Libyan Journal of Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/zljm20

Association between cardio-ankle vascular index and cardiometabolic risk factors in HIV patients in Ghana

Kwame Yeboah, Samuel Essel, Jennifer Agyekum & Bartholomew Dzudzor

To cite this article: Kwame Yeboah, Samuel Essel, Jennifer Agyekum & Bartholomew Dzudzor (2023) Association between cardio-ankle vascular index and cardiometabolic risk factors in HIV patients in Ghana, Libyan Journal of Medicine, 18:1, 2215636, DOI: 10.1080/19932820.2023.2215636

To link to this article: https://doi.org/10.1080/19932820.2023.2215636

LIBYAN JOURNAL OF MEDICINE
2023, VOL. 18, 2215636
https://doi.org/10.1080/19932820.2023.2215636

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Association between cardio-ankle vascular index and cardiometabolic risk factors in HIV patients in Ghana

Kwame Yeboah [a], Samuel Essel[a,b], Jennifer Agyekum [a,c] and Bartholomew Dzudzor [d]

[a]Department of Physiology, University of Ghana Medical School, Accra, Ghana; [b]Department of Physician Assistant Studies, Central University, Accra, Ghana; [c]Medical Laboratory Unit, Mamprobi Hospital, Ghana Health Service, Accra, Ghana; [d]Department of Medical Biochemistry, University of Ghana Medical School, Accra, Ghana

ABSTRACT

Human immunodeficiency virus (HIV) infection is associated with increased cardiovascular diseases (CVDs) even in patients with viral suppression by combination antiretroviral therapy (cART). Arterial stiffness is an independent predictor of CVDs in diseased individuals and the general population. Cardio-ankle vascular index (CAVI) is an index of arterial stiffness that has been shown to predict target organ damage. CAVI is less studied in HIV patients. We compared the levels of arterial stiffness using CAVI and associated factors among cART-treated and cART-naïve HIV patients to those of non-HIV controls. In a case-control design, 158 cART-treated HIV patients, 150 cART-naïve HIV patients and 156 non-HIV controls were recruited from a periurban hospital. We collected data on CVD risk factors, anthropometric characteristics, CAVI, and fasting blood samples to measure plasma glucose, lipid profile, and CD4+ cell counts. Metabolic abnormalities were defined using the JIS criteria. CAVI increased in cART-treated HIV patients compared to cART-naïve HIV patients and non-HIV controls (7.8 ± 1.4 vs 6.6 ± 1.1 vs 6.7 ± 1.4 respectively, $p < 0.001$). CAVI was associated with metabolic syndrome in non-HIV controls [OR (95% CI) = 2.14 (1.04–4.4), $p = 0.039$] and cART-naïve HIV patients [1.47 (1.21–2.38), $p = 0.015$], but not in cART-treated HIV patients [0.81 (0.52–1.26), $p = 0.353$]. In cART-treated HIV patients, a tenofovir (TDF)-based regimen ($\beta = -0.46$, $p = 0.023$) was associated with decreased CAVI and decreased CD4+ cell count ($\beta = -0.23$, $p = 0.047$) was associated with increased CAVI. In a periurban hospital in Ghana, compared to non-HIV controls or cART-naïve HIV patients, cART-treated HIV patients had increased arterial stiffness measured as CAVI. CAVI is associated with metabolic abnormalities in non-HIV controls and cART-naïve HIV patients, but not in cART-treated HIV patients. Patients on TDF-based regimens had decreased CAVI.

ARTICLE HISTORY
Received 23 January 2023
Accepted 15 May 2023

KEYWORDS
Arterial stiffness; CAVI; HIV; cardiometabolic risk factors; cART

1. Introduction

The global infection rate and burden of the human immunodeficiency virus (HIV) have reduced; however, sub-Saharan Africa is responsible for more than two-thirds of the new global HIV infections [1]. Fortunately, due to the widespread availability and access to combination antiretroviral therapy (cART), even in poor resource settings in sub-Saharan Africa, the burden of AIDS-related morbidity and mortality has been markedly reduced [2,3]. However, there is still high morbidity and mortality in HIV patients compared to non-HIV individuals, mainly due to chronic diseases such as cardiovascular disease (CVD) [3]. HIV replication is associated with immune activation, particularly activation of CD4 and CD8 T cells, which leads to increased systemic subclinical inflammation [4]. This may lead to the formation of atherosclerotic plaques and/or stiffening of the large arteries. Arterial stiffness of the medium and large arteries has been associated with the future development of CVD in diseased patients and the general population [5].

The cardio-ankle vascular index (CAVI) is a maker of arterial stiffness derived from the stiffness parameter β, which is reported to have less influence by fluctuation in blood pressure [6]. This makes CAVI unique from other arterial stiffness that is based on pulse wave velocity (PWV), such as carotid-femoral PWV and brachial-ankle PWV [6,7]. CAVI has been reported in several studies to be associated with cardiovascular-related organ damage [8,9] and mortality [10]. Several studies conducted in Africa and other parts of the world have reported arterial stiffness in HIV patients using PWV [2,11–14]. We found only two studies that have recently reported CAVI in the Thai HIV population [15,16], and none in sub-Saharan Africa. There is racial variation of arterial stiffness across lifespan, with blacks reported to have high levels of arterial stiffness compared to Caucasians and Asians at any given age range [17]. In addition, environmental factors such as diet, levels of physical activity and psychosocial parameters can affect arterial stiffness across different

CONTACT Kwame Yeboah kyeboah@ug.edu.gh Department of Physiology, University of Ghana Medical School, Accra, Ghana
Supplemental data for this article can be accessed online at https://doi.org/10.1080/19932820.2023.2215636.

sociodemographic regions [2,14,17]. There is also conflicting report as to whether HIV infection and/or ART medication lead to increase in arterial stiffness [2]. Therefore, we compared arterial stiffness using CAVI between cART-treated and cART-naïve HIV patients with those of non-HIV controls. We also investigated factors associated with changes in CAVI among study participants. We hypothesize that, compared to non-HIV controls, individuals with HIV infection and cART medication may increase arterial stiffness measured as CAVI.

