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Asymptomatic peripheral arterial disease in HIV patients in Ghana: A case-control study

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Background: Peripheral arterial disease (PAD) is common in HIV patients and can be diagnosed noninvasively using the ankle-brachial index (ABI). The burden of PAD has not been investigated in Ghanaian HIV patients. We investigated the prevalence and risk factors associated with PAD in HIV patients at a periurban hospital in Ghana.
Methods: In a case-control design, ABI was measured in 158 cART-treated HIV patients, 150 cART-naïve HIV patients and 156 non-HIV controls with no clinical symptoms of CVDs. PAD was defined as ABI ≤ 0.9. A structured questionnaire was used to collect socio-demographic and clinical data. Fasting venous blood samples were collected to measure plasma levels of glucose, lipid profile, and CD4+ lymphocytes.
Results: The prevalence of PAD was 13.9% among cART-treated HIV patients, 21.3% among cART-naïve HIV patients, and 15.4% among non-HIV controls. Patients with PAD had increased odds of having low CD4+ cell counts [OR (95% CI) = 3.68 (1.41–12.85)]. In cART-treated HIV patients, those on TDF-based [5.76 (1.1–30.01), p = 0.038] and EFV-based [9.28 (1.51–57.12), p = 0.016] regimens had increased odds of having PAD.
Conclusion: In our study population, there was no difference in the prevalence of PAD between cART-treated HIV patients compared to cART-naïve HIV patients or non-HIV controls. Having a low CD4 cell count and being on TDF- or EFV-based regimens were associated with an increased likelihood of having PAD.

Introduction

Sub-Saharan Africa (SSA) has the highest population of people living with HIV (PLWH) worldwide and this is associated with healthcare, socio-economic, and developmental challenges.[1] It was reported in 2017 that 71% of the global total number of PLWH resides in SSA, with 75% of deaths and 65% of new HIV infections occurring in the region.[2] In Ghana, the prevalence of HIV infection is 1.7% and is concentrated mostly in urban and peri-urban areas.[3] Cardiovascular diseases (CVDs) have become a major cause of mortality and morbidity among PLWH as the accessibility and usage of combination antiretroviral therapy (cART) has increased in the past two decades. PLWHs now suffer less from opportunistic infections, and this has improved their standard of living dramatically.[4,5] However, PLWHs are experiencing CVDs such as myocardial infarction, coronary heart disease, cardiac failure, intracranial haemorrhage and ischaemic stroke in greater proportions and at younger ages compared to the uninfected population.[5,6]

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis and causes a lot of deaths globally.[6] PAD is normally diagnosed using clinical symptoms such as intermittent claudication. However, in the majority of patients, PAD may be asymptomatic and laboratory diagnostic assessment like ankle-brachial index (ABI) is required.[7] Previous studies have shown that low ABI (≤0.90) has a specificity greater than 98 % for the diagnosis of PAD and a specificity of 92 % for the prediction of coronary

Abbreviations: ABI, ankle-brachial index; AZT, zidovudine; BMI, body mass index; BP, blood pressure; CI, confidence interval; cART, combination antiretroviral therapy; CVDs, cardiovascular diseases; EVF, efavirenz; FPG, fasting plasma glucose; HIV, human immunodeficiency virus; LPV/r, lopinavir/ritonavir; MetS, Metabolic syndrome; NVP, nevirapine; PAD, peripheral arterial disease; PLWH, people living with HIV; POR, prevalence odds ratio; SSA, sub-Saharan Africa; TDF, tenofovir.

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heart disease and stroke.[8] Despite the high prevalence of HIV in the SSA population, few studies have reported the burden of PAD using ABI in Africa.

The current treatment guidelines for HIV in Ghana require that all PLWHs are treated with antiretroviral therapy (ART) irrespective of their disease staging and/or CD4+ lymphocyte count. The first-line treatment involves the use of tenofovir (TDF)-based regimen that includes its combination with either lamivudine (3TC) or emtricitabine (FTC), as well as either efavirenz (EFV) or nevirapine (NVP). Zidovudine (ZDV)-based regimen is a possible alternative to TDF-based and it is widely used among PLWH in Ghana. Protease inhibitor-based regimens are not commonly used among PLWH in Ghana.[9] Some studies have reported that HIV infection and cART usage are independent factors associated with the development of atherosclerotic lesions in peripheral blood vessels.[10–12] This deleterious effect is even present in HIV patients with viral suppression.[13] In addition, HIV infection and/or cART treatment has been associated with cardiometabolic abnormalities[6,14] which may lead to atherosclerosis in peripheral vessels.[5] There is a paucity of data on the association between cART treatment regimens and PAD in the HIV population in SSA. In this study, we investigated the prevalence and associated factors of PAD in HIV patients, as well as the effect of the cART regimen on PAD. We hypothesize that HIV infection and cART medication are associated with an increased burden of PAD in nondiabetic HIV patients.

