Peripheral artery disease and physical function in women with and without HIV

Emily R. Cedarbaum[a], Yifei Ma[a], Adaora A. Adimora[b], Marcas Bamman[c,d,e,f], Mardge H. Cohen[g], Margaret A. Fischl[h], Deborah Gustafson[i], Kunihiro Matsushita[j], Igho Ofotokun[k], Michael Plankey[l], Eric C. Seaberg[j], Anjali Sharma[m] and Phyllis C. Tien[a,n]

Objectives: Peripheral artery disease (PAD) is associated with decreased physical function and increased mortality in the general population. We previously found that PAD is common in middle-aged women with and without HIV infection, but its association with functional decline is unclear. We examine the contribution of PAD to functional decline in the Women's Interagency HIV Study, controlling for traditional cardiovascular risk factors and HIV-related factors.

Methods: Analysis included 1839 participants (72% with HIV) with measured ankle–brachial index (ABI) and 4 m gait speed. ABI values categorized PAD severity. Linear models with repeated measures estimated the association of PAD severity with log-transformed gait speed after controlling for demographic, behavioral, and metabolic risk factors, and HIV/hepatitis C virus status.

Results: Median age was 50 years and more than 70% were Black. Compared with normal ABI, there was a dose–response relationship between increasing PAD severity and slower gait speed in univariable analyses: 6% slower gait speed for low-normal ABI [95% confidence interval (CI): 4–9%], 10% for borderline PAD (95% CI: 6–13%), 14% for mild PAD (95% CI: 9–18%), and 16% for moderate–severe PAD (95% CI: 5–25%). PAD severity remained associated with slower gait speed in multivariable analyses. HIV/hepatitis C virus co-infection was independently associated with 9% (95% CI: 4–14%) slower gait speed compared with those with neither infection. Among women with HIV, neither $CD4^+$ cell count nor HIV-RNA level was associated with gait speed.

Conclusion: In middle-aged women with and without HIV infection, greater PAD severity is associated with progressively slower gait speed. Early detection of subclinical PAD may decrease the risk of lower extremity functional impairment and its long-term health consequences.

AIDS 2022, **36**:347–354

Keywords: functional status, gait speed, HIV, peripheral artery disease, women's health

[a]Department of Medicine, University of California, San Francisco, San Francisco, California, [b]Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, [c]Department of Cell, Developmental, and Integrative Biology, [d]Department of Medicine, [e]Department of Neurology, University of Alabama, Birmingham, Alabama, [f]Florida Institute for Human & Machine Cognition, Pensacola, Florida, [g]Department of Medicine, Cook County Health and Hospitals System, Stroger Hospital, Chicago, Illinois, [h]Department of Medicine, University of Miami, Miami, Florida, [i]Department of Neurology, State University of New York Downstate Health Sciences University, Brooklyn, New York, [j]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [k]Department of Medicine, Emory University, Atlanta, Georgia, [l]Department of Medicine, Georgetown University Medical Center, Washington, DC, [m]Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, and [n]Medical Service, Department of Veteran Affairs Medical Center, San Francisco, California, USA.

Correspondence to Phyllis C. Tien, MD, VAMC, Infectious Disease Section, University of California, San Francisco, 111W, 4150 Clement Street, San Francisco, CA 94121, USA.

Tel: +1 415 221 4810x22577; fax: +1 415 379 5523; e-mail: Phyllis.tien@ucsf.edu
Received: 6 August 2021; accepted: 5 October 2021.

DOI:10.1097/QAD.0000000000003113

Introduction

Peripheral artery disease (PAD) is common in persons living with HIV (PLWH). We previously reported a PAD prevalence of 7.7% in middle-aged women with and without HIV infection in the United States, on par with prevalence rates in general population studies of women a decade older [1]. These findings are of great clinical concern because PAD is associated with functional decline, decreased quality of life, and greater risk of disability and death [2–14]. Women with PAD may experience faster functional decline and higher prevalence of leg pain than men with PAD [15,16]. Therefore, women with and without HIV infection may experience adverse health consequences of PAD at earlier ages.

Declines in physical function associated with PAD may be explained in part by symptoms of claudication that limit mobility. However, classic claudication is found in only 11% of patients with PAD in the general population [17,18]. Studies using ankle–brachial index (ABI) to assess subclinical PAD or PAD in the absence of symptoms have reported an association with physical function decline, especially limitations in lower extremity function [8,19]. Most studies have been conducted in older populations and few have examined the association of ABI with physical function decline in middle-aged persons with and without HIV infection.

Gait speed (or walking speed at 'usual' pace) is a well established marker of lower extremity function and predicts disability and death in older adults without HIV infection [20–22]. The Multicenter AIDS Cohort Study (MACS) found that men living with HIV had earlier and faster declines in gait speed than HIV seronegative men [23]. Another study of mostly men who used injection drugs in Baltimore found an increased risk of poor functional performance including slower gait speed in PLWH compared with seronegative persons [24]. Studies to date have not examined the contribution of PAD to these functional declines among PLWH.

We aimed to examine the association of PAD severity, measured using ABI, with gait speed in a large nationally representative cohort of middle-aged women with and without HIV infection. Women with HIV are an understudied population that may be affected by PAD and functional decline in specific ways that could impact public health and clinical care.