2. Methods

2.1. Study participants, site and design

This study was conducted from October 2019 through February 2020, and the design was a case-control study 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 classified as those under cART treatment (cART-treated) and newly diagnosed patients who had not yet received cART treatment (cART-naïve). The study was conducted at Atua Government Hospital, a 150-bed primary healthcare facility, located at the Agormanya, a periurban town in the Eastern region of Ghana. The Agormanya area has a high prevalence of HIV infection compared to the national prevalence. The hospital has approximately 3000 HIV patients on its registry. Participants with a diagnosis of diabetes or fasting blood glucose (FPG) > 7 mmol/L, a history of cardiovascular disease or treatment and those with an ankle-brachial index <0.9 were excluded from the study. Ethical approval was obtained from the College of Health Sciences Ethical & Protocol Review Committee (CHS-Et/M.6–5.17/2018–2019) and all participants provided voluntary informed consent before joining the study.

2.2. Data collection

A structured questionnaire was used to obtain data on sociodemographic factors like age, gender, lifestyle factors (smoking, alcohol intake), medical history (hypertension, diabetes, cardiovascular disease), current medication (antihypertensive agents, cART), occupation, education (school cycles completion), marital status. Smoking status was classified as never, past (smoking cessation since more than 1 year before the survey) or current smoking.

Body weight and height were measured using a stadiometer in light clothing with footwear removed, with a body-mass index (BMI) 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). Waist and hip circumferences were measured with a non-elastic tape measure parallel to the floor without compressing the skin. The percentage of body fat was estimated through a bioelectrical impedance analysis with the Body composition monitor (BF- 508, Omron Healthcare, Inc., Vernon Hills, IL, USA). Blood pressure (BP) was measured using a semi-automated blood pressure monitor (average of two measures for each arm at 1-min intervals). Hypertension was defined as those having systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg or taking antihypertensive treatment.

We collected 5 ml of fasting venous blood samples from each participant in appropriate tubes, centrifuged them at 4000 G, and serum/plasma was aliquoted and stored at −80°C until analysis. Fasting plasma glucose (FPG), total cholesterol, high-density lipoprotein cholesterol and plasma triglyceride levels were analysed using a biochemistry analyser (Contec BC 400, China) and commercial reagents (Randox Laboratory Reagents, UK). Low-density lipoprotein (LDL) cholesterol levels were calculated using Friedewald's formula. CD4 cell count was measured using TriTEST reagents following a dual platform protocol and MultiSET and Attractors software using a FACScan flow cytometer (Becton-Dickinson, NJ, USA). Metabolic syndrome was defined by the joint interim statement criteria [18] as having three or more of the following: (1) abdominal obesity (waist circumference ≥94 cm for men & ≥ 80 cm for women); (2) high triglycerides ≥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 ≥130 mmHg and/or diastolic BP ≥85 mmHg); and (5) fasting plasma glucose (FPG) ≥5.6 mmol/l.

CAVI was measured using Vasera 1500N (Fukuda-Denshi, Japan) with the participant resting supine for at least 10 minutes before measurement. Electrocardiogram electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the sternum, and cuffs were wrapped around the upper arms and ankles. CAVI values were computed automatically. Briefly, CAVI corresponds to the stiffness parameter β, calculated from the values of heart-ankle PWV and BP as follows:

$$\beta = (2\rho/\Delta P)\cdot [\ln (P_s/P_d)]\cdot PWV^2$$

Where ρ indicates blood density; ΔP, pulse pressure; ln, natural log; P_s, systolic BP; and P_d, diastolic BP [19,20].

2.3. Sample size calculation

Sample size was computed based on the data from a previous pilot study [21]. A minimum of 133 participants was required in each patient group to detect an

effect size ≥0.4, with a power of 90% and a significance level of 95%.

2.4. Data analysis

IBM SPSS version 28 was used to summarise results as proportions for categorical variables and means and standard deviations (SD) for continuous variables. Shapiro Wilk test was used to check the normality of the quantitative variables, and non-normally distributed variables were transformed appropriately. Mean differences between groups of patients were analysed by ANOVA and ANCOVA to adjust for covariates. The distribution of categorical data was analysed by χ^2 test, and association between variables using Pearson's correlation. Multiple regressions, with all appropriate parameters forced into the model, were performed to determine independent association between patients' characteristics and CAVI. Logistic regression analyses were performed to determine the association between cardiometabolic abnormalities and CAVI. p-values <0.05 were considered statistically significant.

