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Trans Women Have Worse Cardiovascular Biomarker Profiles Than Cisgender Men Independent of Hormone Use and HIV Serostatus

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Abstract

Background: Feminizing hormonal therapy (FHT) and HIV potentially alter cardiovascular disease (CVD) risk in transgender women (TW).

Methods: TW were enrolled in Los Angeles, CA and Houston, TX and frequency-matched to Multicenter AIDS Cohort Study cisgender men (CM) on age, race, substance use and abacavir use. Biomarkers of CVD risk and inflammation were assessed via ELISA. Wilcoxon rank sum

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Authors' Contributions

JEL: concept development, study conduct, analytic plan development, data interpretation, primary manuscript development
RW: statistical analysis, manuscript development
BWB: statistical analysis, manuscript development
EB: performed laboratory assays, manuscript development
ANH: manuscript development
PD: study conduct, manuscript development
JC: manuscript development
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and Fisher's exact tests compared TW and CM. Multivariable linear regression assessed factors associated with biomarker concentrations.

Results: TW (HIV+ n=75, HIV− n=47) and CM (HIV+ n=40, HIV− n=40) had mean age 43–45 years; TW/CM were 90%/91% non-Hispanic Black, Hispanic, or Multi-racial, 26%/53% obese, and 34%/24% current smokers; 67% of TW were on FHT. Among PLWH, TW had higher median extracellular newly-identified receptor for advanced glycation end-products (EN-RAGE), lipoprotein-associated phospholipase A2 (LpPLA2), oxidized LDL (oxLDL), soluble TNF receptor type (sTNFR) I/II, interleukin (IL)-8 and plasminogen activator inhibitor (PAI)-1, but lower soluble CD14, von Willebrand factor (vWF) and endothelin (ET)-1 levels than CM. Findings were similar for participants without HIV (all $p<0.05$). In multivariable analysis, TW had higher EN-RAGE, IL-6, IL-8, P selectin, PAI-1, oxLDL and sTNFRI/II concentrations, and lower vWF, independent of HIV serostatus and current FHT use. Both being a TW and a PLWH were associated with lower ET-1.

Conclusions: Compared to matched cisgender men, trans women have altered profiles of biomarkers associated with systemic inflammation and CVD. Further work is needed to decipher the contributions of FHT to CVD risk in TW with HIV.

Keywords

Feminizing Hormonal Therapy; HIV; Cardiovascular Biomarkers; Trans Women

BACKGROUND

Feminizing hormone therapy (FHT) for transgender women (TW) can be critical to harmonizing gender identity and expression; however, FHT modulates inflammatory and coagulation pathways, causes fat gain, and may increase metabolic disease risk. Indeed, FHT is associated with increased cardiovascular disease (CVD) risk in persons assigned a female sex at birth and TW.[1–8] Cardiometabolic risk in TW is understudied, particularly with contemporary FHT regimens.

HIV is also associated with increased cardiometabolic disease risk, with CVD being a leading cause of morbidity and mortality among people living with HIV (PLWH) on suppressive antiretroviral therapy (ART). [9–14] The mechanisms underlying the heightened risk of CVD in PLWH are not well understood, but are believed to involve traditional as well as HIV− and ART-specific risk factors.[15–18] Chronic HIV is characterized by persistent inflammation and immune activation that can lead to tissue injury and dysfunction, with persistent monocyte activation playing an important role in the pathogenesis of end-organ disease.[19–22] Multiple coagulation pathway abnormalities have also been described.[23–25]

TW are disproportionately affected by HIV, [26] and TW have high rates of traditional CVD risk factors such as smoking,[27–31] but the intersections of chronic HIV−, ART- and modern FHT-induced alterations in immuno-metabolic pathways and their effects on cardiometabolic risk in TW have not been addressed. To better understand the intersections of HIV, ART and FHT with cardiometabolic risk among TW, we designed a cross-sectional,

pilot study of inflammatory and cardiometabolic biomarker measurement in TW and matched cisgender males (CM).

