

# Prevalence and Risk Factors in HIV-infected Persons for Echocardiographic Abnormalities in the Era of Modern HAART

K Mondy<sup>1</sup>, J Gottdiener<sup>2</sup>, ET Overton<sup>1</sup>, K Henry<sup>3</sup>, L Conley<sup>4</sup>, T Bush<sup>4</sup>, J Hammer<sup>5</sup>, C Carpenter<sup>6</sup>, EM Kojic<sup>6</sup>, JT Brooks<sup>4</sup>, and SUN Study Investigators

<sup>1</sup>Washington Univ Sch of Med, St Louis, MO, US; <sup>2</sup>Univ of Maryland, Baltimore, Maryland, US; <sup>3</sup>HIV Program, Hennepin County Med Ctr, Univ of Minnesota, MN, US; <sup>4</sup>CDC, Atlanta, GA, US; <sup>5</sup>Denver Infectious Disease Consultants, Denver, US; <sup>6</sup>The Miriam Hosp, Providence, RI, US



## ABSTRACT (updated)

**Background:** Cardiac function among HIV-infected persons in the contemporary treatment era has not been well characterized.

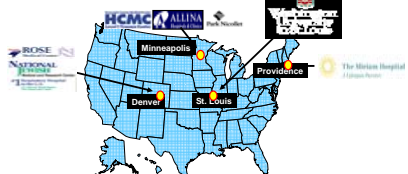
**Methods:** The SUN Study is a prospective cohort of 682 HIV-infected patients receiving care at clinics in Denver, Minneapolis, Providence, and St. Louis. At baseline, all patients underwent standardized echocardiographic examination. Using multivariate logistic regression modeling, we identified independent predictors of left ventricular systolic dysfunction (LVSD = ejection fraction <55%), diastolic dysfunction (DD), pulmonary hypertension (PHTN = right ventricular systolic pressure >30 mmHg), and LV hypertrophy (LVH = LV mass >45 women) and <49 (men) g/m<sup>2</sup>.

**Results:** Characteristics for 643 subjects with available data were: median age 44 years, 23% women, 27% Black, mean body mass index (BMI) 26.4 kg/m<sup>2</sup>, 77% on HAART, mean CD4 cell count (CD4) 519 cells/μL, 54% with HIV viral load <400 copies/mL, 14% hypertensive, 6% diabetic, 44% smokers. Eighteen percent of 640 evaluable subjects had LVSD (111 [18%] mild, 3 [1%] moderate, 0 severe), 25% of 660 evaluable subjects had DD (96 [15%] grade 1 [G1], 9 [1%] G2, 59 [9%] G3), 22% of 316 evaluable patients (i.e., had any tricuspid regurgitant flow present) had Pulm HTN (51 [16%] mild, 16 [1%] moderate, 5 [1%] severe), 6.6% of 604 evaluable subjects had LVH (24 [4%] mild, 8 [1%] each moderate and severe). Multivariate analyses demonstrated the following independent associations: for LVSD – male gender (odds ratio [OR] 2.1), carotid intima-media thickness [IMT] (OR 1.6 if >0.71 mm [median value], and smoking (OR 1.5); for DD – HTN (OR 2.1), and use of inhaled nitrates (OR 0.6); for Pulm HTN – Total Cholesterol (OR 2.6 if >154mg/dL [1st quartile]), Age > 35 years (OR, 2.2), and current use of a boosted PI (OR, 1.8); and for LVH – body mass index (OR 3.5 if ≥26.4 [median value]), use of marijuana (OR 2.0) IMT (OR 1.9 if >0.79 mm [upper quartile]), and current AZT use (OR 1.5) (p<0.05 for all).

**Conclusions:** In this cohort of contemporary HAART-era patients, subclinical abnormalities in cardiac function were detected frequently. Functional abnormalities were mostly associated with expected and often modifiable risks. Our analysis suggests lifestyle modification should become a greater priority in the management of chronic HIV disease.

## Background

- The natural history of HIV infection has been associated with a diverse array of adverse metabolic complications that may increase the risk of developing cardiovascular disease and accelerate risk of other diseases.
- The Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN Study) is a prospective cohort study designed to examine risk factors for complications of treating HIV infection and longer survival.
- Patients are followed from 7 clinics in 4 U.S. cities.
- The primary objectives of this analysis were to characterize baseline cardiac function of subjects by modern echocardiographic methods and to determine clinical, behavioral, and laboratory predictors of prevalent echocardiographic abnormalities.



## Methods

**\*SUN Study Subjects:** Age ≥18, either ARV-naïve with CD4 cell count 100-500 cells/mm<sup>3</sup> or HAART-experienced with CD4 cell count >100 cells/mm<sup>3</sup>, no immunomodulating therapy or AIDS-defining illness in 60 days preceding baseline enrollment.

