Contribution of HIV, HCV, and Vascular Risk Factors to Peripheral Arterial Disease

Emily Cedarbaum[1], Yifei Ma[1], Rebecca Scherzer[1], Jennifer Price[1], Michael Plankey[2], Margaret Fischl[3], Eric Seaberg[4], Mardge H. Cohen[5], Marcas Bamman[6], Jason Lazar[7], Adaora Adimora[8], Michael T. Yin[9], Phyllis C. Tien[1]

WIHS Women's Interagency HIV Study

[1]University of California San Francisco, San Francisco, CA, USA, [2]Georgetown University, Washington, DC, USA, [3]University of Miami, Miami, FL, USA, [4]Johns Hopkins University, Baltimore, MD, USA, [5]Cook County Health & Hospitals System, Chicago, IL, USA, [6]University of Alabama at Birmingham, Birmingham, AL, USA, [7]SUNY Downstate Medical Center, Brooklyn, NY, USA, [8]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [9]Columbia University, New York, NY, USA

Corresponding Author:
Dr. Emily Cedarbaum
UCSF Internal Medicine
San Francisco, CA
E-mail: emily.cedarbaum@ucsf.edu

Introduction

- Peripheral arterial disease is associated with major vascular events (including myocardial infarction), decline in physical function, and mortality.
- Cardiovascular disease (CVD) is now one of the most common non-HIV-related causes of death among persons living with HIV.
- Whether or not HIV infection is associated with greater risk of PAD is unclear.
- Published studies that examine PAD in the setting of HIV infection have reported a prevalence that ranges from 1 – 27%, but these studies have small sample sizes limiting the ability to adequately control for traditional CVD risk factors, rarely include HIV-uninfected controls, and mostly included men. None have also examined the prevalence and risk in HIV/HCV-coinfected persons.
  - In the general population, prevalence of asymptomatic PAD rises after the age of 50 to 3% in those 50 -59 years, 9% in those 60-69 years, 20% in those 70-79 years, and 35% in those >80 years.
- Population-based studies in HIV-uninfected persons have suggested that the prevalence of PAD may be higher in women than in men.
- Compared to men with PAD, women with PAD have been found to have greater walking impairment from leg symptoms, greater leg pain with exertion and rest, and faster rates of functional decline.
- As HIV-infected persons age, it is especially important to characterize the ways in which chronic diseases such as PAD may impact the health of HIV-infected persons.

Purpose

- To determine the association of HIV, HCV, and traditional vascular risk factors with PAD in a large, ethnically and geographically diverse cohort of women with HIV and at risk for HIV infection.
- To determine the association of HIV-related factors with PAD in HIV-infected women.

Methods

Study Population

- **WIHS** is a national, multi-center, prospective cohort study established in 1994 to investigate the progression of HIV in women with and at risk for HIV.
- 1,907 women >40-years-old were enrolled in the study.