METHODS

Study population

TW were recruited from community-based organizations and clinics in Los Angeles, California (APAIT) and Houston, Texas (Thomas Street Health Center) between 2016 and 2018. Participants were enrolled sequentially without regard to HIV serostatus. Inclusion criteria for TW included self-identification as a TW or transfeminine person and ability and willingness to provide informed consent. For TW with HIV, written documentation of HIV serostatus was required, and participants were required to be taking ART. Proof of HIV-1 RNA <50 copies/ml prior to blood draw was not required. Rather, participants were asked if they believed or had proof that they were undetectable at their last clinical visit. If yes, they were allowed to enroll. This was necessary due to the cross-sectional and community-based nature of the study. For TW believed to be HIV negative, documented testing within the last 90 days and/or testing immediately prior to enrollment was required (latter available at the enrollment sites and most persons were retested on the day of enrollment). TW were not required to be on FHT at time of enrollment.

CM were selected from men who have sex with men (MSM) enrolled in the former Multicenter AIDS Cohort Study (MACS). This cohort was chosen due to overlapping HIV risk behaviors with the communities of TW that we were enrolling and because the MACS included men with and without HIV. The MACS began in 1984 to study the natural history of HIV among MSM and to establish a repository of biologic specimens for future study.[32] Participants were enrolled from four sites (Pittsburgh, PA; Baltimore, MD/Washington, DC; Chicago, IL; Los Angeles, CA) over four time periods (1984/85, 1987/90, 2001/03, 2010+), and completed semi-annual visits that included a standardized medical history interview, clinical evaluations, laboratory tests and storage of specimens. CM were frequency-matched to TW on HIV serostatus, age within 5 years, race/ethnicity, recent recreational drug use (yes/no in last 90 days for TW and yes/no in last 6 months for CM) and abacavir use, eliminating the need for matched analyses. MACS men identifying on the transfeminine spectrum by self-reported gender identity were excluded from the pool of potential controls. Specimens and data from CM were collected between April 2012 and September 2014. This time frame was chosen due to: limited availability of samples from men without HIV beginning October 2014, all controls having available specimens during this time frame, and all specimens having been in storage <5 years.

Study Procedures

The study was approved by the institutional review boards of the University of California, Los Angeles (Los Angeles, CA) and UTHealth Houston (Houston, TX). Written informed consent was obtained from TW who were potential participants prior to the initiation of study procedures. Consent for MACS men was covered under their primary MACS consent.

For TW, blood was collected in the fasting state (nothing to eat or drink except water and medications for at least 8 hours) for measurement of comprehensive metabolic panel, lipid panel, and complete blood count according to local standardized practices, and transferred to LabCorp for real-time measurement of the above. $CD4^+$ T lymphocyte count and HIV-1 RNA levels from TW living with HIV were collected from participant medical records (for those who provided consent to contact their primary provider), which were generally available within 90 days of entry.

Blood was collected from TW and stored at −70°C until batched biomarker measurement could occur in the lab of Dr. Nicholas Funderburg (The Ohio State University, Columbus, OH). Control serum and plasma samples were sent from the MACS repository (NIH, Frederick, MD) to Dr. Funderburg's lab. Soluble CD14 (sCD14), soluble CD163 (sCD163), interleukin-6 (IL-6), interleukin-8 (IL-8), soluble TNF receptor type (sTNFR) I/II, P selectin, high molecular weight adiponectin, endothelin-1 (ET-1), extracellular newly-identified receptor for advanced glycation end-products (EN-RAGE), lipoprotein-associated phospholipase A2 (LpPLA2), vascular cell adhesion molecule-1 (VCAM-1) (R&D Systems, Minneapolis, MN, USA), oxidized LDL (oxLDL) (Mercodia, Uppsala, Sweden), plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor (vWF) (Abcam, Cambridge, United Kingdom), and d dimer (Stago, Asnières-sur-Seine, France) were measured on all samples via ELISA. These biomarkers were chosen for their known relationships to cardiovascular disease, inflammatory processes and/or coagulation abnormalities. Twenty percent of all samples were run in duplicate to assess variability, which was consistently <15%.

