Title
HIV infection and cardiovascular disease in women

Journal
Journal of the American Heart Association, 3(5)

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et al.

Publication Date
2014-01-01

Peer reviewed

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Womack, CVD in HIV Infected Women

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Total word count: 4,732

Subject Codes: 8 (Epidemiology), 135 Atherosclerosis Risk Factors

Background: HIV infection is associated with increased risk of cardiovascular disease (CVD) in men. Whether HIV is associated with an increased risk of CVD in women is unclear.

Methods and Results: We analyzed data from the Veterans Aging Cohort Study on 2190 women (32% HIV infected [HIV+]) who were free of CVD at baseline. Participants were followed from their first clinical encounter on/after 04/01/2003 until a CVD event, death, or the last follow-up date (12/31/2009). The primary outcome was CVD [acute myocardial infarction (AMI), ischemic stroke, heart failure]. AMI events were defined using clinical data, ICD-9-CM codes and or death certificate data; ischemic stroke and heart failure were determined using ICD-9-CM codes. We used Cox proportional hazards models to assess the association between HIV and incident CVD, adjusting for age, race/ethnicity, lipids, smoking, blood pressure, diabetes, renal disease, obesity, hepatitis C, and substance use/abuse.

Median follow-up time was 6.0 years. Mean age at baseline of HIV+ and HIV uninfected (HIV-) women was 44.0 vs. 43.2 years, ($p<0.05$). Median time to CVD event was 5.8 vs. 6.1 years ($p<0.001$). There were 86 incident CVD events (53%, HIV+): AMI: 24%; ischemic stroke: 20%; heart failure: 56%. Incident CVD rate/1000 person years was significantly higher among HIV+ (13.5 [95% CI=10.1, 18.1]) than HIV- women (5.3 [95% CI=3.9, 7.2]; $p<0.001$). After adjusting for all covariates, HIV+ women had an increased risk of CVD compared to HIV- (HR=2.8 [95% CI=1.7, 4.6]).

Conclusions: HIV is associated with an increased risk of CVD in women.

Key words: AIDS, CVD risk factors, women

HIV infection has been associated with an increased risk of cardiovascular disease (CVD) in women.[1-3] Whether this association is driven by HIV specific or traditional risk factors remains unclear, as gender-stratified assessments of the associations between risk factors and CVD have not been performed consistently.[1, 3, 4] Where separate analyses were done for men and women, important risk factors for CVD including smoking, hepatitis C status, alcohol and cocaine use, were not included.[2] The inclusion of women diagnosed early in the AIDS epidemic may also confound our ability to understand the impact of earlier analyses on women in the current epidemic as there are significant differences in the timing of ART initiation, the antiretroviral medications available, and the side effects experienced with treatment.[1-3] Finally, a number of the previous analyses have included population comparators who may differ in important ways, such as race and substance use history, from HIV infected women.[1-3, 5] The inclusion of women who are demographically as well as behaviorally similar is of key importance.

We investigated whether HIV and antiretroviral therapy are associated with increased cardiovascular disease events (acute myocardial infarction, ischemic stroke, and heart failure) after adjusting for traditional risk factors and substance use and abuse in a cohort of HIV infected and uninfected women Veterans.

Methods

Sample. The Veterans Aging Cohort Study - Virtual Cohort (VACS-VC) is a prospective, longitudinal observational cohort wherein each HIV infected Veteran is matched on age-, race/ethnicity- and clinical site to two uninfected Veterans.[6] Data for this cohort are extracted from multiple Veterans Health Administration (VHA) sources including the immunology case registry, national patient care database, and the VHA electronic medical record health factor dataset. We confirmed deaths of VACS-VC participants using the VHA vital status file, the social

security administration death master file, the Beneficiary Identification and Records Locator Subsystem, and the VHA Medical Statistical Analysis Systems inpatient datasets. National Death Index data provided cause of death information. This study was approved by the University of Pittsburgh, Yale University, and the VA Connecticut Healthcare System (VACHS) institutional review boards.

For this analysis, we restricted our sample to women. The baseline visit was the first clinical encounter on or after April 1, 2003. All participants were followed from their baseline date to either a CVD event, death, or the last follow-up date as of December 31, 2009.