Methods

Design, setting and population

This study was a case-control design, conducted from October 2019 through February 2020, with HIV patients as cases, and the controls were non-HIV individuals who visited the facility for voluntary testing of their HIV status. HIV patients were categorized as those on cART management (cART-treated) and those who are yet to be put on cART treatment (cART-naïve). The study was conducted at Atua Government Hospital, a 150-bed primary healthcare facility, located in Agormanya, a peri-urban town in the Eastern region of Ghana. The Agormanya area has a higher prevalence of HIV infection (11.6%) compared to the national prevalence which stands at 1.7% in 2020.[3] The hospital has about 1,500 HIV patients on its register. Participants with a diagnosis of any cardiovascular disease or leg pain on exertion (diagnosed or reported at the time of recruitment), and diabetes defined as those treated with insulin or oral hypoglycaemic agents or had fasting blood glucose above 7 mmol/L were excluded from the study. The study was conducted in conformity with the Helsinki Declaration on Human Experimentation, 1964 with subsequent revisions, latest Seoul, October 2008. Ethical approval was granted by the Korle Bu Teaching Hospital Institutional Review Board (Protocol ID number: KBTH-IRB/000131-2018) and all participants provided voluntary informed consent before joining the study.

Data collection

A structured questionnaire was used to obtain data on sociodemographic factors like age, gender, lifestyle factors (smoking, alcohol intake), medical history (previous diagnosis of hypertension, diabetes, cardiovascular diseases), current medication (antihypertensive agents, antidiabetic drugs, statins, antiplatelets), occupation, education and marital status.

Body weight and height were measured using a stadiometer in light clothing with footwear removed and body mass index (BMI) was calculated as weight/height^2 and categorized as underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2). Hypertension was defined as self-reported use of antihypertensive treatment and/or systolic blood pressure (BP) $\geq$ 140 mm Hg and/or diastolic BP $\geq$ 90 mm Hg. We collected fasting blood samples and measured the levels of plasma glucose, lipid profile and CD4+ cell count. Metabolic syndrome (MetS) was defined by the joint interim statement criteria[15] as having three or more of the following: (1) abdominal obesity (waist circumference $\geq$ 94 cm for men & $\geq$ 80 cm for women); (2) high triglycerides $\geq$1.7 mmol/L; (3) low HDL cholesterol: men $<$1.0 mmol/L or women $<$1.3 mmol/L; and (4) High BP (systolic BP $\geq$ 130 mmHg and/or diastolic BP $\geq$ 85 mmHg); and (5) impaired fasting plasma glucose (FPG) $\geq$5.6 mmol/l.

Ankle and brachial BPs were measured with the patient in the supine position after at least 5 min rest. Firstly, the systolic brachial BPs were measured with 8 MHz Doppler (LifeDop, Summit Doppler) in both arms, after which the systolic ankle BPs of the dorsalis pedis and posterior tibial arteries were measured at the level of the malleoli with a Doppler. The ankle-brachial index (ABI) was calculated for each leg by dividing the highest ankle systolic BP by the highest brachial systolic BP.[16] The study participants were categorised into those with PAD (ABI $<$ 0.9), normal (0.9 $\geq$ ABI $<$ 1.3), and stiff arteries (ABI $\geq$ 1.3).

Statistical analysis

Continuous variables with normal distributions were expressed as mean±standard deviation and analysed using ANOVA; variables with nonnormal distribution were expressed as median (interquartile range) and analysed using the Kruskal-Wallis test. Categorical variables were presented as counts (percentages) and analysed using Pearson's chi-square test. Multinominal logistic regression analyses were performed to identify factors associated with abnormal ABI. The magnitudes of the associations were summarized with the odds ratio, together with their 95% confidence intervals (CIs). Statistical analysis was performed using SPSS version 28 (IBM Corporation, Armonk, NY).

Results

General characteristics of study participants

The mean age of the study participants was 38.4 ± 13.7 years with two-thirds being females. There was no difference in mean age among various categories of participants. There was a high proportion of HIV patients who were hypertensive, underweight, and currently or formerly smoked. Compared to non-HIV participants and cART-naïve HIV patients, HIV patients on cART treatment had higher waist circumference, waist-hip ratio, percentage body fat, diastolic and mean BP and heart rate. HIV patients on cART had higher levels of FPG, triglycerides, and total and LDL cholesterol compared with non-HIV participants. ABI categorisation was associated with the grouping of study participants based on HIV status and cART treatment (Table 1).

