ORIGINAL RESEARCH

Effect of Sex on Coronary Endothelial Dysfunction in People Living With HIV

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BACKGROUND: Impaired coronary endothelial function (CEF) predicts cardiovascular events and occurs in people living with HIV (PLWH). Women compared with men living with HIV have worse cardiovascular outcomes, but prior CEF studies included few women. The authors aimed to compare CEF in women with HIV versus without HIV, investigate sex differences in CEF and PCSK9 (proprotein convertase subtilisin/kexin type 9) (a proinflammatory biomarker), and evaluate whether increased serum levels of PCSK9 are associated with CEF in PLWH.

METHODS AND RESULTS: Magnetic resonance imaging was performed to measure CEF (as percent change in coronary cross-sectional area and coronary blood flow during isometric handgrip exercise, an endothelial-dependent stressor) and serum PCSK9 levels were measured in 106 PLWH and 76 people without HIV. CEF was significantly reduced in women with versus without HIV (cross-sectional area change −0.5%±9.7 versus 9.5%±3.2, respectively). After adjustment for age, body mass index, and menopausal status, women with HIV still had reduced CEF (percentage of cross-sectional area: ß −8.3 [−13 to −3.6], P=0.001) compared with women without HIV. PCSK9 was elevated in women living with HIV versus without (306 ng/mL [200–412 ng/mL] versus 180 ng/mL [154–223 ng/mL], P<0.001), and no sex differences in either CEF or PCSK9 were detected in PLWH. Elevated PCSK9 was associated with impaired CEF in PLWH; however, no significant sex differences in the association were detected.

CONCLUSIONS: Among PLWH, coronary endothelial dysfunction is present in women and comparable to men. PCSK9 is higher in women with versus without HIV and a significant inverse relationship between PCSK9 and CEF was shown. Future studies should determine whether PLWH would benefit from interventions to improve endothelial function.

Key Words: coronary endothelial function ■ HIV ■ women

With the advent of contemporary antiretroviral therapy (ART), people living with HIV (PLWH) have reduced mortality and experience an increase in cardiovascular disease (CVD).[1] PLWH have an elevated risk of myocardial infarction, ischemic stroke, and heart failure, among other forms of cardiovascular disease, compared with people without HIV.[1] These risks exceed what may be expected from traditional CVD risk factors alone, which are more prevalent among PLWH.[1] Specifically, the risk of myocardial infarction is reported to be anywhere from 50% to 2-fold higher in PLWH.[1] Notably, while the risk of CVD is higher in all PLWH compared with those without HIV, the excess risk of myocardial infarction may be even greater in women with HIV.[2,3]

Contributors of CVD risk in PLWH are not entirely defined but include metabolic risk factors, chronic inflammation, dysregulated immune activation, and possibly ART.[1] Abnormal coronary endothelial function (CEF) is a marker of early coronary artery disease (CAD) and predicts cardiovascular events.[4,5] More importantly, CEF responds favorably to therapies that

CLINICAL PERSPECTIVES

What Is New?
- Coronary endothelial function is impaired in women with HIV.
- Proprotein convertase subtilisin/kexin type 9 levels are elevated in women and men with HIV, and are inversely associated with coronary endothelial function.

What Are the Clinical Implications?
- In women with HIV, it is important to consider impaired coronary endothelial function as a possible contributor to cardiovascular events.
- These findings may help precipitate use of new therapies to reduce cardiovascular events in women and men with HIV.

Nonstandard Abbreviations and Acronyms

CBF	coronary blood flow
CEF	coronary endothelial function
CSA	cross-sectional area
PCSK9	proprotein convertase subtilisin/kexin type 9
PLWH	people living with HIV

reduce atherosclerotic events.[5,6] While CEF could previously only be measured in the invasive catheterization laboratory during coronary angiography, our group developed a noninvasive magnetic resonance imaging (MRI)–based method to measure changes in coronary cross-sectional area (CSA) and coronary blood flow in response to isometric handgrip exercise, an endothelial-dependent stress.[7] These MRI measures of CEF were shown to be nitric oxide–mediated, thus representing endothelial function, and reproducible.[7,8] We previously reported that CEF is impaired in PLWH with no significant CAD.[9]

