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Effects of HIV Infection on Arterial Endothelial Function: Results from a Large Pooled Cohort Analysis

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Abstract

Objective—To determine the effects of human immunodeficiency virus (HIV) serostatus and disease severity on endothelial function in a large pooled cohort study of people living with HIV infection (PLWH) and HIV− controls.

Approach and Results—We used participant level data from 9 studies: 7 included PLWH (2 treatment-naïve) and 4 had HIV− controls. Brachial artery (BA) flow-mediated dilation (FMD) was measured using a standardized ultrasound imaging protocol with central reading. After data harmonization, multiple linear regression was used to examine the effects of HIV-serostatus, HIV disease severity measures, and cardiovascular disease (CVD) risk factors on FMD. Of 2533 participants, 986 were PLWH (mean 44.4 [standard deviation 11.8] years old) and 1547 were HIV − controls (42.9 [12.2] years old). The strongest and most consistent associates of FMD were BA diameter, age, sex, and body-mass index. The effect of HIV+ serostatus on FMD was strongly influenced by kidney function. In the highest tertile of creatinine (1.0 mg/dL), the effect of HIV+ serostatus was strong (β=−1.59%, 95%CI −2.58 to −0.60%, p=0.002), even after covariate adjustment (β=−1.36%, 95%CI −2.46 to −0.47%, p=0.003). In the lowest tertile (0.8 mg/dL), the effect of HIV+ serostatus was strong (β=−1.90%, 95%CI −2.58 to −1.21%, p<0.001), but disappeared after covariate adjustment. HIV RNA viremia, CD4+ T-cell count, and use of antiretroviral therapy were not meaningfully associated with FMD.

Conclusions—The significant effect of HIV+ serostatus on FMD suggests that PLWH are at increased CVD risk, especially if they have kidney disease.

Graphical Abstract

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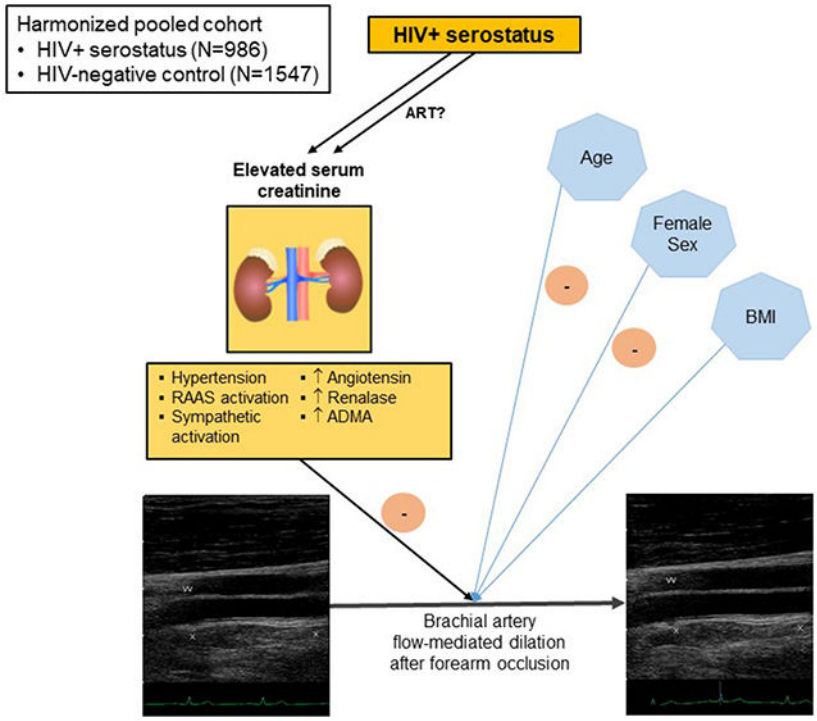

Keywords

Arteries; Endothelial function; Human Immunodeficiency Virus; Cardiovascular Disease; Endothelium/Vascular Type/Nitric Oxide; Risk Factors; Ultrasound; Vascular Disease

Introduction

People living with human immunodeficiency virus (HIV) infection (PLWH) are at increased cardiovascular disease (CVD) risk compared to those without HIV infection[1–3]. CVD has emerged as a leading cause of death among those living with HIV infection[4,5], however, the factors that contribute to CVD among PLWH infection are uncertain[2,6]. Early studies suggested that certain anti-retroviral therapies (ART) increased CVD risk; others pointed to an increased CVD risk factor burden related to ART (*e.g.,* dyslipidemia, insulin resistance) as well as cigarette smoking, kidney disease, cocaine use, and hepatitis C co-infection[2,6–8]. More recently, investigators have focused on inflammation and disordered immune regulation that persist despite viral suppression[9–12]. Identifying the contributors to CVD in PLWH infection has been challenging because the HIV epidemic has evolved over the past 30 years in ways that affect CVD risk. Today, PLWH are diagnosed younger, treated earlier, use ART regimens with less metabolic toxicities, live longer and to older ages, use more lipid-lowering medications, and have a lower prevalence of cigarette smoking – factors that influence CVD risk[12–14].

We sought to characterize the effects of HIV serostatus, HIV disease severity, and CVD risk factors on brachial artery (BA) flow-mediated dilation (FMD), a sensitive measure of arterial endothelial function that is associated with CVD risk factors and that predicts future CVD

events [17–23] in the largest dataset that evaluated CVD risk among PLWH infection reported to date. This dataset used harmonized laboratory and ultrasound measurements from participants in the National Heart, Lung, and Blood Institute's HIV-CVD Initiative[20–24], enhanced by 4 large cohorts from the Acquired Immune Deficiency Syndrome (AIDS) Clinical Trial Group[26–28] and 2 cohorts of HIV-negative individuals[29,30]. It provided the unique opportunity to investigate the extent to which HIV serostatus influences endothelial function after controlling for CVD risk factors and other confounders of CVD risk in PLWH infection compared to people without HIV disease.