Association between HIV status and PAD

When the prevalence of PAD was compared among various categories of study participants in unadjusted logistics regression analyses, cART-naïve HIV patients had an increased prevalence odd ratio (POR) of PAD [POR (95%) = 1.9 (1.03–3.52), p = 0.041] and borderline ABI [1.95 (1.16–3.29), p=0.012] compared to non-HIV controls. In adjusted models, the POR of borderline ABI remain significant [2.22 (1.17–4.21), p = 0.014] but not that of PAD [1.8 (0.8 – 4.02), p = 0.153]. There was no significant change in the POR of PAD [unadjusted model = 1 (0.52–1.92), p = 0.995 & adjusted

Table 1
General characteristics of study participants.

	All Participants	Non-HIV controls	cART-naïve HIV patients	cART-treated HIV patients	p
N	464	156	150	158	
Age, years	38.4±13.7	36.7±14.4	38.2±11.6	39±11.4	0.109
Females, n (%)	312 (67.2)	106 (67.9)	84 (56)	122 (77.2)	0.02
Married, n (%)	198 (42.7)	70 (44.9)	62 (41.3)	66 (41.8)	0.79
Smoking, n (%)					0.029
Current	16 (3.4)	2 (1.3)	4 (2.7)	10 (6.3)	
Former	57 (15.9)	9 (5.8)	22 (14.6)	26 (16.5)	
Never	187 (80.6)	71 (92.9)	124 (82.7)	132 (83.5)	
Alcohol intake, n (%)	102 (22)	38 (24.4)	36 (24)	28 (17.7)	0.55
Waist circumference, cm	87±12	85±11	84±11	90±12# *	0.002
Hip circumference, cm	102±11	103±11	99±11*	103±11	0.074
Body height, cm	164±7	164±8	164±7	162±7	0.194
Waist-hip ratio	0.85±0.08	0.82±0.08	0.84±0.07*	0.88±0.08* #	<0.001
Body weight, kg	60±13.2	68±13.3	64.4±7.3	65.8±14	0.204
BMI, kg/m^2	24.8±5	25.4±4.7	23.7±4.4*	25.3±5.7	0.061
BMI categories, n (%)					0.024
Underweight	34 (7.4)	6 (3.9)	16 (10.7)	12 (7.6)	
Normal	238 (51.5)	70 (45.5)	94 (62.7)	74 (46.8)	
Overweight	116 (25.1)	46 (29.9)	18 (12)	52 (32.9)	
Obese	74 (16)	32 (20.8)	22 (14.7)	20 (12.7)	
Body fat, %	31±12.2	32.4±12.5	27.6±11.8*	32.8±11.6* #	0.014
Systolic BP, mmHg	134±18	132±13	133±19	137±22	0.184
Diastolic BP, mmHg	83±11	80±9	83±12	86±12* #	0.008
Mean BP, mmHg	100±14	98±10	99±14	104±16* #	0.007
Pulse BP, mmHg	51±13	52±10	50±10	51±13	0.672
Heart rate, bpm	74±9	72±8	73±9	80±8* #	<0.001
Hypertension, n (%)	162 (34.9)	48 (30.8)	46 (30.7)	68 (43)	0.031
FPG, mmol/l	5.2±0.8	5±0.9	5.1±0.8	5.6±0.8*	<0.001
Triglycerides, mmol/l	1.4±0.4	1.4±0.3	1.4±0.4	1.6±0.4*	<0.001
Total cholesterol, mmol/l	5.1±1.2	4.8±1.2	5±1.1	5.6±1.1*	<0.001
HDL cholesterol, mmol/l	1.5±0.4	1.6±0.4	1.4±0.4	1.5±0.5	0.128
LDL cholesterol mmol/l	3±0.9	2.6±0.9	3±0.8*	3.3±0.7* #	<0.001
Current CD4 count, cells/mm^2	405 (273 – 562)		430 (327 – 534)	403 (253 – 583)	0.804
Minimum ABI	0.99±0.09	1±0.09	0.98±0.09	0.99±0.09	0.21
Right	1.02±0.1	1.03±0.09	1.01±0.1	1.03±0.1	0.208
Left	1.01±0.09	1.02±0.1	1±0.08	1101±0.01	0.209
ABI categories					0.048
Normal (ABI≥1)	246 (53)	94 (60.3)	66 (44)	86 (54.4)	
Borderline (ABI: 0.90 – 0.99)	240 (30.2)	38 (24.4)	52 (34.7)	50 (31.6)	
PAD (ABI<0.9)	78 (16.8)	24 (15.4)	32 (21.3)	22 (13.9)	
MetS	178 (38.4)	34 (21.8)	42 (28)	102 (64.6)	<0.001

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ABI, ankle-brachial index; PAD, peripheral arterial disease; cART, combination antiretroviral therapy; MetS, metabolic syndrome.
* : p<0.05 compared to non-HIV controls
\# : p< 0.05 compared to cART-naïve HIV patients

model = 1.14 (0.46–2.98), p = 0.789] and borderline ABI [unadjusted model = 1.44 (0.86–2.4), p = 0.165 & adjusted model = 1.57 (0.76–3.26), p = 0.227] between cART-treated HIV patients and non-HIV controls. In addition, there was no change in the POR of PAD [0.85 (0.61–1.19), p = 0.338] and borderline ABI [0.84 (0.65–1.08), p = 0.175] between cART-treated and cART-naïve HIV patients.