Methods

Setting and participants

The Women's Interagency HIV Study (WIHS) (now part of the MACS-WIHS Combined Cohort Study) is a multi-center prospective cohort study that enrolled a total of 4982 women (3678 with HIV infection and 1304 without HIV infection). Enrollment occurred during four recruitment waves: 1994–1995, 2001–2002, 2011–2012, and 2013–2015 from 10 US cities (Bronx and Brooklyn, NY; Chicago, IL; San Francisco, CA; Los Angeles, CA; Washington, DC; Atlanta, GA; Chapel Hill, NC; Miami, FL; Jackson, MS; and Birmingham, AL). Full details of recruitment, retention, and demographics have been published previously [25]. Baseline sociodemographic characteristics and HIV risk factors were similar between HIV-seropositive and HIV-seronegative women. Each WIHS site's institutional review board approved the study protocol and consent form, and each participant gave written informed consent. At semiannual research visits, participants completed a brief physical examination, provided biological specimens, and completed an interviewer-administered questionnaire.

From October 2013 through October 2019, 2010 WIHS participants aged older than 40 years underwent ABI measurements. Among the 2010 participants, 1845 also had measured 4 m timed gait speed. Five participants were excluded due to unknown hepatitis C virus (HCV) status and one participant was excluded due to non-compressible vessels (ABI $>$ 1.4). Among the 1839 remaining participants, all had ABI measurements at one visit, 1590 had ABI measurements at two visits, and 637 had ABI measurements at three visits.

Peripheral artery disease determination

The WIHS ABI protocol has been previously described [1]. Briefly, single measures of SBP were measured utilizing a hand-held Doppler instrument with a 5 mm Hz probe and an aneroid sphygmomanometer at the brachial artery on both arms and the dorsalis pedis and posterior tibial arteries on both legs. All technicians were trained and certified by the same central trainer after practicing on an average of 15 volunteers.

ABI was calculated for the left and the right limbs by dividing the higher pressure of the lower extremity arterial measurements for each side by the higher pressure of either the left or right brachial artery. Lower values correlate with arterial disease in the lower extremities. The lower of the two ABI values (right versus left) was used for analysis. This method is consistent with the American Heart Association/American College of Cardiology Guidelines for measurement of ABI [26]. Categories of PAD severity were based on prior studies [7,27].

Primary outcome: gait speed

Our primary physical performance outcome was 4 m walking speed, which has been found to correlate with 6-min walk test performance [28]. A walking course of 4 m was created at participating sites as part of the WIHS physical performance assessments protocol. Women were asked to walk at their usual speed and a stopwatch was used for timing. Two attempts were completed and the

time for each attempt was recorded in seconds. The faster of the two attempts was used in our analysis.

Predictors and covariates

The primary predictor was PAD severity, which was categorized into five groups based on ABI measurements as per prior studies [7,27]: normal (ABI 1.1–1.4), low-normal (ABI 1.0–<1.1), borderline PAD (ABI 0.9–<1.0), mild PAD (ABI 0.7–<0.9), or moderate–severe PAD (ABI < 0.7).

Several covariates were considered. Infectious disease covariates included HIV serostatus (yes/no) and HCV serostatus (defined by detectable HCV RNA following a positive anti-HCV antibody result and if treated, by detectable HCV RNA at least 6 months after HCV treatment completion). Sociodemographic covariates included age at the time of ABI measurement, sex, and race/ethnicity categorized as Hispanic, non-Hispanic white, non-Hispanic Black, and non-Hispanic other. Behavioral covariates included self-reported alcohol use, categorized as none, light (1–15 g/day), moderate (15–30 g/day), and heavy (>30 g/day), self-reported smoking history (none, current, past), and duration of smoking (pack-years). Anthropometric measures included waist circumference and BMI in kg/m^2. Metabolic variables included diabetes mellitus [defined by (1) self-report of diabetes mellitus medication use; (2) elevated fasting glucose ≥126 mg/dl confirmed by a subsequent fasting glucose ≥126 mg/dl, report of a diabetes mellitus medication, or a confirmed hemoglobin A1C (HbA1C) value ≥6.5%; or (3) self-report of diabetes mellitus confirmed by a subsequent report of diabetes mellitus medication use or two fasting glucose measurements ≥126 mg/dl, or fasting glucose ≥126 mg/dl concurrent with HbA1C ≥ 6.5%], SBP and DBP, hypertension (SBP ≥ 140, DBP ≥ 90, self-reported hypertension, or use of anti-hypertensive medications), statin use, blood lipid measurements, and estimated glomerular filtration rate. Physical activity score was based on a standardized questionnaire [29,30]. Peripheral neuropathy was defined by a combination of self-report of symptoms, deep tendon reflexes, and vibration sense, and categorized as mild, moderate, and severe. In HIV-seropositive participants, HIV-related covariates included current CD4$^+$ cell count, CD4$^+$ cell count nadir, current HIV-RNA level, history of clinical AIDS, and use of anti-retroviral therapy (ART).

Statistical analysis

We first compared baseline sociodemographic and clinical characteristics across the five categories of PAD: normal ABI, low-normal ABI, borderline PAD, mild PAD, moderate–severe PAD. For continuous variables, we compared characteristics using ANOVA for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables. We used the chi-squared test or Fisher exact test for categorical variables.

