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ORIGINAL RESEARCH ARTICLE

Association of Human Immunodeficiency Virus Infection and Risk of Peripheral Artery Disease

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BACKGROUND: The effect of human immunodeficiency virus (HIV) on the development of peripheral artery disease (PAD) remains unclear. We investigated whether HIV infection is associated with an increased risk of PAD after adjustment for traditional atherosclerotic risk factors in a large cohort of HIV-infected (HIV+) and demographically similar HIV-uninfected veterans.

METHODS: We studied participants in the Veterans Aging Cohort Study from April 1, 2003, through December 31, 2014. We excluded participants with known prior PAD or prevalent cardiovascular disease (myocardial infarction, stroke, coronary heart disease, and congestive heart failure) and analyzed the effect of HIV status on the risk of incident PAD events after adjusting for demographics, PAD risk factors, substance use, CD4 cell count, HIV-1 ribonucleic acid, and antiretroviral therapy. The primary outcome is incident peripheral artery disease events. Secondary outcomes include mortality and amputation in subjects with incident PAD events by HIV infection status, viral load, and CD4 count.

RESULTS: Among 91 953 participants, over a median follow up of 9.0 years, there were 7708 incident PAD events. Rates of incident PAD events per 1000 person-years were higher among HIV+ (11.9; 95% confidence interval [CI], 11.5–12.4) than uninfected veterans (9.9; 95% CI, 9.6–10.1). After adjustment for demographics, PAD risk factors, and other covariates, HIV+ veterans had an increased risk of incident PAD events compared with uninfected veterans (hazard ratio [HR], 1.19; 95% CI, 1.13–1.25). This risk was highest among those with time-updated HIV viral load >500 copies/mL (HR, 1.51; 95% CI, 1.38–1.65) and CD4 cell counts <200 cells/mm^3 (HR, 1.91; 95% CI, 1.71–2.13). In contrast, HIV+ veterans with time updated CD4 cell count ≥500 cells/mm^3 had no increased risk of PAD (HR, 1.03; 95% CI, 0.96–1.11). Mortality rates after incident PAD events are high regardless of HIV status. HIV infection did not affect rates of amputation after incident PAD events.

CONCLUSIONS: Infection with HIV is associated with a 19% increased risk of PAD beyond that explained by traditional atherosclerotic risk factors. However, for those with sustained CD4 cell counts <200 cells/mm^3, the risk of incident PAD events is nearly 2-fold higher, whereas for those with sustained CD4 cell counts ≥500 cells/mm^3 there is no excess risk of incident PAD events compared with uninfected people.

Key Words: amputation ■ antiretroviral therapy ■ CD4 cells ■ human immunodeficiency virus ■ mortality ■ peripheral artery disease

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Clinical Perspective

What Is New?

- HIV infection increases the risk of developing peripheral artery disease (PAD).
- Once PAD has developed, HIV infection increases the risk of mortality compared with HIV-uninfected subjects.
- Worsening HIV infection, as measured by CD4 cell count and HIV viral load, is associated with increased incident PAD and mortality.

What Are the Clinical Implications?

- HIV infection increases the risk of developing PAD and mortality.
- Aggressive antiretroviral therapy to reduce viral load and increase CD4 cell counts may reduce the risk of developing PAD.
- Clinicians should solicit clinical complaints and physical signs consistent with PAD to facilitate the diagnosis of PAD in patients with HIV to ensure the addition of guideline-based antiatherosclerotic therapies in the appropriate patients.

The advent of effective antiretroviral therapy (ART) has significantly increased the survival of patients infected with human immunodeficiency virus (HIV). Currently, the life expectancy of these patients approaches that of the general population.[1,2] An increased risk in cardiovascular disease events is present even among well-treated patients with HIV.[3] This fact may represent an important cause that prevents attainment of a normal life span.[4] The mechanisms underlying this excess risk of cardiovascular disease may include the inherent immune activation of HIV infection or other commonly acquired infections like hepatitis C, metabolic changes associated with some of the antiretroviral agents, and an increased prevalence of cardiovascular risk factors.[5] The impact of HIV infection, independent of these other factors, is likely substantial. HIV infection increases rates of myocardial infarction (MI), even among those with few or no cardiovascular disease risk factors,[3] as compared with uninfected people. Worse, standard medical therapy may not provide the same risk reduction as in the general population.[6]

Atherosclerosis is a systemic disease whose phenotype depends on the manifestation of clinical presentation.[7] HIV infection is associated with an increased risk of MI and ischemic stroke.[8] In contrast, there is sparse information concerning the relationship between HIV and the other major presentation of atherosclerosis: peripheral artery disease (PAD).[9,10] Accordingly, we examined the association between HIV and PAD in an older, predominantly male population compared with a demographically and behaviorally similar uninfected population (eg, similar rates of substance use).

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Sample

The Veterans Aging Cohort Study (VACS) is a prospective, longitudinal cohort of HIV-infected and uninfected veterans matched 1:2 for age, race/ethnicity, sex, and clinical site and enrolled in the same calendar year.[11] Participants are identified using a validated algorithm deployed in the US Department of Veterans Affairs (VA) national electronic medical record system.[11] Clinical and demographic data are extracted from the VA Corporate Data Warehouse and the VA electronic medical record health factor data set. Vital status is determined using the VA vital status file, the Social Security Administration death master file, the Beneficiary Identification and Records Locator Subsystem, and the Veterans Health Administration Medical Statistical Analysis Systems inpatient data sets. The Vanderbilt University Medical Center, Yale University, and West Haven VA Medical Center institutional review boards approved this study.

