HORMONE USE AND HIV ALTER CARDIOVASCULAR BIOMARKER PROFILES IN TRANSGENDER WOMEN

#3472

Jordan E. Lake,[1] Ruibin Wang,[2] Benjamin Barrett,[2] Nicholas Funderburg,[3] Emily Bowman,[3] Paula Debroy,[1] Jury Candelario,[4] Linda Teplin,[5] Jessica McGuiness,[6] Robert Bolan,[7] Heather McKay,[2] Michael Plankey,[8] Todd T. Brown,[2] Judith S. Currier[9]

[1]UTHealth, Houston, TX; [2]Johns Hopkins University, Baltimore, MD; [3]The Ohio State University, Columbus, OH; [4]APAIT-Special Services for Groups, Los Angeles, CA; [5]Northwestern University, Chicago, IL; [6]University of Pittsburgh, Pittsburgh, PA; [7]Los Angeles LGBT Center, Los Angeles, CA; [8]Georgetown University, Washington, DC; [9]University of California, Los Angeles, CA

Correspondence:
Jordan E. Lake, M.D., M.Sc.
6431 Fannin St., MSB 2.112
Houston, TX 77030
Jordan.E.Lake@uth.tmc.edu

Background

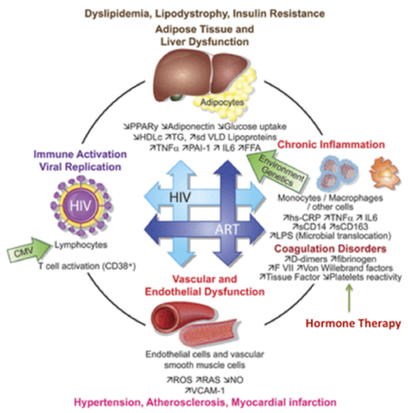

Figure 1. Contributions of HIV and FHT to metabolic and inflammatory disease. Adapted from Hemkens and Bucher. Eur Heart J. 2014.

- Transgender women (TW) are disproportionally affected by HIV and have a high prevalence of modifiable cardiovascular disease (CVD) risk factors.[1,2]
- Feminizing hormonal therapy (FHT) and HIV potentially alter CVD risk in TW.[3]
- We assessed serum biomarkers of CVD risk and inflammation among TW by HIV serostatus and FHT use, compared to cis-gender male (CM) controls.

Methods

Population:

- TW from community-based organizations and clinics in Los Angeles, California and Houston, Texas
- TW were frequency-matched to Multicenter AIDS Cohort Study CM on age, race, substance use and antiretroviral therapy (ART) type.
- All participants with HIV were on ART.
- For regression analyses, TW with HIV (n=51) had HIV-1 RNA<50 copies/mL.

Analysis:

- Serum biomarker profiles were assessed via ELISA.
- Wilcoxon rank sum and Fisher's exact tests compared group differences.
- Multivariable linear regression analyses assessed factors associated with natural log-transformed biomarker concentrations after adjusting for HIV serostatus, gender, age, race/ethnicity, body mass index (BMI), and smoking.

Results

Table 1: Baseline 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	58%	67%	30%	24%
Smoking history (former or current)	80%	86%	50%	48%
Recreational drug use	28%	48%	23%	41%
Alcohol use				
<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		0%		32%
Any AIDS diagnosis		8%		36%
Feminizing Hormonal Therapy			66%	68%

Frequency or median (interquartile range) presented. *When restricting to TW with suppressed HIV-1 RNA, age and smoking and alcohol use frequency more closely resembled CM. TW=transgender women, CM=cis-gender men, NNRTI= non-nucleoside reverse transcriptase inhibitors, PI=protease inhibitors, INTI=integrase strand transfer inhibitors