Associated factors of PAD and borderline ABI

In unadjusted logistic regression models, BMI and having high BP were associated with decreased odds of having PAD while being cART-treated HIV patients, having low CD4 cell count, formal employment or being self-employed were associated with an increase in odds of having PAD. In the adjusted logistic regression models, high BP, low CD4+ cell count and having formal employment or self-employed were associated with increased odds of having PAD. For borderline ABI, individuals with low CD4+ cell count had increased odds of having borderline ABI in unadjusted logistic regression models. In the adjusted models, having hypertension was associated with decreased odds of having borderline ABI, whereas being self-employed, cART naïve or cART-treated HIV patient and having a low CD4+ cell count were associated with increased odds of having borderline ABI (Table 2).

There was no association between metabolic abnormalities and ABI categories among various categories of study participants in Pearson's chi-square analyses. For the components of MetS, high blood BP was associated with decreased odds of having PAD and abdominal obesity was associated with increased odds of having PAD in the entire study participants. Abdominal obesity was associated with increased odds of PAD in cART-treated HIV patients (Table S1, Supplementary material).

Association between PAD and cART regimen in cART-treated HIV patients

The average duration of HIV infection in cART-treated HIV patients was 7.6±4.6 years and the average duration of treatment was 7.2±4.5 years. There was no difference in the duration of HIV infection and cART regimens among various ABI categories (Table S2, Supplementary material). Concerning cART medication regimens, with non-HIV controls as a reference, patients on TDF-based and

Table 2
Factors associated with low and borderline ABI from logistic regression analyses.

	Low ABI [OR (95% CI)]		Borderline ABI [OR (95% CI)]	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Age	0.99 (0.97 – 1.01)	1 (0.96 – 1.04)	1 (0.98 – 1.01)	
Females	0.72 (0.43 – 1.21)	0.83 (0.36 – 1.92)	1.34 (0.85 – 2.12)	1.94 (0.92 – 4.1)
Unmarried	1.08 (0.65 – 1.81)	0.74 (0.36 – 1.54)	1.33 (0.87 – 2.03)	1.1 (0.59 – 2.03)
Alcohol intake	0.84 (0.45 – 1.56)	0.98 (0.42 – 2.3)	0.81 (0.49 – 1.35)	1.05 (0.5 – 2.2)
Current smoking	0.62 (0.13 – 2.9)	0.5 (0.09 – 2.83)	0.69 (0.21 – 2.26)	0.55 (0.14 – 2.24)
Hypertension	0.54 (0.31 – 0.95)*	0.49 (0.22 – 1.08)	0.77 (0.49 – 1.18)	0.48 (0.25 – 091)*
HIV status: reference= non-HIV				
cART-naïve	1.9 (1.03 – 3.52)*	1.02 (0.48 – 2.18)	1 (0.52 – 1.92)	0.67 (0.36 – 1.27)*
cART -treated	1.95 (1.16 – 3.29)*	0.44 (0.15 – 1.28)	1.44 (0.86 – 2.4)	0.37 (0.16 – 0.88)*
CD4+ cell count <200 cells/mm^3	2.73 (1.08 – 8.53)*	3.68 (1.41 – 12.85)*	7.01 (2.89 – 17.04)*	14.94 (5 – 44.74)*
Employment (Reference: unemployed)				
Employed	7.69 (1.79 – 33.03)*	5.69 (1.03 – 22.84)*	1.76 (0.9 – 3.43)	2 (0.7 – 5.67)
Self-employed	6.84 (1.54 – 30.31)*	8.54 (1.53 – 47.73)*	1.73 (0.85 – 3.52)	3.05 (1.04 – 8.97)
Education: reference= No formal education				
Basic/JHS	2.06 (0.8 – 5.31)	2.61 (0.88 – 7.75)	1.35 (0.66 – 2.73)	2.1 (0.88 – 5.01)
SHS/Tech	0.53 (0.14 – 2.04)	0.61 (0.13 – 2.9)	1.47 (0.65 – 3.29)	2.03 (0.65 – 6.3)
Tertiary	1.71 (0.64 – 4.57)	0.8 (0.15 – 4.17)	1.02 (0.48 – 2.15)	2.6 (0.77 – 8.8)
BMI (unit change)	0.92 (0.87 – 0.98)*		0.97 (0.93 – 1.02)	
BMI categories (Reference: normal)				
Underweight	1.94 (0.8 – 4.7)	0.95 (0.29 – 3.03)	0.99 (0.42–2.35)	0.47 (0.22 – 1.04)
Overweight	0.6 (0.32 – 1.15)	0.55 (0.23 – 1.32)	0.54 (0.32–0.91)	0.49 (0.2 – 1.22)
Obese	0.47 (0.21 – 1.08)	0.34 (0.1 – 1.23)	0.6 (0.33–1.1)	1.01 (1 – 1.04)