For this analysis, we included all VACS participants enrolled on or after April 1, 2003, where the baseline was a participant's first clinic visit on or after this date. All participants were followed from their baseline date to development of PAD, death, or censored on December 31, 2014, if living. We truncated our analysis after 2014 to coincide with the end of our Medicare data files. As we have done in previous studies, we excluded participants with prevalent PAD or cardiovascular disease based on the presence of 1 inpatient or outpatient administrative International Classification of Diseases (ICD)-9 or current procedural terminology codes for acute MI, unstable angina, other coronary heart disease, stroke or transient ischemic attack, congestive heart failure, or PAD on or before their baseline date. We additionally excluded participants with negative follow-up time. After these exclusions (n=41 652), our final sample included 91 953 veterans, of whom 31% were HIV+.

Independent Variable

HIV status was determined on the basis of inclusion in the VA Immunology Case Registry as well as a validated metric including ≥1 inpatient or ≥2 outpatient ICD-9 codes for HIV (Table I in the online-only Data Supplement).[11]

Dependent Variables

All participants were followed via their records (ie, evidence of clinical inpatient or outpatient visits from VA, Medicare, or VA fee for service files) for evidence of their first PAD event from their baseline date through the last date of follow-up for this study (December 31, 2014). An incident PAD event was defined as the presence of ≥1 inpatient or ≥2 outpatient VA, VA fee for service, or Medicare ICD-9 or current procedural terminology codes. In this analysis, we used the PAD definition described by Bali et al.[12] Secondary analyses restricted

the Bali et al definition to only those who underwent surgical revascularization or stent placement (eg, femoral-popliteal artery bypass). Among veterans with PAD, we also examined all-cause mortality and rates of amputation. The former was determined from the VA vital status file, which has previously been shown[13] to accurately ascertain mortality. The latter definition was based on current procedural terminology procedure codes from Bali et al.[12]

Covariates

Age, sex, and race/ethnicity were pulled from administrative data. Diabetes mellitus, dyslipidemia, hypertension, renal disease, total bilirubin, anemia, and hepatitis C infection were ascertained using clinical inpatient or outpatient or clinical laboratory data collected closest to the baseline date—an approach for comorbidity extraction in VACS that has been previously described.[3] Body mass index was taken from VA vital sign data and was dichotomized using a cut point of at least 30 kg/m^2. Pharmacy data were utilized to determine administration of cardiac and diabetes mellitus medication as well as antiretroviral therapy.[14] Hypertension was categorized as no hypertension (blood pressure <140/90 mm Hg and no antihypertensive medication), controlled hypertension (<140/90 mm Hg with antihypertensive medication), and uncontrolled hypertension (≥140/90 mm Hg). Using the average of the 3 outpatient clinical measurements closest to baseline, we determined an individual's systolic and diastolic blood pressure.[15] Diabetes mellitus was diagnosed using a previously validated algorithm[16] which includes glucose >200 mg/dL on 2 separate occasions (any duration apart), ICD-9 codes (2 outpatient or 1 inpatient) plus treatment with an oral hypoglycemic or insulin for >30 days, ICD-9 codes (2 outpatient or 1 inpatient) plus glucose >126 mg/dL on 2 separate occasions, or glucose >200 mg/dL on 1 occasion plus treatment with an oral hypoglycemic or insulin for >30 days. Chronic obstructive pulmonary disease was diagnosed based on ≥1 inpatient or ≥2 outpatient ICD-9 codes. From the VA electronic medical record health factor data set, we extracted smoking status. Hepatitis C virus infection was diagnosed on the basis of a positive hepatitis C virus antibody test or ≥1 inpatient or ≥2 outpatient ICD-9 codes for this diagnosis. As described in a previous study,[17] history of alcohol abuse or dependence was defined using ICD-9 codes. ART was categorized by regimen within a window of 180 days before baseline through 7 days postbaseline and included a nucleoside reverse transcriptase inhibitor (NRTI) plus a protease inhibitor, an NRTI plus a non-NRTI, other (ie, use of protease inhibitor, NRTI, or non-NRTI medications but not in combination as described in the other 2 categories), and no ART (reference group).[14] HIV-specific biomarkers CD4 and viral load were collected at baseline and throughout follow-up until the end of 2014.

Statistical Analysis

Descriptive statistics for all variables by HIV and incident PAD event status were analyzed using χ^2 tests for categorical variables and Wilcoxon tests for continuous variables. Next, we plotted the cumulative incidence of PAD over the follow-up period by HIV status, HIV viral load, and CD4 cell count and performed log-rank tests to compare the various groups. We then calculated incident PAD event rates per 1000 person-years stratified by HIV status, baseline CD4+ T cell count, and baseline HIV viral load. Because we used model-based standard errors, we inspected log-log plots and observed no serious violations of the proportional hazards assumption. Then, unadjusted and fully-adjusted Cox proportional hazard regression models were used to compare the risk of incident PAD events in HIV-infected veterans compared with uninfected veterans. Our fully adjusted Cox proportional hazards regression model included age, sex, race/ethnicity, hypertension, diabetes mellitus, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, smoking status, hepatitis C infection, renal disease (as measured by estimated glomerular filtration rate), obesity, hemoglobin, total bilirubin, history of alcohol or cocaine abuse, and chronic obstructive pulmonary disease.