Results

Table 2a: Biomarker Concentrations by Gender in Participants Without HIV

	TW (N=47)	CM (N=40)	P-value
Adiponectin (ng/mL)	3034.7 (1696.8-5015.4)	2723.0 (1307.0-3678.9)	0.344
Human ENRAGE (ng/mL)	9971.1 (8182.2-10796.5)	**2272.5 (877.6-3325.0)**	**<0.001**
LpPLA2 (ng/mL)	243.5 (197.8-289.4)	250.7 (234.7-279.8)	0.268
Oxidized LDL (mg/dL)	52260.8 (38632.2-67630.7)	**34833.5 (29078.1-48335.0)**	**<0.001**
sCD14 (pg/mL)	1687.7 (1296.3-1928.3)	1638.8 (1459.1-1868.6)	0.517
sCD163 (pg/mL)	500.7 (407.5-682.1)	534.1 (407.0-668.1)	0.583
sTNFR I (ng/mL)	1057.5 (920.6-1492.2)	**980.5 (814.0-1120.4)**	**0.037**
sTNFR II (ng/mL)	2698.4 (2242.2-3450.7)	**2220.1 (1971.1-2806.3)**	**0.008**
VCAM-1 (ng/mL)	717.5 (505.4-879.1)	683.4 (509.9-759.4)	0.501
VWF (IU/dL)	1736.4 (1100.6-2308.6)	1957.1 (1481.2-3737.0)	0.057
P-Selectin (ng/mL)	113.9 (91.6-144.6)	**90.0 (73.1-108.1)**	**0.010**
Endothelin-1 (pg/mL)	4.6 (3.0-6.8)	**7.6 (5.3-8.6)**	**0.004**
IL-6 (pg/mL)	4.5 (1.7-9.4)	**1.9 (1.2-4.8)**	**0.048**
IL-8 (pg/mL)	49.6 (31.3-310.5)	**7.1 (3.9-12.8)**	**<0.001**
PAI-1 (ng/mL)	206907.8 (177575.5-252684.4)	**124326.9 (93968.2-146791.6)**	**<0.001**
Insulin (mU/mL)	15.5 (9.4-23.3)	15.0 (9.7-23.1)	0.93

Median and interquartile range presented, TW=transgender women, CM= cis-gender men

Table 2b: Biomarker Concentrations by Gender in Participants with HIV

	TW (N=75)	CM (N=40)	P-value
Adiponectin (ng/mL)	3499.2 (1965.5-5335.0)	2926.0 (1323.3-4454.1)	0.215
Human ENRAGE (ng/mL)	**9498.6 (6875.6-12461.0)**	**912.9 (787.4-2797.4)**	**<0.001**
LpPLA2(ng/mL)	242.6 (208.6-309.4)	220.8 (194.1-254.3)	0.013
Oxidized LDL (mg/dL)	**51166.2 (34108.9-60422.8)**	**37248.1 (31470.8-46385.6)**	**0.007**
sCD14 (pg/mL)	**1878.2 (1524.5-2200.9)**	**2024.0 (1783.6-2353.3)**	**0.026**
sCD163 (pg/mL)	608.1 (384.4-944.0)	727.0 (576.1-843.6)	0.178
sTNFR I (ng/mL)	**1369.0 (1176.0-1604.5)**	**989.4 (787.7-1194.0)**	**<0.001**
sTNFR II (ng/mL)	**3243.1 (2656.9-4344.5)**	**2669.8 (2041.4-3718.3)**	**0.005**
VCAM-1 (ng/mL)	730.0 (576.5-1098.0)	766.9 (613.9-867.4)	0.577
VWF (IU/dL)	**1797.9 (1410.4-2910.9)**	**2719.1 (1916.8-3890.7)**	**0.002**
P-Selectin (ng/mL)	116.0 (91.5-149.4)	97.8 (79.0-129.0)	0.094
Endothelin-1 (pg/mL)	**3.7 (1.9-5.0)**	**5.9 (3.0-7.4)**	**0.005**
IL-6 (pg/mL)	2.5 (1.5-7.7)	3.2 (2.0-7.8)	0.368
IL-8 (pg/mL)	**31.3 (19.7-54.3)**	**10.7 (5.6-17.4)**	**<0.001**
PAI-1 (ng/mL)	**191640.1 (152676.2-260532.7)**	**96152.4 (75255.7-150325.9)**	**<0.001**
Insulin (mU/mL)	19.0 (14.7-30.6)	15.9 (12.4-22.7)	0.29

Median and interquartile range presented, TW=transgender women, CM=cis-gender men

