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ORIGINAL RESEARCH

Increased burden and severity of metabolic syndrome and arterial stiffness in treatment-naïve HIV+ patients from Cameroon

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Background: Human immunodeficiency virus (HIV) and its therapy are associated with increased aortic stiffness and metabolic syndrome (MetS) phenotype in Caucasian patients. We hypothesized that, independently of antiretroviral therapy, HIV infection in native black African patients is associated with increased burden of cardiometabolic risk factors that may accelerate arterial structural damage and translate into increased aortic stiffness.

Patients and methods: Ninety-six apparently healthy Cameroonian subjects (controls) were compared to 108 untreated Cameroonian HIV+ patients (HIV-UT) of similar age. In each participant, pulse wave velocity (Complior), aortic augmentation index (SphygmoCor), brachial blood pressure (Omron 705 IT), fasting plasma glucose (FPG), and lipids were recorded, as well as the prevalence and severity of MetS, based on the American Heart Association/National Heart, Lung, and Blood Institute score ≥3/5.

Results: Prevalence of impaired fasting glucose (FPG 100–125 mg·dL^{-1}) and of diabetes (FPG > 125 mg·dL^{-1}) was higher in HIV-UT than in controls (47% versus 27%, and 26% versus 1%, respectively; both $P < 0.01$). Fasting triglycerides and the atherogenic dyslipidemia ratio were significantly higher in HIV-UT than in controls. Hypertension prevalence was high and comparable in both groups (41% versus 44%, respectively; not significant). HIV-UT patients exhibited a twice-higher prevalence of MetS than controls (47% versus 21%; $P = 0.02$). Age- and sex-adjusted pulse wave velocity was higher in HIV-UT than in controls (7.5 ± 2.2 m/s versus 6.9 ± 1.7 m/s, respectively; $P = 0.02$), whereas aortic augmentation index was significantly lower (6% ± 4% versus 8% ± 7%, respectively; $P = 0.01$).

Conclusion: Similar to Caucasian populations, native Cameroonian HIV-UT patients showed a higher prevalence of MetS and its phenotype, associated with increased aortic stiffness, an early marker of atherosclerosis.

Keywords: metabolic syndrome, HIV, arterial, stiffness, Cameroon

Introduction

Human immunodeficiency virus (HIV) infection and its therapy are associated with an increased risk of cardiovascular diseases (CVDs).[1,2] The underlying pathophysiology has not yet been fully elucidated, but the virus appears to contribute directly to the accelerated development of arteriosclerosis.[3] It may do this by increasing systemic inflammation, hypercoagulation, and platelet activation, leading to endothelial dysfunction.[3–5] Independently of treatment, HIV infection has a direct effect on cholesterol and lipoproteins processing and transport, and may also increase cardiometabolic abnormalities, including visceral fat accumulation, diabetes, dyslipidemia, insulin resistance, and hypertension.[3,6–10] All these abnormalities are either individual components of the metabolic syndrome (MetS) phenotype or of its underlying pathophysiology, and may

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predispose to the development of atherosclerosis; whereas westernized, unhealthy lifestyles and obesity are causally related to the acquisition of a MetS phenotype.

Increased arterial stiffness, assessed by aortic pulse wave velocity (PWV), is a direct marker of atherosclerosis and an independent predictor of cardiovascular (CV) outcomes,[11] and PWV was reported to be more elevated in Caucasian untreated HIV-infected individuals than in healthy controls.[12] Augmentation index (Aix), a direct measure of wave reflection and an aortic stiffness surrogate, is known to be an independent predictor of cardiovascular outcomes.[13] Despite the prevalence of HIV infection, the highest being in sub-Saharan Africa,[14] the related cardiometabolic disorders and atherosclerosis risk has been poorly explored in native populations with HIV, as yet little exposed to westernized lifestyles. We therefore hypothesized that HIV infection in untreated black African patients, born and living in sub-Saharan Africa, is associated with increased burden of cardiometabolic risk factors that may accelerate arterial structural damage and translate into early-onset increased arterial stiffness.