TW self-reported basic demographic information, medical history including substance use history and current medication usage. A separate FHT questionnaire assessed FHT usage, including current or past usage, FHT type and frequency, and mode of acquisition. For MACS CM, variables equivalent to those available for TW were selected.

Analysis

Demographic and clinical characteristics were summarized as median (interquartile range, IQR) or frequency. Given the inflammatory and metabolic perturbations associated with HIV, biomarker results were stratified first by HIV serostatus and then by gender. Wilcoxon rank sum and Fisher's exact tests compared differences between TW and CM. Multivariable linear regression analyses assessed factors associated with individual natural log-transformed biomarker concentrations after adjusting for HIV serostatus, gender, age, race/ethnicity, body mass index (BMI), and smoking. For regression analyses, the population of TW with HIV was limited to those with confirmed HIV-1 RNA <50 copies/ml (undetectable; n=51). All CM with HIV also had undetectable HIV-1 RNA. Statistical significance was defined as a two-sided $p<0.05$. For this hypothesis-generating, pilot study, no adjustments were made for multiple comparisons. Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study population

Demographic and clinical characteristics are presented in Table 1. Briefly, 122 TW (HIV+ n=75, HIV− n=47) were enrolled and had available samples for analysis. Eighty CM (HIV+ n=40, HIV− n=40) were selected as frequency-matched controls. Overall, the population of TW and CM: had mean age of 43 and 45 years, 90% and 91% self-identified as non-Hispanic Black, Hispanic, or Multi-racial; 26% and 53% were obese (body mass index ≥30 kg/m^2), and 34% and 24% were current smokers, respectively. PLWH had current median $CD4^+$ T lymphocyte count 609 cells/uL; 67% of TW were currently on FHT (68% HIV+, 66% HIV−). ART use included 30% non-nucleoside reverse transcriptase inhibitor (NNRTI) −, 29% protease inhibitor (PI)-, and 37% integrase strand transfer inhibitor (INSTI)-based regimens. TW were less likely to be on NNRTI-based ART (among PLWH), be obese, and have smoking history or hypertension, but were more likely to be on INSTI-based ART, have heavy alcohol intake, and be current smokers. Upon medical record review, 32% of TW had recent detectable HIV-1 RNA compared to 0% of CM.

Biomarker Results

Among participants without HIV, TW had significantly higher EN-RAGE, oxidized LDL, sTNFRI/II, IL-6, P selectin, IL-8 and PAI-1 concentrations. Only ET-1 levels were lower in TW (all $p<0.05$, Table 2). Similarly, TW with HIV had higher EN-RAGE, oxidized LDL, sTNFRI/II, LpPLA2, IL-8, and PAI-1 concentrations than CM with HIV. A trend was seen for higher P selectin concentrations among TW. IL-6 levels were similar by gender among participants with HIV. ET-1 concentrations were lower in TW than CM with HIV, but unlike participants without HIV, so were sCD14 and vWF ($p<0.05$, Table 2).

Upon further stratifying TW by current FHT use, several stepwise changes were observed going from CM to TW not on FHT to TW on FHT (Table 3), with additional increases in ENRAGE, oxLDL, sTNFRI, and PAI-1 (Figure 1), and decreases in vWF and ET-1 meeting statistical significance for a difference across groups. However, when comparing biomarker concentrations between TW not on FHT to TW on FHT, no significant differences were observed by FHT status either when pooling TW or stratifying by HIV serostatus.