3. Results

3.1. 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, overweight, and currently or previously smoked. Compared to non-HV participants and cART-naïve HIV patients, HIV patients on cART treatment had higher waist circumference, waist-hip ratio, percentage of body fat, mean diastolic and blood pressures, and heart rate. HIV patients on cART had higher levels of fasting plasma glucose (FPG), triglycerides, and total and LDL cholesterol compared to non-HIV participants. cART-treated HIV patients had higher levels of CAVI and MetS compared to cART-naïve HIV patients or non-HIV participants, but no difference between cART-naïve and non-HIV participants (Table 1). The average duration of HIV infection in cART-treated HIV patients was 7.6 ± 4.6 years and the average duration of cART treatment was 7.2 ± 4.5 years. For the cART medication regimen, 94 (59.5%) patients were treated with TDF/3TC/NVP or EFV regimens, 52 (32.9%) patients were

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
MetS	178 (38.4)	34 (21.8)	42 (28)	102 (64.6)	<0.001
Current CD4 count, cells/mm^2	405 (273–562)		430 (327–534)	403 (253–583)	0.804
CAVI	7.1 ± 1.4	6.6 ± 1.1	6.7 ± 1.4	7.8 ± 1.4*#	<0.001

Note: BMI, body mass index; BP, blood pressure; FPG, fasting blood glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; CAVI, cardio-ankle vascular index; MetS, metabolic syndrome.

*$p < 0.05$ compared to non-HIV controls.

#$p < 0.05$ compared to cART-naïve HIV patients.

on AZT/3TC/NVP or EFV regimens and 12 (7.6%) patients were on LPV/r-based regimens.

3.2. Comparison of CAVI among study participants

There was no difference in the levels of CAVI between male and female participants (7.1 ± 1.3 vs 7 ± 1.4, p = 0.883, respectively). In non-HIV controls (6.8 ± 1.1 vs 6.3 ± 1.1, p = 0.023) and cART-naïve HIV patients (7.1 ± 1.5 vs 6.5 ± 1.3, p = 0.031), CAVI was higher in those with MetS compared to those without MetS, but no differences in CAVI was observed between cART-treated HIV patients with and without MetS (7.7 ± 1.4 vs 8 ± 1.4, p = 0.141). When CAVI levels were compared among various categories of BMI in all study participants, the obese group had lower CAVI than the overweight and normal groups, with the underweight group having the highest CAVI. In non-HIV controls, the underweight group had higher CAVI compared to the other BMI groups. In cART- naïve and cART-treated HIV patients, obese participants had a lower CAVI than normal BMI participants (Figure 1). Similar observations were made when the mean CAVI values were adjusted for covariates in ANCOVA analysis (Supplementary, S1). When HIV patients were classified according to their CD4+ cell count, CAVI was highest in patients with CD4+ cell count <200 cell/mm^3, followed by those with CD4+ cell count 200–500 cells/mm^3, and those with CD4+ cell count >500 cells/mm^3 had the lowest CAVI (Figure 2). Similar observations were made when adjusted for covariates (Supplementary, S2).

3.3. Correlation between CAVI and participants characteristics

In all study participants, CAVI was positively correlated with age, waist-hip ratio, BPs, heart rate, FPG, and total and LDL cholesterol levels; negatively correlated with body weight, hip circumference, BMI, body fat, and CD4+ cell count. In non-HIV controls, CAVI was positively correlated with age, BPs, total and LDL cholesterol, and negatively correlated with hip

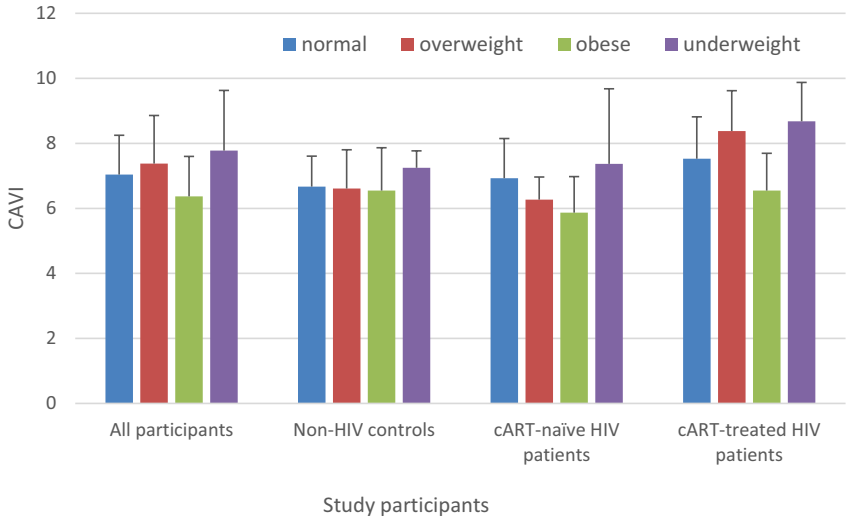

Figure 1. Levels of CAVI among various BMI categories in study participants.

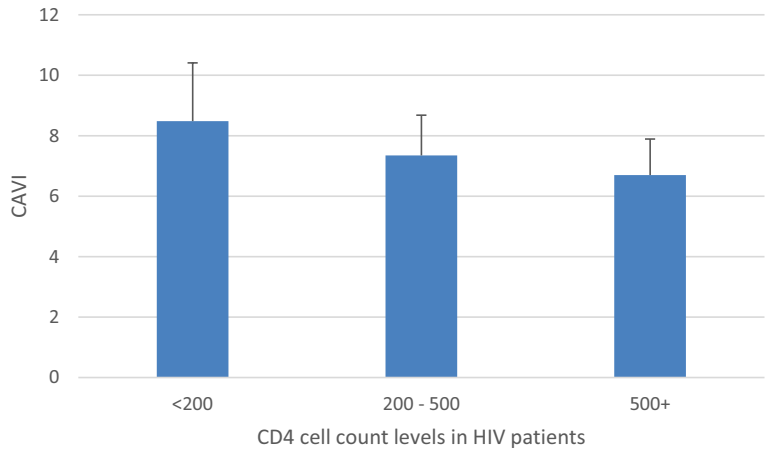

Figure 2. Levels of CAVI levels among CD4+ cell count categories in HIV patients.