As reported in an earlier study, data from the VACS-VC were merged with data from Medicare, Medicaid, and the Ischemic Heart Disease-Quality Enhancement Research Initiative.[7] We excluded participants with prevalent cardiovascular disease on the basis of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for acute myocardial infarction (AMI), unstable angina, cardiovascular revascularization, stroke or transient ischemic attack, peripheral vascular disease, or heart failure on or before their baseline date (n=63). After these exclusions, our final sample included 2190 Veterans (32% HIV infected).

Independent variable. We identified HIV infection by the presence of at least two outpatient or one inpatient ICD-9-CM codes for HIV and confirmation in the VHA immunology case registry.[6]

Dependent variables. Our primary outcome was total CVD defined as the presence of acute myocardial infarction, ischemic stroke, or congestive heart failure.[7] All primary outcomes were defined using VHA, Medicare, and death certificate data. For AMI events within the VHA, we used adjudicated outcomes from the VHA External Peer Review Program. To identify AMI events occurring outside the VHA in patients who were not transferred to the VHA, a Medicare 410.xx ICD-9-CM code was used. For heart failure and ischemic stroke, we used one inpatient

and/or two or more outpatient ICD-9-CM codes: heart failure 428.xx, 429.3, 402.01, 402.11, 402.91, 425.xx; stroke (inpatient) 433.x1, 434.x1, 436, and (outpatient) 438.xx. These CVD ICD-9-CM codes were selected based on prior validation work within and outside the VHA health care system.[8, 9]

Covariates. We determined age, sex and race/ethnicity using administrative data. Hypertension, diabetes mellitus, dyslipidemia, renal disease, and anemia were identified using outpatient and clinical laboratory data collected closest to the baseline date. HMG-CoA reductase-inhibitor and antiretroviral therapy (ART) use were identified using pharmacy data. Smoking and body mass index (BMI; weight in kilograms/height in meters^2) were identified in health factor data that are collected in a standardized form within the VHA. Hypertension was categorized based on use of antihypertensive medication and blood pressure≥140/90 mm Hg derived from the average of the three routine outpatient clinical measurements closest to the baseline date. Diabetes was diagnosed using a previously validated metric that includes glucose measurements, antidiabetic agent use, and/or at least one inpatient and/or two or more outpatient ICD-9-CM codes for this diagnosis.[10] The HMG-CoA reductase-inhibitor use was within 180 days of the baseline date. Current, past, and never smoking, and BMI were assessed using documentation from the VHA electronic medical record health factor data set, which contains information collected from clinical reminders that clinicians are required to complete for patients. Prior work demonstrates high agreement between health factor documentation and self-reported smoking survey data.[11] Hepatitis C virus infection was defined as a positive hepatitis C virus antibody test result or at least 1 inpatient and/or two or more outpatient ICD-9-CM codes for this diagnosis. History of cocaine and alcohol abuse or dependence was identified using ICD-9-CM codes.[12] We collected data on baseline CD4+ T-cell (CD4) counts and HIV-1 RNA values. Baseline ART was categorized by drug class and types of regimens within 180 days of the baseline enrollment date. Antiretroviral regimens were defined as follows: protease

inhibitors (PI) plus nucleoside reverse transcriptase inhibitors (NRTI), nonnucleoside reverse transcriptase inhibitors (NNRTI) plus NRTI, other, and no ART use. We have previously demonstrated that 96% of HIV infected Veterans obtain all of their ART medications from the VHA.[6]