Linear modeling with repeated measures was used to examine both unadjusted and adjusted associations of PAD category with gait speed. ABI was a time-dependent predictor and the outcome of gait speed was measured multiple times and analyzed with repeated measures. All models were fitted using auto correlation structure of order 1 among visits within patients. Nested models were then used to adjust sequentially for HIV, HCV, and the interactive effects of HIV and HCV; demographic factors; behavioral factors; and metabolic factors. Sequential models included all the variables in the previous models, and therefore are nested. Among women with HIV, we additionally examined the impact of HIV-related factors as the last step. Gait speed was log-transformed to approximate normal distribution. The coefficients were then exponentiated to reflect percentage differences. All analyses were performed using SAS system, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Results

The 1839 women included in this study were median age 50 years, the majority were Black, and 51% were obese (BMI ≥ 30 kg/m^2) (Table 1). Nearly half reported current smoking, approximately 25% had diabetes and 50% had hypertension. Among the women with HIV, the majority had well controlled HIV, with mean CD4$^+$ cell count more than 500 cells/μl and undetectable HIV viral loads. Table 1 shows clinical characteristics by PAD severity. Over one-third had ABI values in the normal range (41%), about one-third had low-normal ABI values (36%), 15% had borderline PAD, 6% had mild PAD, and 1.3% had moderate–severe PAD. Smoking, physical inactivity, higher triglyceride levels, lower median HDL cholesterol and LDL cholesterol levels, statin use, diabetes, hypertension, peripheral neuropathy, and report of symptoms consistent with claudication were more common in women with moderate–severe PAD than those in the other ABI categories.

In unadjusted analyses, compared with normal ABI (absence of PAD), each category of increasing PAD severity was associated with progressively slower gait speed (Fig. 1). The median gait speed was fastest in women with normal ABI at 0.25 m/s [interquartile range (IQR): 0.21, 0.29], followed by women with low-normal ABI and women with borderline PAD [0.23 (IQR: 0.19, 0.28) and 0.23 m/s (IQR: 0.18, 0.27), respectively] and slowest in women with mild and moderate–severe PAD [0.20 (IQR: 0.13, 0.26) and 0.22 m/s (IQR: 0.14, 0.26), respectively]. Overall, for each 0.1 U decrease in ABI, there was a 3.5% decrease in gait speed ($P < 0.0001$).

Table 2 shows the association of increasing PAD severity with gait speed compared with women with normal ABI scores, after sequential adjustment for HIV and HCV status, followed by additional adjustment for demographic

Table 1. Demographic and clinical characteristics of 1839 Women's Interagency HIV Study women by ankle–brachial index.

Characteristics Median (IQR) or % (*N*)	Normal ABI 1.10–1.40 ($n=759$)	Low-normal ABI ABI 1.00–1.09 ($n=663$)	Borderline PAD ABI 0.90–0.99 ($n=284$)	Mild PAD ABI 0.70–0.89 ($n=110$)	Moderate–severe PAD ABI ≤ 0.69 ($n=23$)
Demographics					
Age (years)	50 (45, 54)	50 (45, 56)	51 (46, 56)	51 (47, 57)	56 (46, 61)
Race/ethnicity					
Black	67% (510)	75% (497)	74% (210)	85% (93)	65% (15)
White	13% (101)	8% (51)	8% (24)	5% (6)	17% (4)
Hispanic	16% (118)	13% (86)	13% (36)	9% (10)	17% (4)
Other	4% (30)	4% (29)	5% (14)	1% (1)	0% (0)
Behavioral					
Current smoker	35% (266)	44% (295)	53% (150)	47% (52)	52% (12)
Pack-years of smoking	1.3 (0, 10.5)	4.0 (0, 12.6)	6.9 (0, 16.1)	7.8 (0, 14.1)	8.3 (0.9, 24.5)
Alcohol consumption					
None	54% (407)	51% (335)	49% (138)	55% (60)	74% (17)
Light (<15 g/day)	33% (250)	32% (213)	36% (103)	36% (40)	26% (6)
Moderate–heavy (≥15 g/day)	13% (101)	17% (115)	15% (43)	9% (10)	0% (0)
Physical activity total score	90 (0, 213)	65 (0, 204)	48 (0, 144)	48 (0, 144)	18 (0, 192)
Metabolic					
BMI (kg/m^2)	30.3 (25.8, 35.4)	29.9 (25.0, 35.9)	29.2 (24.9, 36.2)	31.1 (25.4, 37.0)	29.3 (25.5, 36.7)
Waist circumference (cm)	100 (89, 111)	98 (87, 111)	97 (87, 110)	101 (90, 114)	102 (95, 112)
Diabetes	23% (174)	20% (133)	19% (55)	25% (27)	35% (8)
Triglycerides (mg/dl)	101 (78, 121)	102 (72, 142)	102 (78, 147)	108 (81, 151)	124 (90, 161)
HDL (mg/dl)	52 (43, 65)	54 (44, 69)	54 (44, 64)	53 (42, 61)	48 (42, 52)
LDL (mg/dl)	100 (78, 121)	100 (77, 123)	101 (78, 122)	101 (81, 136)	97 (85, 134)
Statin use					
Current	22% (157)	27% (177)	20% (58)	27% (30)	39% (9)
Ever	32% (230)	36% (241)	31% (89)	40% (44)	57% (13)
Hypertension	50% (357)	53% (348)	53% (150)	68% (75)	70% (16)
SBP (mmHg)	123 (111, 135)	122 (112, 135)	122 (113, 136)	127 (114, 143)	124 (117, 142)
DBP (mmHg)	76 (70, 83)	76 (70, 83)	75 (69, 82)	78 (71, 85)	71 (67, 79)
Peripheral neuropathy					
Normal	50% (381)	48% (317)	47% (134)	47% (52)	30% (7)
Mild	27% (206)	30% (201)	29% (81)	24% (26)	35% (8)
Moderate–severe	12% (93)	9% (62)	12% (33)	20% (22)	26% (6)
Claudication (left or right)	1% (9)	2% (13)	1% (3)	2% (2)	9% (2)
HIV and HCV related					
HIV monoinfection	66% (498)	63% (420)	58% (166)	65% (72)	43% (10)
HIV/HCV co-infection	6% (49)	10% (67)	12% (34)	7% (8)	35% (8)
HCV monoinfection	3% (21)	3% (19)	4% (10)	3% (3)	0% (0)
HIV/HCV uninfected	25% (191)	24% (157)	26% (74)	25% (27)	22% (5)
$CD4^+$ cell count (cells/μl)					
Current[a]	582 (370, 788)	591 (423, 815)	586 (400, 853)	677 (362, 861)	669 (432, 947)
Nadir	314 (155, 628)	308 (139, 566)	287 (134, 644)	319 (163, 674)	271 (167, 693)
History of AIDS[a]	31% (172)	30% (144)	35% (70)	26% (21)	39% (7)
ART use					
Current	63% (476)	65% (434)	64% (183)	63% (69)	74% (17)
Ever	68% (516)	70% (467)	68% (193)	70% (77)	74% (17)
Undetectable HIV-RNA (≤20)[a]	67% (348)	70% (339)	71% (142)	64% (51)	61% (11)