There is some evidence that lipids, diabetes mellitus, obesity, estimated glomerular filtration rate, or hemoglobin lie along the causal pathway from HIV infection to PAD or other cardiovascular outcomes.[18] Thus, to account for the possible overadjustment from including these factors as adjustment variables in our models, we ran 2 supplemental analyses. In the first, we removed lipids, diabetes mellitus, and obesity as adjustment variables in our models; in the second, we additionally removed estimated glomerular filtration rate and hemoglobin from our models.

Additional analyses further stratified participants by HIV status and levels of HIV biomarkers (viral load and CD4 cell count) at both baseline and time-updated during follow-up. To assess the potential for a dose response attributable to HIV severity, we generated restricted cubic spline plots (unadjusted and multivariable adjusted) with 3 knots displaying PAD risk versus CD4 cell count in HIV-infected veterans. For the time-updated analysis, the follow-up period was broken into segments of time on the basis of updated HIV biomarker laboratory data, where an individual's HIV biomarker values were assigned the most recent values from that date until the next measurement. For example, if an HIV-infected veteran had 9 years of follow-up, and during that time had measurements of viral load ascertained at baseline, 3 years, and 6 years, the baseline value of viral load would be considered constant from baseline to year 3; the year 3 measurement of viral load would be considered constant on the interval of 3 years; and the viral load measurement at year 6 would be used from year 6 to the end of follow-up.

To determine which factors were associated with incident PAD events in HIV-infected individuals, we then limited our Cox proportional hazards regression models to infected veterans. For these models restricted to HIV-infected participants, we further adjusted for HIV-specific factors (HIV viral load, CD4 count, and ART regimen) at baseline and as time-varying covariates (CD4 count and HIV viral load only).

Finally, we explored whether HIV-infected individuals were at a higher risk of death and amputation after an incident PAD event. For the former analysis, we stratified participants on the basis of their viral load and CD4 count closest to the date of the incident PAD events through examination of Kaplan–Meier curves and the log-rank test. For the latter, we only stratified by HIV status because there were too few amputation events to stratify by HIV viral load and CD4 cell count status.

Table 1. Baseline Characteristics of VACS Participants Stratified by HIV Status

Baseline Characteristic*	HIV Infected (n=28 714)	HIV Uninfected (n=63 239)
Age, y		
Mean (SD)	47.5 (9.9)	48.0 (9.6)
Median	48.0	48.0
Male sex, %	97.0	96.8
Race/ethnicity, %		
Black	48.0	48.2
White	39.0	37.9
Hispanic	7.2	8.0
Other	5.8	5.9
Framingham risk factors, %		
Hypertension		
None	50.0	37.8
Controlled	26.5	31.9
Uncontrolled	23.5	30.3
Diabetes mellitus		
None	91.5	87.4
Diabetes without insulin	5.8	8.6
Diabetes with insulin	2.7	4.0
Lipids, mg/dL†		
LDL cholesterol <100	45.9	31.2
LDL cholesterol 100–129	30.1	33.7
LDL cholesterol 130–159	16.4	22.9
LDL cholesterol ≥160	7.6	12.1
HDL cholesterol ≥60	11.2	14.9
HDL cholesterol 40–59	38.1	48.1
HDL cholesterol <40	50.7	37.1
Triglycerides ≥150	45.4	37.2
Smoking, %†		
Current	55.0	50.0
Former	15.3	16.8
Never	29.7	33.3
Other risk factors, %		
HCV infection, %	27.7	12.0
Renal disease, mL/min/1.73m²†		
eGFR ≥60	95.1	96.3
eGFR 30–59	4.2	3.4
eGFR <30	0.7	0.3
Obesity (BMI ≥ 30 kg/m²),† %	15.5	39.3
Anemia, g/dL†		
Hemoglobin ≥14	57.6	74.5
Hemoglobin 12–13.9	31.5	22.6
Hemoglobin 10–11.9	8.7	2.5
Hemoglobin <10	2.2	0.4
Bilirubin, mg/dL		
Mean (SD)	0.7 (0.6)	0.7 (0.6)
Median	0.6	0.6
History of alcohol abuse, %	23.9	26.0
History of cocaine abuse, %	18.0	15.1
COPD, %	7.6	7.9
HIV-specific variables‡		
CD4 cell count, cells/mm³†		
Mean (SD)	431.0 (297.6)	—
Median	389.0	—
HIV-1 RNA, copies/mL†		
Mean (SD)	73 305.5 (1 003 933.7)	—
Median	1320.0	—
ART regimen, %		
NRTI + PI	17.9	—
NRTI + NNRTI	14.5	—
NRTI + NNRTI + PI & other combinations	9.4	—
No ART	58.3	—
Atazanavir usage	1.4	—

SI conversion factors: To convert HDL and LDL to millimoles per liter, multiply by 0.0259; hemoglobin to grams per liter, multiply by 10; and triglycerides to millimoles per liter, multiply by 0.0113. ART indicates antiretroviral therapy; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; and RNA, ribonucleic acid.