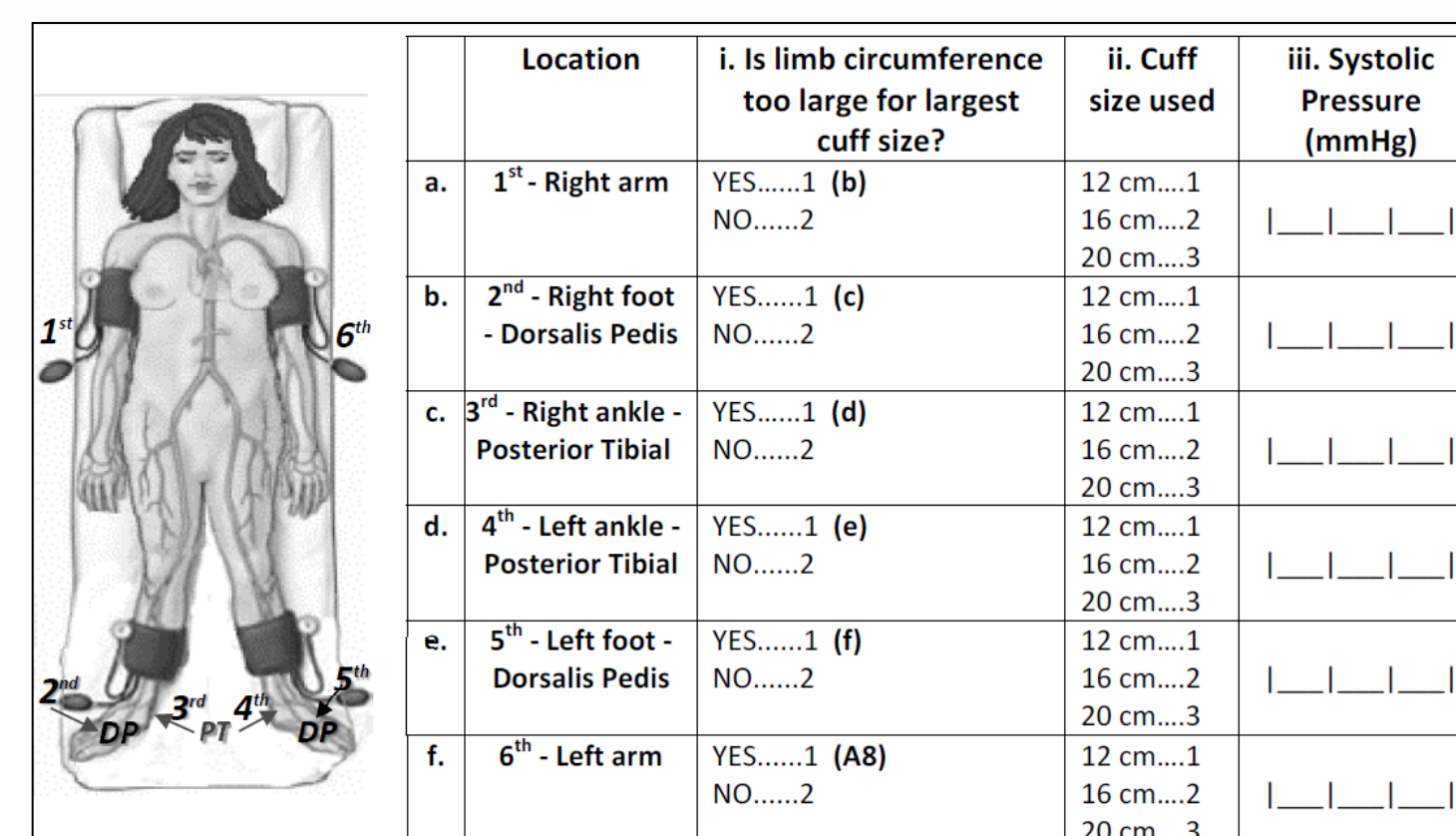### Study Design

- Cross-sectional study

Measurements

Primary Predictors
- HIV status, HCV status
- HIV-related factors such as CD4 count, viral load
- Demographic factors, behavioral factors
- Metabolic factors, vascular risk factors

Outcomes
- Peripheral arterial disease by ABI:
  - Abnormal ABI: (PAD): ≤0.9
  - Borderline ABI: 0.91- <1.0
  - Normal ABI: 1.0-1.4
  - Noncompressible vessels: >1.4

Statistical Analysis

- Univariable and multivariable logistic regression models were used to determine the association of HIV and HCV with PAD.
- Adjusted sequentially Staged models were used to sequentially control forfor demographic factors, behavioral factors, vascular factors, and liver fibrosis.
- Multivariable logistic regression was performed including the entire group and a test for interaction was used to determine the factors associated with PAD by HIV and HCV status.

Results

Table 1. Demographic and clinical characteristics of 1,907 WIHS women by HIV and HCV infection status.