Materials and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

The following studies and their brief descriptions were included in this analysis: ACTG studies A5152s[26] (PLWH, ART-naïve adults, 19-59 years old), A5260s[21] (PLWH, ART-naïve adults 19-72 years old), A5293[25] (PLWH, ART-suppressed adults 33-59 years old, with dyslipidemia), A5331[27] (PLWH, ART-suppressed adults 21-63 years old), and A5314[28] (PLWH. ART-suppressed adults 42-73 years old at increased CVD risk); University of Hawaii studies H001 and H009[20,23] (PLWH and HIV−; 40-73 years old); Indiana University studies PFX A, B, and C[24] (PLWH and HIV−,18-59 years old); CARDIO-DIAB[29] (HIV−, 18-48 years old), and the Wisconsin Smokers Health Study-1[30] (HIV− current tobacco users, 18-79 years old). The two cohorts of HIV-negative participants were selected from available data sets that were enriched with young adults and smokers to provide better comparability to the relatively young age and smoking heaviness prevalent in PLWH during the approximately 15 years of the HIV epidemic that these data were collected. The HIV-CVD Initiative[22] included the University of Hawaii, Indiana University, and A5260s studies. Each study was approved by the human subjects research Institutional Review Board at each participating site. Each participant provided informed consent prior to participation.

BA Ultrasonography

All BA ultrasound data were obtained by core lab (University of Wisconsin)-certified sonographers using the exact same scanning and measuring techniques[20–30]. Sonographers completed on-line and in-person training sessions then performed mock studies to demonstrate protocol adherence, correct use of ultrasound instrumentation and controls, high quality imaging, and landmark reproducibility prior to scanning subjects. They maintained certification through a rigorous quality assurance program that included continuous quality control including continuous assessment of sonographer image quality, reproducibility, and ultrasound phantom scans.

BA ultrasound studies used the lower arm occlusion method[31]. Fasted subjects who refrained from cigarette smoking and exercise for ≥8 hours and rested supine in a temperature-controlled room for 10 minutes prior to imaging. A blood pressure cuff was placed on the proximal right forearm approximately 1 cm distal to the antecubital fossa. The

arm was extended 90° from the thorax and placed on an arm board with the elbow positioned downwards and the hand rotated so thumb pointed towards the ceiling. Using a high-resolution linear array vascular ultrasound transducer, the brachial artery was located above the elbow and scanned in longitudinal sections with the focus zone set to the depth of the far wall. Time-gain compensation and overall gain settings were used to optimize images of the lumen/arterial wall interface. Extra-vascular landmarks were identified and labeled to assure reproducible segmental brachial artery imaging. After recording baseline B-mode images of the artery and spectral Doppler flow images, the forearm cuff was inflated to 250 mmHg for 5 minutes to induce reactive hyperemia. Immediately after deflation, spectral Doppler images were obtained to verify hyperemia. Peak brachial artery FMD was measured for at least 60 and up to 90 seconds after cuff deflation.

Ultrasound systems were required to acquire and store images in digital (DICOM) format with ECG-gating and to use a linear-array vascular ultrasound transducer with a frequency >7 MHz[31]. Although some imaging sites had different ultrasound systems, BA diameter and flow measurements obtained during BA reactivity testing are large and above the limits of resolution of modern ultrasound systems and are not affected notably by instrumentation as long as the ultrasound system requirements from the core lab were met and the imaging protocol that standardized imaging gains and presets were followed. All equipment had baseline and 6-monthly phantom scan analyses to exclude temporal drift.

FMD (%) was calculated as the ratio between the 60-second post cuff release BA diameter and the baseline diameter[31]. Peak hyperemic flow velocity (PHFV) was measured as the peak velocity of the spectral Doppler blood flow signal from the first three consecutive complete, stable beats after cuff release[32,33]. PHFV values only were available from the studies of PLWH. All imaging was performed digitally and images were transferred to the core lab by secure file transfer protocol for offline measurement in triplicate. Measurement reproducibility was excellent and has been reported previously[21,26,30].

Laboratory testing

Standard clinical laboratory tests were performed using validated assays at Clinical Laboratory Improvement Amendments-approved clinical laboratories. All studies had lipoprotein measurements performed by nuclear magnetic resonance spectroscopy (formerly LipoScience, Raleigh, NC). The HIV-CVD Initiative studies had inflammatory biomarkers (*i.e.,* high sensitivity C-reactive protein, interleukin-6) measured at the University of Vermont.

Data Analysis

All variables were described as means (standard deviations) with ranges. Variables with highly skewed distributions (*e.g.,* C-reactive protein, HIV RNA) were $\log_{10}$ transformed. HIV RNA values below the limit of detection were set at the lower limit of detection before transformation. Frequency distributions and descriptive statistics for all variables were reviewed for each study to confirm their validity and comparability and to identify and eliminate biologically implausible outlier values. Sequential multivariable linear mixed regression models were used to evaluate the effect of HIV serostatus on FMD to account for

clustering within each study and to permit robust confidence intervals (model 0). The beta coefficient, 95% confidence interval, and sample sizes were evaluated as the following variables were added sequentially based on an *a priori* modeling plan: Model 1 = BA diameter, age, sex, body-mass index, race/ethnicity; Model 2 = non-high-density lipoprotein cholesterol, systolic and diastolic blood pressures, heart rate, glucose, and Model 3 = creatinine. For sensitivity analyses, we created additional linear mixed models to explore the effects of adjustments for use of antihypertensive, lipid-lowering, and antiglycemic medications, low-density and high-density lipoprotein particle sizes, $\log_{10}$ transformed C-reactive protein, and interleukin-6 levels. We also assessed for modification of the effect of HIV serostatus by age by introducing an age*HIV serostatus interaction term after Model 3. Sensitivity analyses also included sequential linear mixed models that individually left out each of the 7 studies of PLWH to ensure our results were not driven by a single outlying study.