Statistical analysis. Descriptive statistics for all variables by HIV status were assessed using two-sample t- tests or the nonparametric counterparts for continuous variables and the chi-square or Fisher exact test for categorical variables. We calculated incidence rates of total CVD per 1000 person-years and median age at time of CVD event stratified by HIV status. We used Cox proportional hazards models to estimate the hazard ratio (HR) and 95% confidence intervals (CI) to assess whether HIV infection was associated with incident total CVD after adjusting for age and race/ethnicity, and then for Framingham risk factors.[8,13] In our third model, we adjusted for demographic characteristics, Framingham risk factors, comorbid disease, and substance abuse or dependence. We conducted similar secondary analyses that separately compared uninfected women to HIV infected women stratified by baseline CD4+ T cell count, baseline HIV-1 RNA level, and baseline HIV-1 RNA level and baseline ART status. On ART at baseline was defined as on any ART regimen (PI+NRTI, NNRTI+ NRTI, other ART medications) versus not on any ART at baseline. We also examined the rates of CVD among HIV infected Veterans who were on ART and not on ART at baseline compared to uninfected Veterans. Missing covariate data were included in the analyses using multiple imputation techniques that generated five data sets with complete covariate values to increase the robustness and efficiency of the estimated HR.

Results

After restricting the VACS-VC sample to women (n=2253) and excluding those with baseline cardiovascular disease (n=63), our final sample included 2190 women. The prevalence of several cardiovascular risk factors differed by HIV status (Table 1). HIV infected women

Veterans had a higher prevalence of low HDL cholesterol, elevated triglycerides, smoking, HCV infection, hemoglobin <12 g/dL, alcohol and cocaine abuse/dependence, and a lower prevalence of hypertension and obesity (BMI≥30 kg/m^2) ($p<0.05$ for all).

During a median follow up of 6.0 years, there were 86 CVD events (53% HIV infected). Of these events, 24% were AMI, 20% were ischemic stroke and 56% were heart failure. Incident CVD per 1000 person years was significantly higher among HIV infected (13.5 [95% CI=10.1, 18.1]) compared to uninfected women Veterans (5.3 [95% CI=3.9, 7.2]), ($p<0.001$), (Figure 1). The median age at time of the CVD event for HIV infected versus uninfected women was (49.3 years versus 52.1 years, $p=0.05$). The median Framingham risk score was 3% for both HIV infected and uninfected women ($p=0.2$).

After adjusting for Framingham risk factors (age, lipids, smoking, blood pressure, and diabetes), other comorbidities (renal disease, obesity, hepatitis C virus infection), substance use and abuse (cocaine and alcohol), and demographic factors, HIV infected women Veterans had a significantly increased risk of total CVD compared to uninfected women Veterans (HR=2.8 [95% CI=1.7, 4.6]) (Table 2).

Compared with uninfected women, HIV infected women had a significantly increased risk of CVD, regardless of CD4 count at baseline (≥500 cells/mm^3, 200-499 cells/mm^3, and <200 cells/mm^3) (Table 3). Among HIV infected women, there was a stepwise increase in point estimates of CVD risk with decreasing baseline CD4 count (HR=2.3 [95% CI=1.3, 4.4]; HR=2.9 [95% CI=1.5, 5.7]; HR=3.8 [95% CI=1.9, 7.6], respectively), but these differences were not statistically significant. In addition, HIV infected women with unsuppressed HIV-1 RNA (≥ 500 cpm) were at greater risk for CVD compared with uninfected women (HR=3.7 [95% CI=2.2, 6.5]), although CVD risk did not differ by level of HIV-RNA suppression ($p>0.05$; Table 3). Being on ART at baseline did not appear to change these relationships (Table 3).

The rate of incident CVD per 1000 person years among HIV infected women who were on ART at baseline compared to those who were not on ART at baseline were similar (12.8 [95% CI=8.0, 20.7] vs. (14.0 [95% CI=9.7, 20.1], respectively) and were significantly higher than the rate of incident CVD among uninfected women (5.3 [95% CI=3.9, 7.2]), ($p<0.05$).

Discussion

HIV infected women had higher rates and risks of total CVD compared to uninfected women. This increased risk persisted after adjustment for demographic factors, Framingham risk factors, other comorbidities, and substance (alcohol and cocaine) use and abuse.

While multiple prior studies have linked HIV infection to AMI, coronary heart disease, ischemic stroke and heart failure, the majority of the participants in these studies were men.[7, 14] Few studies have focused on women and even fewer included CVD events. Our results are consistent with earlier studies that linked HIV infection to an increased risk of CHD, ischemic stroke, and subclinical atherosclerosis among women.[1, 2, 15]

Our findings extend these results by examining this association in a national sample of HIV infected and uninfected women from the same health care system. In addition, we were able to adjust our analyses for demographic and Framingham risk factors, as well as comorbid conditions, smoking, and substance use and abuse variables (cocaine, and alcohol). We assessed incident CVD events, and included analyses stratified by HIV-1 RNA, CD4 count and ART use.