In multivariable analysis adjusting for HIV serostatus, age, race/ethnicity, BMI, and smoking status, being a TW was associated with higher ENRAGE, oxLDL, sTNFRI/II, P selectin, IL-6, IL-8 and PAI-1 concentrations, and lower sCD14, sCD163, vWF and ET-1 concentrations (Table 4). A positive HIV serostatus was associated with higher sCD14 and lower ET-1 concentrations (both $p<0.02$). In a model restricted to TW and adding FHT use status as an additional covariate, current FHT use was not independently associated with any of the biomarkers concentrations (data not shown).

Discussion

In this cohort of TW both on and off FHT, significant aberrations in biomarkers reflecting inflammation, cardiovascular health and coagulation pathways were observed compared to matched CM and independent of HIV serostatus. Although pathophysiology cannot be

inferred from this cross-sectional assessment, these provocative data highlight the potential for adverse cardiovascular events among TW and the need for further research.

Importantly, both FHT and HIV are associated with increased cardiovascular and thrombo-embolic event risk. [1–14] However, in this cohort TW demonstrated significant alterations in biomarker profiles vs matched CM regardless of FHT use and independent of HIV serostatus. Demographic and clinical factors potentially affecting biomarker profiles include BMI and smoking status, with TW less likely to be overweight or obese and more likely to be current smokers than CM. Diabetes mellitus frequency was similar between TW and CM, and rates of hypertension were lower among TW. Supporting our belief that observed differences in this cohort are not due to traditional components of CVD risk is an analysis from The Behavioral Risk Factor Surveillance System, in which no significant differences in rates of myocardial infarction were observed in TW compared to CM after adjusting for traditional CVD risk factors.[33]

Unmeasured factors, however, could contribute. For example, in this group of predominantly TW of color, multiple intersecting contributors to minority stress could predispose TW to poorer health outcomes,[34] some possibly mediated by the pathways reflected in the measured biomarkers. Indeed, The Intersectional Transgender Multilevel Minority Stress Model illustrates how multiple marginalized identities intersect with social determinants of health to impact cardiovascular health.[35] Despite this knowledge, the physiologic mechanisms of non-traditional cardiovascular risk remain poorly defined, yet their understanding is critical to optimizing health for transgender persons.

The most striking differences in biomarker concentrations between TW and CM were EN-RAGE, oxLDL and PAI-1 concentrations. EN-RAGE is a pro-inflammatory ligand of the receptor for advanced glycation end products (RAGE) and Toll-like receptor 4 (TLR4) that has been associated with incident CVD events independently of traditional CVD risk factors and associated biomarkers of inflammation.[36–38] OxLDL plays a key role in atherogenic and pro-apoptotic processes.[39] PAI-1 is the principal inhibitor of plasminogen, with elevations linked to hypofibrinolytic states and acute cardiovascular events.[40] Complex relationships between these molecules exist: EN-RAGE and oxLDL both bind CD36 and activate TLR4, EN-RAGE may regulate CD36 expression, and oxLDL can bind RAGE, all leading to and reinforcing inflammatory pathways involved in CVD.[41] Several stressor pathways, including IL-6 release,[42] lead to increased PAI-1 expression. OxLDL induces IL-6 release,[43] and IL-6 leads to increases in EN-RAGE.[44] The tight pathologic relationships between these biomarkers lends credence to the hypothesis that elevations of these biomarkers in TW are related to and represent increased cardiovascular risk. Additionally, sexual dimorphism in EN-RAGE concentrations has not been reported, suggesting elevated EN-RAGE levels in this group of TW cannot be accounted for by increased estradiol levels/relative testosterone deficiency.[45, 46]

ET-1 plays a diverse role in CVD development and is modulated by sex hormones. ET-1 is lower in adults assigned female at birth than adults assigned male at birth, and increases throughout the menopausal transition. The role of testosterone is more complex: people assigned female at birth with hyperandrogenism have higher ET-1 concentrations, but

people assigned male at birth with hypogonadism have higher ET-1 levels that decline with testosterone supplementation.[47] Given higher estrogen levels and relative hypogonadism in our TW vs CM, it is not surprising that we observed lower ET-1 among TW. Additionally, though differences in ET-1 levels were not statistically different by FHT use status in our cohort (likely due to small sample size), TW on FHT did have lower ET-1 levels than those not on FHT (data not shown).