*All characteristics were statistically different among HIV-infected and uninfected veterans ($P<0.05$) using χ^2 test or Wilcoxon rank sum test except sex ($P=0.11$) and COPD ($P=0.19$).

†All variables had complete data except the following: Hypertension data were available on 28 278 (HIV-infected) and 60 000 (uninfected); LDL cholesterol data were available on 22 972 (HIV-infected) and 47 660 (uninfected); HDL cholesterol data were available on 23 309 (HIV-infected) and 48 229 (uninfected); triglyceride data were available on 23 695 (HIV-infected) and 48 254 (uninfected); smoking data were available on 19 270 (HIV-infected) and 42 435 (uninfected); eGFR data were available on 27 083 (HIV-infected) and 55 302 (uninfected); BMI data were available on 27 963 (HIV-infected) and 58 869 (uninfected); anemia data were available on 27 334 (HIV-infected) and 54 603 (uninfected); bilirubin data were available on 26 824 (HIV-infected) and 52 491 (uninfected); CD4 cell count data were available on 23 769 (HIV-infected); and HIV-1 RNA data were available on 24 369 (HIV-infected).

‡Because uninfected veterans do not have HIV-specific biomarkers or ART regimens, these cells contain only dashes.

In the present investigation, we used multivariate imputation by chained equation (MICE) techniques that generated 5 complete data sets to handle missing covariate data while keeping the correlation structure intact. For continuous variables, regression-based predictive mean matching was utilized to produce biologically plausible imputed values while the discriminant function with a noninformative Jeffrey's prior was used to impute categorical variables. A 2-sided *P* value of <0.05 was used to determine statistical

significance, and all analyses were performed using SAS version 9.4 (Cary, NC).

RESULTS

In this analysis, there were 91 953 veterans (31% infected with HIV) who were free of prevalent cardiovascular disease at baseline. Compared with veterans without HIV infection, HIV+ veterans had a lower prevalence of hypertension, obesity, diabetes mellitus, and lower low-density lipoprotein cholesterol levels and a higher prevalence of low high-density lipoprotein cholesterol, cigarette smoking, anemia, cocaine abuse, chronic kidney disease, and hepatitis C infection (Table 1). Chronic obstructive pulmonary disease was similar between groups. Among the HIV+ veterans, the median CD4 cell count was 389 mm^3, median HIV-1 ribonucleic acid $\times 10^3$ copies/mL was 1320, and 42% were on antiretroviral therapy at baseline.

During a median follow up of 9.0 years, 7708 participants developed an incident PAD event, with 2609 events occurring in the HIV+ participants (Table 2). Among the veterans who developed incident PAD events, there was no difference in in racial/ethnic background or in the prevalence of smoking status, chronic obstructive pulmonary disease, total bilirubin, and alcohol abuse by HIV status. However, veterans with HIV who developed an incident PAD event were less likely to have hypertension, diabetes mellitus, and obesity than uninfected veterans who developed an incident PAD event (Table II in the online-only Data Supplement).

The rate of incident PAD events per 1000 person-years was significantly increased for veterans with HIV infection at 11.9 (95% confidence interval [CI],11.5–12.4) compared with those without HIV infection, 9.9 (95% CI, 9.6–10.1; Figure 1). HIV infection was associated with an increased risk of PAD; the hazard ratio (HR) was 1.22 (95% CI, 1.16–1.28) in unadjusted analysis. After adjustment for demographic characteristics, cardiovascular disease risk factors, and other potential confounders, the association between HIV infection and the risk of incident PAD events remained essentially unchanged (HR, 1.19; 95% CI, 1.13–1.25; Table 2). In a sensitivity analysis restricting the definition of incident PAD events to surgical revascularization and stent placement, HIV infection was borderline significantly associated with incident PAD events (HR, 1.20; 95% CI, 0.97–1.48; Table III in the online-only Data Supplement).

In supplemental models where we do not adjust for lipids, diabetes mellitus, or body mass index, we observe that HIV+ veterans have 1.17 (95% CI, 1.11–1.23) times the hazard of PAD compared with HIV-uninfected veterans. Similarly, when no longer adjusting for lipids, diabetes mellitus, body mass index, estimated glomerular filtration rate, or hemoglobin, we find that HIV+ veterans are at 1.25 (95% CI, 1.19–1.31) times the hazard of an incident PAD event compared with HIV-uninfected veterans.