We further explored the notable effect of creatinine in model 3 on the association between HIV serostatus on FMD. We did this in two ways that permitted us to evaluate creatinine as a confounder and to ensure that creatinine was not acting as a collider. First, we created reduced models that only included HIV serostatus, age, creatinine, and smoking status, as many of the adjustment factors were collinear with creatinine and could have led to underestimating this association. Second, we performed comprehensive regression modeling that introduced creatinine stratified at three levels: above/below the cohort's median creatinine value, by tertiles, and above the cohort's 95th percentiles versus below the cohort's median value. Secondary analyses used the same modeling strategy and evaluated BA and PHFV (in PLWH) as outcome variables. We used a similar modeling strategy to assess the individual effects of CD4+ T-cell concentration, $\log_{10}$ HIV RNA concentration, undetectable HIV RNA, and use of ART on each of the 3 BA outcome measures and also looked for interactions with age.

Results

Participant Characteristics

Overall participant characteristics and by HIV serostatus are in Table 1. Characteristics by individual study are in Supplemental Table 1. Participants and data availability are in Figure 1.

Effects of HIV Serostatus and CVD Risk Factors on Brachial Artery FMD

The effect of HIV serostatus on FMD was not statistically significant alone or after adjustments in models 1 and 2 (Table 2). Larger BA diameter ($p<0.0001$ in all models), increasing age, female sex, and lower body-mass index were the strongest and most consistent predictors of lower FMD in all models. However, after adjusting for creatinine, HIV-positive serostatus was significantly associated with lower FMD ($\beta=-0.89\%$, 95% confidence intervals [CI] −1.61 to −0.17%, $p=0.015$). The significant association of HIV-positive serostatus with lower FMD was robust to adjustment for use of antihypertensive, lipid-lowering, and antiglycemic medications, lipoprotein particle sizes, and IL-6 levels, none of which were associated independently with FMD. Furthermore, adding C-reactive

protein level to model 3 (N=1656) strengthened the association of HIV-positivity with lower FMD (β=−1.20%, 95% CI −1.85 to −0.55%, p<0.0001); this finding also was robust to all further adjustments (Figure 2), even though the association of CRP with FMD was weak and not statistically significant. There was no evidence of an age*HIV serostatus interaction in any model. Individually leaving out each of the studies that included PLWH did not materially affect the point estimate and confidence intervals for the effect of HIV serostatus on FMD.

Effects of Kidney Function on the Relationship between HIV Serostatus and Brachial Artery FMD

As in Table 1, creatinine levels were higher in PLWH than in HIV-negative participants (p<0.001) and the inverse correlation between creatinine level and FMD was slightly stronger in PLWH (r=−0.14) than in HIV-negative participants (r=−0.05). In reduced models that only included HIV serostatus, age, race, and creatinine, HIV serostatus (β=−1.25, standard error 0.39, p=0.001) and creatinine (β=−0.72, standard error 0.32, p=0.024) were independent associates of FMD ((Supplemental Table 2). These models essentially were unchanged after adding smoking status (Supplemental Table 3).

As in Table 3A, the effect of serum creatinine on the association between HIV-positive serostatus and FMD in the highest tertile of creatinine (>1.0 mg/dL) was strong (model 0, β=−1.59%, 95%CI −2.58 to −0.60%), statistically significant (p=0.002), and minimally affected by the multiple adjustments in models 1 and 2. However, in the middle and lowest tertiles of creatinine (Tables 3B and 3C, respectively), the effect size of the association between HV serostatus and FMD was markedly diminished and not statistically significant after adjustments in models 1 and 2. A similar pattern of larger and statistically significant inverse associations between HIV serostatus and FMD were observed for creatinine above the median of 0.9 mg/dL (but not below) and for creatinine above the 95th percentile of 1.2 mg/dL and the 67th percentile of 1.0 mg/dL (but not below it) (Supplemental Tables 3 and 4). Formal interaction testing of HIV serostatus by creatinine level was not statistically significant, likely due to low statistical power to detect an interaction.

Effects of HIV Serostatus and CVD Risk Factors on Other Brachial Artery Measures

HIV serostatus was not associated strongly with BA diameter alone or in any models. BA diameter was associated strongly with increasing age, male sex, larger body-mass index (p<0.001 for each), and higher diastolic blood pressure (p=0.004) (data not shown).

Effects of Measures of HIV Disease Severity and ART on FMD and Other Measures

HIV RNA viremia, undetectable HIV RNA, CD4+ T-cell count, and use of ART were not associated significantly with FMD alone or in any models. No meaningful interactions with age were identified for any of these 4 measures of HIV disease severity. We did not identify a major effect of hepatitis co-infection status on FMD. HIV RNA viremia (p<0.001), undetectable HIV RNA (p=0.002), and use of ART (p=0.007) were associated inversely with BA diameter, but these associations were not significant after adjusting for age. HIV RNA viremia, undetectable HIV RNA, CD4+ T-cell count, and use of ART were not associated significantly with PHFV alone or in any models.