Our results are consistent with prior studies reporting HIV infection as an independent risk factor for CVD in men, suggesting that HIV infection increases the risk of CVD regardless of gender. Those with HIV-1 RNA $\geq$ 500 cpm appear to be at particularly high risk. In addition, antiretroviral therapy, Framingham risk factors, and important comorbidities such as hypertension, renal disease, substance use, and anemia may all contribute to CVD in men and women.[7] What

remains to be established is whether or not HIV infected women are at greater risk than HIV infected men, whether those with lower CD4 counts are at greater risk than those with higher, and whether or not CVD risk among those with fully suppressed HIV-1 RNA differs from that of uninfected individuals or from those with detectable HIV-1 RNA.

Although the exact mechanisms for increased CVD risk in HIV infected women are not known, prior studies in men have suggested inflammation, immune activation, immunodeficiency, altered coagulation, dyslipidemia, insulin resistance, and endothelial dysfunction as potential mechanisms.[16-18] HIV infected women also have increased immune activation markers (soluble CD163) that are associated with pre-clinical CVD, compared with uninfected women.[19, 20] Prior studies among uninfected women also suggest that depression[21, 22] (which has a higher prevalence among HIV infected versus uninfected women[22]), earlier menopause[23] (which may be more prevalent among HIV infected versus uninfected women[24]), and other drivers of decreased estrogen such as substance use[24, 25] are all associated with incident CVD events.[26] Whether these factors contribute to the excess risk of CVD among HIV infected women, however, is not known.

Currently, women represent one out of every four people living with HIV infection in the United States and 20% of all new infections.[5] Minority women are disproportionately affected by the HIV infection epidemic. Heart disease and cerebrovascular disease are the first and third leading causes of death among U.S. women ages 18 or older, respectively. For these reasons, future studies will be needed to elucidate the mechanisms of cardiovascular disease in this high risk population. Without this knowledge, CVD risk stratification strategies for HIV infected women will not be optimal.

There are several limitations that warrant discussion. First, unlike prior studies in men infected with HIV, we did not find significant associations between several traditional and HIV-specific

risk factors and total CVD in this study. The lack of significance likely reflects our relatively small number of total events (n=86). However, when we compared these results to our larger study among HIV infected and uninfected male and female Veterans[7], the associations between the majority of these risk factors and CVD risk were of similar direction and magnitude. We also did not have sufficient power to examine individual types of CVD events separately in this analysis. However, prior studies among men have demonstrated that HIV is significantly associated with each component of our CVD variable (AMI, ischemic stroke, and heart failure). On balance, this study presents data from one of few cohorts of HIV infected women that includes adjudicated, clinical CVD events, detailed information on comorbidities, substance use and abuse, HIV specific biomarkers and a comparator group of uninfected women from the same national health care system. Our use of ICD-9 codes for determining incident CVD events may have resulted in some misclassification; however, the codes selected have been validated in prior studies.[8] Moreover, our study incorporated VHA, Medicare, and national death index cause of death data to maximize our capture of incident CVD events. Lastly, examining the impact of antiretroviral therapy, including individual medications, in detail was not possible due to the number of events in the HIV population.

In summary, HIV infected women have increased rates and risk of incident CVD events as compared to uninfected women after adjustment for demographic characteristics, Framingham risk factors, other comorbidities and substance use and abuse. Future studies should focus on the identification of risk factors contributing to this excess risk of CVD among HIV infected women and strategies designed to prevent CVD in this high risk population.

Acknowledgements

We would like to thank the Veterans for participating in the Veterans Aging Cohort Study. Without their participation and the commitment of the study's staff and coordinators, this research would not be possible.