One potential contributor to CVD in PLWH is PCSK9 (proprotein convertase subtilisin/kexin type 9), which is traditionally recognized for its importance in cholesterol metabolism.[10] However, recent studies suggest an additional, low-density lipoprotein receptor–independent adverse effect on endothelial cell function.[11] Our group and others reported that PCSK9, which has been linked to systemic inflammation, is elevated in PLWH and associated with abnormal CEF.[11] Unfortunately, prior studies included few women with HIV.[11] Some studies demonstrated that reduced ovarian reserve in women is associated with subclinical atherosclerotic plaque, and that hormonal dysregulation, characterized by prolonged amenorrhea and premature menopause, is present in women with HIV.[12] However, it is unclear whether CEF is impaired in women with HIV as compared with women without HIV, independent of menopausal status. Furthermore, it is unknown whether there are sex differences in the extent of CEF impairment and PCSK9 elevation observed in PLWH and whether the association of CEF with PCSK9 is different in women versus men with HIV. We aimed to investigate: (1) whether CEF is reduced in women with HIV compared with women without HIV, (2) the extent of CEF impairment and PCSK9 elevation between men and women with HIV, and (3) to evaluate the interaction of sex in the relationship of PCSK9 with CEF among PLWH.

METHODS

Data used in this study are available from the investigators upon reasonable request.

Patient Selection and Enrollment

Both HIV-seropositive adults and participants without HIV (aged ≥21 years) were recruited from outpatient clinics at Johns Hopkins Medicine. Both controls and PLWH were recruited from community-based clinics in Baltimore, Maryland, within the same geographical region from Johns Hopkins Medicine, primarily serving patients living in Baltimore. Controls were matched based on age (by decade) and sex. In the current study, self-defined biologic sex was used to categorize women and men. Participants were included if they had no prior history of clinical CAD (coronary revascularization, myocardial infarction, or angina) and, if available within the prior 2 years, no obstructive (luminal stenosis >50%) CAD on a clinically indicated coronary angiography or coronary computed tomography angiography study. Although use of ART in PLWH was not required, the majority of study participants with HIV were taking chronic stable ART and, if so, there was no change in the ART regimen for at least 3 months before the study. Additionally, all PLWH had a last known $CD4^+$ cell count >200 mm^3 and the majority had undetectable viral load. For both groups, individuals with self-reported recreational drug use or cigarette smoking within the 2 months before the MRI were excluded. All participants provided written and verbal consent. The current study was approved by the Johns Hopkins' institutional review board. The results from 25 PLWH were included in a previously published study.[11]

MRI Protocol

A commercial 3.0-T MR scanner was used (Achieva; Phillips). The study's MRI protocol has previously been described.[7] Briefly, participants underwent a noncontrast MRI study of CEF at rest and during continuous

isometric handgrip exercise. The MRI study was used to measure coronary CSA, coronary flow velocity, and coronary blood flow (CBF) in response to isometric handgrip exercise stress, which was defined as continuous isometric handgrip exercise for 4 to 8 minutes at 30% of a participant's maximum effort, as determined before entering the MRI. Baseline and stress images were analyzed to measure CSA, and CBF was computed using the following equation: coronary CSA × coronary artery peak diastolic velocity × 0.3.[7,13] MRI measures were performed by individuals blinded to the clinical and laboratory information.

Clinical Examination and Laboratory Measurements

Participants were required to fast for a minimum of 6 hours before their study visit to avoid any possible influence of diet on endothelial function. Participants were advised to refrain from taking antihypertensive medications on the day of the scan. All participants underwent a thorough history and physical examination. Venipuncture was performed on the day of the MRI and subsequently stored for batched analysis. Fasting lipid panel and serum PCSK9 level were obtained. For participants with HIV, measurement of CD4+ cell count and HIV RNA viral load were also performed, unless available within the prior 6 months in the electronic medical record.

PCSK9 Measurement

PCSK9 concentration levels were measured on serum aliquots stored at −80 °C using a commercial ELISA kit (R&D Systems, Catalog Number DPC900). The minimum detectable dose of human PCSK9 ranged from 0.030 ng/mL to 0.219 ng/mL and the intra-assay and interassay coefficients of variation were 5.4%±1.2% and 4.8%±1.9%, respectively.[14] All of the measurements were performed using a fully automated ELISA system (DS2, Dynex Technologies, Inc.).