Discussion

In a large pooled cohort study with harmonized brachial artery ultrasound and laboratory techniques, we demonstrated that FMD, a measure of arterial endothelial function that predicts future CVD events, was lower in PLWH than in HIV− controls, after adjusting for factors associated with CVD risk. This association was robust to multiple covariate adjustments and sensitivity analyses performed to detect bias. The effect of HIV+ serostatus on FMD was strongly influenced by kidney function, but not measures of HIV disease severity. These findings are consistent with observational studies that identified increased CVD risk in PLWH[1–3] and emphasize the importance of even a mild degree of kidney function as a modifier of CVD risk in PLWH[8,34]. In our fully adjusted model, the beta coefficient for HIV+ serostatus was notably higher than for age, body-mass index, and non-high-density lipoprotein-cholesterol, as well as other CVD risk factors that were not associated significantly with FMD, though less than that of female sex (though with overlapping 95% CIs). As in Figure 1, the point estimate for the effect of serostatus on FMD became more negative with CVD risk factor adjustment, suggesting that CVD risk factor differences between PLWH and those without HIV obscure the effect of HIV infection on FMD. Once these risk factors were accounted for with statistical adjustment, the effect size and confidence in the effect of HIV serostatus on FMD was clarified.

The large increase in effect size for HIV serostatus that emerged with adjustment for serum creatinine is especially noteworthy. Adding serum creatinine to the models that adjusted for CVD risk factors marginally changed their associations with FMD, but the effect size for HIV serostatus increased and became statistically significant without notably narrowing the 95% confidence intervals. Our reduced models and stratified analyses identified a strong and consistent effect of renal function on the relationship between HIV serostatus and FMD, such that the effect of HIV serostatus on FMD is larger in people with even mild creatinine elevations; or, alternatively, the effect of kidney disease on FMD is greater in people with HIV disease. Our original modeling strategy focused on potential confounders of HIV serostatus and FMD and used extensive covariate adjustments *prior to* introducing the creatinine variable as a late confounder. We discovered that our data sample had “negative confounding” such that the true association between kidney disease and HIV serostatus masked the true association between HIV serostatus and FMD. Indeed, many of those covariates are influenced by kidney disease, which was significantly more prevalent in our HIV+ cohort. Adjusting for serum creatinine also may have reduced channeling bias due to ART prescriptions as HIV-infected patients with kidney disease preferentially were treated with abacavir, a nucleoside reverse transcriptase inhibitor that may increase CVD risk[35,36], rather than tenofovir, a preferred CVD risk-neutral nucleotide reverse transcriptase inhibitor that raises serum creatinine levels[37]. Of note, the effects of abacavir and tenofovir on FMD are not clear[38,39] and this study’s design was not able to address the specific effects of ART agents and classes on FMD in PLWH.

Our observation that even mild differences in renal function significantly impacts the relation between HIV serostatus and FMD is consistent with data from the D:A:D study that identified strong relations between moderate and advanced renal dysfunction and CVD risk in PLWH[8,34]. Our findings suggest that endothelial function related to even mild kidney

disease may play a role in HIV-associated CVD risk. Several factors related to advancing kidney disease are associated with reduced nitric oxide-mediated arterial dilation beyond shared risk factors like hypertension, including activation of the renin-angiotensin-aldosterone system, increased sympathetic activation, and increased levels of angiotensin, renalase, and asymmetric dimethylarginine[40,41].

We did not observe significant age modification of the association between HIV serostatus and FMD, in contrast with a pooled cohort study that showed a stronger association between HIV-positive serostatus and carotid intima-media thickness in younger compared to older adults[42]. Endothelial function is a precedent to carotid wall thickening in the cascade of arterial injury that leads to atherosclerosis[16,43]; the effect of risk factors like HIV infection on FMD may not differ by age if the injury it mediates is permissive to or a foundation upon which other CVD risk factors accelerate arterial injury with aging. Indeed, we consistently observed the expected inverse relationship between FMD and increasing age, consistent with the hypothesis that HIV infection leads to accelerated or accentuated arterial aging[44]. We also observed progressive, inverse strengthening of the effect of HIV serostatus on FMD as we introduced CVD risk factors, all consistent with an independent effect of HIV infection on endothelial function across the age spectrum of this study.

Adding CRP to the models further strengthened the association of HIV serostatus with FMD, but like creatinine, its association with FMD was weak and not statistically significant in the context of a highly adjusted model with other variables that also are related to CRP. Although CRP is associated with increased CVD event risk in PLWH[45,46], recent studies demonstrate that CRP levels are markers, not mediators, of CVD[47,48]. CRP levels were higher among PLWH than those without HIV infection, but were not correlated with FMD in either group (data not shown). It is not clear why the effect estimate of HIV serostatus on FMD became stronger when CRP was added to model 3. If CRP is a measure of residual subclinical inflammation that causes arterial injury among people with treated and suppressed HIV infection or is an adverse effect of certain ART that we could not discern in this study, controlling for it may further reduce confounding in the estimate of the association of HIV infection on the endothelium.

In contrast to observational studies showing that HIV viremia and CD4+ T-cells measures are associated with increased CVD risk[2,49], these markers of HIV disease severity were not associated with FMD in our study. It is not clear why, but the absence of these associations is consistent in each of the component studies. It is possible that the HIV disease severity markers we measured don't adequately reflect the impact of HIV disease on FMD at the time we measured them or impact FMD much less than other risk factors (*i.e.,* upon entry into a clinical trial of initial ART, of lipid-lowering therapy, or of anti-inflammatory therapy for high CVD risk). It also is possible that nitric oxide-dependent dilation of a large conduit artery does not reflect the arterial injury and increased CVD risk associated with uncontrolled HIV infection as well as it reflects injury from traditional CVD risk factors.

Our study had several strengths. It is the largest study to date evaluating the effects of HIV serostatus and measures of HIV disease activity on endothelial dysfunction, a key step in atherogenesis that contributes its initiation, perpetuation, and clinical manifestations[16,43].