**\*Methods/Data Collection:** Baseline resting echocardiography with tissue doppler imaging, carotid intima media thickness, patient demographics, behavioral risk factors, and fasting laboratory data were analyzed for the SUN cohort (n=667, tables 1-2); subgroup analyses were performed for the following echocardiographic abnormalities: left ventricular systolic dysfunction, diastolic dysfunction, pulmonary hypertension, and left ventricular hypertrophy. Sources of data included anonymous patient interview and laboratory data obtained at baseline study visit as well as abstraction of data from outpatient medical records. Echocardiographic and carotid data were read at central reading sites (U. of Maryland, Baltimore and U. of Southern California, respectively).

**\*Statistics:** Chi-square or Fisher's exact tests were used for categorical variables. Continuous variables were compared using the Student's t-test or Mann-Whitney U test. Multivariate logistic regression were used to identify independent predictors of echocardiographic outcomes from among factors significant in univariate analyses. All p values were two-tailed. Analysis was performed using SAS software version 9.1.

## Results: Echocardiographic Characteristics of Subjects (Table 1)

Characteristic	No. (%)	Mean ± S.E.M.	Median (Range)
<b>Systolic function (LVEF)</b>			
Normal: ≥55%	523 (82)	61.0 ± 0.2	60.2 (55.0 – 77.1)
Mild: 45-55%	114 (18)	53.3 ± 0.1	53.6 (45.4 – 55.0)
Moderate: 30-45%	3 (<1)	38.1 ± 3.9	42.7 (31.4 – 43.2)
Severe: <30%	0 (0.0)	N/A	N/A
<b>Diastolic function</b>			
Grade 0: normal	470 (74)	N/A	N/A
Grade 1: impaired relaxation	96 (15)	N/A	N/A
Grade 2: pseudonormal	9 (<1)	N/A	N/A
Grade 3: restrictive	59 (9)	N/A	N/A
<b>Pulmonary HTN (RVP mmHg)</b>			
Normal: < 31	136 (43)	27.1 ± 0.3	27.5 (14.4 – 31.0)
Borderline 31- 35	108 (34)	33.1 ± 0.1	33 (31.1 – 36.0)
Mild: 36-40	51 (16)	38.2 ± 0.2	37.9 (36.1 – 40.9)
Moderate: 41-50	16 (<1)	44.6 ± 0.7	44.8 (41.1 – 49.9)
Severe: ≥50	5 (<1)	67.8 ± 7.5	57.1 (64.8 – 90.3)
<b>Left ventricular mass (g/m<sup>2</sup>)</b>			
Normal: (<45 W; <49 M)	564 (93)	32.8 ± 0.3	32.6 (10.2 – 48.8)
Mild abnormal: (45-51 W; 49-55 M)	24 (4)	49.2 ± 0.5	49.1 (45.3 – 55.9)
Moderate: (52-58 W; 56-63 M)	8 (1)	58.0 ± 1.1	57.1 (50.4 – 62.8)
Severe abnormal: (≥59 W; ≥64 M)	8 (1)	83.3 ± 10.7	68.7 (60.7 – 151.4)
<b>Left atrial volume (ml/m<sup>2</sup> BSA)</b>			
Normal: <29	360 (61)	23.3 ± 0.2	23.6 (11.0 – 29.0)
Mild abnormal: 29-33	121 (21)	31.4 ± 0.1	31.4 (28.1 – 34.6)
Moderate abnormal: 34-39	64 (11)	36.4 ± 0.2	36.4 (34.2 – 39.9)
Severe abnormal: ≥40	45 (8)	45.1 ± 0.9	43.3 (40.1 – 71.2)

\*Pulmonary hypertension could only be evaluated in those subjects with the presence of tricuspid regurgitant flow. S.E.M. = standard error of the mean value