Table 2. Correlation between CAVI and characteristics of study participants.

	All participants		Non-HIV controls		cART-naïve HIV patients		cART-treated HIV patients	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age	0.72	<0.001	0.72	<0.001	0.67	<0.001	0.67	<0.001
Weight	−0.23	<0.001	−0.1	0.242	−0.41	<0.001	−0.25	0.003
Height	−0.05	0.344	−0.02	0.852	−0.21	0.02	0.18	0.033
Waist circumference	0.05	0.315	0.14	0.118	−0.14	0.146	−0.11	0.201
Hip circumference	−0.23	<0.001	−0.17	0.049	−0.32	<0.001	−0.31	<0.001
WHR	0.33	<0.001	0.35		0.25	0.007	0.2	0.021
BMI	−0.21	<0.001	−0.08	0.339	−0.33	<0.001	−0.33	<0.001
Body fat	−0.15	<0.001	−0.08	0.342	−0.29	0.002	−0.27	0.002
Systolic BP	0.3	<0.001	0.36	<0.001	0.2	0.027	0.17	0.055
Diastolic BP	0.35	<0.001	0.47	<0.001	0.33	<0.001	0.23	0.006
Mean BP	0.36	<0.001	0.46	<0.001	0.28	0.003	0.23	0.008
Pulse BP	0.05	0.142	0.06	0.474	−0.04	0.704	0.06	0.503
Heart rate	0.13	0.01	0.14	0.114	0.14	0.123	−0.17	0.052
FPG	0.15	0.003	−0.02	0.809	0.21	0.025	−0.03	0.69
Total cholesterol	0.14	0.006	0.19	0.027	−0.01	0.591	−0.05	0.535
Triglycerides	0.09	0.094	0.08	0.373	0.05	0.56	−0.15	0.084
HDL cholesterol	−0.01	0.885	0.05	0.55	0.03	0.737	−0.14	0.097
LDL cholesterol	0.19	<0.001	0.23	0.007	−0.09	0.322	0.06	0.498
CD4 cell count	−0.45	<0.001			−0.69	<0.001	−0.38	<0.001
Duration of HIV infection							0.32	<0.001
cART treatment duration							0.31	<0.001

Note: WHR, waist-hip ratio; BMI, body mass index; BP, blood pressure; FPG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; cART, combination antiretroviral therapy.

circumference. In cART-naïve HIV patients, CAVI was positively correlated with age, waist-hip ratio, blood pressure indices and fasting blood glucose, and negatively correlated with body weight and height, hip circumference, BMI, body fat and CD4+ cell count. In cART-treated HIV patients, CAVI was positively correlated with age, body height, waist-hip ratio, systolic and diastolic BP, duration of HIV infection, and cART treatment; and negatively correlated with body weight, hip circumference, BMI, body fat, and CD4+ cell count (Table 2).

3.4. Determinant of CAVI from multiple linear regression

In multivariate regression analyses among all study participants with all parameters forced into the models, CAVI was significantly associated with increased age, systolic BP, and cART-treated HIV patients compared to non-HIV controls and smokers compared to non-smokers while CAVI decreased with increasing BMI. In non-HIV controls, CAVI was associated with increasing age and systolic BP, as well as decreasing BMI. In cART-naïve HIV patients, CAVI was associated with an increase in age and systolic BP while CAVI decreased with an increase in body height, BMI, and CD4+ cell count. In cART-treated HIV patients, CAVI was associated with increased age and systolic BP, and decreased body height, BMI, triglycerides, and CD4 cell count. CAVI decreased in patients on the TDF-based regimen compared to the AZT-based regimen (Table 3).

Association between CAVI and cardiometabolic abnormalities

Table 3. CAVI Determinants from multivariate linear regression analyses in various Study Groups.

	All participants			Non-HIV controls			cART-naïve HIV patients			cART-treated HIV patients		
	B±SE	β	p	B±SE	β	p	B±SE	β	p	B±SE	β	p
HIV status (Reference: Non-HIV participants)												
cART-naïve	−0.09 ± 0.11	−0.06	0.409									
cART-treated	0.23 ± 0.12	0.167	0.039									
Age	0.06 ± 0.01	0.64	<0.001	0.05 ± 0.01	0.7	<0.001	0.05 ± 0.01	0.41	<0.001	0.07 ± 0.01	0.55	<0.001
Female gender	0.04 ± 0.12	0.03	0.767	0.01 ± 0.22	0.01	0.975	0.09 ± 0.18	0.07	0.617	0.31 ± 0.33	0.22	0.364
Alcohol usage	0.18 ± 0.11	0.13	0.08	0.18 ± 0.14	0.17	0.194	0.17 ± 0.18	0.13	0.345	0.3 ± 0.3	0.21	0.33
Current smoking	0.48 ± 0.23	0.35	0.039	−0.45 ± 0.49	−0.41	0.367	0.77 ± 0.41	0.57	0.061	0.57 ± 0.53	0.41	0.288
Systolic BP	0.02 ± 0.01	0.22	<0.001	0.02 ± 0.01	0.23	0.004	0.01 ± 0.01	0.15	0.01	0.01 ± 0.01	0.23	0.042
Body height	−0.01 ± 0.01	−0.07	0.071	−0.01 ± 0.01	−0.06	0.526	−0.05 ± 0.01	−0.25	<0.001	0.01 ± 0.02	0.07	0.502
BMI	−0.1 ± 0.01	−0.39	<0.001	−0.09 ± 0.02	−0.41	<0.001	−0.08 ± 0.02	−0.27	<0.001	−0.1 ± 0.02	−0.44	<0.01
Total cholesterol	0.05 ± 0.05	0.04	0.361	0.13 ± 0.07	0.14	0.098	−0.11 ± 0.08	−0.09	0.193	0.26 ± 0.16	0.21	0.113
Triglycerides	−0.16 ± 0.16	−0.04	0.324	−0.43 ± 0.27	−0.12	0.111	0.22 ± 0.24	0.06	0.367	−0.96 ± 0.44	−0.26	0.034
FPG	−0.03 ± 0.05	−0.01	0.819	0.03 ± 0.07	0.02	0.714	−0.13 ± 0.1	−0.07	0.196	−0.09 ± 0.18	−0.05	0.631
$\sqrt[3]{\text{CD4count}}$							−0.58 ± 0.09	−0.41	<0.001	−0.23 ± 0.12	−0.23	0.047
cART regimen (Reference: AZT/3TC/NVP or EFV)												
TDF/3TC/NVP or EFV										−0.64 ± 0.28	−0.46	0.023
LPV/r-based										0.32 ± 0.42	0.23	0.45