We measured FMD using the same brachial artery reactivity testing protocol in all participants. Brachial artery FMD correlates strongly with coronary artery FMD[50]. Indeed, PLWH have abnormal coronary flow reserve that responds rapidly to proprotein convertase subtilisin/kexin type 9 inhibition, even in the absence of hypercholesterolemia[51,52]. Each participating site was certified by the same core lab that performed all measurements. Our participants had a wide range of ages from young adulthood through older age and were recruited over 15 years of changing treatments for HIV disease; controls were enriched in cigarette smokers to be more comparable to PLWH in this study.

The approximately 1% lower FMD effect size for HIV serostatus that we identified is clinically meaningful. In the Multi-Ethnic Study of Atherosclerosis of CVD-free middle-aged healthy adults and in the Cardiovascular Health Study of older adults, a 1% lower FMD was associated with an approximately 10-11% increased risk of a future CVD event in middle-aged adults free clinical CVD[18,19]. Furthermore, administration of pravastatin to hypercholesteremic patients with HIV infection led to an approximately 1% improvement in FMD after 8 weeks[53,54], suggesting that the magnitude of the HIV serostatus effect on FMD is clinically important.

Our study also had limitations. As a pooled cohort study, we couldn't assess the effects of individual ART classes due to the wide range of treatments in the cohort and limited sample sizes of specific ART regimens, as well as the possibility of medication channeling. We also cannot rule out the effect of other unmeasured confounders or underestimates of the effects of CVD risk factors on FMD due its variability as a biological measure, even when acquired and measured using highly standardized protocols. There were important differences between the PLWH and the HIV-control groups with respect to age, sex, race and smoking status. Though these were adjusted for in our analyses, we cannot exclude the possibility of some residual confounding. The minimal impact of smoking status on the effect of HIV serostatus on FMD suggests that smoking status is not likely to be a collider variable in these analyses. Because PLWH in our study were recruited into their cohorts over approximately 15 years and were enriched in ART-naive individuals, their overall characteristics differ from clinical populations today. Women and non-Whites, as well as people with hepatitis co-infection were relatively underrepresented which may affect generalizability of our findings. Also, measurement variation in ultrasound machines and due to sonographers may have limited our ability to discern the effects of individual markers of HIV disease severity on FMD.

Conclusions

In the largest study of the effects of HIV serostatus and CVD risk factors on endothelial function performed to date, HIV seropositivity was associated independently with impaired endothelial function, suggesting that HIV infection increases CVD risk beyond associated risk factors. The effect of HIV+ serostatus on FMD was influenced strongly by even mild reductions in kidney function, which had a greater effect in PLWH than in people without HIV disease. These findings suggest that endothelial function related to even mild kidney disease may play a role in HIV-associated CVD risk. Our findings support observational data

and provide mechanistic insight into the observation that PLWH are at increased CVD risk, especially if they have kidney disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACTG	AIDS Clinical Trials Group
AIDS	Acquired Immune Deficiency Syndrome
ART	antiretroviral therapy
BA	brachial artery
CVD	cardiovascular disease
FMD	flow-mediated dilation
HIV	human immunodeficiency virus
PHFV	peak hyperemic flow velocity
PLWH	people living with HIV

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Highlights

- HIV seropositivity was associated independently with impaired endothelial function, suggesting that HIV infection increases CVD risk beyond associated risk factors.
- The effect of HIV+ serostatus on FMD was influenced strongly by even mild reductions in kidney function, which had a greater effect in PLWH than in people without HIV disease.
- These findiings suggest that endothelial function related to even mild kidney disease may play a role in HIV-associated CVD risk.
- The magnitude of the association of HIV serostatus with FMD is clinically relevant.
- Our findings support observational data and provide mechanistic insight into the observation that PLWH are at increased CVD risk, especially if they have kidney disease.