ABI, ankle–brachial index; ART, antiretroviral therapy; HCV, hepatitis C virus; IQR, interquartile range; PAD, peripheral artery disease.
[a]Current $CD4^+$, undetectable HIV-RNA ≤ 20, and history of AIDS are available for HIV+ patients only.

and behavioral factors, and finally, additional adjustment for metabolic factors. After adjustment for HIV and HCV status, each category of increasing PAD severity was associated with slower gait speed: 6% slower for low-normal ABI [95% confidence interval (CI):4, 9%], 9% slower for borderline PAD (95% CI: 6, 12%), 13% slower for mild PAD (95% CI: 9, 17%), and 15% slower for moderate–severe PAD (95% CI: 4, 24%). With additional adjustment for demographic and behavioral factors, each category of increasing PAD severity remained significantly associated with slower gait speed. In fully adjusted models, each PAD category remained associated with slower gait speed: 6% slower for low-normal ABI (95% CI: 4, 9%), 10% for borderline PAD (95% CI: 7, 14%), 12% for mild PAD (95% CI: 8, 17%), and 11% for moderate–severe PAD (95% CI: 0, 22%), but the association of moderate–severe PAD with gait speed did not reach statistical significance.

When we examined the association of HIV and HCV infection status with gait speed in multivariable analysis, we found that HIV monoinfection was associated with only 1% slower gait speed, HCV monoinfection with 7% slower gait speed, and HIV/HCV co-infection 9% slower gait speed compared with women with neither infection; only the latter association was statistically significant (Table 3). Other individual factors associated with slower gait speed in multivariable analysis included older age,

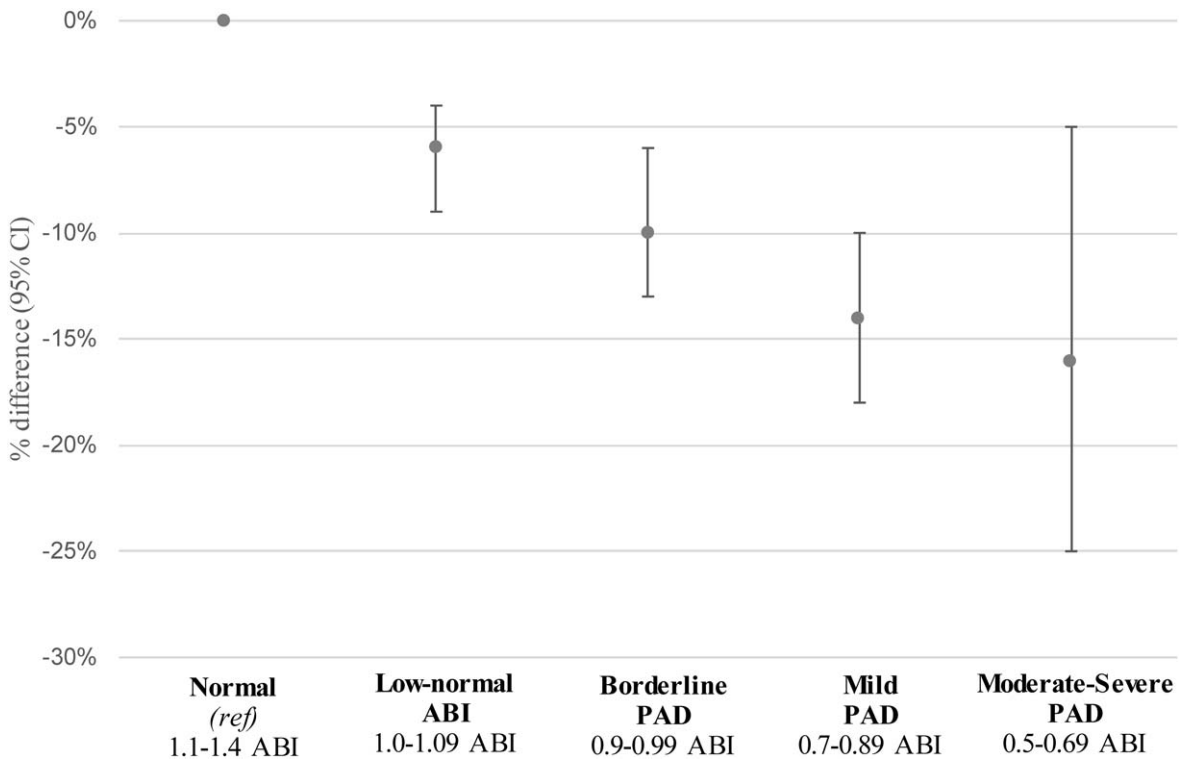

Fig. 1. Peripheral artery disease is associated with slower gait speed in women with and without HIV infection. Linear modeling with repeated measures was used to examine the unadjusted associations of peripheral artery disease category with 4 m gait speed. The coefficients were then exponentiated to reflect percentage differences. There was a dose–response relationship between peripheral artery disease severity and slower gait speed. PAD, peripheral artery disease.