When further stratifying HIV+ veterans by baseline CD4 cell count and viral load, we found that those with greater disease severity were at the highest risk of an incident PAD event compared with HIV-uninfected veterans (Table 2and Figure 1) and compared with HIV+

Table 2. Rates and Risk of PAD by HIV Status

Group	N*	PAD Events*	Rate/1000PY [95% CI]*	Unadjusted PAD Risk [95% CI]	Adjusted PAD Risk [95% CI]†	Time-Updated Adjusted PAD Risk [95% CI]‡
Stratified by HIV status and CD4 cell count						
HIV–	63 239	5099	9.9 [9.6, 10.1]	1.00	1.00	1.00
HIV+, CD4≥500	8372	755	11.0 [10.2, 11.8]	1.12 [1.04, 1.21]	1.14 [1.06, 1.22]	1.03 [0.96, 1.11]
HIV+, 200≤CD4<500	9986	945	11.8 [11.1, 12.6]	1.21 [1.14, 1.30]	1.20 [1.12, 1.29]	1.19 [1.10, 1.28]
HIV+, CD4<200	5411	495	13.3 [12.1, 14.5]	1.42 [1.31, 1.55]	1.28 [1.16, 1.40]	1.91 [1.71, 2.13]
HIV+, missing CD4§	4945	414	12.5 [11.3, 13.8]	—	—	—
Stratified by HIV status and viral load						
HIV–	63 239	5099	9.9 [9.6, 10.1]	1.00	1.00	1.00
HIV+, VL<500	10 850	1101	12.4 [11.7, 13.1]	1.25 [1.17, 1.33]	1.15 [1.07, 1.23]	1.11 [1.04, 1.17]
HIV+, VL ≥500	13 519	1128	11.4 [10.7, 12.1]	1.20 [1.12, 1.28]	1.23 [1.15, 1.33]	1.51 [1.38, 1.65]
HIV+, missing VL§	4345	380	12.2 [11.0, 13.5]	—	—	—

CI indicates confidence interval; HIV, human immunodeficiency virus; PAD, peripheral arterial disease; PY, person years; and VL, viral load.

*Values correspond to the analysis using baseline values of CD4 and HIV viral load, not the time-updated analysis.

†Adjusted for age, sex, race/ethnicity, hypertension, diabetes mellitus, low- and high-density lipoprotein cholesterol, triglycerides, hepatitis C virus infection, smoking status, renal disease, obesity, anemia, total bilirubin, cocaine dependence or abuse, alcohol dependence or abuse, and chronic obstructive pulmonary disease.

‡Adjusted for all factors in (†) but CD4 and viral load are time updated.

§Missing category used only for calculation of incidence rates. For models, missing CD4 cell counts were imputed.