Note: BMI, body mass index; BP, blood pressure; FPG, fasting blood glucose; cART, combination antiretroviral therapy; AZT, zidovudine; 3TC, Lamivudine; TDF, tenofovir; NVP, nevirapine; EVF, efavirenz; LVP/r, Lopinavir/ritonavir. All parameters were forced into the linear regression model.

The association between CAVI and cardiometabolic abnormalities were examined using logistic regression analyses. In all participants, a unit change in CAVI was associated with increased odds of impaired fasting glucose, high systolic BP, high triglycerides, and MetS in the unadjusted model. After adjustments, high systolic BP and MetS remained associated with CAVI. In non-HIV controls, a unit change in CAVI was associated with increased odds of MetS in unadjusted and adjusted models. In cART-naïve HIV patients, CAVI was associated with high systolic BP, high triglycerides and MetS in unadjusted and adjusted models. In cART-treated HIV patients, only high systolic BP was associated with CAVI in unadjusted and adjusted models (Table 4).

4. Discussion

The main findings from this study are: CAVI increased in cART-treated HIV patients compared to cART-naïve HIV patients and non-HIV controls. In study participants, regardless of HIV or cART status, CAVI was associated with increased age and systolic BP, as well as decreased BMI. CAVI was associated with metabolic syndrome in non-HIV controls and cART-naïve HIV patients, but not in cART-treated HIV patients. In cART-treated HIV patients, the TDF-based regimen was associated with decreased CAVI and decreased CD4+ cell count was associated with increased CAVI.

In this study, we found that CAVI increases in HIV patients treated with cART, but is similar among cART-naïve HIV patients and non-HIV controls. CAVI is a sensitive marker of arterial stiffness and several studies have shown that it predicts CVD in patients and the general population [9,10]. From our literature search, we found just two studies that reported CAVI in HIV patients. These studies were carried out in the Thai population and reported no differences in CAVI between HIV patients and non-HIV controls [15,16], which contrasts with what we observed in our study population. Previous studies conducted in the sub-Saharan African population have reported arterial stiffness in HIV patients using PWV. Similar to the findings of our study, Msoka et al. reported higher levels of arterial stiffness, measured as aortic PWV, in Tanzanian HIV patients compared to controls [22]. A similar finding of elevated arterial stiffness was reported in Cameroonian HIV patients using carotid-femoral PWV [14]. In contrast to our findings, studies conducted in South Africa [4,11], Cameroon [23] and Ethiopia [12] reported similar levels of arterial stiffness between HIV patients and non-HIV controls. Recent metanalysis reported that arterial stiffness measured as carotid-femoral PWV is increased in

Table 4. Association between CAVI and metabolic abnormalities from logistics regression models.