Hispanic ethnicity, Black race, more pack-years of smoking, larger waist circumference, and a history of statin use. Being in the highest tertile of physical activity was associated with faster gait speeds compared with women reporting no physical activity. There was no association of diabetes or hypertension with gait speed.

Among women with HIV infection, associations of PAD category with gait speed were similar to those observed in the full sample of women. In multivariable analyses, PAD category was associated with slower gait speed: 6% slower for low-normal ABI (95% CI: 2, 9%), 9% slower for borderline PAD (95% CI: 5, 13%), 12% slower for mild PAD (95% CI: 6, 17%), and 11% slower for moderate–severe PAD (95% CI: −4, 24%), although the association in the latter group did not reach significance. Reporting a history of ART was associated with a 13% faster gait speed (95% CI: 2, 24%). There was little association of $CD4^+$ cell nadir and HIV viral load with gait speed.

Discussion

In this large cohort of middle-aged US women with and without HIV, we found that increasing PAD severity was associated with progressively slower gait speed, even after adjustment for HIV and HCV status, demographic, behavioral, and metabolic risk factors. We found a 0.05 m/s difference in median gait speed between women with normal ABI compared with women with mild PAD. A gait speed change of 0.05 m/s has been shown to be a meaningful difference in the general population of older adults [31]. Of clinical concern is that ABI values previously defined as being low-normal and as borderline PAD were associated with progressively slower gait speed, suggesting that lower extremity functional declines occur in women with subclinical and asymptomatic PAD. Given our previous report of a high PAD prevalence that was similar to seronegative women a decade older, our findings could have important clinical implications regarding earlier onset of disability and potentially mortality, linked to lower extremity functional declines [1].

Our findings are notable for several reasons. First, we demonstrated that increasing PAD severity was associated with increasing lower extremity functional impairment in women who were relatively young in age. Second, this relationship was observed in those with early, subclinical PAD as measured by low ABI values. While one study also showed that low-normal values of ABI and borderline, mild, moderate, and severe PAD were associated with decreasing rates of mobility, the mean age of adults in that study was older than 70 years [7]. In other population studies among older adults, borderline ABI values have been associated with subclinical atherosclerosis and

Table 2. Association of peripheral artery disease category with 4 m gait speed after controlling for HIV and hepatitis C virus status, demographic, behavioral, and metabolic risk factors.

	% Difference (95% CI)[a]	*P* value
Adjusted for HIV and HCV[b]		
Low-normal ABI	−6% (−9, −4%)	**<0.001**
Borderline PAD	−9% (−12, −6%)	**<0.001**
Mild PAD	−13% (−17, −9%)	**<0.001**
Moderate–severe PAD	−15% (−24, −4%)	**0.011**
Adjusted for HIV and HCV, and demographics[c]		
Low-normal ABI	−6% (−9, −4%)	**<0.001**
Borderline PAD	−9% (−12, −6%)	**<0.001**
Mild PAD	−13% (−17, −8%)	**<0.001**
Moderate–severe PAD	−14% (−24, −3%)	**0.015**
Adjusted for HIV and HCV, demographics, and behavioral factors[d]		
Low-normal ABI	−6% (−8, −3%)	**<0.001**
Borderline PAD	−9% (−12, −5%)	**<0.001**
Mild PAD	−12% (−16, −7%)	**<0.001**
Moderate–severe PAD	−13% (−23, −2%)	**0.022**
Adjusted for HIV and HCV, demographics, behavioral, and metabolic factors[e]		
Low-normal ABI	−6% (−9, −4%)	**<0.001**
Borderline PAD	−10% (−14, −7%)	**<0.001**
Mild PAD	−12% (−17, −8%)	**<0.001**
Moderate–severe PAD	−11% (−22, 0%)	0.060

ABI, ankle–brachial index; CI, confidence interval; HCV, hepatitis C virus; PAD, peripheral artery disease. Bold values indicate statistical significance ($P < 0.05$).
[a]% Difference from normal ABI reference group.
[b]HIV and HCV: HIV-monoinfection, HCV-monoinfection, and HIV/HCV co-infection.
[c]Demographics: age and race/ethnicity.
[d]Behavioral factors: pack-years of smoking, alcohol consumption, and physical activity score.
[e]Metabolic factors: diabetes, hypertension, waist circumference, statin use, and estimated glomerular filtration rate.

Table 3. Factors associated with 4 m gait speed in the entire cohort, controlling for HIV and hepatitis C virus status, demographics, behavioral, and metabolic factors.