Statistical Analysis

Demographic and clinical characteristics were compared between women and men with and without HIV. Normality was assessed using Skewness and Kurtosis test and histogram. Normally distributed continuous variables are reported as mean±SD, with comparisons performed with Student t test. Non-normally distributed continuous variables are reported as median (interquartile range), with comparisons performed with Wilcoxon rank sum test. Categorical variables are reported as absolute numbers (percentages) and comparisons performed with Fisher exact test.

We then compared parameters of CEF, specifically stress-induced CSA and CBF, between women with and without HIV, and separately between men with and without HIV. Additionally, these parameters were then compared between women with HIV and men with HIV, to evaluate for sex differences in CEF. In women, we also performed multivariable robust linear regression, adjusting for age, menopause status, and body mass index, to assess the independent association of HIV with CEF parameters. For women, we performed additional stratified analysis for CEF comparison for women with and without HIV by menopause status as well as by race.

Next, we compared PCSK9 levels in women with and without HIV and evaluated for correlation of PCSK9 with stress-induced change in CSA and CBF change in women with HIV. The same analyses were performed for men. To evaluate for an interaction of sex with PCSK9, age-adjusted robust regression analysis was performed employing an interaction term (for sex and PCSK9), among individuals with HIV. All statistical analyses were conducted using Stata 16.1 (StataCorp LLC).

RESULTS

A total of 106 PLWH and 76 people without HIV were studied. Women with HIV (n=33) were more likely to be smokers and of Black race (Table 1) compared with women without HIV (n=45). Body mass index and prevalence of most CVD risk factors (hypertension, diabetes, and lipid values) were comparable between women with and without HIV. Notably, more women with HIV were postmenopausal compared with women without HIV (P<0.002) despite similar ages (Table 1). The majority of women with HIV reported ART use (94%). Additional data on medication use and median coronary calcium score values are available in Table S1.

CEF Assessment

Stress-induced percent change in CSA was 9.5%±3.2% in women without HIV and −0.5%±9.7% in women with HIV (P<0.001). Stress-induced percent change in CBF was 35.4%±21.1% in women without HIV and 1.9%±18.6% in women with HIV (P<0.001). Adjusted robust linear regression analysis for women confirmed that the association of percent of CSA and percent of CBF with HIV was independent of menopause status, age, and body mass index (Table 2). Subsequent analyses for women further adjusting for history of smoking, alcohol use, and history of substance use similarly showed that the association of percent of CSA and percent of CBF with HIV was independent (Table S2). For women, analysis stratified by menopause status similarly showed that CEF was impaired in women with

Table 1. Demographics and HIV-Specific Characteristics for Women and Men Without and With HIV

	Women			Men		
	Without HIV (n=45)	With HIV (n=33)	*P* value	Without HIV (n=31)	With HIV (n=73)	*P* value
Age, y	49.6±15.1	51.3±9.5	0.55	45.3±15.6	50.8±11.3	0.05
Race, n (%)			<0.001			0.001
White	29 (64)	2 (6)		14 (45)	20 (27)	
Black	15 (33)	31 (94)		12 (39)	49 (67)	
Other*	1 (2)	0 (0)		5 (16)	4 (5)	
BMI, kg/m²	27.1±5.3	29.4±5.6	0.06	27.8±4.4	27.4±3.9	0.70
Comorbidities, n (%)						
Hypertension	9 (20)	11 (33)	0.20	6 (19)	32 (44)	0.026
Diabetes	1 (2)	2 (6)	0.57	0 (0)	5 (7)	0.32
Smoking history	6 (13)	17 (52)	<0.001	1 (3)	45 (62)	<0.001
Alcohol use	1 (2)	8 (24)	0.004	2 (6)	47 (64)	<0.001
Substance use history	0 (0)	14 (42)	<0.001	0 (0)	26 (36)	<0.001
Hepatitis C	0 (0)	14 (42)	0.06	0 (0)	26 (36)	0.25
Postmenopausal status, n (%)	21 (47)	27 (82)	0.004	N/A	N/A	…
Lipid panel						
Cholesterol, mg/dL	197 (168–208)	192 (163–208)	0.52	175 (174–209)	166 (150–195)	0.68
Triglycerides, mg/dL	112 (85–145)	89 (72–118)	0.47	129 (100–168)	108 (85–150)	0.34
HDL, mg/dL	56 (48–67)	54 (48–65)	0.58	50 (39–53)	47 (41–55)	0.98
LDL, mg/dL	115 (97–125)	102 (89–137)	0.72	112 (104–129)	99 (77–121)	0.07
Left ventricular ejection fraction, %	66±3	61±3	0.011	53±1	62±6	0.07
HIV-specific factors						
Length of time since HIV diagnosis, y	N/A	5 (1.5–16.5)	…	N/A	2 (1–2.5)	…
CD4 count	N/A	774 (617–1002)	…	N/A	641 (483–861)	…
Undetectable viral load (<100 copies per µL), n (%)	N/A	29 (88)	…	N/A	66 (90)	…
ART use, n (%)		31 (94)			64 (88)	
Protease inhibitor	N/A	4 (12)	…	N/A	1 (1.4)	…
NNRTI	N/A	3 (9)	…	N/A	14 (19)	…
NRTI	N/A	24 (73)	…	N/A	60 (83)	…
Integrase inhibitor	N/A	27 (82)	…	N/A	55 (75)	…
Entry inhibitor	N/A	20 (61)	…	N/A	1 (1.4)	…