Methods

The study design was cross-sectional and included 204 volunteer subjects aged >18 years (55 males/149 females) recruited from the HIV clinic of Yaoundé Central Hospital, Cameroon, between September 2009 and May 2010. Two groups were analyzed in parallel: a group of 96 apparently healthy subjects (controls) was compared to a group of 108 HIV-positive patients, untreated with antiretroviral drugs (HIV group), with similar mean age ± standard deviation (SD) (41 ± 12 years [controls] versus 39 ± 10 years [HIV]). Patients were included who had serologically documented HIV infection; and controls were apparently healthy subjects with recently documented (within the past year) seronegative status for HIV. Exclusion criteria for the two groups included: previously documented hypertension, diabetes, dyslipidemia; a history of cigarette smoking or regular alcohol consumption; current use of antidiabetics, antihypertensives, lipid-lowering drugs, or any others CV drugs; first-degree familial history of diabetes or early-onset coronary heart disease; and history of antiretroviral therapy (ART). Each volunteer provided a signed, informed consent, and the study was approved by the Institutional Review Board of the Yaoundé Central Hospital and Cameroonian Ministry of Public Health.

For each study participant, sociodemographic and clinical variables were recorded, including age, sex, and duration since HIV diagnosis (as a surrogate for HIV infection duration). All participants underwent a physical examination by a single operator who measured the following parameters: weight, height, body mass index (BMI), waist circumference (as proxy for visceral fat), hip circumference, waist-to-height ratio, and conicity index ([waist circumference {m}/0.109] √[weight {kg}/height {m}]), the latter two being validated surrogates for central adiposity distribution. (Reference values for conicity index, from lean controls [n = 79] with normal glucose tolerance [NGT]: 1.22 ± 0.09 m^2/kg [mean ± SD]; 1.16–1.26 m^2/kg [interquartile range] and 1.03–1.43 m^2/kg [range]). Hypertension prevalence was defined as systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg.[15] The presence of a MetS was defined by a score ≥3/5 for the following items: (1) impaired fasting glucose or diabetes; (2) hypertension; (3) enlarged waist; (4) elevated fasting triglycerides (TGs); (5) decreased high-density lipoprotein cholesterol (HDL-C) (according to 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 harmonized definition), with the mean MetS score used as a surrogate for whole-body insulin resistance.[16]

Biochemical parameters

In all participants, a venous blood sample was collected after an overnight fast to measure the concentration of the following biochemical variables: fasting plasma glucose (FPG), lipids (total cholesterol [C], HDL-C, TGs, LDL-C [low-density lipoprotein C; computed from Friedewald's formula]), and non-HDL-C (by subtracting HDL-C from total C). NGT, impaired fasting glucose, and diabetes were defined as FPG <100 $mg \cdot dL^{-1}$, 100–125 $mg \cdot dL^{-1}$, and >125 $mg \cdot dL^{-1}$, respectively. The prevalence of atherogenic dyslipidemia was defined as the combination of low HDL-C (<40 $mg \cdot dL^{-1}$ [males] and <50 $mg \cdot dL^{-1}$ [females]) plus high fasting TGs (≥150 $mg \cdot dL^{-1}$), whereas atherogenic dyslipidemia severity, as a continuous variable, was determined by the log(TGs)/HDL-C ratio (normal values for the latter, obtained from 79 lean healthy subjects without familial histories for diabetes or early-onset cardiovascular disease: 0.036 [mean]; 0.012 [SD]; 0.014 [minimum]; 0.067 [maximum]).[17] Urinary Na^+ and urinary K^+ were determined from a spot urine sample. CD_4^+ cell counts (most recent value and nadir whenever possible) were recorded. All samples were analyzed at the central biochemical laboratory of ULB-Erasme Hospital, Brussels, Belgium.

Hemodynamic measurements

To ensure a steady state, all hemodynamic measurements were performed in the morning after 15 minutes of supine rest in a quiet room. All participants were instructed to abstain from strong physical effort and from drinking caffeine, tea, or any alcoholic beverage for at least 2 hours before hemodynamic measurements. All measurements were performed by the same investigator in triplicate and averaged for analysis.