	% Difference (95% CI)[a]	*P* value
PAD		
Low-normal ABI	−6% (−9, −4%)	**<0.001**
Borderline PAD	−10% (−14, −7%)	**<0.001**
Mild PAD	−12% (−17, −8%)	**<0.001**
Moderate–severe PAD	−11% (−22, 0%)	0.060
Infection status		
HIV monoinfection	−1% (−4, 3%)	0.667
HCV monoinfection	−7% (−15, 2%)	0.134
HIV/HCV co-infection	−9% (−14, −4%)	**0.002**
Demographic factors		
Age	−0.3% (−0.5, −0.1%)	**0.017**
Race/Ethnicity (ref = white)		
Black	−8% (−13, −4%)	**0.001**
Hispanic	−15% (−20, −9%)	**<0.001**
Other race	0% (−8, 9%)	0.987
Behavioral factors		
Physical activity (ref = no activity)		
Lowest tertile	3% (−1, 6%)	0.130
Middle tertile	1% (−2, 5%)	0.555
Highest tertile	8% (4, 12%)	**<0.001**
Pack years of smoking	−0.2% (−0.3, −0.1%)	**0.008**
Metabolic factors		
Waist circumference (per 10 cm)	−3% (−4, −2%)	**<0.001**
Hypertension	−1% (−4, 2%)	0.454
Diabetes	−3% (−7, 0%)	0.088
Statin use (ever)	−6% (−9, −3%)	**<0.001**

ABI, ankle–brachial index; CI, confidence interval; HCV, hepatitis C virus; PAD, peripheral artery disease. Bold values indicate statistical significance ($P < 0.05$).
[a]% Difference from normal ABI reference group.

endothelial dysfunction [7,27]. When we adjusted for metabolic risk factors, low-normal ABI values and borderline PAD remained independently associated with slower gait speed, suggesting that other unmeasured factors besides traditional cardiovascular risk factors may contribute to the association of subclinical PAD with lower extremity functional declines. PAD has been associated with skeletal muscle damage from ischemia–perfusion injury in microvascular beds, leading to lower calf muscle area and increased calf muscle fat [32]. Future investigation will examine whether factors such as lower extremity muscle volume might explain the association of subclinical PAD with lower extremity functional declines.

Another study of men and women without HIV infection found that increased physical activity improved ABI values in those with borderline ABI values who underwent a cardiovascular intervention [33]. Future study will evaluate the impact of ABI improvements on physical function. Whether ABI monitoring can be used as a tool for early detection and prevention of lower extremity functional declines in women at high risk for PAD needs further study.

As expected, we found that several vascular risk factors other than PAD were independently associated with lower extremity functional declines including smoking, waist circumference, and history of statin use, which could be a marker of dyslipidemia. These factors may contribute to reduced lower extremity vascular perfusion resulting from atherosclerosis. Being Black and of Hispanic ethnicity have also been associated with slower gait speed in men with and at risk for HIV, and with physical function declines in a general aging population cohort [23,34,35]. These studies have postulated that socioeconomic disparities may be a reason.

There was little association of HIV monoinfection with slower gait speed, although we found that HIV/HCV co-infection was associated with slower gait speed even after adjustment for demographic, behavioral, and clinical factors. This suggests that the effect of HIV/HCV co-infection on gait speed may be primarily driven by HCV rather than HIV. We initially hypothesized that peripheral neuropathy could be a cause of slower gait speed in women with HIV or HCV, but the study was not powered to make these conclusions. While peripheral neuropathy is common in HIV and HCV infection [36–38], HIV/HCV co-infection has been associated with distal sensory polyneuropathy compared with women with HIV alone [39]. Among women with HIV infection, we found that anti-retroviral drug use was associated with faster gait speed, possibly due to improved health. However, we did not observe a significant association of $CD4^+$ cell count

or HIV viral load with gait speed. Our findings may warrant additional investigation of the potential role of systemic inflammation associated with chronic viral infection on functional impairment.

While our study has a number of strengths including the large sample with repeated ABI measures and detailed covariate measurements, there are some limitations. First, our findings examining the relationship of PAD severity with gait speed may not be generalizable to men. Second, our study examined gait speed, which is only one measure of physical function, but also allowed examination of lower extremity PAD with lower extremity functional declines. Finally, there are likely unmeasured factors associated with gait speed for which we were not able to account.

Conclusion

In this cohort of middle-aged women with and without HIV infection, worsening PAD severity was associated with progressively slower gait speed, independent of HIV and HCV status, demographic, behavioral, and metabolic risk factors. Of clinical concern is that lower extremity functional declines were noted even in those with early and subclinical PAD. Early detection of subclinical PAD using ABI measurements in women at high risk for PAD could have major implications for decreasing the risk of lower extremity functional impairment and its long-term health consequences.

Acknowledgements

Data in this article were collected by the Women's Interagency HIV Study (WIHS), now the MACS/WIHS Combined Cohort Study (MWCCS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH). MWCCS (Principal Investigators): Atlanta CRS (Ighovwerha Ofotokun, Anandi Sheth, and Gina Wingood), U01-HL146241; Baltimore CRS (Todd Brown and Joseph Margolick), U01-HL146201; Bronx CRS (Kathryn Anastos and Anjali Sharma), U01-HL146204; Brooklyn CRS (Deborah Gustafson and Tracey Wilson), U01-HL146202; Data Analysis and Coordination Center (Gypsyamber D'Souza, Stephen Gange and Elizabeth Golub), U01-HL146193; Chicago-Cook County CRS (Mardge Cohen and Audrey French), U01-HL146245; Chicago-Northwestern CRS (Steven Wolinsky), U01-HL146240; Northern California CRS (Bradley Aouizerat, Jennifer Price, and Phyllis Tien), U01-HL146242; Los Angeles CRS (Roger Detels and Matthew Mimiaga), U01-HL146333; Metropolitan Washington CRS (Seble Kassaye and Daniel Merenstein), U01-HL146205; Miami CRS (Maria Alcaide, Margaret Fischl, and Deborah Jones), U01-HL146203; Pittsburgh CRS (Jeremy Martinson and Charles Rinaldo), U01-HL146208; UAB-MS CRS (Mirjam-Colette Kempf, Jodie Dionne-Odom, and Deborah Konkle-Parker), U01-HL146192; UNC CRS (Adaora Adimora), U01-HL146194. The MWCCS is funded primarily by the National Heart, Lung, and Blood Institute (NHLBI), with additional co-funding from the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), National Institute on Aging (NIA), National Institute of Dental & Craniofacial Research (NIDCR), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Mental Health (NIMH), National Institute on Drug Abuse (NIDA), National Institute of Nursing Research (NINR), National Cancer Institute (NCI), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute on Minority Health and Health Disparities (NIMHD), and in coordination and alignment with the research priorities of the National Institutes of Health, Office of AIDS Research (OAR). MWCCS data collection is also supported by UL1-TR000004 (UCSF CTSA), UL1-TR003098 (JHU ICTR), UL1-TR001881 (UCLA CTSI), P30-AI-050409 (Atlanta CFAR), P30-AI-073961 (Miami CFAR), P30-AI-050410 (UNC CFAR), P30-AI-027767 (UAB CFAR), and P30-MH-116867 (Miami CHARM). The study was also supported by the National Institute of Allergy and Infectious Diseases [K24 AI 108516 (PCT)].