We also observed lower sCD14 and vWF concentrations among TW than CM among PLWH only. A sexual dimorphism in sCD14 levels has been documented, with higher levels generally observed in people assigned female at birth that are not greatly affected by menopause.[48] Additionally, in one study of transgender people, feminizing therapies increased vWF whereas testosterone treatment decreased vWF levels.[49] Thus, our findings cannot readily be explained by sex hormone differences between TW and CM, and HIV complicates the picture, with sCD14 and vWF levels elevated among PLWH.[50, 51] Future studies are needed to confirm or deny these findings.

While the aforementioned differences between TW and CM were observed, additional statistically significant differences within TW by FHT use status were not seen in this cohort. This may be due, in part, to the relatively small sample sizes of the groups, particularly when additionally stratified by HIV serostatus, and/or the high rates of current FHT use (67%). However, most data on CVD in TW on FHT is in the context of 17-α-ethinyl estradiol use, which is no longer recommended for FHT due to its perturbations of inflammatory and coagulation biomarker and lipid concentrations.[52] 17-β estradiol has milder effects on inflammatory and atherosclerotic pathways, and is the current standard of care. However, 17-α-ethinyl estradiol use is still observed, and TW engaging in medically-unsupervised FHT use may not have access to standard of care therapies. In this study, incomplete reporting of current FHT components prevented further exploration of biomarker levels by FHT type.

Limitations of this study include its cross-sectional design and lack of detailed FHT use information. FHT use was self-reported with confirmation by medical record where available. However, confirmation was not available for all participants, and some participants were taking medically-unsupervised FHT, the true components of which were unknown. Additionally, serum estradiol and testosterone concentrations were not available for this cohort, and we cannot completely exclude the possibility that an acute HIV acquisition was missed by rapid testing of persons believed to be HIV-negative. Lastly, time in storage was a few years longer for MACS men. However, samples had not previously been thawed and biomarkers we chose are not anticipated to have had substantial additional degradation during the additional storage period.

Although the sample size is fairly small, it is large among studies of TW. Strengths include having data from TW with and without HIV, on and off FHT, and from diverse racial, ethnic and geographic backgrounds. Well-matched controls are another significant strength. However, future research is needed to further characterize differences in cardiovascular risk by gender and FHT use and type, including research on surrogate measures of risk, such as circulating biomarkers.

Conclusions

Compared to matched CM, TW have altered profiles of biomarkers associated with systemic inflammation and CVD, even after adjusting for key risk factors. HIV and FHT may further complicate CVD risk. Although pathophysiology cannot be inferred from these cross-sectional assessments, these provocative data highlight the potential for adverse cardiovascular events among TW. Clinical data and longitudinal studies are needed to understand the mechanisms of CVD risk among TW.