Brachial BPs and heart rate

Brachial systolic and diastolic BP and heart rate (HR) were recorded at the right arm with appropriate cuff size with the use of an automated sphygmomanometer (HEM-705 CP; Omron Corporation, Tokyo, Japan). Pulse pressure was calculated as systolic minus diastolic BP, and mean arterial pressure as diastolic BP plus one-third of pulse pressure value. All values were obtained from brachial measurements.

Carotid-femoral PWV

Carotid-femoral PWV was measured by the same investigator (DL) using sequential recordings of the arterial pressure waveform at the carotid and femoral arteries, with the use of a validated[18] noninvasive device (Complior; Artech Medical, Pantin, France), which performs pressure wave recordings and automatically calculates PWV. The distance was defined as the distance from the suprasternal notch to femoral artery minus distance from carotid artery to the suprasternal notch. Pulse transit time was averaged over 10 consecutive beats. PWV corresponds to the ratio of the distance (meters) to the transit time (seconds). Intraobserver coefficient of variation for PWV for the same investigator (DL) was previously reported.[19]

Aortic augmentation index corrected for HR and BP

Aortic augmentation index corrected for HR (Aix), BP, and transit time was obtained from noninvasive pulse wave analysis by means of radial applanation tonometry calibrated by the brachial BP (SphygmoCor version 6.1 software; AtCor Medical Pty Ltd, West Ryde, NSW, Australia), as described previously.[19] The reproducibility of derived Aix has been validated previously.[20] In our hands (DL), the mean ± SD intraobserver within-session coefficient of variation for derived Aix measures using SphygmoCor was 7.1 ± 8.6 (n = 30).

Statistical methods

Data are presented as mean (± SD) or as proportion (%). The significance of differences between means was assessed by Student's *t*-test or alternately by Welch's *t*-test for data sets with significant differences in SD, and by Fisher's exact test for differences in proportions, with TG values log-transformed prior to statistical analysis. A multiple regression analysis was performed to assess the independent determinant of the PWV and Aix. All relevant variables that correlated with PWV and Aix at $P < 0.01$ were included in that model. Results were considered significant at $P < 0.05$.

Results

Patient characteristics

Sex distribution was not statistically different between control subjects and HIV patients. Men and women represented 28% (n = 27) and 72% (n = 69) of the control group and 26% (n = 28) and 74% (n = 80) of the HIV group, respectively. Mean duration since HIV diagnosis was 19.3 (28.4) months. Height was comparable between groups, whereas weight was lower by an absolute mean of 10.5 kg in HIV ($P < 0.01$) compared with the controls, to such an extent that BMI was markedly lower in HIV patients than in controls ($P = 0.02$). Waist circumference was smaller by an average 9 cm in HIV patients than in controls ($P < 0.01$). Conicity index was comparable between groups, whereas the waist-to-height ratio, another surrogate for central adiposity, was lower in HIV patients ($P < 0.01$) (Table 1).

Table 2 describes the cardiometabolic phenotype of the two study groups. Based on FPG, the proportion of participants with NGT was higher in controls than in HIV patients ($P < 0.01$), whereas the prevalence of impaired fasting glucose and diabetes was markedly increased in HIV (both $P < 0.05$). Atherogenic dyslipidemia prevalence

Table 1 Patients' characteristics

	Controls	HIV	*P*-value
n	96	108	
Age (years)	41 ± 12	39 ± 11	0.21
Sex (%) (male, female)	28, 72	26, 74	0.75
Weight (kg)	75.3 ±15.4	64.8 ± 13.4	<0.01
Height (m)	1.64 ± 0.09	1.63 ± 0.10	0.45
BMI (kg/m^2)	28.1 ± 5.9	25.1 ± 12.1	0.02
BMI < 27.5 kg/m^2 (%)	51	79	<0.01
Waist circumference (cm)	90 ± 13	81 ± 10	<0.01
Hip circumference (cm)	112 ± 26	106 ± 25	0.09
Waist-to-hip ratio	0.84 ± 0.22	0.80 ± 0.19	0.16
Conicity index (m^2/kg)	1.24 ± 0.24	1.20 ± 0.18	0.17
Waist-to-height ratio	0.55 ± 0.09	0.50 ± 0.08	<0.01

Note: Data are mean ± SD or proportions (%).
Abbreviations: HIV, untreated patients with human immunodeficiency virus; n, number; BMI, body mass index; SD, standard deviation.

