ST2 and GDF-15 are Associated with Structural Heart Disease and Mortality in HIV-Infected Individuals

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Background

With the advent HAART, the HIV population is now growing older, and in parallel with this trend, cardiovascular disease has emerged as an important health concern among HIV-infected individuals. Previous studies have associated markers of inflammation, coagulation, and renal disease with cardiovascular events and mortality in HIV-infected individuals, but these markers lack cardiac specificity and may not represent the direct pathway between HIV infection and cardiovascular disease. Novel markers of cardiac stress have recently identified non-infected ambulatory persons at risk for structural heart disease and mortality, but have yet to be studied in the HIV population.

Methods

Patient selection 332 HIV-infected study subjects were recruited from 9/2004 through 3/2011 from the SCOPE study, an ongoing prospective cohort study at San Francisco General Hospital. 50 uninfected controls were recruited with enrollment targeted to match demographics of HIV population.

Assessment of cardiac dysfunction Transthoracic echocardiograms were performed on subjects at the time of enrollment. We defined systolic dysfunction as an ejection fraction <50%, pulmonary hypertension as PASP >35mmHg, and diastolic dysfunction as ≥ stage 1 (impaired relaxation).

Analysis of Biomarkers Eight biomarkers were selected because of reported associations with cardiovascular events or death in either the general population and/or in HIV-infected individuals. The biomarkers included: ST2 (fibrosis); GDF-15 (apoptosis); NT-proBNP (myocyte stretch); high sensitivity Troponin I (myocardial injury); hsCRP and IL-6 (inflammation); Cystatin C (renal dysfunction); and D-dimer (thrombosis).

Mortality Data Mortality data was obtained through the Social Security Death Index and/or CDC National Death Index 1 year after last patient visit.

Statistical analysis

Multivariable linear regression models were used to investigate factors associated with levels of each biomarker and other continuous parameters. Cox proportional hazards regression models were used to investigate the associations between biomarker levels with diastolic dysfunction, pulmonary hypertension, and all-cause mortality. All analyses were also restricted to treated, virally suppressed HIV patients. Analyses were conducted using SAS v9.2 (SAS Institute, Inc.,Cary, NC)

Results

Table 1: Characteristics of All Participants

	HIV+ (N = 332)	Controls (N = 50)
Age (years)	49 (42-54)	46 (40-57)
Male gender	265 (80%)	44 (88%)
Race		
Caucasian	186 (56%)	33 (66%)
African American	**105 (32%)**	**4 (8%)**
Other	41 (13%)	13 (26%)
Body Mass Index (kg/m2)	25 (23-29)	26 (24-29)
Systolic Blood Pressure	120 (111-130)	122 (114-128)
Medical History		
Current tobacco use	117 (35%)	12 (24%)
Coronary artery disease	13 (4%)	0
Diabetes mellitus	27 (8%)	4 (8%)
Hypertension	**112 (34%)**	**3 (6%)**
Dyslipidemia	97 (29%)	12 (24%)
Laboratory Findings		
LDL (mg/dL)	101 (76-128)	106 (89-114)
HDL (mg.dL)	47 (39-55)	46 (44-62)
Triglycerides (mg/dL)	**149 (100-258)**	**92 (66-166)**
Total Cholesterol(mg/dL)	185 (152-216)	177 (169-191)

Values are represented as medians (interquartile range), unless otherwise noted
Bolded, yellow values represent significant differences

Table 2: Characteristics of HIV Participants

	HIV+ (N = 332)
Duration of HIV infection (yrs)	14 (10-18)
Antiretroviral use	261 (79%)
Protease Inhibitor use	242 (73%)
Current CD4 count (cells/mm^3)	469 (294-668)
Nadir CD4 count (cells/mm^3)	160 (41-300)
Plasma HIV RNA < 75 copies/ml	178 (68%)
Hepatitis C Infection	87 (26%)
Previous Intravenous Drug Use	131 (39%)
Previous Opportunistic Infection	93 (28%)

Values are represented as medians (interquartile range), unless otherwise noted

Table 3: HIV Effect on Biomarker Levels

Biomarker	Unadjusted HIV %Effect	Adjusted HIV %Effect
ST2	7.1 (-3.0, 18.2)	8.8 (-1.1, 19.7)
NT-proBNP	**151.0 (96.7, 220.4)**	**130.2 (82.3, 190.7)**
GDF-15	**237.7 (189.5, 293.8)**	**231.5 (183.9, 286.9)**
hsTnI	**94.6 (11.1, 240.9)**	**90.1 (6.4, 239.4)**
hsCRP	**54.9 (6.1, 126.3)**	**53.8 (4.7, 126.0)**
IL-6	22.8 (-7.5, 63.1)	20.3 (-9.6, 60.1)
Cystatin C	**39.4 (27.6, 52.3)**	**39.5 (27.6, 52.4)**
D-Dimer	**40.3 (18.9, 65.7)**	**36.0 (17.5, 57.4)**

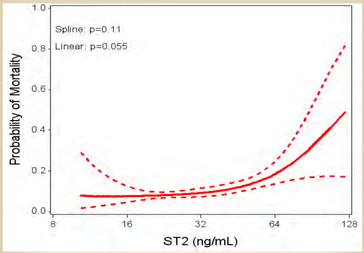
Values are represented as percent estimates (confidence intervals)
Bolded, yellow values represent significant differences

Table 4: Associations between Biomarkers with Diastolic Dysfunction, Pulmonary Hypertension, and Death in HIV