Conflicts of interest

E.R.C., Y.M., M.B., M.H.C., M.A.F., D.G., I.O., M.P., E.C.S.: none. A.A.A.: Merck (receipt of personal funds for consulting), Gilead (institution received funds for research). K.M.: received personal fee from Fukuda Denshi outside of the submitted work. A.S.: grant funding from Gilead Sciences. P.C.T.: grant funding for research from Merck.

References

1. Cedarbaum E, Ma Y, Scherzer R, Price JC, Adimora AA, Bamman M, *et al*. **Contributions of HIV, hepatitis C virus, and traditional vascular risk factors to peripheral artery disease in women.** *AIDS* 2019; **33**:2025–2033.
2. Qu B, Liu Q, Li J. **Systematic review of association between low ankle–brachial index and all-cause cardiovascular, or noncardiovascular mortality.** *Cell Biochem Biophys* 2015; **73**:571–575.
3. Ankle Brachial Index C, Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, *et al*. **Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis.** *JAMA* 2008; **300**:197–208.
4. Fan H, Hu X, Yu W, Cao H, Wang J, Li J, *et al*. **Low ankle–brachial index and risk of stroke.** *Atherosclerosis* 2013; **229**:317–323.
5. Gronewold J, Hermann DM, Lehmann N, Kroger K, Lauterbach K, Berger K, *et al*. **Ankle–brachial index predicts stroke in the**