Continuous variables are represented as mean±SD if normally distributed or median (interquartile range) if nonnormally distributed. ART indicates antiretroviral therapy; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N/A, not available; NNRTI, nonnucleoside reverse transcriptase inhibitor; and NRTI, nucleoside reverse transcriptase inhibitor.

*Other race/ethnicity includes Hispanic and Asian/Pacific Islander.

compared with women without HIV in both premenopausal and postmenopausal groups (Table S3). Overall, stress-induced percentage changes in CSA and CBF were comparable in men and women with HIV (Figure 1A and 1B). Analysis stratified by race also showed that CEF was impaired in both Black and White women with HIV compared with those without HIV. Among Black women, stress-induced percent change in CSA was 7.4%±5.5% in women without HIV (n=15) and −1.0%±10.2% in women with HIV (n=31) (*P*=0.005), and among White women

was 11.9%±7.2% in women without HIV (n=29) and 6.0%±0.4% in women with HIV (n=2) (*P*=0.5).

PCSK9 and CEF

Levels of PCSK9 were higher in women with HIV compared with those without HIV (306 ng/mL [200–412 ng/mL] versus 180 ng/mL [154–223 ng/mL], *P*<0.001, respectively) (Figure 1C). We then evaluated the association of PCSK9 with percent change in CSA and percent of CBF during stress. There was a significant relationship between PCSK9 and percent of CSA

Table 2. Unadjusted and Adjusted Association of HIV With CEF in Women

	Percent CSA unadjusted ß coefficient (95% CI)	Percent CSA adjusted for age, BMI, and menopause status) ß coefficient (95% CI)	Percent CBF unadjusted ß coefficient (95% CI)	Percent CBF adjusted for age, BMI, and menopause status) ß coefficient (95% CI)
HIV	−8.7 (−12.5 to −4.9)*	−8.3 (−12.9 to −3.6)*	−31.3 (−40.4 to −22.2)*	−30.2 (−40.8 to −1−9.8)*
Age, y		−0.1 (−0.3 to 0.1)		−0.02 (−0.5 to 0.5)
BMI, kg/m²		−0.3 (−0.7 to 0.1)		0.3 (−0.6 to 1.1)
Postmenopausal status		−0.5 (−7.1 to 6.1)		−7.2 (−22.2 to 7.7)

BMI indicates body mass index; CBF, coronary blood flow; CEF, coronary endothelial function; and CSA, coronary cross-sectional area.

*Values represent statistically significant values with $P<0.05$.

change in PLWH overall (Figure 2). When stratified by sex, using robust linear regression, the relationship of PCSK9 with percent of CSA was significant in men with HIV (β=−0.035 [−0.067 to −0.003], $P=0.030$) but not in women with HIV (β=−0.016 [−0.046 to 0.014], $P=0.28$). Similarly, Spearman correlation coefficient was −0.29 ($P=0.014$) for men and −0.27 ($P=0.14$) for women. However, we then evaluated findings further with age-adjusted robust linear regression and employed an interaction term to assess for the interaction of PCSK9 with sex, and we did not find a statistically significant difference in the association of PCSK9 with percent of CSA between men and women with HIV (β=0.01 [−0.03 to 0.06], $P=0.53$). We did not detect an association of PCSK9 with percent of CBF in men or women with HIV using robust linear regression (β=0.00 [−0.06 to 0.06], $P=0.99$).