* : p<0.05. All the parameters were forced into the multivariable logistic regression model for the adjusted odds ratio. ABI, ankle-brachial index; cART, combination antiretroviral therapy; BMI, body mass index.

Table 3
Association between low ABI and cART regimen in cART-treated HIV patients.

	Normal ABI, n (%)	Low ABI, n (%)	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)*	p
TDF-based	80 (58.8)	20 (90.9)	7 (1.57 – 31.2)	0.004	5.76 (1.1 – 30.01)	0.038
AZT-based	54 (39.7)	2 (9.1)	0.15 (0.03 – 0.68)	0.011	0.18 (0.03 – 0.96)	0.044
EFV-based	82 (60.3)	20 (90.9)	6.59 (1.48 – 29.3)	0.011	9.28 (1.51 – 57.12)	0.016
NVP-based	44 (32.4)	2 (9.1)	0.21 (0.05 – 0.94)	0.048	0.13 (0.02 – 0.8)	0.027

* Adjusted for age, gender, marital status, alcohol and smoking status, employment, educational level, BMI categories and CD4+ cell level.
d4T, stavudine; AZT, zidovudine; TDF, tenofovir; NVP, nevirapine; EVF, efavirenz.
The major confounders in the multivariable regression models
TDF-based regimen [OR (95% CI)]: male gender [4.14 (1.04–16.36), p = 0.043] and unmarried [2.23 (1.06–6.32), p = 0.039].
AZT-based regimen group: male gender [3.73 (1.14–11.01), p = 0.034].
EFV-based regimen group: unmarried [1.73 (1.05–5.71), p = 0.037] and unemployed [1.56 (1.08–4.39), p = 0.038].
NVP-based regimen group: male gender [4.2 (1.12–15.68), p = 0.033] and unmarried [2.7 (1.18–8.74), p = 0.019].

EFV-based regimens had increased odds of having PAD, while those on AZT-based and NVP-based regimens had decreased odds of having PAD in both unadjusted and adjusted logistic regression models (Table 3).

Lamivudine was part of the medication regimen for 154 (97.5%) patients, and hence, we did not analyse it. Stavudine and emtricitabine were taken by 2 and 4 patients respectively, and hence, we did not include them in our analyses.

In mediation analyses employing 1000 bootstrapped samples, the indirect effect between cART treatment and low ABI through MetS was significant [β_{a*b} (95% CI) = -0.034 (-0.066, -0.001), p=0.045]. Given that the direct effect of cART treatment and low ABI was not significant [β_c (95% CI) = 0.06 (-0.024, 0143), p=0.249], the mediation present was partial and not full. There was no direct [β_c (95% CI) = 0.06 (-0.024, 0143), p=0.301] or indirect [β_{a*b} (95% CI) = -0.007 (-0.017, 0.003), p=0.185] association between cART-naïve HIV status and low ABI.

Discussion

The major findings of this study are that the prevalence of PAD was higher in cART-naïve HIV patients and non-HIV participants compared to cART-treated HIV patients. However, MetS was common among cART-treated HIV patients compared to cART-naïve HIV patients and non-HIV controls. Participants who had CD4+ cell count <200 cells/mm^3, those formally- or self-employed had increased odds of having PAD. Also, HIV patients on TDF-based and EFV-based regimens had increased odds of PAD while those on AZT-based and NVP-based regimens had decreased odds of having PAD. Furthermore, MetS partially mediated the relationship between cART-treatment HIV patients and PAD.

Few studies that have reported the prevalence of PAD in the sub-Saharan African HIV population employed cross-sectional designs without any comparative non-HIV controls. In a case-control study conducted on Nigerian HIV patients, the prevalence of PAD in cART-treated HIV patients was 14.6%, similar to what was found in this study. However, what was found in non-HIV controls was 2%, lower than the prevalence of PAD found in our non-HIV controls. This discrepancy may be due to their cut-off definition for PAD (<0.9) compared to our cut-off (≤0.9). Furthermore, the sample size of their non-HIV controls was too small (a third of the sample size of their HIV patients), limiting the comparability of the outcomes.[10] In Burundi HIV patients, the prevalence of PAD was reported to be 17.3%[16], higher than what was found in our cART-treated HIV patients but lower than the cART-naïve HIV patients in our study. Surprisingly, the prevalence of PAD in Cameroonian HIV patients was low (6.9%) compared to most studies conducted in other African populations.[17] These wide variations in the prevalence may be attributed to the methodology used in patient selection and ABI assessment, especially how PAD was defined across various studies.

