CIRCULATING BIOMARKERS AND CARDIAC DYSFUNCTION IN WOMEN WITH OR AT RISK FOR HIV

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BACKGROUND

- People with HIV are at greater risk for cardiovascular disease (CVD), including cardiac dysfunction, compared with those without HIV
  - Underlying mechanisms not well-understood
  - Risks may be further elevated in women with HIV
- To better understand role of HIV in development of cardiac dysfunction, we measured 8 circulating cardiac, metabolic or inflammatory biomarkers in women either with or at risk for HIV
  - We assessed the association of each biomarker with measures of subclinical cardiac dysfunction, and effect modification by HIV serostatus
  - We evaluated the relationship of each biomarker with HIV and related parameters

METHODS

Study population and inclusion criteria

- WIHS Women's Interagency HIV Study — A longitudinal cohort study of women with or at risk for HIV at 10 U.S. sites
- In this substudy, **709** participants from the Bronx, Brooklyn, and San Francisco sites underwent trans-thoracic echocardiography between 2014 and 2018

Biomarkers of interest

Biomarker	Hypothesized role	Assoc. outcomes
Cardiac/metabolic biomarkers		
NT-proBNP	Cardiomyocyte stretch	Heart failure, death
High sensitivity troponin I (hsTnI)	Cardiomyocyte injury	CVD, heart failure, death
Soluble ST2 (sST2)	Cardiac stress and inflammation, fibrosis	CVD, heart failure, death
Non-esterified free-fatty acids (NEFA)	Insulin resistance, excess lipolysis, ectopic fat deposition	Diabetes, heart failure
Inflammation/immune biomarkers		
C-reactive protein (CRP)	Systemic inflammation	CVD
Interleukin-6 (IL-6)	Systemic inflammation	Heart failure, death
Soluble CD14 (sCD14)	Macrophage activation, inflammation	Atherosclerosis, death
Growth/differentiation factor-15 (GDF-15)	Inflammation, oxidative stress	Heart failure, atrial fibrillation, death

We identified previously unreported associations of several key biomarkers with cardiac dysfunction in the context of HIV in women, including differing associations of GDF-15 with LV systolic dysfunction by HIV serostatus

Outcomes of interest

1. Left ventricular (LV) systolic dysfunction: LV ejection fraction <54%
2. Isolated LV diastolic dysfunction: American Society of Echocardiography 2016 guidelines definition
3. Pulmonary hypertension: Peak tricuspid regurgitation velocity >2.8 m/s

Statistical methods

- Biomarkers log-transformed, Z-score standardized
- Modified Poisson regression and linear regression models, adjusting for demographic, behavioral and cardiometabolic factors
- Two-way interaction terms assessed effect modification by HIV serostatus
- Multiple imputation for missing data

RESULTS

Participant characteristics (N=709, 68% with HIV)

Characteristic	With HIV (N=484)	Without HIV (N=225)
Median age, yrs (IQR)	53 (48-59)	51 (44-57)
Black (non-Hispanic) race	64%	67%
Hispanic ethnicity	22%	23%
Income <$30,000/year	76%	74%
History of HCV infection	29%	21%
Current smoker	37%	46%
Median BMI, kg/m^2 (IQR)	29 (25-36)	31 (26-37)
LV systolic dysfunction	6%	4%
LV diastolic dysfunction	9%	8%
Pulmonary hypertension	12%	9%

BMI = body mass index, HCV = hepatitis C virus, IQR = interquartile range.

- Among women with HIV (N=484)
  - Median CD4 count: 649 (IQR 442-869)
  - 95% currently using ART, with 56% on an integrase strand transfer inhibitor (INSTI) regimen
  - 69% with undetectable viral load (<20 cp/mL)
  - 46% with history of clinical AIDS
- sCD14 and GDF-15 levels significantly higher in women with HIV than without HIV (p<0.0001)

RESULTS, CONTINUED

Adjusted associations of markers with cardiac dysfunction (N=709)

	Left ventricular systolic dysfunction		Left ventricular diastolic dysfunction		Pulmonary hypertension	
	Prevalence ratio (95% CI)	P-value	Prevalence ratio (95% CI)	P-value	Prevalence ratio (95% CI)	P-value
Cardiac/metabolic biomarkers						
NT-proBNP	**1.53 (1.10, 2.12)**	**0.01**	**1.83 (1.32, 2.55)**	**<0.01**	**1.79 (1.44, 2.21)**	**<0.01**
hsTnI	1.44 (0.89, 2.33)	0.14	**2.74 (1.24, 6.04)**	**0.01**	1.26 (0.86, 1.84)	0.23
sST2	1.16 (0.87, 1.54)	0.31	1.07 (0.79, 1.45)	0.67	1.16 (0.94, 1.43)	0.17
NEFA	**1.44 (1.04, 1.99)**	**0.03**	0.75 (0.53, 1.05)	0.10	0.98 (0.80, 1.22)	0.88
Inflammation/immune biomarkers						
hsCRP	**1.51 (1.13, 2.01)**	**0.01**	0.88 (0.61, 1.28)	0.50	1.20 (0.95, 1.52)	0.13
IL-6	1.25 (0.94, 1.66)	0.13	1.13 (0.69, 1.84)	0.64	**1.32 (1.09, 1.61)**	**0.01**
sCD14	**1.58 (1.14, 2.17)**	**0.01**	1.21 (0.79, 1.84)	0.38	1.16 (0.88, 1.53)	0.29
GDF-15	1.28 (0.91, 1.78)	0.15	1.01 (0.63, 1.62)	0.96	**1.57 (1.16, 2.13)**	**<0.01**

Adjusted for HIV serostatus, age, race/ethnicity, education, study site, history of injection drug use, crack/cocaine use, current smoking, current alcohol use, history of HCV infection, body mass index, systolic blood pressure, total and HDL cholesterol, use of antihypertension or anticholesterol medications, history of diabetes, eGFR, menopause status. CI = confidence interval.

- Differing associations of GDF-15 with LV systolic dysfunction among women with HIV (N=484, adj. PrevR 1.73, 95% CI 1.29-2.32) than without HIV (N=225, adj. PrevR 0.29, 95% CI 0.09-0.96), p_{ix}=0.09

Adjusted associations of markers with HIV-related factors (N=484)

- Higher sCD14, GDF-15, NT-proBNP, and sST2 levels significantly associated with lower current CD4 count
- Higher sCD14 associated with greater cumulative HIV viremia
- Higher hsTnI associated with AIDS, lower cumulative HIV viremia
- Higher sCD14, GDF-15, and NEFA associated with less INSTI use

CONCLUSIONS

- We found several previously unreported associations of circulating biomarkers with cardiac dysfunction in the context of HIV in women, including differing associations of GDF-15 with LV systolic dysfunction by HIV serostatus
- sCD14, GDF-15 higher in women with HIV than women without HIV, associated with lower CD4 count and less INSTI use
- Longitudinal studies would help to confirm and extend the findings of this cross-sectional study

Funding
R01-HL-132794
K01-HL-137557
U01-HL-146204
U01-HL-146202
U01-HL-146242
U01-HL-146193

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