Funding sources

This work was supported by the Yale Center for Clinical Investigation and the Clinical and Translational Science Award Grant Number UL1 RR024139 from the National Center for Research Resources; National Institute of Nursing Research Grant Number K01 NR013437; National Heart, Lung, and Blood Institute Grant Number HL095136; and the National Institute on Alcohol Abuse and Alcoholism Grant Numbers AA013566-10, AA020790, and AA020794, all components of the National Institutes of Health.

Disclaimer

The NIH did not participate in the design and conduct of the study; collection, management, analysis, or the interpretation of the data; nor did the NIH prepare, review or approve of this manuscript. The views expressed in this article are those of the authors and do not necessarily reflect the position or policies of the Department of Veterans Affairs.

Disclosures: None

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Table 1. Characteristics of Women VACS participants stratified by HIV status*†

Characteristic	**Uninfected** **N=1480**	**HIV Infected** **N=710**
Age at baseline, y		
Mean (SD)	44.0 (7.7)	43.2 (7.7)
Median (IQR)	44.0 (40.0-48.0)	44.0 (39.0-48.0)
Race/ethnicity		
African American	59.4	61.6
White	30.8	28.7
Other	9.8	9.7
Framingham risk score		
Mean (SD)	3.1 (3.0)	3.2 (3.1)
Median (IQR)	3 (1-5)	3 (1-5)
Framingham Risk Factors, %		
Hypertension	28.0	22.9
Diabetes Mellitus	12.6	10.4
Lipids, mg/dL		
LDL cholesterol >=160	12.3	8.2
HDL cholesterol <50	41.1	53.8
Triglycerides ≥ 150	23.4	33.6
Smoking, %		
Current	40.5	59.2
Past	12.3	10.2
Never	47.2	30.6
Other risk factors, %		
Current HMG CoA reductase-inhibitor use	7.3	4.7
HCV infection	5.7	24.4
EGFR[‡]< 60 mL/min/1.73m2, %	3.7	5.6
Body mass index ≥ 30, %	44.6	25.3
Hemoglobin <12g/dL	17.5	29.7
History of substance use, %		
Alcohol abuse/dependence	5.0	13.8
Cocaine abuse/dependence	3.6	13.5
HIV-specific biomarkers		
CD4 cell count, mm3		
Mean (SD)		468 (352)
Median (IQR)		420 (212-654)
HIV-RNA, copies/mL		
Mean (SD)		57866 (150888)
Median (IQR)		1900 (325-30600)
ART[§] regimen, %		
PI + NRTI		15.2
NNRTI+ NRTI		21.7
Other		4.4
No ART use		58.7

*P<0.05 for all comparisons by HIV status except race (p=0.59), diabetes (p=0.14), and median Framingham risk score (p=0.30)

†All variables had complete data except hypertension (HIV- N=1449; HIV+ N=702), LDL cholesterol (HIV- N=1055; HIV+ N=537), HDL-cholesterol (HIV- N=1081; HIV+ N=558), triglycerides (HIV- N=1128; HIV+ N=587), smoking (HIV- N=1390; HIV+ N=679), eGFR (HIV- N=1284, HIV+ N=662), BMI (HIV- N=1447; HIV+ N=699), hemoglobin (HIV- N=1277, HIV+ N=651), CD4 cell count (HIV+ N=512), HIV-1 RNA (HIV+ N=539)

‡ EGFR: Estimated glomerular filtration rate

§ ART: Antiretroviral therapy

Table 2. The Association between HIV and incident total CVD*

Characteristic	Model 1 (Demographics)	Model 2 (Framingham risk factors)	Model 3 (All predictors)
HIV	2.8 (1.8, 4.3)	3.1 (2, 4.9)	2.8 (1.7, 4.6)
Age	2.1 (1.6, 2.7)	1.7 (1.3, 2.3)	1.7 (1.3, 2.3)
White	1.0	1.0	1.0
Black	1.4 (0.9, 2.3)	1.3 (0.8, 2.1)	1.3 (0.7, 2.2)
Other	0.5 (0.1, 1.6)	0.4 (0.1, 1.4)	0.4 (0.1, 1.4)
Hypertension		2.5 (1.6, 4.0)	2.4 (1.5, 3.8)
Diabetes		1.6 (1.0, 2.7)	1.6 (0.9, 2.7)
LDL≥160 mg/dL		1.3 (0.7, 2.4)	1.3 (0.7, 2.5)
HDL<50 mg/dL		0.9 (0.5, 1.5)	0.8 (0.5, 1.4)