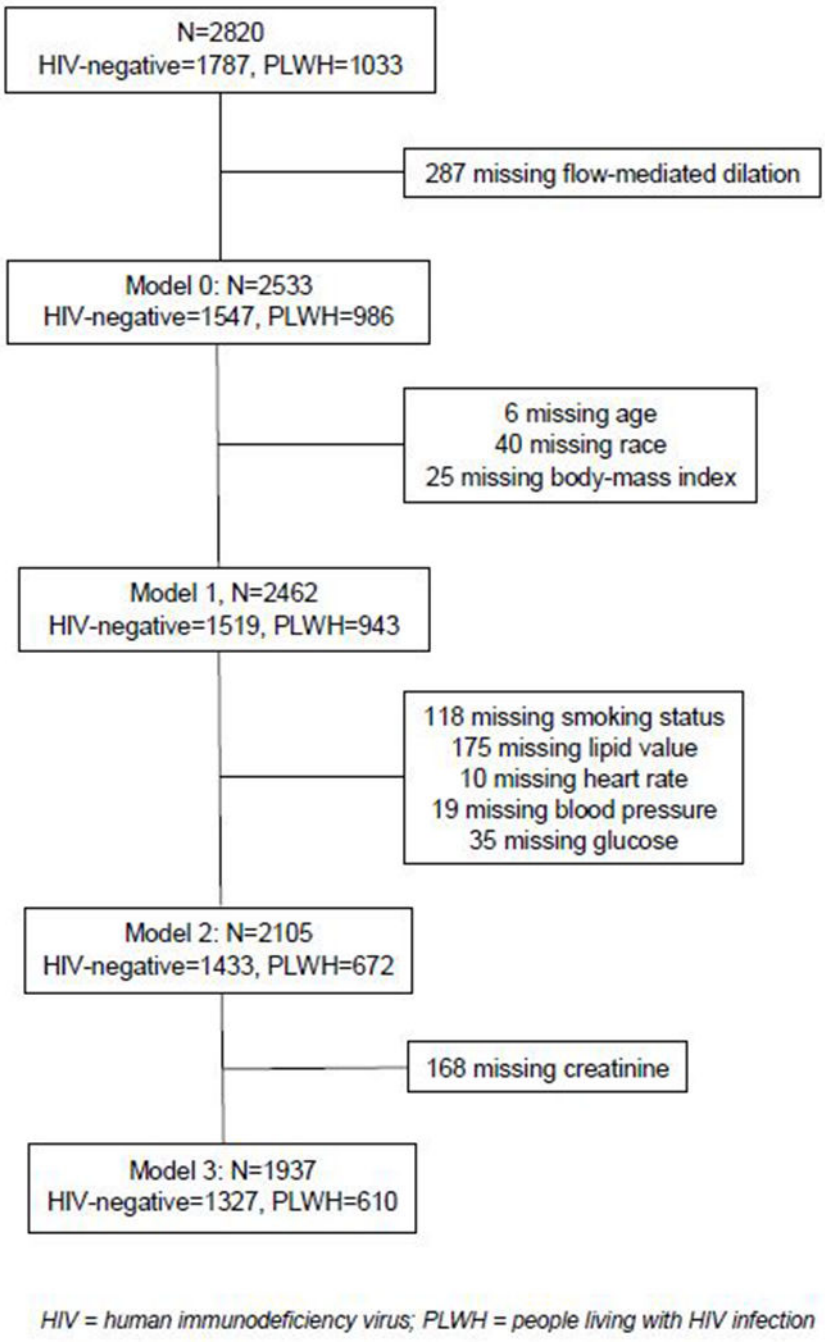

Figure 1. Participants and Data Availability

HIV = human immunodeficiency virus; PLWH = people living with HIV infection

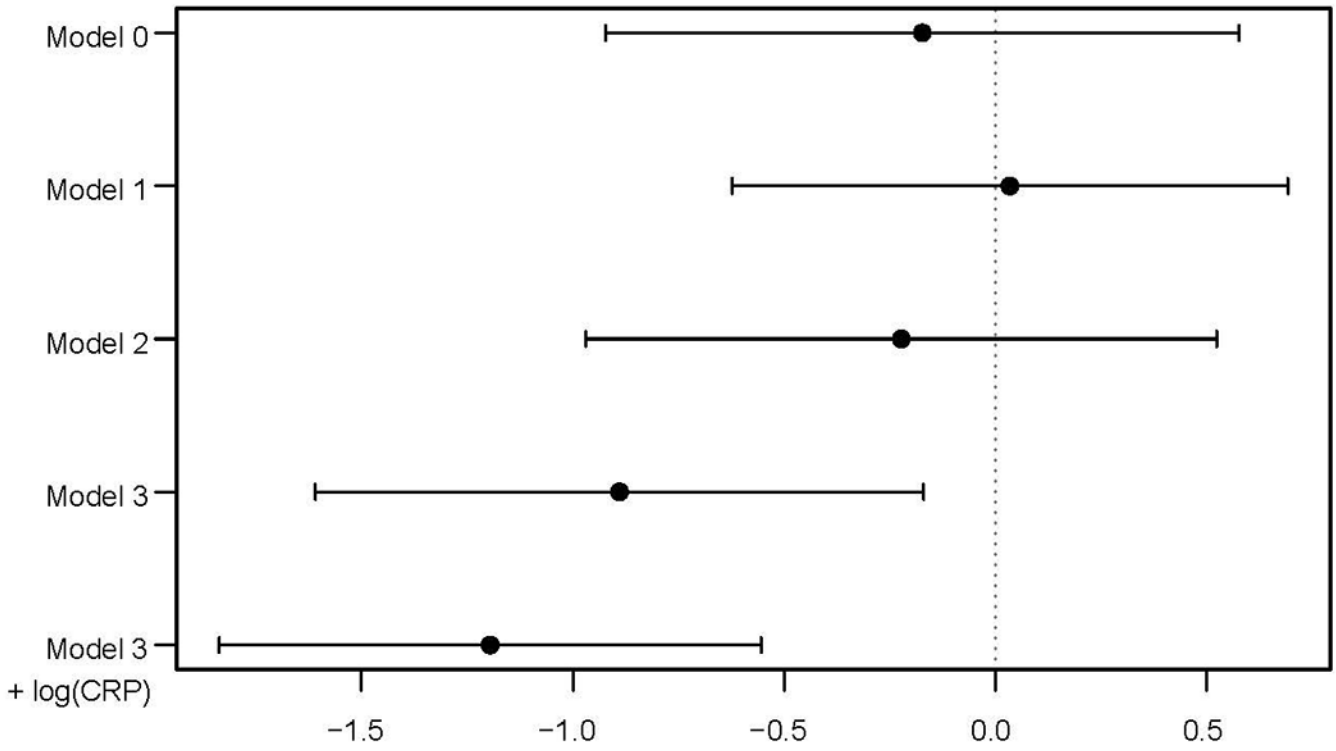

Figure 2.
Effects of HIV Serostatus on Brachial Artery Flow-Mediated Dilation Models as in Table 2

Table 1.