	Unadjusted model		Multivariable adjusted model	
	OR (95% CI)	p	OR (95% CI)	p
All study participants				
Impaired fasting glucose	1.24 (1.08–1.42)	0.002	1.09 (0.89–1.34)	0.393
High systolic BP	1.46 (1.26–1.69)	<0.001	1.69 (1.33–2.15)	<0.001
Abdominal obesity	1.1 (0.96–1.25)	0.117	1.06 (0.75–1.51)	0.749
Low HDL	1.01 (0.88–1.17)	0.846	1.14 (0.92–1.41)	0.221
High triglycerides	1.25 (1.08–1.44)	0.002	1.18 (0.92–1.51)	0.19
Metabolic syndrome	1.27 (1.11–1.46)	<0.001	1.19 (1.09–1.53)	0.013
Non-HIV controls				
Impaired fasting glucose	1.02 (0.74–1.39)	0.923	1.34 (0.75–2.38)	0.326
High systolic BP	1.85 (1.3–2.61)	<0.001	1.62 (0.76–3.47)	0.214
Abdominal obesity	1.01 (0.75–1.36)	0.95	0.68 (0.22–2.13)	0.51
Low HDL	0.81 (0.56–1.16)	0.254	1.62 (0.85–3.07)	0.142
High triglycerides	0.9 (0.61–1.33)	0.604	0.7 (0.34–1.45)	0.334
Metabolic syndrome	1.19 (1.07–1.56)	0.022	2.14 (1.04–4.4)	0.039
cART-naïve HIV patients				
Impaired fasting glucose	1.44 (1.11–1.85)	0.005	1.33 (0.88–2)	0.176
High systolic BP	1.61 (1.23–2.12)	<0.001	1.84 (1.24–2.72)	0.002
Abdominal obesity	1.04 (0.83–1.31)	0.721	1.75 (0.97–3.15)	0.063
Low HDL	0.88 (0.68–1.15)	0.354	0.91 (0.59–1.39)	0.656
High triglycerides	1.22 (1.09–1.62)	0.016	1.45 (1.12–2.54)	0.029
Metabolic syndrome	1.26 (1.07–1.63)	0.031	1.47 (1.21–2.38)	0.015
cART-treated HIV patients				
Impaired fasting glucose	0.87 (0.69–1.1)	0.248	1.15 (0.76–1.76)	0.503
High systolic BP	1.36 (1.06–1.73)	0.014	1.51 (1.01–2.24)	0.044
Abdominal obesity	0.91 (0.71–1.16)	0.451	0.52 (0.26–1.07)	0.075
Low HDL	0.99 (0.79–1.25)	0.924	1.05 (0.69–1.59)	0.826
High triglycerides	0.96 (0.77–1.21)	0.751	1.06 (0.7–1.6)	0.791
Metabolic syndrome	0.84 (0.66–1.06)	0.143	0.81 (0.52–1.26)	0.353

Note: IFG, impaired fasting glucose; BP, blood pressure; HDL, high-density lipoprotein cholesterol; cART, combination antiretroviral therapy.

The multivariable models were adjusted for sex, age, BMI, alcohol intake, smoking status, educational level, marital status, employment status, CD4 cell count (only in cART-naïve and cART-exposed HIV patients) and cART regimen (only in cART-exposed patients). The duration of HIV infection and cART management were excluded from the model due to their low tolerance and high valence inflation factor in model diagnostics.

cART-treated HIV patients compared to cART-naïve HIV patients and non-HIV controls [2], confirming the findings of our study.

In this study, we found that age and systolic BP increase CAVI regardless of HIV or cART status. The influence of age on CAVI is similar to what had been reported in previous studies of patients and healthy populations [7,24]. Ageing is associated with several mechanisms that might have resulted in increased arterial stiffness, such as fatigue and fracture after long-standing arterial pulsation in the central arteries [25], increased arterial calcification and endothelial dysfunction [25,26], and accumulation of advanced glycated end-products in vascular matrix proteins [26]. We also found that total plasma cholesterol and LDL cholesterol correlated with CAVI in non-HIV controls but not in HIV patients. This is in agreement with the findings of a study by Soska et al. that reported a weak relationship between CAVI and total cholesterol and LDL in non-HIV participants [27]. HIV infection and the use of cART likely affect lipid metabolism, resulting in inflammation, and this may blunt the relationship between arterial stiffness and plasma cholesterol. However, previous studies in the Ghanaian diabetic population failed to find any association between parameters of lipid profile and CAVI because most diabetic patients were on lipid-lowering treatment [24,28].

We also found that the presence of MetS was associated with higher CAVI in non-HIV controls and cART-naïve HIV patients, but not in cART-treated HIV patients. This contrast to the findings of Msoka et al who reported that arterial stiffness was similar in non-HIV controls and cART-naïve HIV patients with and without MetS, but higher in cART-treated HIV patients with MetS [22]. The contradiction between our findings and that of Msoka et al may be attributed to the different methods used to assess arterial stiffness and the heterogeneity of the populations studied; we did not use the strict hepatic, renal and haematological screening protocol employed in the Msoka et al study and we also included HIV patients irrespective of their CD4+ cell count. The findings of our study imply that in non-HIV controls and cART-naïve HIV patients, the presence of metabolic abnormalities may partially explain the increased arterial stiffness as reported in the Caucasian population [29,30].

In this study, obese individuals had lower CAVI compared to those with normal BMI, and BMI was negatively associated with CAVI in regression analysis. Similar findings were reported in HIV patients in South Africa, where low BMI was associated with increased arterial stiffness measured as carotid-femoral PWV [13]. This observation may be explained by the phenomenon of 'return to health' which describes desirable weight gain after the resolution of a debilitating catabolic illness such as HIV infection that restores body fat and protein stores [31]. Previous studies reported that early initiation of cART medication prevented the cachectic and wasted state that characterised HIV infection, resulting in suppression of viral replication, a significant reduction in inflammation, and normalisation of CD4+ cell count [32]. This is likewise supported by what we observed in this study that HIV patients with low CD4+ cell count had higher CAVI compared to those with normal levels. Therefore, there is the possibility that weight gain and high BMI may represent improved cardiovascular health in HIV patients. However, we also observed a lower CAVI in non-HIV obese controls, which implies that further studies are needed to investigate the relationship between BMI and arterial stiffness in Africans.

Multivariate analysis in cART-treated HIV patients showed that the TDF-based regimen was associated with a decrease in CAVI compared to those on the AZT-based regimen. The AZT-based regimen has been shown to cause oxidative damage, a major mechanistic pathway of arterial stiffness, through the induction of mitochondrial dysfunction by inhibition of DNA polymerase-γ activity [33]. Furthermore, a metabolic study showed that the pathway through which the AZT-based regimen leads to oxidative stress is by altering the metabolism of glutamine and glutamate, glutathione, arginine biosynthesis, as well as the metabolism of alanine, aspartate and glutamate [34]. Interestingly, it has been demonstrated in a meta-analysis that the TDF-based regimen has better viral suppression tolerability compared to the AZT-based regimen [35,36], making it suitable for treatment in HIV patients.