We did not find any difference in the prevalence of PAD in cART-treated HIV patients compared to non-HIV controls. This is consistent with the study conducted in Thailand that reported no difference in the prevalence of PAD between HIV patients and non-HIV controls.[13] Interestingly, the Danish HIV studies[18] and the Women's Interagency HIV Study[19] also reported a similar low prevalence of PAD in HIV patients, but both studies had no comparative non-HIV controls. In contrast to the findings of this study, some case-control design studies have reported a high prevalence of PAD in HIV patients compared to non-HIV controls. In the Copenhagen comorbidity in HIV infection study, HIV infection doubled the odds of having PAD compared to uninfected controls[20] and the incident rate of subclinical PAD is 3.6% within a median follow-up of 2 years.[21] In addition, the Veterans Aging Cohort Study, which utilized a longitudinal study design, reported an increased risk of PAD in HIV-infected patients compared to non-HIV participants[12]. In the African population, two postgraduate dissertations of studies conducted in Nairobi[22] and Eldoret[23], Kenya, reported a higher prevalence of PAD in HIV patients to be 18 and 19.2% compared to that in non-HIV controls, which was 6.8% and 7.5% respectively. The finding of a high prevalence of PAD in cART-naïve HIV patients in our study is consistent with the hypothesis that HIV infection and replication are associated with inflammation and immune activation which lead to the development of atherosclerosis.[24] Indeed, a randomized controlled trial in cART-naïve HIV patients found that initiation of cART treatment resulted in improvement of endothelial dysfunction, measured as flow-mediated dilation of the brachial artery, at weeks four and 24 of the trial duration.[25]

Concerning HIV factors assessed in this study, only participants with low CD4+ cell counts (<200 cells/mm^3) had significantly increased odds of having PAD, consistent with what was reported in other studies.[12,16,17] This supports the proposition that the severity or staging of HIV infection may partly be responsible for the development of PAD.[12,16] However, our study did not find any association between the durations of HIV infection and cART treatment on the prevalence of PAD, unlike what was reported in other studies.[12,16] In cART-treated HIV patients, the presence of MetS was associated with reduced odds of having PAD with MetS indirectly mediating the relationship between cART treatment and PAD. This is contrary to what was reported in studies conducted in Switzerland[26] and Nigeria[10] where MetS in cART-treated HIV patients increased the likelihood of having PAD.

Among the cART-treated HIV patients, those on TDF- and EFV-based regimens had increased odds of having PAD. This is consistent with the findings of Aragonè et al., who reported that Spanish HIV patients on TDF-based regimens, compared to other cART regimens, had increased progression of atherosclerosis assessed as carotid artery intima-media thickness (cIMT).[11] Another study in Ethiopian HIV patients reported that those on EFV-based regimens showed high levels of atherosclerosis (increased cIMT) and endothelial dysfunction (impaired flow-mediated dilatation).[27] The atherosclerotic potential of the TDF-based regimens is supported by the findings of Potměšil et al, who demonstrated that acyclic nucleoside phosphonate antivirals, such as TDF, activate the expression of monocyte chemotactic proteins and transcriptional factor nuclear factor-κB[28], potent mediators of atherosclerosis.

The findings of this study may be interpreted taking account of these major limitations. First, the study was conducted in a single healthcare facility and hence, the burden of PAD reported cannot be generalized to the entire Ghanaian HIV population. Also, ABI was measured at one time, and therefore, we cannot infer causality between HIV infection and PAD; it is possible that some HIV patients had PAD before the infection. In addition, PAD was assessed using resting ABI, which has been shown to underestimate the burden of PAD in HIV patients.[29] Moreover, the sample size was not adequate for us to make a definite conclusion about the role of various cART regimens on PAD prevalence. It is recommended that future studies utilize a multicentre longitudinal design to investigate the development of PAD and the effect of cART medication in a large number of patients to confirm or refute the findings of the study. Likewise, the use of post-exercise ABI in further studies can help determine the actual prevalence of PAD in our population.