Triglycerides≥150 mg/dL		1.2 (0.7, 2.1)	1.2 (0.7, 2.1)
Non-smoker		1.0	1.0
Current smoker		0.9 (0.6, 1.5)	1 (0.6, 1.6)
Past smoker		1.3 (0.7, 2.4)	1.3 (0.7, 2.5)
HMG CoA reductase inhibitor			1.1 (0.5, 2.2)
Hepatitis C			1.1 (0.6, 2.0)
EGFR<60 mL/min/1.73m2			3 (1.5, 6.2)
BMI≥30 kg/m^2			1.2 (0.7, 1.9)
Cocaine abuse/dependence			2.5 (1.1, 5.4)
Alcohol abuse/dependence			0.5 (0.2, 1.3)
Hemoglobin <12 g/dL			1.7 (1.0, 2.8)

* Hazard ratio (95% confidence interval)

Table 3: Association between HIV status, HIV specific covariates and incident total CVD

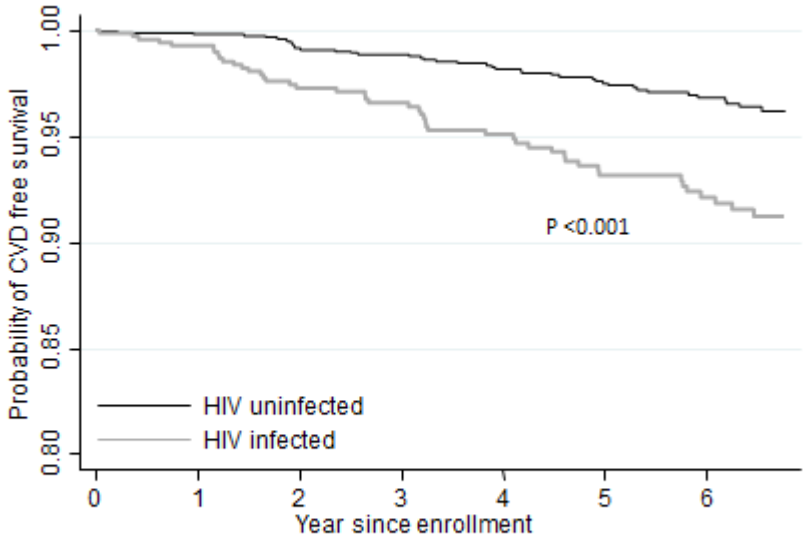
Model		HR (95% CI)
A	HIV-	1
	HIV+, CD4+ T-cell count ≥500 cells/mm^3	2.3 (1.3, 4.4)†
	HIV+, CD4+ T-cell count 200-499 cells/mm^3	2.9 (1.5, 5.7)†
	HIV+, CD4+ T-cell count <200 cells/mm^3	3.8 (1.9, 7.6)†
B	HIV-	1
	HIV+, HIV-1 RNA<500 cpm	1.6 (0.6, 4.1)†
	HIV+, HIV-1 RNA≥500 cpm	3.7 (2.2, 6.5)†
C	HIV-	1
	HIV+, HIV-1 RNA<500 cpm, on ART	1.6 (0.7, 3.9)†
	HIV+, HIV-1 RNA≥500 cpm, on ART	4.4 (2.0, 10.0)†
	HIV+, not on ART	3.0 (1.8, 5.1)†

*Model hazard ratios adjusted for age, race/ethnicity, hypertension, diabetes, LDL cholesterol, HDL cholesterol, triglycerides, HMG CoA reductase use, smoking, hepatitis C, estimated glomerular filtration rate, body mass index, cocaine and alcohol abuse or dependence, hemoglobin.

ART- antiretroviral therapy

† Tests for differences in CVD risk among the HIV infected women were not statistically significant (p>0.05)

Figure 1. Cardiovascular disease-free survival by HIV status



Number at risk							
HIV uninfected	1480	1421	1341	1227	1092	967	759
HIV infected	710	666	598	534	478	413	343

X