Participant Characteristics

	Overall (N=2533)	PLWH (N=986)	HIV− (N=1547)
Age, years	43.5 (12.1)	44.4 (11.8)	42.9 (12.2)
Female, n	975 (38.5)	128 (13)	847 (54.8)
Body-mass index, kg/m^2	27.9 (6.5)	27.0 (5.4)	28.5 (7.0)
Race, n			
White	1898 (74.9)	596 (60.4)	1302 (84.2)
Black	469 (18.5)	287 (29.1)	182 (11.8)
American Indian or Alaska Native	14 (0.5)	6 (0.6)	8 (0.6)
Asian/Pacific Islander	39 (1.5)	28 (2.8)	11 (0.7)
Other	71 (2.8)	30 (3)	41 (2.7)
Hispanic, n	237 (9.4)	190 (19.3)	47 (3)
Smoking status			
Current smoker, n	1703 (67.2)	327 (33.2)	1376 (88.9)
Ever smoked, n	1989 (78.5)	554 (56.2)	1435 (92.8)
Non-high-density lipoprotein cholesterol, cholesterol, mg/dL	132.9 (36.9)	126.7 (35.6)	136.4 (37.2)
Heart rate, bpm	63.6 (10.6)	65.2 (10.7)	62.5 (10.4)
Systolic blood pressure, mmHg	121.9 (15.5)	120.0 (13.5)	123.2 (16.5)
Diastolic blood pressure, mmHg	73.8 (9.3)	74.0 (9.2)	73.6 (9.3)
Glucose, mg/dL	91.9 (16.0)	89.3 (14.5)	93.2 (16.5)
Creatinine, mg/dL	0.94 (0.26)	0.96 (0.21)	0.92 (0.28)
C-reactive protein, mg/L	0.85 (5.11)	1.85 (3.12)	0.59 (5.47)
Interleukin-6, pcg/mL	2.3 (3.1)	2.2 (2.3)	3.5 (10.0)
Medication use, n			
Antihypertensive	328 (12.9)	263 (26.7)	65 (4.2)
Lipid-lowering	305 (12)	241 (24.4)	64 (4.1)
Diabetes mellitus	85 (3.4)	54 (5.5)	31 (2)
Brachial artery measures			
Flow-mediated dilation,	5.2 (3.8)	4.3 (2.8)	5.8 (4.2)
Baseline diameter, cm	0.41 (0.07)	0.44 (0.06)	0.39 (0.07)
Peak hyperemic flow velocity, cm/s	145.4 (34.0)	145.8 (34.2)	142.5 (32.4)
HIV parameters			
HIV RNA, log copies/mL	*	2.9 (1.6)	*
HIV RNA suppressed, n	*	521 (52.8)	*
CD4+ T-cells, /mm^3	*	505.4 (303.9)	*
Antiretroviral therapy use, n	*	557 (56.5)	*
Hepatitis co-infection			
Hepatitis B	98 (3.9)	96 (9.7)	*

	Overall (N=2533)	PLWH (N=986)	HIV− (N=1547)
Hepatitis C	41 (1.6)	38 (3.9)	*

All values are mean (standard deviation) or N (%);

* = not available; C-reactive protein values are geometric means;

bpm = beats per minute; HIV =human immunodeficiency virus, PLWH = people living with HIV, RNA = ribonucleic acid

Table 2.

Models of the Effect of HIV Serostatus and Cardiovascular Disease Risk Factors on Brachial Artery Flow-Mediation Dilation

	β	95% Lower CI	95% Upper CI	P-value
Model 0 (n=2533)				
HIV-positive serostatus	−0.17	−0.92	0.58	0.651
Model 1 (n=2462)				
HIV-positive serostatus	0.03	−0.62	0.69	0.919
Baseline brachial artery diameter (cm)	−23.45	−26.21	−20.69	<0.001
Age (/5 years)	−0.10	−0.17	−0.03	0.003
Female sex	−1.11	−1.53	−0.70	<0.001
Body-mass index (/5 kg/m^2)	0.22	0.11	0.33	<0.001
White race (vs. not white)	0.16	−0.17	0.49	0.355
Model 2 (n=2105)				
HIV-positive serostatus	−0.22	−0.97	0.52	0.558
Baseline brachial artery diameter (cm)	−23.44	−26.56	−20.33	<0.0001
Age (/5 years)	−0.11	−0.19	−0.03	0.005
Female sex	−1.27	−1.73	−0.81	<0.0001
Body-mass index (/5 kg/m^2)	0.18	0.05	0.31	0.006
White race (vs. not white)	0.14	−0.24	0.52	0.479
Current smoker (vs. not)	0.12	−0.34	0.58	0.605
Non-high-density lipoprotein cholesterol (/10 mg/dL)	0.07	0.02	0.11	0.004
Heart rate (/10 bpm)	0.23	0.08	0.38	0.003
Systolic blood pressure (/10 mmHg)	0.03	−0.09	0.15	0.636
Diastolic blood pressure (/5 mmHg)	−0.08	−0.19	0.02	0.127
Glucose (/10 mg/dL)	0.02	−0.08	0.12	0.684
Model 3 (n=1937)				
HIV-positive serostatus	−0.89	−1.61	−0.17	**0.015**
Baseline brachial artery diameter (cm)	−24.23	−27.56	−20.90	<0.001
Age (/5 years)	−0.09	−0.17	−0.01	0.027
Female sex	−1.48	−1.99	−0.98	<0.001
Body-mass index (/5 kg/m^2)	0.26	0.10	0.41	<0.001
White race (vs. not white)	0.18	−0.23	0.59	0.393
Current smoker (vs. not)	−0.04	−0.53	0.46	0.888
Non-high-density lipoprotein cholesterol (/10 mg/dL)	0.06	0.01	0.11	0.013
Heart rate (/10 bpm)	0.22	0.06	0.38	0.007
Systolic blood pressure (/10 mmHg)	0.03	−0.01	0.16	0.618
Diastolic blood pressure (/5 mmHg)	−0.11	−0.23	0.00	0.055
Glucose (/10 mg/dL)	0.00	−0.11	0.11	0.985

	β	95% Lower CI	95% Upper CI	P-value
Creatinine (/0.5 mg/dL)	−0.01	−0.33	0.32	0.972

CI = confidence interval, HIV = human immunodeficiency virus

Table 3.