DISCUSSION

The current study demonstrates that CEF in women with HIV is impaired as compared with women without HIV (Figure 3). The degree of CEF impairment is similar in men and women with HIV, as measured by both percent change in CSA and CBF with endothelial-dependent stress. Women with HIV are also more
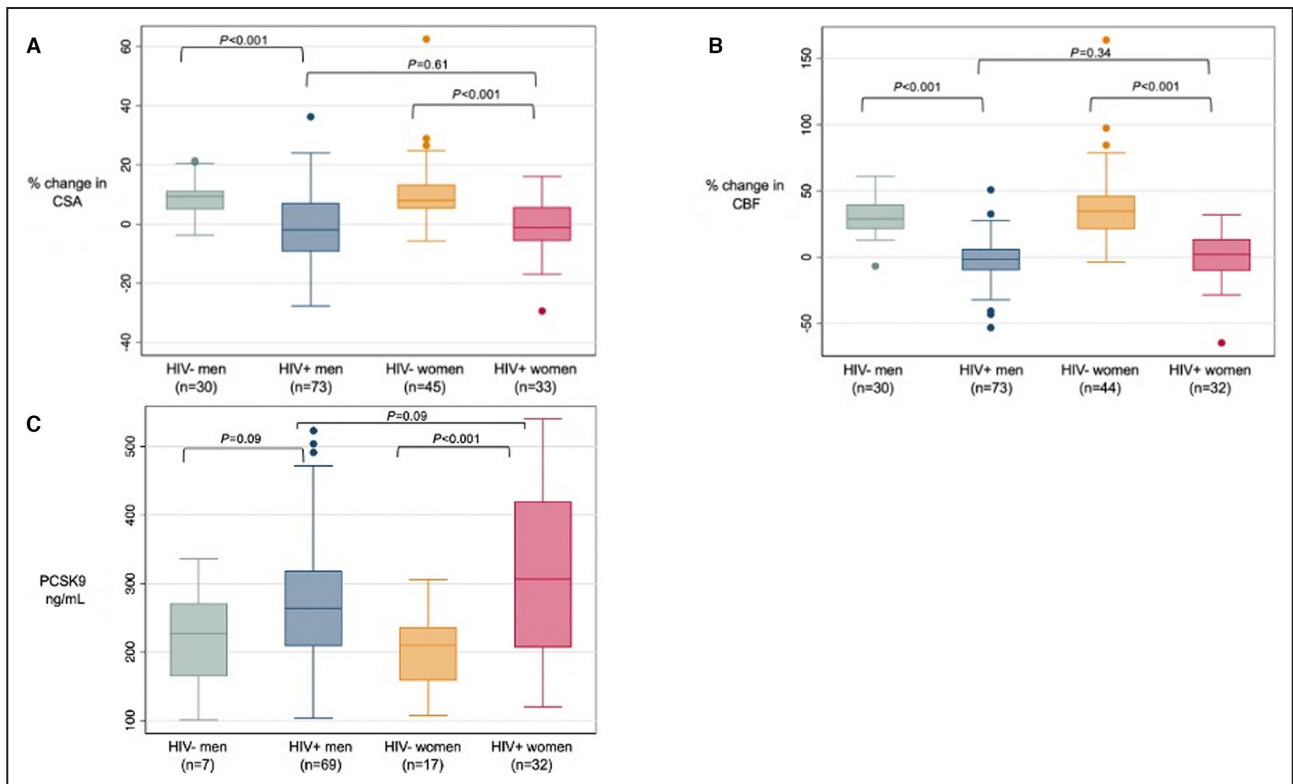