## Results: Patient Characteristics (Table 2)

Characteristic	No. (%)
<b>Age (mean ± SEM)</b>	41.0 ± 0.4
<b>Gender</b>	
Men	495 (77)
Women	148 (23)
<b>Race</b>	
White, non-Hispanic	388 (61)
Black, non-Hispanic	173 (27)
Hispanic	64 (10)
Unknown	12 (2)
<b>Years Since HIV Diagnosis (mean ± SEM)</b>	6.0 ± 0.2
<b>History of Opportunistic Infection</b>	121 (19)
<b>Co-infection with Hepatitis B</b>	21 (5.0)
<b>Co-infection with Hepatitis C</b>	70 (13)
<b>Current Smoker</b>	282 (44)
<b>Current Drug Use</b>	
Cocaine	63 (10)
Marijuana	160 (25)
IVDU	7 (1)
Inhaled nitrates	107 (17)
<b>On HAART</b>	493 (77)
HIV RNA<400 copies	350 (71)
<b>Type of HAART*</b>	
Ritonavir-boosted PI	183 (29)
Unboosted PI	50 (8)
NNRTI	237 (38)
3 or more NRTIs	112 (18)
<b>Time (years) on HAART (mean ± SEM)</b>	
NRTIs	3.0 ± 0.1
PIs	1.6 ± 0.9
NNRTIs	1.4 ± 0.8
<b>CD4 Count (mean cells/mm<sup>3</sup> ± SEM)</b>	
current	519 ± 11.1
naïve	221 ± 6.5
<b>BMI (mean kg/m<sup>2</sup> ± SEM)</b>	26.4 ± 0.2
<b>Fasting Glucose (mean mg/dL ± SEM)</b>	95 ± 1.1
<b>Fasting Total Cholesterol (mean mg/dL ± SEM)</b>	185 ± 2.0
<b>Fasting LDL (mean mg/dL ± SEM)</b>	109 ± 1.6
<b>Fasting HDL (mean mg/dL ± SEM)</b>	43 ± 0.6
<b>Fasting TG (mean mg/dL ± SEM)</b>	178 ± 5.5
<b>Current Use of Lipid-lowering Therapy</b>	72 (11)
<b>Diagnosis of Hypertension</b>	92 (14)
<b>On Antihypertensive Therapy</b>	107 (17)
<b>Diagnosis of Diabetes</b>	38 (6)
<b>History of Myocardial Infarction</b>	2 (<1)
<b>Mean Carotid IMT (mm ± SEM)</b>	0.73 ± 0.01
<b>Median Carotid IMT</b>	0.71

\*Some patients were receiving both PIs and NNRTIs.

## Results (Multivariate Analysis) : Predictors of Echocardiographic Abnormalities (Table 3)

Significant Predictors of Left Ventricular Systolic Dysfunction (EF<55%)				
Predictor	Odds Ratio	95% C.I.	P Value	
Gender male	2.05	1.19 – 3.71	0.013	
Carotid IMT > 0.71 mm (median)	1.64	1.08 – 2.51	0.022	
Current smoking	1.54	1.02 – 2.35	0.041	
Significant Predictors of Diastolic Dysfunction (Grade 1-3)				
Predictor	Odds Ratio	95% C.I.	P Value	
Hypertension	2.06	1.32-3.19	0.001	
Poppers in last 30 days	0.56	0.35 – 0.86	0.034	
Significant Predictors of Pulmonary Hypertension				
Predictor	Odds Ratio	95% C.I.	P Value	
Total Cholesterol >154 mg/dL (lower quartile)	2.58	1.37 – 5.09	0.004	
Age >35 years (lower quartile)	2.22	1.23 – 4.03	0.008	
Boosted PI	1.90	1.12 – 3.29	0.019	
Significant Predictors of Left Ventricular Hypertrophy				
Predictor	Odds Ratio	95% C.I.	P Value	
BMI >25.4 (median)	3.53	2.30 – 5.52	<0.001	
Marijuana in last 6 months	2.01	1.35 – 3.03	<0.001	
Carotid IMT >0.79 mm (upper quartile)	1.90	1.24 – 2.93	0.003	
Current AZT use	1.54	1.04 – 2.27	0.030	
Significant Predictors of Left Atrial Enlargement				
Predictor	Odds Ratio	95% C.I.	P Value	
Hepatitis C	2.27	1.31 – 4.06	0.004	
Marijuana in last 6 months	1.74	1.17 – 2.60	0.006	
Age >46 years (upper quartile)	1.73	1.13 – 2.67	0.012	
VAT/SAT < 0.58 (median)	1.49	1.03 – 2.17	0.036	

## Conclusions

- In the era of modern HAART, subtle abnormalities in cardiac function were prevalent within this patient cohort.
- Echocardiographic abnormalities were predicted not only by traditional cardiac risk factors but also modifiable risk factors including illicit drug use.
- Of the ARV therapy evaluated, the only associations were current use of ritonavir-boosted PIs with pulmonary hypertension and current AZT use with left ventricular hypertrophy.
- The current analysis suggests lifestyle modification should be a high priority in the management of chronic HIV disease.
- Further longitudinal assessment of cardiac function is anticipated in this HIV-infected cohort to determine whether these cardiac abnormalities remain stable over time.

**Acknowledgements:** We wish to gratefully acknowledge all SUN study investigators and their support staff, Cerner Corporation, and all of the study participants that have devoted their time and effort to this research endeavor.