Perspectives for nursing practice

The task shift of HIV care in sub-Saharan Africa from physicians to nursing staff has dramatically improved access to ART, retention in care and the suppression of viremia.[30] However, most special nurses in ART clinics do not have the requisite training and logistics to screen for PAD among HIV patients. ABI is a simple and noninvasive, yet effective screening technique that can be used to detect PAD and general atherosclerosis in HIV patients.[5,6] Incorporation of ABI assessment into HIV care can help early identify patients with subclinical PAD for management and slows the disease progression of those with PAD.[16] In addition, during patient education, nurses may highlight the management of metabolic and other CVD risk factors for the prevention of PAD.

Conclusion

In our study population, the prevalence of PAD in cART-treated HIV patients is similar to that of cART-naïve and non-HIV controls. Patients with low CD4+ cell count had an increased likelihood of having PAD. MetS partially mediated the association between cART-treated HIV patients and PAD. HIV patients being treated with TDF- and EFV-based regimens had an increased likelihood of having PAD.

Ethical approval and consent to participate

The study was conducted in conformity with the Helsinki Declaration on Human Experimentation, 1964, with subsequent revisions, latest Seoul, October 2008. Ethical approval was granted by the Korle Bu Teaching Hospital Institutional Review Board (Protocol ID number: KBTH-IRB/000131-2018). All the study participants provided voluntary informed consent before joining the study.

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Availability of data

Dataset supporting the conclusions of this paper is available and can be requested from the corresponding author.

Consent for publication

Consent for publication was not requested from participants because no individual participant's data in any form such as images, voice recordings or videos are not included in this manuscript.

Declaration of Competing Interest

The authors have no conflict of interest to disclose.

CRediT authorship contribution statement

Kwame Yeboah: Conceptualization, Formal analysis, Data curation, Writing – original draft. **Latif Musah:** Data curation, Writing – review & editing. **Samuel Essel:** Data curation, Writing – review & editing. **Jennifer Adjepong Agyekum:** Formal analysis, Data curation, Writing – review & editing. **Kweku Bedu-Addo:** Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jvn.2023.07.001.