Characteristics Median (IQR) or %	HIV/HCV coinfected (n=291)	HCV-monoinfected (n=94)	HIV-monoinfected (n=1094)	Control (n=428)
Demographics				
Age (yrs)	55 (51, 58)	54 (48, 59)	49 (45, 54)	50 (45, 55)
Race				
African American	69%	71%	71%	74%
White	14%	7%	11%	7%
Other¶	2%	6%	4%	5%
Hispanic	15%	15%	15%	14%
Post-menopausal	79%	70%	51%	49%
Lifestyle				
Current smoker	56%	73%	35%	46%
Pack-years of smoking	30 (18, 38)	31 (24, 38)	13 (0, 27)	18 (0, 31)
Alcohol consumption				
None	58%	53%	56%	41%
Light (<15gm/day)	26%	26%	32%	39%
Moderate (15-30 gm/day)	6%	5%	4%	8%
Heavy (>30gm/day)	10%	16%	7%	13%
Metabolic				
BMI (kg/m²)	27 (24, 32)	32 (26, 36)	30 (26, 36)	32 (27, 37)
Waist circumference (cm)	95 (85, 106)	102 (92, 112)	99 (89, 112)	103 (90, 113)
Hip circumference (cm)	101 (92, 110)	107 (98, 116)	106 (97, 115)	108 (100, 118)
Diabetes	23%	33%	21%	24%
HOMA-IR	2.98 (1.84, 5.21)	5.17 (2.02, 7.17)	2.55 (1.47, 4.21)	2.12 (1.17, 4.47)
Triglycerides (mg/dL)	111 (87, 155)	106 (74, 133)	103 (76, 145)	99 (71, 146)
HDL (mg/dL)	55 (42, 68)	51 (44, 66)	52 (43, 64)	55 (44, 67)
LDL (mg/dL)	85 (65, 108)	86 (68, 111)	104 (83, 125)	106 (83, 124)
Statin use				
Current	7%	3%	17%	14%
Ever	22%	23%	32%	31%
EGFR	83 (65, 102)	94 (79, 108)	92 (77, 108)	96 (82, 109)
APRI	0.46 (0.28, 0.81)	0.40 (0.24, 0.63)	0.23 (0.16, 0.31)	0.19 (0.14, 0.25)
Hypertension	63%	64%	51%	53%
SBP	123 (112, 138)	126 (116, 144)	121 (111, 134)	123 (113, 140)
DBP	77 (72, 85)	78 (71, 84)	75 (69, 82)	77 (70, 83)
HIV related **				
CD4 T cell count (cells/mm³)				
Current	589 (382, 787)	-	590 (392, 817)	-
Nadir	206 (102, 328)	-	221 (101, 353)	-
History of AIDS	41%	-	31%	-
Current ARV use	84%	-	90%	-
Undetectable HIV RNA	64%	-	69%	-

HCV, hepatitis C virus; IQR, interquartile range; BMI, body mass index; ¶ Includes Asian, Pacific Islander, Native American, Alaskan and other study participants

Table 2. Staged model of the association of HIV and HCV infection with PAD

After adjustment for demographic, behavioral, and vascular factors, the associations of HIV/HCV coinfection, HCV monoinfection, and HIV monoinfection were all in the negative direction and not significant. Further adjustment for liver fibrosis using the indirect serum fibrosis marker APRI had little effect on the estimates in all three infection groups.

Adjusted Models* (ref: Control)	HIV/HCV coinfected OR (95% CI)	HCV monoinfected OR (95% CI)	HIV monoinfected OR (95% CI)
Demographic Adjusted	1.09 (0.77, 1.54) p=0.62	1.00 (0.60, 1.66) p=0.995	1.03 (0.79, 1.33) p=0.84
Demographic Adjusted + Behavioral	1.03 (0.73, 1.46) p=0.87	0.89 (0.53, 1.49) p=0.65	1.06 (0.81, 1.37) p=0.68
Demographic Adjusted + Behavioral + Vascular	0.93 (0.61, 1.41) p=0.72	0.80 (0.44, 1.46) p=0.47	0.90 (0.67, 1.22) p=0.50
Demographic Adjusted + Behavioral + Vascular + Liver	0.96 (0.61, 1.50) p=0.85	0.79 (0.42, 1.48) p=0.46	0.92 (0.68, 1.25) p=0.59