Figure 1. Comparison of coronary endothelial function and PCSK9 (proprotein convertase subtilisin/kexin type 9) in men and women with/without HIV.
Box plot showing median quartile and interquartile range in participants with and without HIV. **A**, The percent change in coronary cross-sectional area (CSA) with isometric handgrip exercise. **B**, The percent change in coronary blood flow (CBF) with isometric handgrip exercise. **C**, The distribution of PCSK9 (ng/mL) among men and women with and without HIV.
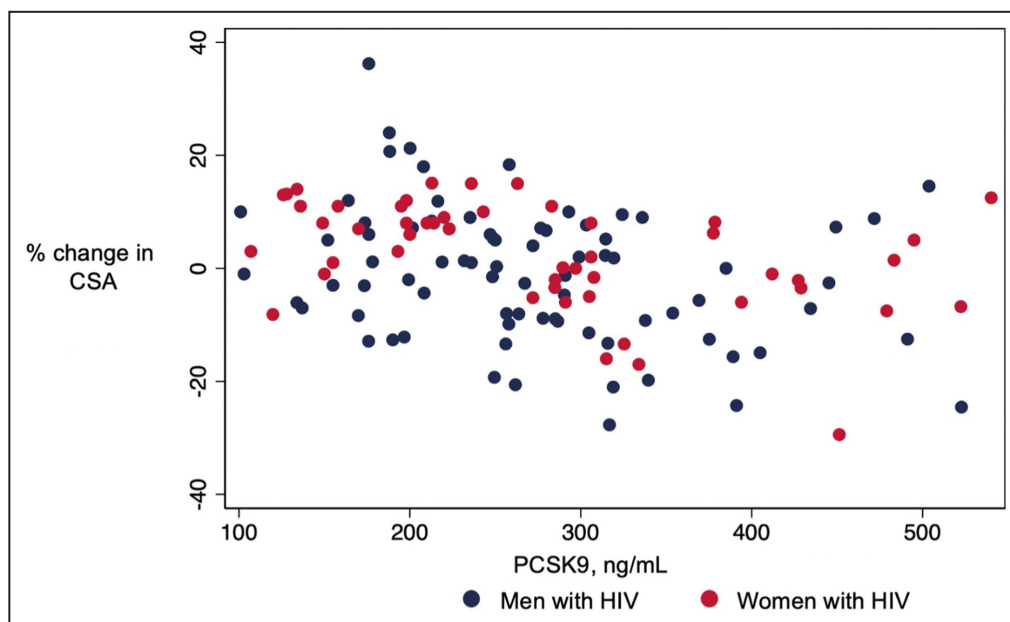
Figure 2. Correlation of PCSK9 (proprotein convertase subtilisin/kexin type 9) (ng/mL) with percent of stress-induced change in coronary cross-sectional area (CSA) by sex.
The figure shows a scatterplot of PCSK9 level vs percent change in coronary CSA in response to isometric handgrip stress (measure of coronary endothelial function). Men with HIV are represented in blue and women with HIV in red. Spearman coefficient in the overall cohort is −0.27 (P=0.0061).

likely to be menopausal at a younger age compared with women without HIV, although the association of CEF with HIV is independent of menopausal status. Furthermore, we also report that PCSK9 levels are elevated in women with HIV compared with women without HIV. Finally, we detected a significant inverse relationship between PCSK9 and percent of CSA change, a measure of CEF in PLWH.

Abnormal CEF contributes to the development of atherosclerotic CVD and independently predicts cardiovascular events.[4,5] Notably, measurements of peripheral artery endothelial function only modestly correlate with CEF.[6] Our current findings support previous work from our group demonstrating that CEF is impaired in people with HIV without CAD.[9,11] Prior literature suggests a trend towards women with HIV having a higher risk of CVD than men with HIV, although statistical significance was not achieved.[15] It is plausible that women with HIV may have accelerated cardiovascular risk attributable to reduced ovarian reserve and earlier menopause, compared with women without HIV.[16] In the current study, we found that while women with HIV were more likely to be menopausal at a similar age to women without HIV, CEF remained impaired independent of menopausal status. These findings suggest that the association of HIV with impaired CEF is independent of menopausal status, and is possibly caused by other factors such as chronic systemic inflammation, immune activation, or ART regimen.

In a prior study from our group performed primarily in men, we demonstrated that HIV infection was associated with higher levels of PCSK9, which, in turn, was associated with impaired CEF.[11] In our present study, although there was an inverse association between elevated PCSK9 and impaired CEF in PLWH, we did not detect a significant difference in the relationship between men and women, although this analysis may be limited by the sample size in women. Prior studies in non-HIV populations have reported that PCSK9 levels are increased in women (especially those who are postmenopausal) compared with men.[17,18] Other studies have shown that PCSK9 levels in women may be inversely related to sex hormones, with levels increased in postmenopausal women.[19,20] Our study contributes to the literature revealing no significant sex differences in PCSK9 levels in PWLH in a cohort of virally suppressed stable outpatients. However, further studies are needed to evaluate whether the relationship between sex hormones and PCSK9 levels are different in PLWH.