Table 2 Cardiometabolic phenotype

	Controls	HIV	*P*-value
MetS (%)	21	47	0.02
MetS score (0/5 to 5/5)	1.7 ± 1.0	2.3 ± 1.1	<0.01
Hyperglycemia	0.41	0.81	<0.01
Enlarged waist	0.43	0.20	<0.01
Elevated triglycerides	0.07	0.14	0.17
Low HDL-C	0.45	0.75	<0.01
High blood pressure	0.34	0.40	0.46
Normal fasting glucose (%)	72	27	<0.01
Impaired fasting glucose (%)	27	47	0.05
Diabetes (%)	1	26	<0.01

Note: Data are mean (SD) or proportions (%), or scores (0/5 to 5/5 for MetS score, and 0/5 to 1/5 for the five individual components of the MetS).
Abbreviations: HIV, untreated patients with human immunodeficiency virus; MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation.

was lower in controls than in HIV patients ($P = 0.03$). HIV patients exhibited a higher prevalence of MetS than controls ($P = 0.02$).

Laboratory values

Mean FPG was markedly higher in HIV than in controls ($P < 0.01$). Total cholesterol (C) was lower in HIV ($P = 0.01$), whereas LDL-C and non-HDL-C were comparable between groups. HDL-C was significantly lower, by an absolute mean of 7 $mg \cdot dL^{-1}$ in HIV ($P < 0.01$). The atherogenic ratios (total C/HDL-C) and (non-HDL-C/HDL-C), atherogenic dyslipidemia ratio (log[TGs]/HDL-C), and fasting TGs were significantly higher in HIV (all $P < 0.05$). Urinary Na^+ excretion was lower in HIV than in controls ($P < 0.01$), whereas urinary K^+ did not differ between groups (Table 3).

Table 3 Laboratory values

	Controls	HIV	*P*-value
Fasting plasma glucose ($mmol \cdot L^{-1}$)	5.2 ± 0.9	6.8 ± 3.2	<0.01
Total cholesterol ($mg \cdot dL^{-1}$)	167 ± 43	151 ± 47	0.01
LDL-C ($mg \cdot dL^{-1}$)	103 ± 34	96 ± 39	0.17
Non-HDL-C ($mg \cdot dL^{-1}$)	118 ± 39	117 ± 39	0.85
HDL-C ($mg \cdot dL^{-1}$)	49 ± 17	34 ± 17	<0.01
Total-C · HDL-C^{-1}	4.11 ± 2.95	6.71 ± 6.98	<0.01
Non-HDL-C · HDL-C^{-1}	3.06 ± 2.96	5.71 ± 6.98	<0.01
TGs ($mg \cdot dL^{-1}$)	67 ± 35	155 ± 432	0.03
Log(TGs) ($mg \cdot dL^{-1}$)	1.78 ± 0.19	1.94 ± 0.33	<0.01
TGs <150 $mg \cdot dL^{-1}$ (%)	94	87	0.15
Log(TGs) · HDL-C^{-1}	0.048 ± 0.044	0.114 ± 0.169	0.02
Atherogenic dyslipidemia (%)	3	11	0.03
CD_4^+ lymphocytes ($\times 10^6 \cdot L^{-1}$)	~	353 ± 215	~
Urinary Na^+ ($mmol \cdot L^{-1}$)	116 ± 59	91 ± 52	<0.01
Urinary K^+ ($mmol \cdot L^{-1}$)	74 ± 32	67 ± 33	0.12

Note: Data are mean (SD) or proportions (%).
Abbreviations: HIV, untreated patients with human immunodeficiency virus; C, cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TGs, triglycerides; Na^+, sodium; K^+, potassium; SD, standard deviation.

