.14 (0.78-1.66)	0.49		1.14 (0.73-1.80)	0.56	
Severe CAD: 70% Stenosis	81 (42.9%)	132 (41.4%)	1.06 (0.74-1.53)	0.74		1.09 (0.75-1.59)	0.63		1.02 (0.65-1.61)	0.92	
3 Vessel CAD or L main	35 (18.5%)	52 (16.3%)	1.17 (0.73-1.87)	0.52		1.24 (0.76-2.01)	0.39		1.20 (0.69-2.08)	0.52	
PCI performed	48 (25.4%)	52 (16.3%)	1.75 (1.12-2.72)	0.01		1.86 (1.19-2.93)	<0.001		1.85 (1.12-3.04)	0.02	

* Model 1: Unadjusted

** Model 2: Adjusted for age, sex, race

*** Model 3: Adjusted for age, sex, race, hypertension, diabetes, total cholesterol, HDL cholesterol, antihypertensive use, statin use, stress modality performed, and previous percutaneous coronary intervention or coronary artery bypass grafting

Table 4
Odds ratios for coronary artery disease and percutaneous coronary intervention following abnormal echocardiographic stress testing: HIV-infected vs. uninfected patients

	HIV-infected (N = 42)	Uninfected controls (N = 85)	Model 1: unadjusted		Model 2	
			Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Moderate CAD: 50% stenosis (%)	22 (52.4%)	39 (45.9%)	1.30 (0.62–2.72)	0.49	1.25 (0.51–3.06)	0.63
Severe CAD: 70% stenosis	17 (40.4%)	31 (36.5%)	1.18 (0.56–2.52)	0.66	0.93 (0.38–2.27)	0.88
3 Vessel CAD or L main	5 (11.9%)	10 (11.8%)	1.01 (0.32–3.18)	0.98	1.01 (0.27–3.84)	0.98
PCI performed	12 (28.6%)	13 (15.3%)	2.21 (0.91–5.41)	0.08	2.07 (0.75–5.75)	0.16

* Model 1: Unadjusted

** Model 2: Adjusted for age, sex, race, hypertension, diabetes, total cholesterol, HDL cholesterol, antihypertensive use, statin use, and previous percutaneous coronary intervention or coronary artery bypass grafting

Table 5

Odds ratios for coronary artery disease and percutaneous coronary intervention following abnormal nuclear perfusion stress testing: HIV-infected vs. uninfected patients

	HIV-infected (N = 147)	Uninfected controls (N = 234)	Model 1: unadjusted		Model 2	
			Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Moderate CAD: 50% stenosis (%)	77 (52.4%)	121 (51.7%)	1.03 (0.68–1.55)	0.90	1.07 (0.63–1.83)	0.80
Severe CAD: 70% stenosis	64 (43.5%)	101 (43.1%)	1.02 (0.67–1.54)	0.94	1.02 (0.60–1.73)	0.95
3 Vessel CAD or L main	30 (20.4%)	42 (18.0%)	1.17 (0.70–1.98)	0.55	1.21 (0.65–2.26)	0.54
PCI performed	36 (24.5%)	39 (16.7%)	1.62 (0.97–2.70)	0.06	1.86 (1.03–3.36)	0.04

* Model 1: Unadjusted

** Model 2: Adjusted for age, sex, race, hypertension, diabetes, total cholesterol, HDL cholesterol, antihypertensive use, statin use, and previous percutaneous coronary intervention or coronary artery bypass grafting