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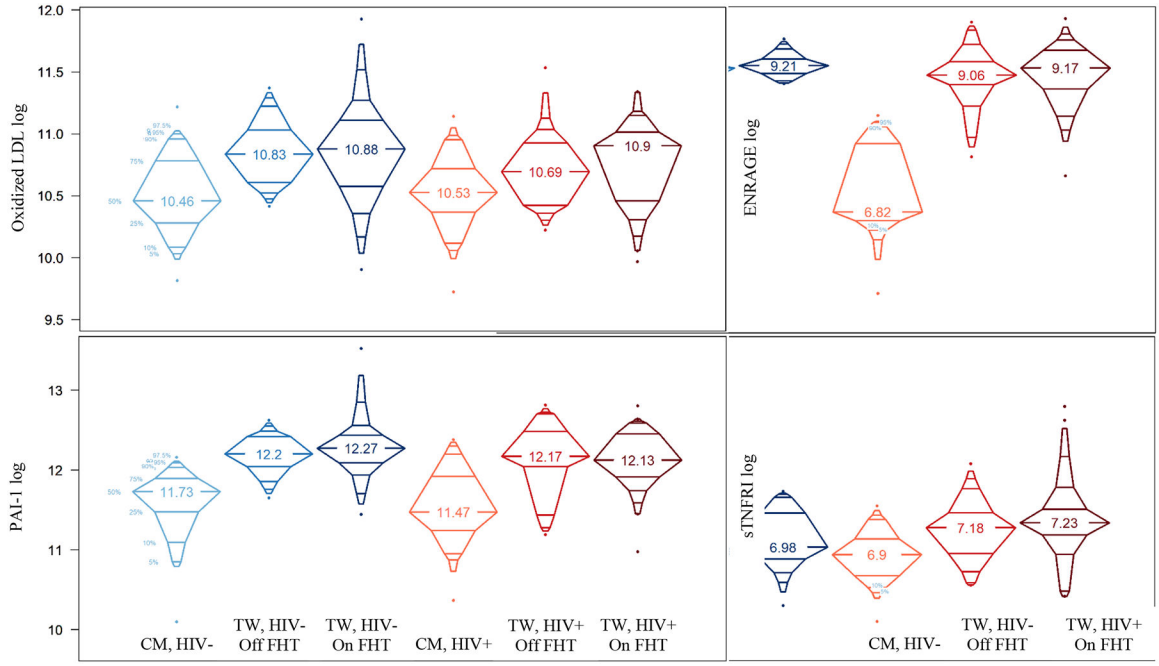

Figure 1:

Differences in Biomarker Concentrations by Gender, FHT Use and HIV Serostatus

FHT=feminizing hormonal therapy, TW=transgender women, CM=cisgender males

Table 1.

Clinical and Demographic Characteristics

	CM, HIV− (N=40)	CM, HIV+ (N=40)	TW, HIV− (N=47)	TW, HIV+* (N=75)
Age	43 (35, 52)	48 (43, 54)	40 (32, 48)	43 (37, 52)
Black race	13%	23%	13%	27%
Hispanic ethnicity	65%	60%	64%	57%
Overweight/obese (BMI >25 kg/m^2)	58%	67%	30%	24%
Former smoker	60%	58%	22%	11%
Current smoker	20%	28%	28%	37%
Recreational drug use	28%	48%	23%	41%
Alcohol use				
>0 & <14 drinks/week	73%	78%	37%	45%
>=14 drinks/week	5%	3%	11%	8%
Hypertension	40%	39%	17%	33%
Diabetes mellitus	13%	19%	15%	13%
ART regimen				
NNRTI-based		43%		24%
PI-based		45%		20%
INSTI-based		13%		49%
CD4$^+$ T lymphocyte count (cells/μL)		650 (466,846)		580 (391,841)
CD4$^+$ T lymphocyte nadir <200 (cells/μL)		48%		54%
Detectable HIV-1 RNA (≥50 copies/ml)		0%		32%
Any AIDS diagnosis		8%		36%
Feminizing Hormonal Therapy			66%	68%

Frequency or median (interquartile range) presented.

*When restricting to TW with undetectable HIV-1 RNA, age, current smoking and high-risk alcohol use frequency more closely resembled CM.
TW=transgender women, CM=cisgender males, NNRTI= non-nucleoside reverse transcriptase inhibitors, PI=protease inhibitors, INTI=integrase strand transfer inhibitors

Table 2:

Biomarker Concentrations by Gender and HIV Serostatus

	PLWH			PWOH		
	TW (N=75)	**CM (N=40)**	***P*-value**	**TW (N=47)**	**CM (N=40)**	***P*-value**
Adiponectin (ng/mL)	3499.2 (1965.5–5335.0)	2926.0 (1323.3–4454.1)	0.215	3034.7 (1696.8–5015.4)	2723.0 (1307.0–3678.9)	0.344
Human ENRAGE (pg/mL)	9498.6 (6875.6–12461.0)	912.9 (787.4–2797.4)	<0.001	9971.1 (8182.2–10796.5)	2272.5 (877.6–3325.0)	<0.001
LpPLA2(ng/mL)	242.6 (208.6–309.4)	220.8 (194.1–254.3)	0.013	243.5 (197.8–289.4)	250.7 (234.7–279.8)	0.268
Oxidized LDL (mU/L)	51166.2 (34108.9–60422.8)	37248.1 (31470.8–46385.6)	0.007	52260.8 (38632.2–67630.7)	34833.5 (29078.1–48335.0)	<0.001
sCD14 (ng/mL)	1878.2 (1524.5–2200.9)	2024.0 (1783.6–2353.3)	0.026	1687.7 (1296.3–1928.3)	1638.8 (1459.1–1868.6)	0.517
sCD163 (ng/mL)	608.1 (384.4–944.0)	727.0 (576.1–843.6)	0.178	500.7 (407.5–682.1)	534.1 (407.0–668.1)	0.583
sTNFR I (pg/mL)	1369.0 (1176.0–1604.5)	989.4 (787.7–1194.0)	<0.001	1057.5 (920.6–1492.2)	980.5 (814.0–1120.4)	0.037
sTNFR II (pg/mL)	3243.1 (2656.9–4344.5)	2669.8 (2041.4–3718.3)	0.005	2698.4 (2242.2–3450.7)	2220.1 (1971.1–2806.3)	0.008
VCAM-1 (ng/mL)	730.0 (576.5–1098.0)	766.9 (613.9–867.4)	0.577	717.5 (505.4–879.1)	683.4 (509.9–759.4)	0.501
VWF (mU/mL)	1797.9 (1410.4–2910.9)	2719.1 (1916.8–3890.7)	0.002	1736.4 (1100.6–2308.6)	1957.1 (1481.2–3737.0)	0.057
P-Selectin (ug/mL)	116.0 (91.5–149.4)	97.8 (79.0–129.0)	0.094	113.9 (91.6–144.6)	90.0 (73.1–108.1)	0.010
Endothelin-1 (pg/mL)	3.7 (1.9–5.0)	5.9 (3.0–7.4)	0.005	4.6 (3.0–6.8)	7.6 (5.3–8.6)	0.004
IL-6 (pg/mL)	2.5 (1.5–7.7)	3.2 (2.0–7.8)	0.368	4.5 (1.7–9.4)	1.9 (1.2–4.8)	0.048
IL-8 (pg/mL)	31.3 (19.7–54.3)	10.7 (5.6–17.4)	<0.001	49.6 (31.3–310.5)	7.1 (3.9–12.8)	<0.001
PAI-1 (pg/mL)	191640.1 (152676.2–260532.7)	96152.4 (75255.7–150325.9)	<0.001	206907.8 (177575.5–252684.4)	124326.9 (93968.2–146791.6)	<0.001

Median and interquartile range presented, TW=transgender women, CM=cisgender males, PLWH=people living with HIV, PWOH=people without HIV

Table 3:

Biomarker Concentrations by Gender, FHT Use and HIV Serostatus *

	PLWH				PWOH			
	TW on FHT (N=51)	**TW not on FHT (N=24)**	**CM (N=40)**	***P*-value**	**TW on FHT (N=31)**	**TW not on FHT (N=16)**	**CM (N=40)**	***P*-value**
ENRAGE (pg/mL)	9642.3 (6834.2–12857.7)	8596.5 (7345.9–10696.7)	912.9 (787.4–2797.4)	<0.001	10021.4 (8182.2–11471.4)	9652.8 (8018.3–10254.8)	2272.5 (877.6–3325.0)	<0.001
LpPLA2 (ng/mL)	235.9 (208.6–304.3)	263.6 (199.5–318.8)	220.8 (194.1–254.3)	0.040	243.5 (195.5–287.4)	241.5 (217.5–305.2)	250.7 (234.7–279.8)	0.499
Oxidized LDL (mU/L)	54347.4 (34837.7–60737.1)	44096.3 (32866.8–55587.9)	37248.1 (31470.8–46385.6)	0.023	52924.3 (38632.2–67630.7)	50779.3 (39381.7–65883.7)	34833.5 (29078.1–48335.0)	0.004
sTNFRI (pg/mL)	1385.7 (1212.3–1604.5)	1315.2 (992.9–1574.3)	989.4 (787.7–1194.0)	<0.001	1071.4 (941.6–1575.1)	1022.6 (880.6–1197.8)	980.5 (814.0–1120.4)	0.061
sTNFRII (pg/mL)	3225.9 (2634.0–4396.9)	3300.2 (2801.3–4205.0)	2669.8 (2041.4–3718.3)	0.017	2698.4 (2242.2–3921.1)	2842.9 (2318.5–3380.6)	2220.1 (1971.1–2806.3)	0.031
VWF (mU/mL)	1750.7 (1289.6–2644.3)	1901.0 (1599.4–3444.1)	2719.1 (1916.8–3890.7)	0.005	1573.5 (940.5–2186.8)	1970.3 (1343.1–2449.5)	1957.1 (1481.2–3737.0)	0.078
Endothelin-1 (pg/mL)	3.6 (1.3–4.8)	4.1 (2.1–5.2)	5.9 (3.0–7.4)	0.012	4.5 (2.8–6.1)	5.1 (3.0–8.3)	7.6 (5.3–8.6)	0.007
IL-8 (pg/mL)	31.3 (20.6–45.1)	31.3 (16.4–90.4)	10.7 (5.6–17.4)	<0.001	35.4 (31.3–297.0)	89.8 (31.3–355.6)	7.1 (3.9–12.8)	<0.001
PAI-1 (pg/mL)	184436.3 (148166.6–259048.4)	193237.3 (169630.9–267712.5)	96152.4 (75255.7–150325.9)	<0.001	213929.0 (177999.5–254385.6)	198819.6 (165473.8–250659.3)	124326.9 (93968.2–146791.6)	<0.001

* Limited to subset of biomarkers with statistical significance across at least 1 HIV serostatus

Median and interquartile range presented, FHT=feminizing hormonal therapy, TW=transgender women, CM=cisgender males, PLWH=people living with HIV, PWOH=people without HIV

Table 4:

Adjusted Associations Between Gender (TW vs CM) and Biomarker Concentrations

	Difference in Log Biomarker (95% CI)	*P*-value
Adiponectin (ng/mL)	0.06 (−0.20, 0.33)	0.648
ENRAGE (pg/mL)	1.82 (1.58, 2.06)	<0.001
LpPLA2 (ng/mL)	0.06 (−0.03, 0.15)	0.209
Oxidized LDL (mU/L)	0.26 (0.12, 0.39)	<0.001
sCD14 (ng/mL)	−0.09 (−0.19, −0.00)	0.048
sCD163 (ng/mL)	−0.27 (−0.47, −0.08)	0.007
sTNFR I (pg/mL)	0.20 (0.07, 0.34)	0.003
sTNFR II (pg/mL)	0.17 (0.03, 0.30)	0.017
VCAM-1 (ng/mL)	−0.05 (−0.17, 0.07)	0.425
VWF (mU/mL)	−0.41 (−0.63, −0.19)	<0.001
P-Selectin (ug/mL)	0.26 (0.08, 0.45)	0.006
Endothelin-1 (pg/mL)	−0.35 (−0.64, −0.05)	0.021
IL-6 (pg/mL)	0.53 (0.12, 0.94)	0.012
IL-8 (pg/mL)	2.08 (1.49, 2.67)	<0.001
PAI-1 (pg/mL)	0.67 (0.50, 0.83)	<0.001

Adjusted for HIV serostatus, age, race/ethnicity, BMI, and smoking status; TW=transgender women, CM=cisgender males