Hemodynamic parameters

The prevalence of hypertension was high and comparable in both groups, despite the exclusion in the control group of participants with a known history of hypertension. Brachial, central, and mean arterial BP were significantly higher in the control group (all $P < 0.01$). Heart rate was faster, by an absolute mean of 10 beats per minute (bpm), in HIV patients compared to controls ($P < 0.01$). Age- and sex-adjusted PWV was faster in HIV patients than in controls ($P = 0.02$), indicating increased arterial stiffness and predicting atherosclerosis risk in HIV patients (Table 4). There were no significant differences in mean arterial pressure, central systolic blood pressure (SBP), central diastolic blood pressure (DBP), central pulse pressure, PWV, or central pressure index between patients with shorter versus longer known duration of HIV infection.

Determinants of PWV and Aix

The relations between Aix, PWV, and cardiovascular variable in the two groups are shown in Tables 5 and 6. Multiple regression analysis showed that LDL-C and age in the HIV group, and total cholesterol and fasting plasma glucose in the control group, were independent predictors of PWV (Table 7). Brachial SBP, brachial DBP, and age were independent predictors of Aix in the HIV group, explaining 80% of variability; whereas male sex, brachial SBP, brachial DBP, and BMI were negatively and independently associated with Aix in the control group, accounting for 86% of the changes in Aix (Table 8).

Discussion

This study explored for the first time the impact of HIV infection on MetS, its phenotype components, and the association

Table 4 Central and peripheral hemodynamics

	Controls	HIV	*P*-value
Brachial SBP (mmHg)	128 ± 24	117 ± 20	<0.01
Brachial DBP (mmHg)	83 ± 14	77 ± 13	<0.01
Heart rate (bpm)	68 ± 11	78 ± 13	<0.01
Mean arterial BP (mmHg)	98 ± 16	91 ± 15	<0.01
Central SBP (mmHg)	118 ± 24	107 ± 19	<0.01
Central DBP (mmHg)	84 ± 14	78 ± 13	<0.01
PWV ($m \cdot s^{-1}$)	6.9 ± 1.7	7.5 ± 2.2	0.02
Aix (%)	8 ± 7	6 ± 4	<0.01

Note: Data are mean (SD).
Abbreviations: HIV, untreated patients with human immunodeficiency virus; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute; BP, blood pressure; PWV, pulse wave velocity; Aix, augmentation index (corrected for heart rate); SD, standard deviation.

Table 5 Relation between the augmentation index, aortic pulse wave velocity, and cardiovascular variable in the control group

Variables	Aix		PWV	
	r	*P*-value	*r*	*P*-value
Age (years)	0.55	<0.01	0.06	0.55
Weight (kg)	0.179	0.08	–0.027	0.79
Height (m)	–0.382	<0.01	–0.043	0.68
BMI (kg/m^2)	0.42	<0.01	0.02	0.84
Waist circumference (cm)	0.040	0.70	–0.018	0.86
Brachial SBP (mmHg)	0.496	<0.01	0.024	0.81
Peripheral DBP (mmHg)	0.472	<0.01	0.053	0.61
Heart rate (bpm)	0.129	0.20	0.06	0.56
Total C (mg · dL^{-1})	0.026	0.8	0.38	0.02
TGs (mg · dL^{-1})	–0.11	0.93	0.167	0.20
LDL-C (mg · dL^{-1})	–0.39	0.76	0.353	0.06
HDL-C (mg · dL^{-1})	0.031	0.81	0.211	0.10
Fasting plasma glucose (mmol · l^{-1})	–0.012	0.911	0.009	0.94
Urinary Na^+ (mmol · L^{-1})	–0.54	0.65	–0.121	0.31
Urinary K^+ (mmol · L^{-1})	0.286	0.01	0.046	0.70
Aix (%)			0.78	0.45
PWV (m · s^{-1})	0.78	0.45		

Abbreviations: Aix, augmentation index corrected for heart rate; PWV, pulse wave velocity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; C, cholesterol; TGs, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Na^+, sodium; K^+, potassium.

with subclinical atherosclerosis among untreated black HIV+ natives living in sub-Saharan Africa. The major finding is that treatment-naïve Cameroonian HIV+ patients showed a high prevalence of MetS and related cardiometabolic abnormalities, together with increased arterial stiffness assessed by PWV.