*demographic: age, sex, race; behavioral: smoking and alcohol; vascular: waist circumference, DM, HDL, LDL, GFR, pulse pressure (=systolic blood pressure – diastolic blood pressure); liver: AST-platelet ratio index (APRI)

Figure 1. Prevalence of PAD ranged from 26 - 29%. In unadjusted models, HIV/HCV coinfection, HCV monoinfection, and HIV monoinfection were associated with a non-statistically significant 1.18 (95% CI:0.84, 1.64), 1.09 (95% CI:0.66, 1.80) and 1.00 (95% CI:0.78, 1.29) greater odds of PAD compared to uninfected controls.
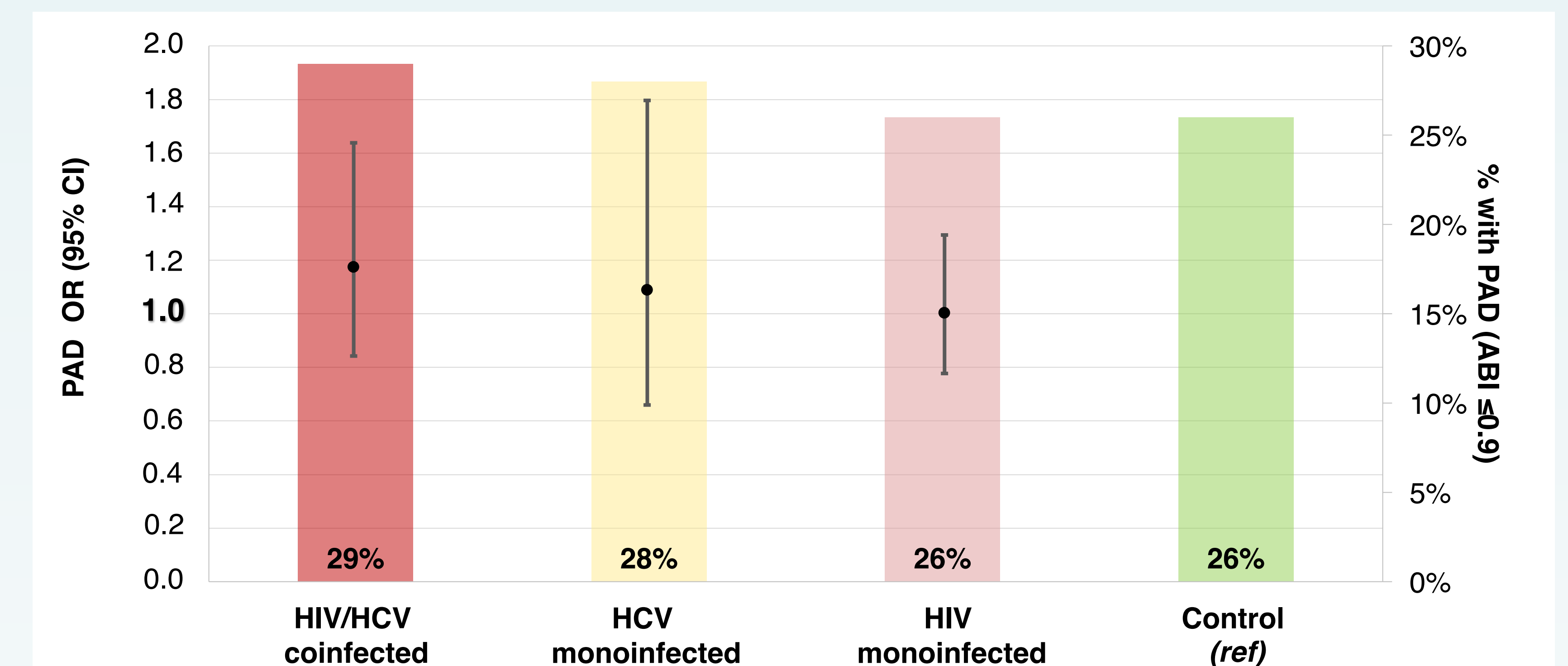