general population in addition to classical risk factors. *Atherosclerosis* 2014; **233**:545–550.
6. Matsushita K, Ballew SH, Sang Y, Kalbaugh C, Loehr LR, Hirsch AT, *et al*. **Ankle–brachial index and physical function in older individuals: the Atherosclerosis Risk in Communities (ARIC) study.** *Atherosclerosis* 2017; **257**:208–215.
7. McDermott MM, Guralnik JM, Tian L, Liu K, Ferrucci L, Liao Y, *et al*. **Associations of borderline and low normal ankle–brachial index values with functional decline at 5-year follow-up: the WALCS (Walking and Leg Circulation Study).** *J Am Coll Cardiol* 2009; **53**:1056–1062.
8. McDermott MM, Guralnik JM, Ferrucci L, Tian L, Liu K, Liao Y, *et al*. **Asymptomatic peripheral arterial disease is associated with more adverse lower extremity characteristics than intermittent claudication.** *Circulation* 2008; **117**:2484–2491.
9. Wu A, Coresh J, Selvin E, Tanaka H, Heiss G, Hirsch AT, *et al*. **Lower extremity peripheral artery disease and quality of life among older individuals in the community.** *J Am Heart Assoc* 2017; **6**:e004519.
10. Morris DR, Rodriguez AJ, Moxon JV, Cunningham MA, McDermott MM, Myers J, *et al*. **Association of lower extremity performance with cardiovascular and all-cause mortality in patients with peripheral artery disease: a systematic review and meta-analysis.** *J Am Heart Assoc* 2014; **3**:e001105.
11. Jain A, Liu K, Ferrucci L, Criqui MH, Tian L, Guralnik JM, *et al*. **Declining walking impairment questionnaire scores are associated with subsequent increased mortality in peripheral artery disease.** *J Am Coll Cardiol* 2013; **61**:1820–1829.
12. Gardner AW, Montgomery PS, Wang M, Xu C. **Predictors of health-related quality of life in patients with symptomatic peripheral artery disease.** *J Vasc Surg* 2018; **68**:1126–1134.
13. Jain A, Liu K, Ferrucci L, Criqui MH, Tian L, Guralnik JM, *et al*. **The Walking Impairment Questionnaire stair-climbing score predicts mortality in men and women with peripheral arterial disease.** *J Vasc Surg* 2012; **55**:1662–1673.e2.
14. McDermott MM, Tian L, Liu K, Guralnik JM, Ferrucci L, Tan J, *et al*. **Prognostic value of functional performance for mortality in patients with peripheral artery disease.** *J Am Coll Cardiol* 2008; **51**:1482–1489.
15. McDermott MM, Ferrucci L, Liu K, Guralnik JM, Tian L, Kibbe M, *et al*. **Women with peripheral arterial disease experience faster functional decline than men with peripheral arterial disease.** *J Am Coll Cardiol* 2011; **57**:707–714.
16. McDermott MM, Greenland P, Liu K, Criqui MH, Guralnik JM, Celic L, *et al*. **Sex differences in peripheral arterial disease: leg symptoms and physical functioning.** *J Am Geriatr Soc* 2003; **51**:222–228.
17. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, *et al*. **Peripheral arterial disease detection, awareness, and treatment in primary care.** *JAMA* 2001; **286**:1317–1324.
18. Regensteiner JG, Hiatt WR, Coll JR, Criqui MH, Treat-Jacobson D, McDermott MM, *et al*. **The impact of peripheral arterial disease on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program.** *Vasc Med* 2008; **13**:15–24.
19. McDermott MM, Tian L, Ferrucci L, Liu K, Guralnik JM, Liao Y, *et al*. **Associations between lower extremity ischemia, upper and lower extremity strength, and functional impairment with peripheral arterial disease.** *J Am Geriatr Soc* 2008; **56**:724–729.
20. Cummings SR, Studenski S, Ferrucci L. **A diagnosis of dismobility – giving mobility clinical visibility: a Mobility Working Group recommendation.** *JAMA* 2014; **311**:2061–2062.
21. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, *et al*. **Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery.** *J Gerontol A Biol Sci Med Sci* 2000; **55**:M221–M231.
22. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, *et al*. **Gait speed and survival in older adults.** *JAMA* 2011; **305**:50–58.
23. Schrack JA, Althoff KN, Jacobson LP, Erlandson KM, Jamieson BD, Koletar SL, *et al*. **Accelerated longitudinal gait speed decline in HIV-infected older men.** *J Acquir Immune Defic Syndr* 2015; **70**:370–376.
24. Greene M, Covinsky K, Astemborski J, Piggott DA, Brown T, Leng S, *et al*. **The relationship of physical performance with HIV disease and mortality.** *AIDS* 2014; **28**:2711–2719.
25. Adimora AA, Ramirez C, Benning L, Greenblatt RM, Kempf MC, Tien PC, *et al*. **Cohort profile: the Women's Interagency HIV Study (WIHS).** *Int J Epidemiol* 2018; **47**:393–394i.
26. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, *et al*. **Measurement and interpretation of the ankle–brachial index: a scientific statement from the American Heart Association.** *Circulation* 2012; **126**:2890–2909.
27. McDermott MM, Liu K, Criqui MH, Ruth K, Goff D, Saad MF, *et al*. **Ankle–brachial index and subclinical cardiac and carotid disease: the multiethnic study of atherosclerosis.** *Am J Epidemiol* 2005; **162**:33–41.
28. Chen X, Stoner JA, Montgomery PS, Casanegra AI, Silva-Palacios F, Chen S, *et al*. **Prediction of 6-min walk performance in patients with peripheral artery disease.** *J Vasc Surg* 2017; **66**:1202–1209.
29. Sidney S, Jacobs DR Jr, Haskell WL, Armstrong MA, Dimicco A, Oberman A, *et al*. **Comparison of two methods of assessing physical activity in the Coronary Artery Risk Development in Young Adults (CARDIA) Study.** *Am J Epidemiol* 1991; **133**:1231–1245.
30. Hoegerman GS, Lewis CE, Flack J, Raczynski JM, Caveny J, Gardin JM. **Lack of association of recreational cocaine and alcohol use with left ventricular mass in young adults. The Coronary Artery Risk Development in Young Adults (CARDIA) study.** *J Am Coll Cardiol* 1995; **25**:895–900.
31. Perera S, Mody SH, Woodman RC, Studenski SA. **Meaningful change and responsiveness in common physical performance measures in older adults.** *J Am Geriatr Soc* 2006; **54**:743–749.
32. McDermott MM. **Lower extremity manifestations of peripheral artery disease: the pathophysiologic and functional implications of leg ischemia.** *Circ Res* 2015; **116**:1540–1550.
33. Heikkila A, Venermo M, Kautiainen H, Aarnio P, Korhonen P. **Physical activity improves borderline ankle–brachial index values in a cardiovascular risk population.** *Ann Vasc Surg* 2016; **32**:50–56.
34. Masters MC, Perez J, Tassiopoulos K, Andrade A, Ellis R, Yang J, *et al*. **Gait speed decline is associated with hemoglobin A1C, neurocognitive impairment, and black race in persons with HIV.** *AIDS Res Hum Retroviruses* 2019; **35**:1065–1073.
35. Thorpe RJ Jr, Koster A, Kritchevsky SB, Newman AB, Harris T, Ayonayon HN, *et al*. **Race, socioeconomic resources, and late-life mobility and decline: findings from the Health, Aging, and Body Composition study.** *J Gerontol A Biol Sci Med Sci* 2011; **66**:1114–1123.
36. Mathew S, Faheem M, Ibrahim SM, Iqbal W, Rauff B, Fatima K, *et al*. **Hepatitis C virus and neurological damage.** *World J Hepatol* 2016; **8**:545–556.
37. Stavros K, Simpson DM. **Understanding the etiology and management of HIV-associated peripheral neuropathy.** *Curr HIV/AIDS Rep* 2014; **11**:195–201.
38. Ellis RJ, Rosario D, Clifford DB, McArthur JC, Simpson D, Alexander T, *et al*. **Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER Study.** *Arch Neurol* 2010; **67**:552–558.
39. Anziska Y, Helzner EP, Crystal H, Glesby MJ, Plankey M, Weber K, *et al*. **The relationship between race and HIV-distal sensory polyneuropathy in a large cohort of US women.** *J Neurol Sci* 2012; **315**:129–132.