Table 6 Relation between augmentation index, aortic pulse wave velocity, and cardiovascular variable in the HIV group

Variables	Aix		PWV	
	r	*P*-value	*r*	*P*-value
Age (years)	0.511	<0.01	0.107	0.29
Weight (kg)	0.160	0.09	–0.094	0.35
Height (m)	–0.192	0.05	–0.043	0.68
BMI (kg/m^2)	0.281	<0.01	0.02	0.84
Waist circumference (cm)	0.071	0.47	0.081	0.42
Brachial SBP (mmHg)	0.460	<0.01	0.053	0.60
Brachial DBP (mmHg)	0.281	<0.01	0.078	0.44
Heart rate (bpm)	–0.062	0.52	–0.114	0.26
Total C (mg · dL^{-1})	–0.047	0.64	0.179	0.09
TGs (mg · dL^{-1})	0.069	0.5	0.16	0.88
LDL-C (mg · dL^{-1})	–0.111	0.28	0.227	0.03
HDL-C (mg · dL^{-1})	–0.054	0.60	0.143	0.18
Fasting plasma glucose (mmol · L^{-1})	0.100	0.31	0.042	0.68
Urinary Na^+ (mmol · L^{-1})	–0.291	0.04	0.11	0.30
Urinary K^+ (mmol · L^{-1})	–0.228	0.02	0.076	0.48
Aix (%)			0.011	0.91
PWV (m · s^{-1})	0.011	0.91		

Abbreviations: Aix, augmentation index corrected for heart rate; PWV, pulse wave velocity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minutes; C, cholesterol; TGs, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Na^+, sodium; K^+, potassium.

Table 7 Determinants of aortic PWV in multiple regression model

	β	*P*-value
HIV group		
LDL-C	0.02 ± 0.05	<0.001
Age	0.067 ± 0.023	<0.0047
Controls group		
Total cholesterol	0.011 ± 0.005	0.0455
Fasting plasma glucose	0.025 ± 0.012	0.0414

Notes: HIV group-included variables: LDL-C and age ($R^2 = 0.16$; $P < 0.05$). Controls group-included variables: total cholesterol and fasting plasma glucose ($R^2 = 0.17$; $P < 0.05$).

Abbreviations: PWV, pulse wave velocity; HIV, human immunodeficiency virus; LDL-C: low-density lipoprotein cholesterol.

Only a handful of reports to date investigated HIV-induced abnormalities in blood hemodynamics in native black autochthonous Africans. Lazar et al studied arterial wave reflection in untreated HIV+ Rwandan women and did not observe increased arterial stiffness in comparison with HIV- controls.[21] Fourie et al reported an inflammatory injury pointing to endothelium dysfunction of never-treated HIV-1-infected South Africans of African ancestry, but did not assess its association with the MetS or its components.[22]

Numerous studies suggested an increase of the burden of hypertension in the general population of sub-Saharan Africa.[23,24] In the present study, the prevalence of hypertension was worryingly high, and comparable in the two groups. Fourie et al[22] and Mufunda et al[24] studied African untreated HIV patients and did not report increased BP compared with the general population, contrary to another report on HIV+ patients receiving ART.[25] High dietary salt intake contributes to a substantial component of the rise in BP with age[26] and is a major determinant of hypertension in black individuals.[27] In the present study, the lower mean BP observed in

Table 8 Determinants of Aix in multiple regression model

	β	*P*-value
HIV group		
Brachial SBP	–0.47 ± 0.04	<0.001
Brachial DBP	–1.32 ± 0.25	<0.001
Age	0.069 ± 0.01	<0.004
Controls group		
Male sex	–2.82 ± 0.72	<0.001
Brachial SBP	–0.50 ± 0.06	<0.001
Brachial DBP	–2.25 ± 0.45	0.001
BMI	–0.12 ± 0.059	0.03

Notes: HIV group-included variables: brachial SBP, brachial DBP, and age ($R^2 = 0.80$; $P < 0.05$). Controls group-included variables: male sex, brachial SBP, brachial DBP, and BMI ($R^2 = 0.86$; $P < 0.05$).