Table 3. Association of demographic, lifestyle, and vascular risk factors with PAD in the entire cohort and by HIV and HCV status after multivariable adjustment

Overall, older age, Black race, greater pack year smoking history, and wider pulse pressure remained significantly associated with PAD; diabetes was associated with lower odds. There was little difference in these effects across the four infection groups, except for older age. Every decade increase in age in HIV/HCV-coinfected women was associated with an increased risk of PAD that was beyond that observed in the other groups.

	Overall	HIV/HCV coinfected	HCV mono	HIV mono	Control	p-value*
Age (per decade)	1.02 (1.00, 1.04)	2.09 (1.29, 3.38)	1.80 (0.91, 3.59)	1.05 (0.82, 1.35)	1.07 (0.75, 1.54)	**0.027**
African American	2.06 (1.39, 3.07)	1.94 (0.86, 4.34)	3.03 (0.33, 27.64)	2.00 (1.19, 3.36)	1.38 (0.53, 3.59)	0.88
Menopause	1.11 (0.80, 1.55)	0.95 (0.65, 1.39)	1.14 (0.59, 2.22)	0.78 (0.16, 3.94)	4.20 (0.49, 35.76)	0.14
Smoking in pack-year (per year)	1.02 (1.01, 1.03)	1.03 (1.01, 1.05)	1.00 (0.96, 1.05)	1.02 (1.00, 1.03)	1.02 (1.00, 1.04)	0.71
Waist circumference (per 5cm)	1.03 (0.99, 1.07)	1.03 (0.94, 1.12)	1.08 (0.93, 1.26)	1.03 (0.99, 1.08)	1.01 (0.95, 1.08)	0.80
HOMA IR (per doubling)	0.96 (0.84, 1.09)	0.95 (0.71, 1.26)	0.91 (0.62, 1.34)	0.93 (0.81, 1.07)	0.94 (0.76, 1.16)	0.71
Diabetes**	0.67 (0.51, 0.88)	0.33 (0.16, 0.67)	0.67 (0.25, 1.81)	0.91 (0.64, 1.29)	0.50 (0.28, 0.88)	0.041
HDL (per 10 mg/dL)	0.93 (0.86, 1.01)	1.07 (0.92, 1.24)	0.71 (0.51, 0.98)	0.93 (0.84, 1.02)	0.93 (0.81, 1.08)	0.17
LDL (per 10 mg/dL)	1.01 (0.98, 1.05)	1.01 (0.92, 1.12)	1.04 (0.90, 1.20)	0.97 (0.92, 1.02)	1.10 (1.02, 1.18)	0.075
Pulse pressure	1.01 (1.00, 1.02)	1.02 (1.00, 1.03)	1.02 (0.99, 1.05)	1.00 (0.99, 1.01)	1.02 (1.00, 1.03)	0.52
APRI (per doubling)	0.95 (0.84, 1.08)	0.82 (0.64, 1.04)	1.49 (1.00, 2.23)	0.96 (0.79, 1.16)	0.97 (0.70, 1.35)	0.11

*p-value: based on type 3 analysis, testing whether the effect of covariates are similar across disease group.
**DM/Homa IR are in separate models

In HIV-infected women, we did not observe an association of HIV-related factors such as CD4 count, viral load, and duration of HIV infection with PAD (data not shown).

Conclusions

- Contrary to our expectations, HIV and HCV are not associated with PAD after controlling for demographic, behavioral, and vascular factors.
- The high PAD prevalence in this nationally representative cohort of women with and at risk for HIV infection is striking; general population studies show a >25% prevalence at ages >20 years older than the WIHS cohort.
- Our findings suggest that smoking cessation and blood pressure control are important early targets in women with and at risk for HIV.
- Longitudinal ABI data collection is currently underway to investigate progression and development of PAD over time in HIV-infected and HIV-uninfected women.

Acknowledgements