4.1. Limitations of the study

The uniqueness of this study is that it is the first to report on CAVI in sub-Saharan HIV population. The limitation of this study is that it was carried out in a single healthcare facility and therefore the levels of arterial stiffness measured as CAVI cannot be generalised to the entire Ghanaian HIV population. CAVI was measured at one time, and therefore we cannot infer causality between HIV infection and CAVI; some HIV patients may have increased arterial stiffness from other causes before HIV infection. The sample size was not large enough for us to make a definite conclusion about the effect of various cART regimens in CAVI. It is recommended that future studies use a multicentre longitudinal design to investigate the development of arterial stiffness and the effect of cART medication in a large number of patients to confirm or refute the findings of the study. Furthermore, other arterial stiffness indices can be used to compare their agreement with CAVI as a marker of arterial stiffness in the Ghanaian HIV population.

5. Conclusion

In a periurban hospital in Ghana, compared to non-HIV controls or cART-nave HIV patients, cART-treated HIV patients had increased arterial stiffness measured as CAVI. CAVI is associated with metabolic abnormalities in non-HIV controls and cART-naïve HIV patients, but not in cART-treated HIV patients. CAVI increased with increasing age and systolic BP, as well as decreasing BMI. Patients on a TDF-based regimen had decreased CAVI compared to those on an AZT-based regimen. Multicentre longitudinal studies should be conducted to investigate the impact of HIV infection and various cART regimen on arterial stiffness and cardiovascular end-organ damage in HIV patients in sub-Saharan Africa.

Abbreviations

BMI	body mass index
BP	blood pressure
Cart	combination antiretroviral therapy
CAVI	cardio-ankle vascular index
CVD	cardiovascular diseases
FPG	fasting blood glucose
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
LDL	low-density lipoprotein
MetS	metabolic syndrome
PWV	pulse wave velocity

Acknowledgments

We thank all the participants in the HIV clinics at Atua Government Hospital who voluntarily participated in this study. We thank community health volunteers and healthcare providers at HIV clinics for their overwhelming support during the study. Our heartfelt thanks go to Mrs Nneka Essel for her assistance.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

There was no funding for this study.

Authors' contributions

KY conceptualized the study, analysed the data and drafted the manuscript. SE collected the data and revised the manuscript. JAA analyzed the data and made scientific contributions to the manuscript. BD reviewed the manuscript and made scientific contributions to the manuscript. All authors approved the content of the manuscript.

Availability of data

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

ORCID

Kwame Yeboah http://orcid.org/0000-0001-5240-0645
Jennifer Agyekum http://orcid.org/0000-0003-0051-985X
Bartholomew Dzudzor http://orcid.org/0000-0003-2325-7063

References

[1] Joint United Nations Programme on HIV/AIDS. Global HIV & AIDS statistics — Fact sheet. Geneva, Switzerland: UNAIDS; 2021 [cited 2023 January 10]. Available from: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf
[2] Defo AK, Chalati MD, Labos C, et al. Association of HIV infection and antiretroviral therapy with arterial stiffness: a systematic review and meta-analysis. Hypertension. 2021;78(2):320–332.
[3] Bijker R, Jiamsakul A, Uy E, et al. Cardiovascular disease-related mortality and factors associated with cardiovascular events in the TREAT Asia HIV Observational Database (TAHOD). HIV Med. 2019;20 (3):183–191. DOI:10.1111/hiv.12687
[4] Fourie CMT, Schutte AE, Smith W, et al. Endothelial activation and cardiometabolic profiles of treated and never-treated HIV infected Africans. Atherosclerosis. 2015;240(1):154–160.
[5] Kim ED, Ballew SH, Tanaka H, et al. Short-term prognostic impact of arterial stiffness in older adults without prevalent cardiovascular disease. Hypertension. 2019;74(6):1373–1382.
[6] Shirai K, Utino J, Otsuka K, et al. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). J Atheroscler Thromb. 2006;13(2):101–107.
[7] Shirai K, Suzuki K, Tsuda S, et al. Comparison of cardio–ankle vascular index (CAVI) and CAVI0 in large healthy and hypertensive populations. J Atheroscler Thromb. 2019;26(7):603–615.
[8] Aiumtrakul N, Supasyndh O, Krittayaphong R, et al. Cardio-ankle vascular index with renal progression and mortality in high atherosclerosis risk: a prospective cohort study in CORE-Thailand. Clin Exp Nephrol. 2022;26(3):247–256.
[9] Satoh-Asahara N, Kotani K, Yamakage H, et al. Cardio-ankle vascular index predicts for the incidence of cardiovascular events in obese patients: a multicenter prospective cohort study (Japan Obesity and Metabolic Syndrome Study: jOMS). Atherosclerosis. 2015;242(2):461–468.
[10] Murakami K, Inayama E, Itoh Y, et al. The role of cardio-ankle vascular index as a predictor of mortality in patients on maintenance hemodialysis. Vasc Health Risk Manag. 2021;17:791–798.
[11] Botha S, Fourie CMT, van Rooyen JM, et al. Cardiometabolic changes in treated versus never treated HIV-Infected black South Africans: the PURE study. Heart Lung & Circulation. 2014;23 (2):119–126.
[12] Gleason RL Jr., Caulk AW, Seifu D, et al. Current Efavirenz (EFV) or Ritonavir-Boosted Lopinavir (LPV/r) use correlates with elevate markers of atherosclerosis