Abbreviations: Aix, augmentation index (corrected for heart rate); HIV, human immunodeficiency virus; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

treatment-naïve Cameroonian HIV+ individuals could partly arise from lower dietary salt intake, because urinary Na^+ excretion was significantly lower than that of controls.

Another original finding of the present study is the higher prevalence of dyslipidemia, with increased atherogenic ratios as well as atherogenic dyslipidemia, not previously documented in situ in untreated HIV+ black Africans. Atherogenic dyslipidemia increases CV risk even when LDL-C is not elevated or controlled with statins.[19] This finding may contribute to increased atherosclerosis risk in HIV+ patients, long before ART is implemented, especially when elevated fasting TGs coincide with low HDL-C levels,[28] as observed in this study.[29,30] Even though sub-Saharan Africans have spontaneously lower triglyceridemia, our data are consistent with previous observations of similar lipid patterns, albeit more marked, in Caucasian HIV+ patients.[9,12]

Impaired glucose tolerance and diabetes are major comorbidities of CVD.[31] Our study showed a higher prevalence of impaired fasting glucose in comparison with controls, at odds with previous studies in African treatment-naïve HIV patients.[22,24] In Caucasian HIV+ individuals, glucose homeostasis abnormalities were mostly ascribed to ART, especially when protease inhibitors were present.[32]

The MetS phenotype is closely related to insulin resistance and compensatory hyperinsulinemia. The presence of a MetS, especially when its score is high (4/5 and 5/5), raises residual cardiovascular risk and is an established determinant of adverse cardiovascular outcomes.[10,33] The MetS is more prevalent in the presence of HIV infection,[9,10,34] as confirmed in the present study. Obesity is a major driver for the underlying abnormalities of the MetS in the general population,[33,35] as well as in HIV-infected individuals.[9,10,25,34] In this latter population, ART, particularly stavudine and protease inhibitors, directly contribute to impair insulin sensitivity.[9,10,28] Other potential factors that may aggravate the MetS phenotype include acquired nonalcoholic steatohepatitis, hepatic insulin resistance and TG-rich particles overproduction associated with coinfection by hepatitis viruses. Serological data on hepatitis status in HIV patients were not available in the present study.

Despite lower indices for central adiposity and lack of ART use in the present study, HIV infection drastically increased the prevalence of the MetS and the severity of its score, the latter as a surrogate of whole-body insulin resistance. Our results suggest a possible influence of environmental, sociocultural, and/or genetic factors, as well as HIV infection, on MetS expression. On the other hand, the prevalence of obesity and central adiposity, and the mean BMI and waist circumference, were lower in HIV individuals than in controls, in line with observations carried out in treatment-naïve HIV+ Caucasians.[36,37] Fat redistribution and non-treatment-related acquired lipodystrophies are potential confounders in driving some of the discrepancies between global versus regional adiposity indices and MetS prevalence.

In the present study, treatment-naïve HIV+ patients had early-onset aortic stiffness, which corresponds to the early stage of subclinical atherosclerosis. Increased aortic stiffness is associated with cardiovascular risk factors and is an established marker of early arterial pathology. Thus, alterations in arterial stiffness predate hypertension and are linked to cardiovascular events in various settings.[11–13] Increased arterial stiffness observed among untreated Cameroon HIV+ individuals was consistent with recent reports on treatment-naïve Caucasians.[12,14] The high prevalence of atherogenic dyslipidemia observed in the present study may have contributed to increased arterial stiffness in HIV+ patients. Furthermore, HIV status by itself is associated with low-grade subclinical inflammatory injury of the endothelium, with endothelial dysfunction and accelerated atherosclerosis.[4,22]