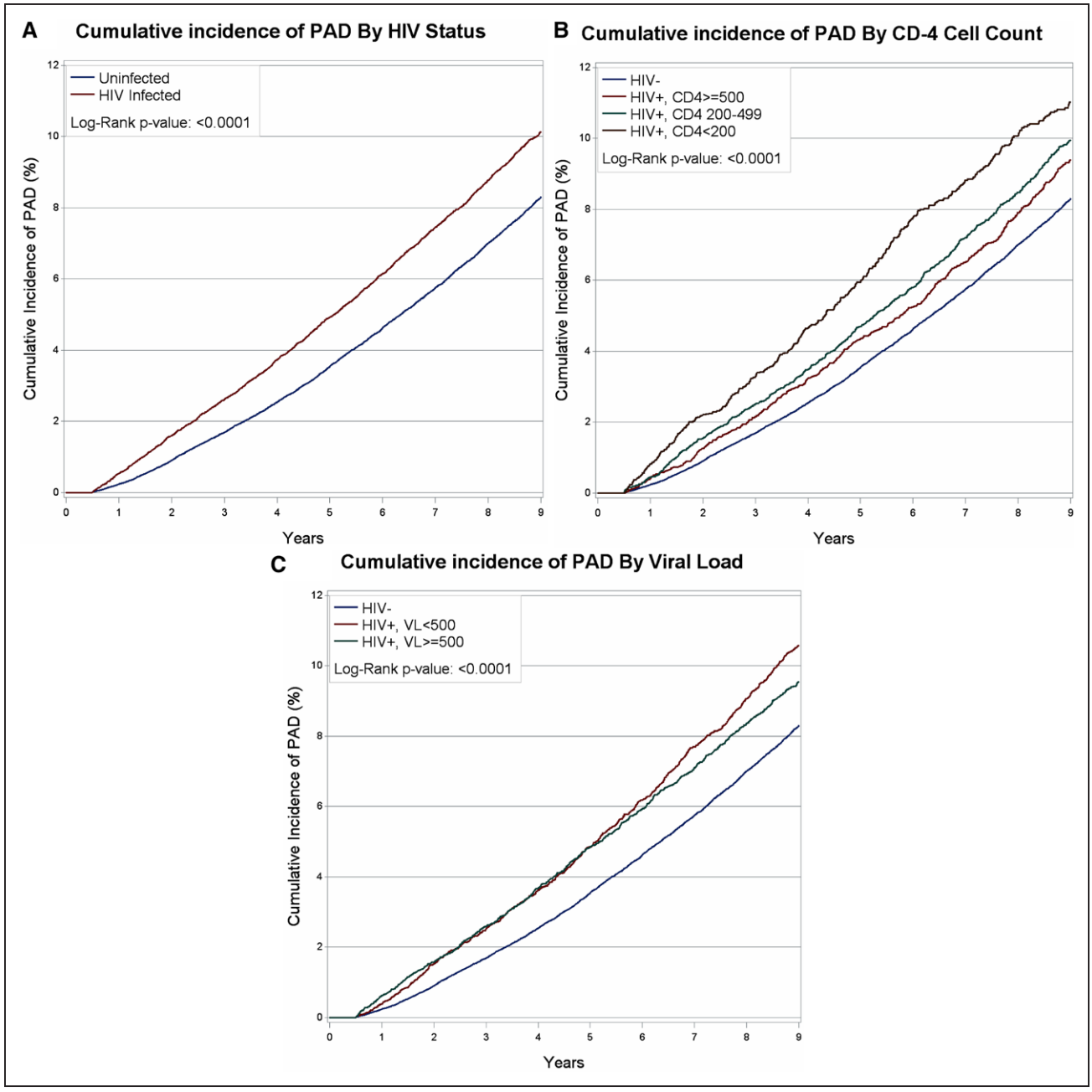

Figure 1. Cumulative incidence plots of incident peripheral artery disease (PAD) events by HIV status.
A, Kaplan–Meier survival curves illustrating the time to first PAD incident over 9.0 median years of follow-up for HIV+ compared with HIV-uninfected (HIV–) veterans. **B,** Kaplan–Meier survival curves illustrating the time to first incident PAD event over 9.0 median years of follow-up stratified by HIV status and CD4 cell count. **C,** Kaplan–Meier survival curves illustrating the time to first incident PAD event over 9.0 median years of follow-up stratified by HIV status and viral load.

veterans with CD4 counts ≥500 cells/mm^3 (Figure I in the online-only Data Supplement). In time-updated analyses, there was a clear dose response to low CD4 cell counts and elevated HIV viral loads. In fact, HIV-infected veterans with sustained low CD4 cell counts had nearly twice the risk of PAD compared with uninfected people (Table 2). In contrast, among those who achieved sustained CD4 cell counts ≥500 cells/mm^3, there was no increased risk of incident PAD events compared with uninfected veterans (HR, 1.03; 95% CI, 0.96–1.11; Table 2).

When limiting the population to HIV+ veterans, older age, hypertension, diabetes mellitus, elevated triglyceride concentrations, current smoking, hepatitis C virus coinfection, chronic kidney disease, anemia, and chronic obstructive pulmonary disease increased the hazard for incident PAD events (Table 3). Similarly, time-updated low CD4 cell counts and unsuppressed HIV viral load were both associated with an increased risk of incident PAD events (Table 3).

After an incident PAD event, HIV+ veterans had higher mortality rates than uninfected veterans (Figure 2).

Table 3. Associations Between Clinical Characteristics and Incident PAD Events Among HIV-Infected Veterans*

Characteristic	Hazard Ratio [95% CI]*	
	Using Baseline Covariates	Time-Updated CD4 and VL
Age, 10 y	1.57 [1.50, 1.65]	1.58 [1.50, 1.66]
Male sex	0.95 [0.74, 1.22]	0.93 [0.73, 1.19]
Race/ethnicity		
Black vs. White	0.97 [0.89, 1.07]	0.96 [0.87, 1.05]
Hispanic vs. White	0.95 [0.81, 1.11]	0.95 [0.82, 1.11]
Other vs. White	0.82 [0.66, 1.03]	0.82 [0.66, 1.03]
Hypertension		
Controlled vs. none	1.34 [1.21, 1.48]	1.37 [1.24, 1.52]
Uncontrolled vs. none	1.53 [1.39, 1.69]	1.55 [1.41, 1.72]
Diabetes mellitus		
Without insulin vs. none	1.72 [1.51, 1.94]	1.72 [1.51, 1.97]
With insulin vs. none	1.92 [1.62, 2.28]	1.95 [1.64, 2.31]
Lipids, mg/dL		
LDL cholesterol: 100–129 vs. <100	0.97 [0.88, 1.08]	0.99 [0.89, 1.09]
LDL cholesterol: 130–159 vs. <100	1.06 [0.94, 1.20]	1.07 [0.93, 1.22]
LDL cholesterol: ≥160 vs. <100	1.08 [0.92, 1.26]	1.09 [0.93, 1.28]
HDL cholesterol: 40–59 vs. ≥60	0.94 [0.80, 1.09]	0.93 [0.80, 1.09]
HDL cholesterol: <40 vs. ≥60	1.03 [0.87, 1.20]	1.02 [0.87, 1.19]
Triglycerides: ≥150 vs. <150	1.13 [1.04, 1.23]	1.15 [1.05, 1.25]
Smoking		
Current vs. never	1.61 [1.37, 1.89]	1.59 [1.36, 1.87]
Former vs. never	1.23 [0.99, 1.52]	1.22 [0.99, 1.51]
HCV infection	1.40 [1.28, 1.53]	1.37 [1.25, 1.50]
Renal disease, mL/min/1.73m^2		
eGFR 30–59 vs. ≥60	1.39 [1.18, 1.63]	1.37 [1.17, 1.62]
eGFR <30 vs. ≥60	3.99 [3.09, 5.15]	3.86 [2.72, 5.49]
Obesity, BMI ≥ 30 kg/m^2	1.01 [0.90, 1.13]	1.03 [0.92, 1.15]
Anemia, g/dL*		
Hemoglobin 12–13.9 vs. ≥14	1.11 [1.01, 1.22]	1.09 [0.99, 1.20]
Hemoglobin 10–11.9 vs. ≥14	1.43 [1.24, 1.65]	1.37 [1.19, 1.59]
Hemoglobin <10 vs. ≥14	1.64 [1.25, 2.15]	1.55 [1.17, 2.05]
Bilirubin, mg/dL	1.00 [0.92, 1.08]	0.99 [0.92, 1.08]
History of alcohol abuse	1.11 [0.99, 1.25]	1.11 [0.99, 1.25]
History of cocaine abuse	1.06 [0.93, 1.20]	1.04 [0.91, 1.18]
COPD	1.43 [1.27, 1.61]	1.40 [1.23, 1.59]
CD4 cell count, cells/mm^3		
200–499 vs. ≥500	1.05 [0.95, 1.15]	1.13 [1.03, 1.25]
<200 vs. ≥500	1.10 [0.98, 1.24]	1.74 [1.55, 1.96]
HIV-1 RNA, copies/mL		
≥500 vs. <500	1.05 [0.94, 1.16]	1.17 [1.06, 1.30]
ART regimen		
NRTI + PI vs. no ART	1.03 [0.93, 1.15]	1.06 [0.96, 1.16]
NRTI + NNRTI vs. no ART	1.04 [0.93, 1.17]	1.06 [0.95, 1.19]
Other vs. no ART	1.09 [0.96, 1.24]	1.04 [0.87, 1.23]