Outcome	Demographic adjusted RR (95% CI)	Fully adjusted RR (95% CI)
Diastolic Dysfunction		
ST2	**1.43 (1.06, 1.92)**	**1.36 (1.00, 1.85)**
NT-proBNP	1.01 (0.93, 1.11)	1.00 (0.91, 1.10)
hsCRP	1.06 (0.97, 1.16)	1.08 (0.98, 1.18)
GDF-15	1.08 (0.96, 1.22)	1.05 (0.92, 1.19)
Cystatin C	1.19 (0.90, 1.57)	1.11 (0.80, 1.54)
IL-6	1.09 (0.99, 1.20)	1.09 (0.98, 1.20)
D-dimer	1.17 (0.99, 1.38)	1.17 (0.98, 1.39)
Detectable Troponin	1.19 (0.83, 1.73)	1.10 (0.75, 1.60)
Pulmonary Hypertension		
ST2	1.18 (0.83, 1.67)	1.21 (0.84, 1.75)
NT-proBNP	**1.15 (1.04, 1.26)**	**1.18 (1.04, 1.32)**
hsCRP	1.07 (0.96, 1.19)	1.03 (0.90, 1.17)
GDF-15	**1.19 (1.03, 1.37)**	**1.18 (1.01, 1.39)**
Cystatin C	1.33 (0.97, 1.83)	**1.54 (1.04, 2.29)**
IL-6	1.02 (0.91, 1.14)	1.03 (0.91, 1.17)
D-dimer	1.11 (0.90, 1.37)	1.06 (0.85, 1.33)
Detectable Troponin	0.76 (0.45, 1.26)	0.84 (0.49, 1.42)
All-cause Mortality	**Demographic adjusted HR (95% CI)**	**Fully adjusted HR (95% CI)**
ST2	**2.08 (1.22, 3.56)**	**1.89 (1.04, 3.44)**
NT-proBNP	**1.32 (1.13, 1.54)**	1.20 (1.00, 1.45)
hsCRP	1.13 (0.93, 1.37)	1.18 (0.96, 1.45)
GDF-15	**1.48 (1.17, 1.88)**	**1.35 (1.02, 1.79)**
Cystatin C	1.70 (0.98, 2.96)	1.14 (0.50, 2.59)
IL-6	1.17 (0.91, 1.50)	1.02 (0.81, 1.29)
D-dimer	**1.78 (1.26, 2.51)**	1.40 (0.94, 2.09)
Detectable Troponin	1.55 (0.74, 3.27)	1.21 (0.54, 2.74)

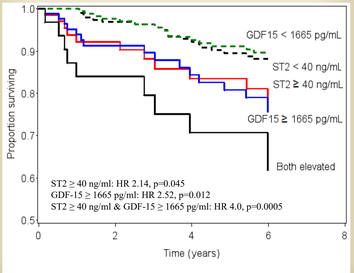
Bolded, yellow values represent significant differences

Figure 1: Association of ST2 and GDF-15 Levels with Mortality in HIV Participants



Spline p-values test non-linearity. Solid lines denote predicted probability of mortality and dotted lines represent 95% confidence interval bounds.

Figure 2: Kaplan-Meier Survival Curves for HIV Patients, Stratified by ST2 and GDF-15 Levels



Discussion

Discussion: HIV patients were a median 49 years, 80% were male, 34% had hypertension, 29% had dyslipidemia and 35% used tobacco (Table 1). The median duration of HIV infection was 14 years, the nadir CD4+ T cell count was 160 cells/mm^3, the current CD4 count was 469 cells/mm^3 and 68% had undetectable HIV RNA levels (Table 2). Compared with controls, HIV participants had higher levels of all biomarkers, although differences in ST2 and IL-6 levels did not reach full significance ($p<0.05$ for all except ST2, $p=0.083$ and IL-6, $p=0.21$) (Table 3). Associations between biomarkers and outcomes for HIV patients are displayed in Table 4. Among HIV patients, 45% had diastolic dysfunction (DD); only ST2 was associated with DD in fully-adjusted analysis (RR=1.36). Systolic dysfunction was rare in this cohort (5%) and showed no associations with the biomarkers. Pulmonary hypertension was present in 27% of HIV patients versus 2% of controls ($p<.0001$) and was associated with GDF-15 (RR=1.18), NT-proBNP (RR=1.18), and Cystatin C (RR 1.54). 33 deaths occurred among HIV subjects over a median 5.8 years of follow-up, whereas only 1 death occurred among controls. In fully-adjusted analysis, only ST2 (HR 1.89) and GDF-15 (HR 1.35) were individually associated with mortality (Figure 1). Using ROC analyses, thresholds exceeding 40 ng/ml for ST2 and 1665 pg/ml for GDF-15 were each predictive of mortality (HR=2.14 for ST2 ≥40 ng/ml, HR=2.52 for GDF-15 ≥1665 pg/ml). This association was strengthened when both thresholds were surpassed (HR=4.0) (Figure 2). Results for all analyses were similar when restricted to treated, virally-suppressed HIV-infected patients.

Conclusion

Among ambulatory HIV patients, cardiac biomarker levels were greater compared with controls. ST2 was strongly associated with diastolic dysfunction, while GDF-15, NT-proBNP and Cystatin C were associated with pulmonary hypertension. ST2 and GDF-15 were each predictive of mortality and this relationship strengthened when these biomarkers were used in combination. ST2 and GDF-15 may be useful biomarkers of structural heart disease and overall mortality in HIV-infected patients.

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