Figure 1: Differences in Biomarker Concentrations by Gender and HIV Serostatus

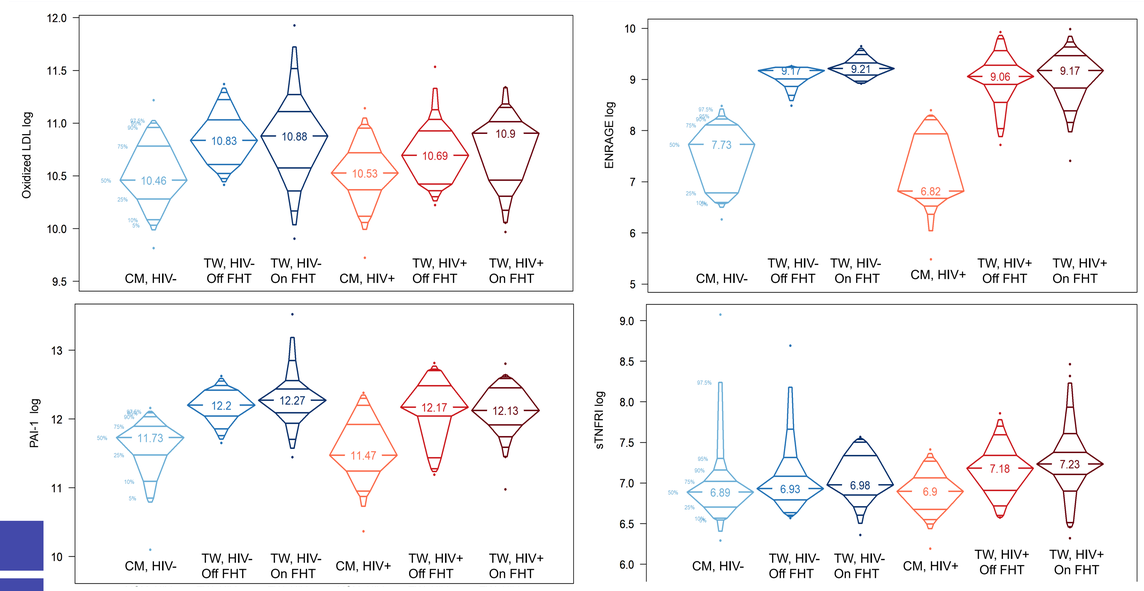

Table 3: Biomarker Concentrations by Gender, FHT Use and HIV Serostatus

	HIV+				HIV-			
	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 (ng/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 (mg.dL)	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 (ng/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 (ng/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 (IU/dL)	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 (ng/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

Median and interquartile range presented, FHT=feminizing hormonal therapy, TW=transgender women, CM=cis-gender men

Table 4: Adjusted Associations for 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 (ng/mL)	**1.82 (1.58, 2.06)**	**<0.001**
LpPLA2 (ng/mL)	0.06 (-0.03, 0.15)	0.209
Oxidized LDL (mg/dL)	**0.26 (0.12, 0.39)**	**<0.001**
sCD14 (pg/mL)	**-0.09 (-0.19,-0.00)**	**0.048**
sCD163 (pg/mL)	**-0.27 (-0.47,-0.08)**	**0.007**
sTNFR I (ng/mL)	**0.20 (0.07, 0.34)**	**0.003**
sTNFR II (ng/mL)	**0.17 (0.03, 0.30)**	**0.017**
VCAM-1 (ng/mL)	-0.05 (-0.17, 0.07)	0.425
VWF (IU/dL)	**-0.41 (-0.63,-0.19)**	**<0.001**
P-Selectin (ng/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 (ng/mL)	**0.67 (0.50, 0.83)**	**<0.001**
Insulin (mU/mL)	-0.01 (-0.41, 0.38)	0.942

Adjusted for HIV status, age, race/ethnicity, BMI, and smoking status.

Summary & Conclusions

- **Compared to matched cis-gender males, transgender women have altered profiles of biomarkers associated with systemic inflammation and CVD that seem to be influenced by both FHT and HIV.**
- **TW had significantly higher ENRAGE, oxidized LDL, sTNFRI, sTNRFII, IL-8 and PAI-1 concentrations, regardless of HIV serostatus.**
- **Stepwise increase of oxidized LDL, ENRAGE, PAI-1, and sTNFRI were seen, with CM < TW not on FHT < TW on FHT.**
- **Clinical outcomes data and mechanistic studies are needed to understand the contributions of FHT and HIV to CVD risk among TW.**

References and Acknowledgements

[1]*Lancet Infect Dis* 2013;13(3):214-22 [2]*Arch Sex Behav.* 2005;34:679-90 [3]*Clin Endocrinol.* 2010; 72(1):1-10

The investigators thank the study staff and participants for their generous time and support. This work was funded by the Gilead Research Scholars Program in HIV and K23 AI110532 to JEL, R25 MH087222 to JLC, 5P30 AI028697, U01 HL146201, U01 HL146193, U01 HL146240, U01 HL146333 and U01 HL146208.