ART indicates antiretroviral therapy; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PAD, peripheral arterial disease; PI, protease inhibitor; RNA, ribonucleic acid; and VL, viral load.

*Adjusted for all listed characteristics.

Those with immunosuppression or unsuppressed HIV viral load at the time of an incident PAD event had the highest mortality rates. In fact, 50% of HIV+ veterans with a CD4 count <500 cells/mm^3 died within 4 years after incidence of PAD diagnosis. In contrast, mortality rates did not vary by HIV status when HIV+ veterans had CD4 count ≥500 cells/mm^3 at the time of an incident PAD event. Of note, there was no increased risk of amputations after incident PAD events among HIV+ compared with uninfected veterans (Figure II in the online-only Data Supplement).

DISCUSSION

HIV infection is associated with an increased risk of PAD. This risk persists despite a similar or reduced atherosclerotic risk factor burden among HIV+ veterans. This risk increases in a dose–response fashion with increasing HIV viral loads or lowering of CD4 cell counts. In fact, HIV+ veterans with sustained CD4 counts <200 cells/mm^3 have nearly twice the risk of PAD whereas HIV+ veterans with sustained CD4 counts ≥500 cells/mm^3 do not have an excess risk of incident PAD events compared with uninfected veterans. Mortality rates after PAD diagnosis are high regardless of HIV status; however, for those with low CD4 cell counts or unsuppressed HIV viremia, ≈50% are deceased within 5 years. In contrast, rates of amputation after incident PAD events diagnosis are similar for both HIV+ and uninfected veterans.

This is the first large study reporting that HIV infection increases the risk of incident PAD events and mortality after the diagnosis of PAD. We and others have previously reported increases in the rates of MI, stroke, heart failure, and sudden cardiac death in HIV+ persons.[3,8,19] The present study extends prior work by demonstrating an increased risk of atherosclerosis in the second major clinical manifestation. The limited data involving HIV and PAD[20] likely reflects the underdiagnosis and treatment of PAD from the general population to patients infected with HIV.[21] The dearth of diagnostic scrutiny