in HIV-Infected subjects in Addis Ababa, Ethiopia. PLoS ONE. 2015;10(4):e0117125.
[13] Huisman HW, Schutte R, Venter HL, et al. Low BMI is inversely associated with arterial stiffness in Africans. British Journal Of Nutrition. 2015;113(10):1621–1627.
[14] Lemogoum D, Ngatchou W, Borne PVD, et al. Cardiometabolic phenotype and arterial stiffness in HIV-Positive black African Patients. Open J Prev Med. 2014;04(04):11. DOI:10.4236/ojpm.2014.44024
[15] Aurpibul L, Srithanaviboonchai K, Rerkasem K, et al. Prevalence of subclinical atherosclerosis and risk of atherosclerotic cardiovascular disease in older adults living with HIV. AIDS Res Human Retroviruses. 2019;35 (11–12):1136–1142.
[16] Jewpakanon T, Satitthummanid S, Songmuang SB. Subclinical left ventricular dysfunction virologically supressed HIV-infected patients receiving antiretroviral therapy. J Am Coll Cardiol. 2022;79(9_Supplement):1348.
[17] Schutte AE, Kruger R, Gafane-Matemane LF, et al. Ethnicity and arterial stiffness. Arteriosclerosis Thrombosis Vasc Biol. 2020;40(5):1044–1054.
[18] Alberti KG, Eckel RH, Grundy SM, et al. 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.
[19] Sun C-K. Cardio-ankle vascular index (CAVI) as an indicator of arterial stiffness. Integr Blood Press Control. 2013;6:27.
[20] Shirai K, Utino J, Saiki A, et al. Evaluation of blood pressure control using a new arterial stiffness parameter, Cardio-ankle Vascular Index (CAVI). Curr Hypertens Rev. 2013;9(1):66–75.
[21] Yeboah K, Musah L, Essel S, et al. P98 impaired pulmonary function is associated with increased cardio-ankle vascular index in HIV patients in Ghana. Artery Research. 2020;25(Supplement 1):S139.
[22] Msoka TF, Van Guilder GP, Smulders YM, et al. Antiretroviral treatment and time since HIV-1 diagnosis are associated with large artery stiffness in sub-Saharan African HIV-1 patients. Artery Research. 2016;16:34–41.
[23] Ngatchou W, Lemogoum D, Ndobo P, et al. Effects of antiretroviral therapy on arterial stiffness in Cameroonian HIV-infected patients. Blood Press Monit. 2013;18 (5):247–251. DOI:10.1097/MBP.0b013e328363ee43
[24] Yeboah K, Antwi DA, Gyan B, et al. Arterial stiffness in hypertensive and type 2 diabetes patients in Ghana: comparison of the cardio-ankle vascular index and central aortic techniques. BMC Endocr Disord. 2016;16 (1):53.
[25] Atkinson J. Age-related medial elastocalcinosis in arteries: mechanisms, animal models, and physiological consequences. J Appl Physiol. 2008;105(5):1643–1651.
[26] Lee H-Y, Oh B-H. Aging and arterial stiffness. Circ J. 2010;74(11):2257–2262.
[27] Soska V, Dobsak P, Dusek L, et al. Cardio-ankle vascular index in heterozygous familial hypercholesterolemia. J Atheroscler Thromb. 2012;19(5):453–461.
[28] Yeboah K, Antwi DA, Gyan B. Arterial stiffness in non-hypertensive type 2 diabetes patients in Ghana. Int J Endocrinol. 2016;2016:6107572.
[29] Schillaci G, Socio GVLD, Pucci G, et al.: Aortic stiffness in untreated adult patients with human immunodeficiency virus infection. Hypertension 2008, 52 (2):308–313.
[30] Gomez-Sanchez L, Garcia-Ortiz L, Patino-Alonso MC, et al. Association of metabolic syndrome and its components with arterial stiffness in Caucasian subjects of the MARK study: a cross-sectional trial. Cardiovasc Diabetol. 2016;15(1):148.
[31] Kumar S, Samaras K. The impact of weight gain during HIV treatment on risk of pre-diabetes, diabetes mellitus, cardiovascular disease, and mortality. Front Endocrinol (Lausanne). 2018;9:9.
[32] Tate T, Willig AL, Willig JH, et al. HIV infection and obesity: where did all the wasting go? Antivir Ther. 2012;17(7):1281–1289.
[33] Zhao D, Ding Y, Lin H, et al. Mitochondrial Haplogroups N9 and G are associated with metabolic syndrome among human immunodeficiency virus-infected patients in China. AIDS Res Human Retroviruses. 2019;35(6):536–543.
[34] Sitole L, Fortuin R, Tugizimana F. Metabolic profiling of HIV infected individuals on an AZT-based antiretroviral treatment regimen reveals persistent oxidative stress. J Pharm Biomed Anal. 2022;220:114986.
[35] Alzate Angel JC, Duque Molina MM, García García HI. Zidovudine/Lamivudine vs. Abacavir/Lamivudine vs. Tenofovir/Emtricitabine in fixed-dose combinations as initial treatment for HIV patients: a systematic review and network meta-analysis. Colombia Médica. 2017;48 (2):70–81.
[36] Dadi TL, Kefale AT, Mega TA, et al. Efficacy and tolerability of tenofovir disoproxil fumarate based regimen as compared to zidovudine based regimens: a systematic review and meta-analysis. AIDS Res Treat. 2017;2017:5792925.