PCSK9 has emerged as an important biomarker in HIV, and recent studies have shown that PCSK9 is secreted by vascular endothelial cells and leads to secretion of proinflammatory cytokines in a variety of tissues.[21] It is postulated that PCSK9 has pleiotropic effects that modulate the underlying inflammatory mechanisms of atherosclerotic disease. This may play a particularly important role in PLWH who have chronic persistent inflammation and elevated
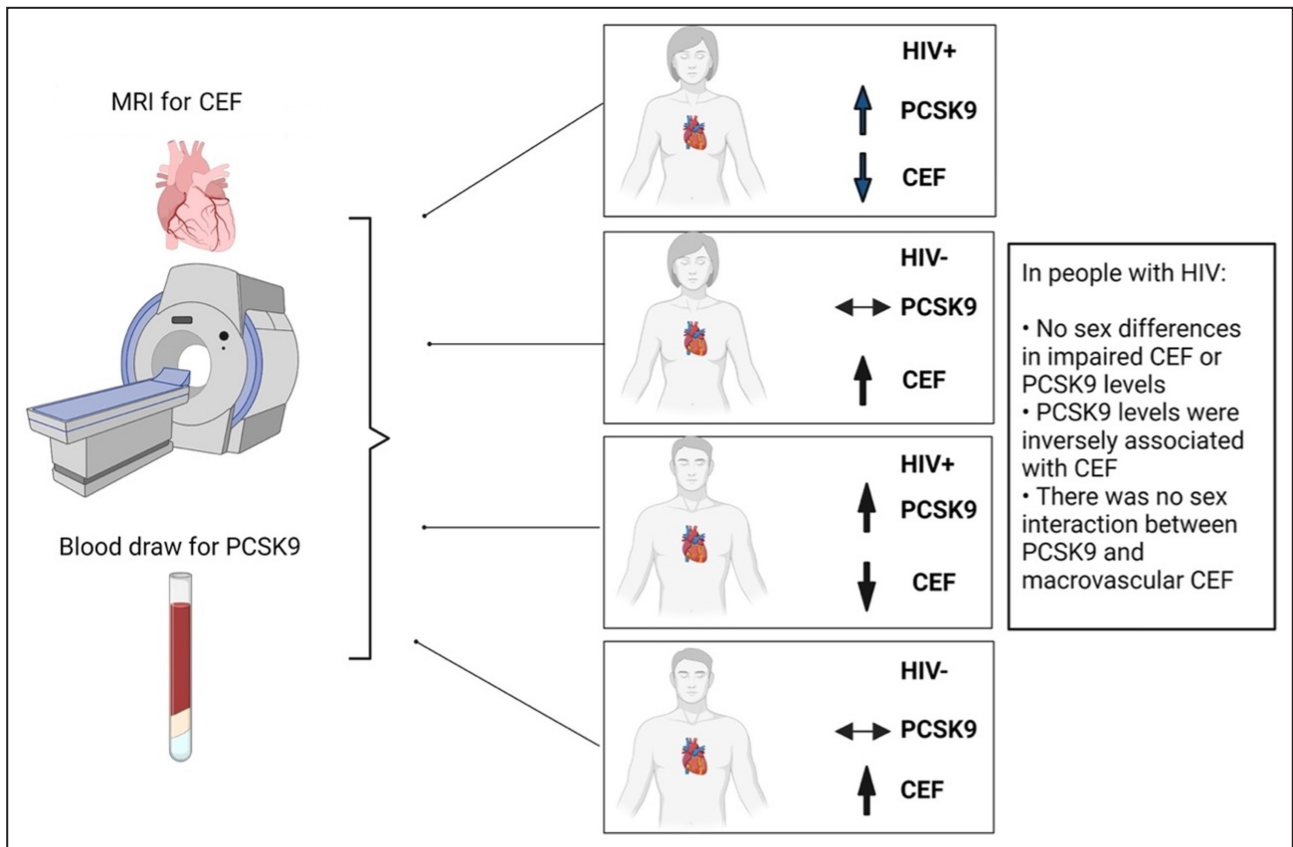
Figure 3.   Summary of key findings comparing coronary endothelial function between women and men with and without HIV.
CEF indicates endothelial function; MRI, magnetic resonance imaging; and PCSK9, proprotein convertase subtilisin/kexin type 9.