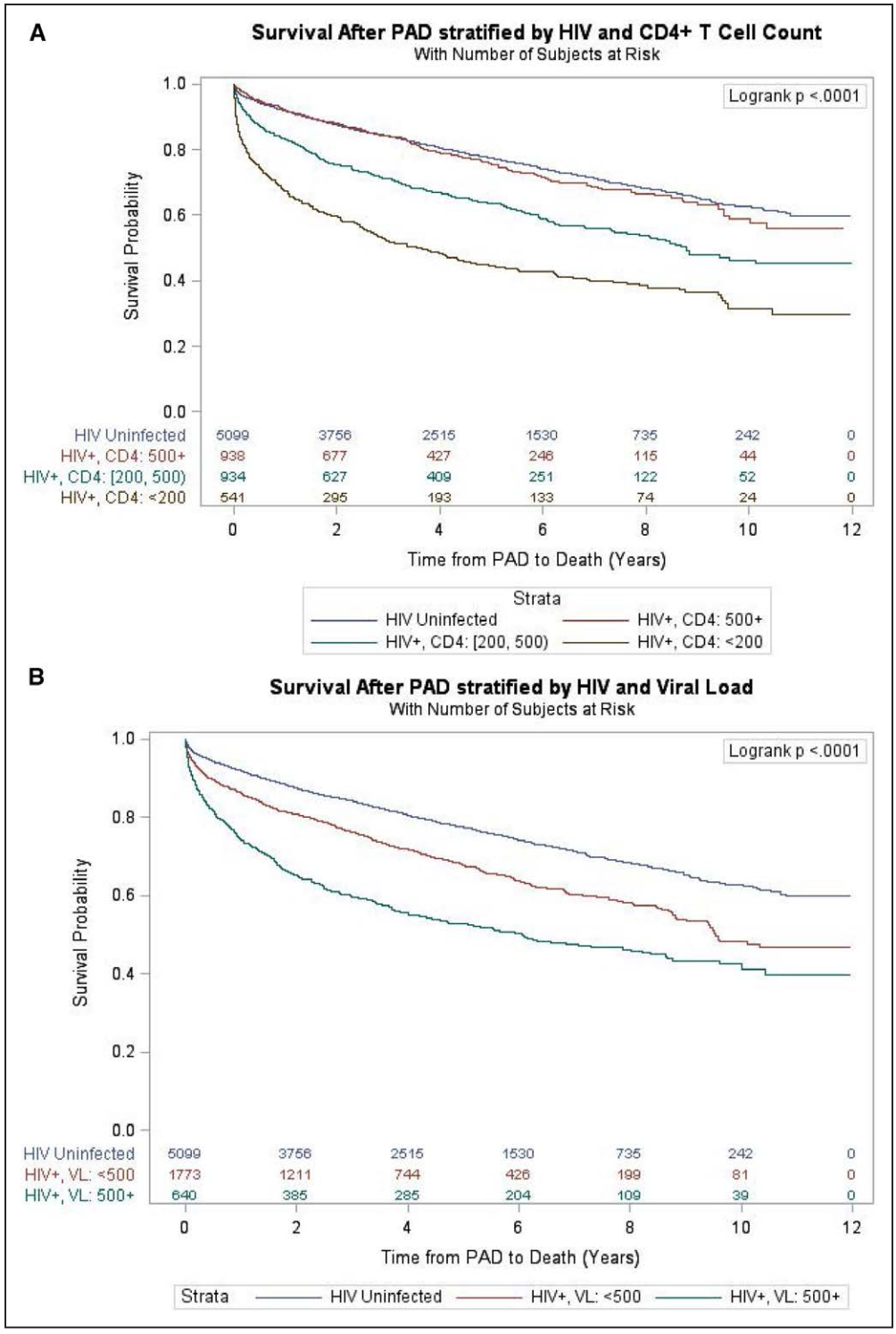

Figure 2. Mortality risk after peripheral artery disease (PAD) diagnosis stratified by HIV status and HIV biomarkers.
Kaplan–Meier survival curves illustrating the time to mortality over 3.7 median years of follow-up for veterans stratified by (**A**) HIV and CDR4 T cell count and (**B**) HIVD and viral load.

squanders 2 therapeutic opportunities: first, the occasion to institute broad atherosclerotic risk factor modification therapies, and second, the chance to ensure the use of antiretroviral therapy in a patient population likely to require frequent medical care.[22]

In our study, atherogenic risk factors, including older age, hypertension, diabetes mellitus, current smoking, and advanced chronic kidney disease increased the risk of PAD. However, the HIV+ patients with PAD did not have a risk factor profile more adverse than those PAD

patients without HIV. These findings suggest that HIV, per se, impairs vascular function and promotes systemic atherosclerosis. HIV-infected patients have been shown to manifest endothelial dysfunction,[23] platelet activation,[24] increased inflammation,[25] monocyte activation, and a prothrombotic tendency.[25] Other possibilities include the use of earlier generation antiretroviral therapy with the development of adverse metabolic changes. The exact mechanisms by which HIV increases atherogenesis in general and PAD specifically remain unclear.

In the general population, PAD affects 8 to 10 million people in the United States and represents the second most common clinical manifestation of atherosclerosis after MI.[26] In contrast to MI or stroke, patients with PAD experience a significant increase in adverse limb events (eg, claudication, critical limb ischemia, acute limb ischemia, and amputation) as well as mortality.[27] In this study, mortality rates among those with incident PAD events were high regardless of HIV status. For those with poorly controlled HIV infection the mortality rates were even higher. In contrast, amputation rates after PAD did not differ by HIV status. Whether major adverse limb events are truly the same for HIV+ and uninfected veterans is not clear because we examined the least common phenotype within the major adverse limb events category. The fact that microvascular disease (ie, nephropathy and neuropathy) in PAD is associated with an increased risk of major adverse limb events and that HIV+ people are at risk for microvascular disease supports further examination of major adverse limb event outcomes among HIV+ people with PAD.

There are some limitations of this work to be noted. First, there is no agreement in the literature for the exact ICD-9 codes to use to define PAD.[28–40] We chose to use the criterion defined by Bali and colleagues for its high negative predictive value[12] to decrease borderline cases. Despite this, there is likely some misclassification and the field of PAD epidemiology would benefit from agreement among its investigators. We note that these data cannot be overly generalized to women, the mortality analyses were unadjusted, and treatments received after PAD diagnosis are not reported. Finally, because these are observational data, we cannot exclude the possibility of residual or unmeasured confounding.

Our data suggest that HIV infection is a risk factor for incident PAD events in addition to and independent of the well-established risk factors for atherosclerosis. The risk of PAD is highest among those with high HIV viral loads and low CD4 cell counts. In contrast, HIV-infected people with sustained high CD4 cell counts do not have an excess risk of PAD compared with uninfected people. After the development of PAD, mortality rates are high regardless of HIV status but highest for those with untreated HIV infection. These results suggest that patients with HIV and PAD require aggressive treatment of both conditions to decrease mortality. Moreover, novel treatments may be required to reduce the increased mortality of HIV patients who are seemingly well-controlled.

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