The Aix, a surrogate measure of arterial stiffness, was unexpectedly lower in HIV+ patients. Our finding was in agreement with previous observations reported by Lazar et al[21] in their investigation of arterial stiffness in HIV-infected, never-treated Rwandan women. Although their study involved only women, our present study included both men and women with comparable magnitude between the two groups. Thus, the observed lower Aix cannot be attributable to sex influence. Discrepancy between Aix and PWV was previously described in diabetic[38] and elderly patients.[39] Carotid-femoral PWV is the gold standard measure of aortic stiffness, whereas Aix is a marker of reflected waves derived from pressure waveform. Aix is a composite measure that depends on PWV, reflection site, and reflected wave amplitude. It may therefore appear unaltered in HIV-infected patients, in the setting of faster wave speed and reduced wave reflection, resulting from impedance mismatch at the point of reflection, due to peripheral vasodilatation.[21] It seems likely that the effect of faster PWV observed in untreated HIV patients may have been attenuated, or probably overcome, by lesser central systolic augmentation in the aorta as a result of lower peripheral arterial resistances elicited by their lower brachial SBP.

Globally, the observed discrepancy as well as limited association between PWV and Aix in the present study demonstrates that Aix is not a sensitive and reliable measure of

arterial stiffness in black African HIV-infected patients. Our finding complies with our previous observations reporting that Aix is not a surrogate of arterial stiffness during β-adrenergic stimulation by isoproterenol, compared with PWV, in both black African and Caucasian subjects.[40] Furthermore, the validity of transfer function used in SphygmoCor to estimate central aortic Aix in the Caucasian population is still debated and might introduce some degree of inaccuracy. Its normal range needs to be adapted and validated in black African subjects born and living in sub-Saharan Africa. Further research is required to consolidate our findings, to unravel the underlying mechanism, and to establish the role of peripheral arterial vasodilatation in the mechanism of wave reflections in HIV-infected patients.

This study highlights a series of potentially modifiable cardiovascular risk factors among sub-Saharan HIV-infected, never-treated African patients. This vulnerable population is at risk for both HIV-induced infectious diseases and HIV-related cardiometabolic outcomes, on top of sharing conventional risk factors for noncommunicable diseases otherwise increasingly prevalent in the general African population, such as high BP, sedentary lifestyle, food insecurity, excess caloric intake, and high saturated fat intake. Risk modification strategies, including screening, smoking avoidance, regular exercise, and therapeutic dietary changes may be especially effective if implemented early, when subclinical atherosclerosis develops, as reflected by early-onset aortic stiffness. This also means that, as elsewhere, clinicians should be particularly aware of considering the use of lipid-lowering drugs when needed, including fibrates for dyslipidemia, and to opt for antiretroviral agents with the lowest propensity to impair glucose homeostasis, insulin sensitivity, or fat and lipids handling.[41]

The present study has several potential limitations, including sample size, transversal design, use of surrogates markers for central fat assessment, definition of glucose homeostasis based on a single glucose measurement instead of repeat or postload assessment, and lack of laboratory measurement of subclinical inflammatory markers, such as high-sensitivity C-reactive protein, interleukin-6, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and plasminogen activator inhibitor-1. Further studies involving a larger population with the assessment of these parameters are needed to confirm our findings. Because of funding and obvious logistical constraints, we recruited only at one center in Cameroon, and our results might therefore not be representative of other HIV+ patients from Cameroon or other sub-Saharan countries. However, the marked differences in cardiometabolic phenotype and PWV between patients and controls suggest that the conclusions of the present study are unlikely to be confounded only by these study limitations. Another study limitation is the predominance of the female sex in the studied population; it is increasingly recognized that the threshold value for pathological waist circumference currently used for black African populations may overpredict abdominal fat excess in women.[42]

Conclusion

In conclusion, HIV infection is associated with a high prevalence of MetS in treatment-naïve Cameroonian patients. The high frequency of atherogenic dyslipidemia, hypertension, and abnormal glucose homeostasis, together with increased frequency and severity of the metabolic syndrome in this population is associated with increased aortic PWV, an early marker of subclinical atherosclerosis. Because these acquired abnormalities are all modifiable by lifestyle or pharmacological interventions, these patients could benefit from preventive screening and targeted interventions to reduce their cardiometabolic risk.

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Disclosure

The authors report no conflicts of interest in this work.

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