References

1. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392(10159):1789–1858.
2. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392(10159):1736–1788.
3. Ghana AIDS Commission. National and sub-national HIV and AIDS estimates and projections 2020 report. Accra: Ghana AIDS Commission; 2021. Available from: https://www.ghanaids.gov.gh/pages/publications. Accessed October 10, 2022.
4. The antiretroviral therapy cohort collaboration: life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372(9635):293–299.
5. Alonso A, Barnes AE, Guest JL, Shah A, Shao IY, Marconi V. HIV infection and incidence of cardiovascular diseases: an analysis of a large healthcare database. *J Am Heart Assoc*. 2019;8(14):e012241.
6. Feinstein MJ, Hsue PY, Benjamin LA, Bloomfield GS, Currier JS, Freiberg MS, Grinspoon SK, Levin J, Longenecker CT, Post WS. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the american heart association. *Circulation*. 2019;140(2):e98–e124.
7. Yeboah K, Puplampu P, Ainuson J, Akpalu J, Gyan B, Amoah AGB. Peripheral artery disease and exertional leg symptoms in diabetes patients in Ghana. *BMC Cardiovasc Disord*. 2016;16(1):68.
8. Doobay AV, Anand SS. Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes. *Arter Thromb Vasc Biol*. 2005;25(7):1463–1469.
9. Ghana Health Service. *Edited by National AIDS/STI Control Programme*. 2019 edn. Consolidated guidelines for HIV care in Ghana: test, treat & track. Accra: Ministry of Health, Ghana; 2019 August.
10. Agu CE, Uchendu IK, Nsonwu AC, Okwuosa CN, Achukwu PU. Prevalence and associated risk factors of peripheral artery disease in virologically suppressed HIV-infected individuals on antiretroviral therapy in Kwara state, Nigeria: a cross sectional study. *BMC Public Health*. 2019;19(1):1143.
11. Aragonès G, Pardo-Reche P, Fernández-Sender L, Rull A, Beltrán-Debón R, Rodríguez-Gallego E, Camps J, Joven J, Alonso-Villaverde C. The deleterious influence of tenofovir-based therapies on the progression of atherosclerosis in HIV-infected patients. *Mediat Inflamm*. 2012;2012:372305.
12. Beckman JA, Duncan MS, Alcorn CW, So-Armah K, Butt AA, Goetz MB, Tindle HA, Sico JJ, Tracy RP, Justice AC, et al. Association of human immunodeficiency virus infection and risk of peripheral artery disease. *Circulation*. 2018;138(3):255–265.
13. Aurpibul L, Sugandhavesa P, Srithanaviboonchai K, Sitthi W, Tangmunkongvorakul A, Chariyalertsak C, Rerkasem K. Peripheral artery disease in HIV-infected older adults on antiretroviral treatment in Thailand. *HIV Med*. 2019;20(1):54–59.
14. Dzudzor B, Essel S, Musah L, Agyekum JA, Yeboah K. Metabolic syndrome and combination antiretroviral therapy in HIV patients in Periurban Hospital in Ghana: a case-control study. *AIDS Res Treat*. 2023;2023:1566001.
15. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WPT, Loria CM, Smith Jr SC. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. *Circulation*. 2009;120(16):1640–1645.
16. Desormais I, Harimenshi D, Niyongabo T, Lacroix P, Aboyans V, Preux PM. HIV clinical stages and lower extremity arterial disease among HIV infected outpatients in Burundi. *Sci Rep*. 2021;11(1):8296.
17. Kamdem F, Mapoure Y, Hamadou B, Souksouna F, Doualla MS, Jingi AM, Kenmegne C, Lekpa FK, Fenkeu JK, Imandy G, et al. Prevalence and risk factors of peripheral artery disease in black Africans with HIV infection: a cross-sectional hospital-based study. *Vasc Health Risk Manag*. 2018;14:401–408.
18. Knudsen A, Malmberg CAE, Kjær A, Lebech AM. Low prevalence of peripheral arterial disease in a cross-sectional study of Danish HIV-infected patients. *Infect Dis*. 2015;47(11):776–782.
19. Sharma A, Holman S, Pitts R, Minkoff HL, DeHovitz J, Lazar J. Peripheral arterial disease in HIV-infected and uninfected women. *HIV Med*. 2007;8(8):555–560.
20. Knudsen AD, Gelpi M, Afzal S, Ronit A, Roen A, Mocroft A, Lundgren J, Nordestgaard B, Sillesen H, Lebech AM, et al. Brief report: prevalence of peripheral artery disease is higher in persons living with HIV compared with uninfected controls. *JAIDS J Acquir Immune Defic Syndr*. 2018;79(3):381–385.
21. Suarez-Zdunek MA, Høgh J, Kirkegaard-Klitbo DM, Jensen AMR, Rupert A, Trøseid M, Gerstoft J, Nielsen SD, Knudsen AD. High incidence of subclinical peripheral artery disease in people with HIV. *AIDS*. 2022;36(10):1355–1362.
22. Kaittany F. *Peripheral Arterial Disease in HIV Positive and Negative Subjects at The Aga Khan University Hospital*. Nairobi. Nairobi, Kenya: Aga Khan University; 2010.
23. Francis O. *Prevalence and Risk Factors for Peripheral Arterial Disease Among HIV Infected Patients at the Moi Teaching and Referral Hospital, Eldoret, Kenya*. Eldoret, Kenya: Moi University; 2020.
24. Stein JH, Currier JS, Hsue PY. Arterial disease in patients with human immunodeficiency virus infection: what has imaging taught us? *JACC Cardiovasc Imaging*. 2014;7(5):515–525.
25. Torriani FJ, Komarow L, Parker RA, Cotter BR, Currier JS, Dubé MP, Fichtenbaum CJ, Gerschenson M, Mitchell CKC, Murphy RL, et al. Endothelial function in human immunodeficiency virus-infected antiretroviral-naive subjects before and after starting potent antiretroviral therapy: the ACTG (AIDS clinical trials group) study 5152s. *J Am Coll Cardiol*. 2008;52(7):569–576.
26. Periard D, Cavassini M, Taffé P, Chevalley M, Senn L, Chapuis-Taillard C, de Vallière S, Hayoz D, Tarr PEfor the Swiss HIVCS. High prevalence of peripheral arterial disease in HIV-infected persons. *Clin Infect Dis*. 2008;46(5):761–767.
27. Gleason RL, Caulk AW, Seifu D, Rosebush JC, Shapiro AM, Schwartz MH, Eckard AR, Amogne W, Abebe W. Efavirenz and ritonavir-boosted lopinavir use exhibited elevated markers of atherosclerosis across age groups in people living with HIV in Ethiopia. *J Biomech*. 2016;49(13):2584–2592.
28. Potměšil P, Holý A, Kmoníčková E, Křížková J, Zídek Z. Acyclic nucleoside phosphonate antivirals activate gene expression of monocyte chemotactic protein 1 and 3. *J Biomed Sci*. 2007;14(1):59–66.
29. Qaqa AY, DeBari VA, Isbitan A, Mohammad N, Sison R, Slim J, Perez G, Shamoon FE. The role of postexercise measurements in the diagnosis of peripheral arterial disease in HIV-infected patients. *Angiology*. 2011;62(1):10–14.
30. Fairall L, Bachmann MO, Lombard C, Timmerman V, Uebel K, Zwarenstein M, Boulle A, Georgeu D, Colvin CJ, Lewin S, et al. Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): a pragmatic, parallel, cluster-randomised trial. *Lancet*. 2012;380(9845):889–898.