Models of the Effect of HIV Serostatus and Cardiovascular Disease Risk Factors on Brachial Artery Flow-Mediation Dilation by Tertiles of Serum Creatinine

A. Highest tertile (Creatinine >1.0 mg/dL)				
	β	**95% Lower CI**	**95% Upper CI**	**P-value**
Model 0 (n=860)				
HIV-positive serostatus	−1.59	−2.58	−0.60	**0.002**
Model 1 (n=833)				
HIV-positive serostatus	−0.97	−1.67	−0.27	**0.007**
Baseline brachial artery diameter (cm)	−18.17	−22.23	−14.11	<0.001
Age (/5 years)	−0.02	−0.04	0.00	0.0248
Female sex	−1.18	−1.89	−0.46	0.0013
Body-mass index (/5 kg/m^2)	0.05	0.01	0.10	0.0148
White race (vs. not white)	0.39	−0.12	0.90	0.1352
Model 2 (n=745)				
HIV-positive serostatus	−1.36	−2.26	−0.47	**0.003**
Baseline brachial artery diameter (cm)	−18.64	−23.14	−14.15	<0.001
Age (/5 years)	−0.09	−0.19	0.02	0.113
Female sex	−1.47	−2.24	−0.70	<0.001
Body-mass index (/5 kg/m^2)	0.07	0.02	0.12	0.010
White race (vs. not white)	0.22	−0.36	0.80	0.457
Current smoker (vs. not)	−0.46	−1.18	0.26	0.213
Non-high-density lipoprotein cholesterol (/10 mg/dL)	0.04	−0.03	0.10	0.280
Heart rate (/10 bpm)	0.12	−0.11	0.35	0.300
Systolic blood pressure (/10 mmHg)	−0.01	−0.03	0.01	0.395
Diastolic blood pressure (/5 mmHg)	0.00	−0.03	0.04	0.923
Glucose (/10 mg/dL)	−0.01	−0.03	0.00	0.093
B. Middle tertile (Creatinine 0.8-1.0 mg/dL)				
	β	**95% Lower CI**	**95% Upper CI**	**P-value**
Model 0 (n=607)				
HIV-positive serostatus	−1.48	−2.15	−0.81	**<0.001**
Model 1 (n=553)				
HIV-positive serostatus	−0.59	−1.30	0.12	0.105
Baseline brachial artery diameter (cm)	−22.92	−28.87	−16.97	<0.001
Age (/5 years)	−0.01	−0.04	0.01	0.246
Female sex	−1.09	−1.97	−0.22	0.014
Body-mass index (/5 kg/m^2)	0.05	0.00	0.10	0.037
White race (vs. not white)	0.40	−0.31	1.11	0.270
Model 2 (n=553)				

A. Highest tertile (Creatinine >1.0 mg/dL)				
	β	**95% Lower CI**	**95% Upper CI**	**P-value**
HIV-positive serostatus	−0.36	−1.26	0.53	0.424
Baseline brachial artery diameter (cm)	−23.24	−29.54	−16.93	<0.001
Age (/5 years)	−0.11	−0.25	0.03	0.114
Female sex	−1.12	−2.03	−0.21	0.016
Body-mass index (/5 kg/m^2)	0.02	−0.04	0.07	0.585
White race (vs. not white)	0.34	−0.43	1.11	0.384
Current smoker (vs. not)	0.15	−0.65	0.96	0.710
Non-high-density lipoprotein cholesterol (/10 mg/dL)	0.11	0.02	0.19	0.018
Heart rate (/10 bpm)	0.28	−0.01	0.58	0.063
Systolic blood pressure (/10 mmHg)	0.02	−0.01	0.05	0.187
Diastolic blood pressure (/5 mmHg)	−0.06	−0.10	−0.01	0.009
Glucose (/10 mg/dL)	0.02	0.00	0.04	0.098
C. Lowest tertile (Creatinine <0.8 mg/dL)				
	β	**95% Lower CI**	**95% Upper CI**	**P-value**
Model 0 (n=728)				
HIV-positive serostatus	−1.90	−2.58	−1.21	**<0.001**
Model 1 (n=709)				
HIV-positive serostatus	−0.75	−2.01	0.50	0.239
Baseline brachial artery diameter (cm)	−33.92	−40.40	−27.45	<0.001
Age (/5 years)	−0.01	−0.04	0.02	0.419
Female sex	−2.29	−3.33	−1.25	<0.001
Body-mass index (/5 kg/m^2)	0.08	0.03	0.13	<0.001
White race (vs. not white)	0.05	−0.71	0.81	0.900
Model 2 (n=639)				
HIV-positive serostatus	−0.98	−2.13	0.16	0.093
Baseline brachial artery diameter (cm)	−34.56	−41.61	−27.52	<0.001
Age (/5 years)	−0.05	−0.21	0.10	0.497
Female sex	−2.53	−3.66	−1.40	<0.001
Body-mass index (/5 kg/m^2)	0.07	0.02	0.13	0.009
White race (vs. not white)	0.03	−0.81	0.86	0.950
Current smoker (vs. not)	0.62	−0.35	1.59	0.208
Non-high-density lipoprotein cholesterol (/10 mg/dL)	0.06	−0.04	0.15	0.243
Heart rate (/10 bpm)	0.19	−0.13	0.51	0.235
Systolic blood pressure (/10 mmHg)	0.00	−0.02	0.02	0.769
Diastolic blood pressure (/5 mmHg)	−0.02	−0.06	0.03	0.489
Glucose (/10 mg/dL)	0.00	−0.02	0.02	0.785

CI = confidence interval, HIV = human immunodeficiency virus