PCSK9 levels.[11] One study showed that PCSK9 levels remain elevated in PWLH who were newly initiated on ART, suggesting that HIV itself, rather than its treatment, influences levels.[22] Previous clinical trials have revealed that treatment with the PCSK9 inhibitor evolocumab is safe and effective in PLWH and improves impaired CEF.[22,23] Our study shows that women with HIV have increased PCSK9 levels and reduced CEF independent of menopausal status. Future studies are needed to evaluate whether women with HIV should be considered for PCSK9 inhibitor therapy if clinically indicated, similar to that for men with HIV.

The primary limitation of our study is the relatively modest sample size, limiting the number of risk factors we could adjust for in the analysis. Participants with HIV differed in some demographic factors, particularly in regard to smoking history or substance use in the past and alcohol use. While additional analyses were performed adjusting for these, residual confounding is possible. Furthermore, the smaller sample size in HIV-positive women limited our ability to ascertain whether there was a sex difference in the association between PCSK9 and CEF in PLWH. Additionally, this is a cross-sectional study and therefore we cannot determine

causality of endothelial dysfunction. We also note that the majority of participants in our study with HIV were taking ART, making it difficult to determine the effects of ART itself or of different classes of ART on CEF. However, prior studies have reported that newly initiated ART improves brachial endothelial function, suggesting that other HIV-related factors may play a more important role in mediating endothelial dysfunction in PLWH.[24] Last, sex was self-identified and we have limited information on the congruence of sex and gender identifications. Similarly, we have limited information on social determinants of health, which may potentially play a role as well.

In conclusion, we report for the first time that women with HIV have impaired CEF and increased PCSK9 levels compared with women without HIV. We observed that CEF is significantly reduced in both premenopausal and postmenopausal women with HIV compared with women without HIV. Furthermore, no sex differences in CEF and PCSK9 were detected in PLWH, which is a novel finding in context of prior studies in non-HIV cohorts showing sex differences in both measures.[17,18,25] Finally, we report that while CEF is significantly, inversely associated with PSCK9 level, we detected no significant difference in the relationship according to sex.

ARTICLE INFORMATION

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Disclosures

There are no relevant disclosures or conflicts of interest to report.

Supplemental Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Data on Medication Use and Coronary Calcium Score

	WOMEN			MEN		
	Without HIV (n=45)	With HIV (n=33)	p-value	Without HIV (n=31)	With HIV (n=73)	p-value
Aspirin	1	4	0.16	0	14	0.009
Statin	8	15	0.012	5	27	0.06
Antihypertensive medications	9	11	0.14	6	32	0.026
ACEi/ARB	0	3	-	0	10	-
Beta-Blocker	1	2	-		4	-
Median Coronary Calcium Score*	0 (0-0)	0 (0-0)	N/A	0 (0-60)	0 (0-8)	0.81

ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers

*Calcium score was not available in all participants. Values were available for 2 women without HIV, 13 women with HIV, 2 men without HIV and 21 men with HIV.

Table S2. Unadjusted and Expanded Adjusted Association of HIV with Coronary

Endothelial Function in Women

	% CSA* Unadjusted ß Coefficient (95% CI)	% CSA* Adjusted for age, BMI[†] , race, alcohol use, history of substance use, history of smoking, and menopause status ß Coefficient (95% CI)	%CBF† Unadjusted ß Coefficient (95% CI)	% CBF† Adjusted for age, BMI‡, race, alcohol use, history of substance use, history of smoking, and menopause status ß Coefficient (95% CI)
HIV	**-8.7 (-13,-4.9)**	**-7.3 (-13,-1.5)**	**-31 (-40,-22)**	**-30 (-44,-15)**

*CSA = coronary cross-sectional area change with stress; †CBF = coronary blood flow

change with stress; ‡BMI = body mass index

Values in bold represent statistically significant values with p<0.05.

Table S3. Coronary Endothelial Function in Pre- and Postmenopausal Women with

and without HIV

	Premenopausal Women			Postmenopausal Women		
	Without HIV (n=22)	With HIV (n=6)	p-value	Without HIV (n=21)	With HIV (n=26)	p-value
%CSA*	13.8$\pm$13.2	-2.3$\pm$9.9	0.001	7.4$\pm$6.3	-0.2$\pm$2.0	0.004
%CBF†	49.7$\pm$33.8	2.5$\pm$23.9	0.004	31.6$\pm$18.6	1.0$\pm$17.9	<0.001

*%CSA = coronary cross-sectional area change with stress

†%CBF = coronary blood flow change with stress