Comparison of endothelial function and cardiometabolic profiles of people living with HIV in two South African regions: the EndoAfrica study

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Abstract

Background: People living with HIV (PLWH) are at risk for cardiovascular disease, but regional differences have not been studied in South Africa. We compared endothelial function and cardiometabolic markers in PLWH and HIV-free controls from two distinct South African regions.

Methods: We measured flow-mediated dilation (FMD), cardiometabolic, immunological and viral markers in age- and gender-matched PLWH on antiretroviral therapy (n = 100/group) and HIV-free participants (n = 50/group) in samples from cohort studies in the North West and Western Cape provinces.

Results: Endothelial function and cardiometabolic profiles were not worse in PLWH than in HIV-free individuals, and %FMD was not associated with cardiometabolic, viral or immunological markers. PLWH from the North West region had lower %FMD but overall better metabolic profiles.

Conclusion: Ethnic, cultural and socio-economic differences need further investigation to understand the possible protective role of antiretroviral treatment on the vasculature and to direct region-specific HIV and AIDS guidelines in South Africa.

Keywords: antiretroviral therapy, cardiovascular risk, epidemiology, flow-mediated dilation

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Africa is at the centre of the human immunodeficiency virus (HIV) epidemic[1] and in 2019, 7.97 million South Africans were living with HIV.[2] Fortunately, with advances in the management of HIV and the introduction of antiretroviral therapy (ART), the life expectancy of people living with HIV (PLWH) has improved.[3] However, with the increase in life expectancy, individuals are exposed to cardiovascular risk factors, such as an unfavourable lipid[4] and pro-inflammatory profile[5] for longer, leading to a rise in cardiovascular disease (CVD) risk.[6] PLWH have a higher risk for atherosclerosis,[7] myocardial infarction[8] and stroke[9] than uninfected individuals. A mix of various factors, including the HIV itself,[10] ART[11,12] and unhealthy lifestyles,[10] creates the perfect conditions for a higher incidence of CVD in PLWH.

Endothelial dysfunction is recognised as a precursor for CVD and a predictor of future cardiovascular events.[13,14] Endothelial dysfunction is characterised by a decrease in endothelium-dependent vasodilation[14] and can be measured as reduced flow-mediated dilation (FMD).[15,16] Traditional risk factors, including tobacco use,[17] hyperglycaemia[18] and hypercholesterolaemia,[19] have been associated with impaired endothelial function.

PLWH have a higher prevalence of endothelial dysfunction[20,21] and cardiovascular risk markers[5,22,23] compared to their uninfected counterparts. However, studies were predominantly conducted in Western populations with prevailing HIV-1, subtype B, and not in individuals with HIV-1, subtype C virus, which predominates in southern Africa.[24] There are significant differences in the biological make-up between the HIV-1, subtype B and C virus.[25-27] These biological differences may play a role in the link between HIV infection and endothelial dysfunction.

South Africa is a multi-ethnic and multi-lingual society characterised by socio-economic disparities. These demographic and environmental factors often also manifest in distinct regional differences among South Africa's nine provinces. Previous studies have shown that the prevalence of cardiovascular risk markers may be influenced by the demographic realities of South Africa[28,29] and that treated PLWH may not have worse

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endothelial function than HIV-free participants.[30] Therefore, in this article, we aimed to compare the endothelial function, as measured by FMD, and the related cardiometabolic profile of PLWH and HIV-free individuals from two different provincial settings in South Africa.

Methods

In this study, we included participants between the ages of 18 and 60 years from two different regional cohorts in South Africa, which form part of the EndoAfrica study [30,31] The North West and Western Cape legs of the EndoAfrica study followed the same study design, as described in more detail previously.[30,31] In the North West province, participants of African descent were recruited from clinics in and near Potchefstroom and from HIV support groups in the area. For the Western Cape cohort, participants were recruited from the primary-care clinics and care centres in Cape Town and the local community health centre in Worcester, and included individuals of mixed ancestry.

Exclusion criteria were PLWH on second-line ART, women who were pregnant or less than three months postpartum, and participants diagnosed with tuberculosis, pneumocystis pneumonia, and/or venereal diseases such as syphilis. To account for the confounding effects of age and gender on endothelial function[32] and cardiometabolic markers,[33,34] we matched participants from the North West province (self-identifying as black) who were living with HIV and received ART (n = 100) or who were HIV free (n = 50), with participants from the Western Cape province (self-identifying as of mixed ancestry) for age and gender. All participants living with HIV received first-line ART, which included nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI), as prescribed by the South African National Antiretroviral Treatment Guidelines.[35]

The EndoAfrica study was approved by the ethics committees of both the North-West and Stellenbosch universities and complied with the Declaration of Helsinki. We received additional approval for this sub-study from the Human Research Ethics Committee of the North-West University.

Questionnaire and anthropometric measurements: All measurements were performed on the same day while participants were in a fasting state. A standardised questionnaire was completed to collect demographic and lifestyle information. Anthropometric measurements were obtained with standardised procedures.[36] They included body height (stadiometer, SECA, Hamburg, Germany), weight (SECA 813 Electronic scale SECA, Hamburg, Germany) and waist circumference (Lufkin steel anthropometric tape, W606PM; Lufkin, Apex, USA).

Cardiovascular measurements: Non-invasive FMD of the brachial artery was measured with an Esaote MyLab™ Five ultrasound system (Esaote, Italy) and 12-MHz linear probe. The FMD procedure was based on a previously described protocol.[37] The %FMD (the difference between maximum brachial artery diameter and mean baseline artery diameter, expressed as a percentage of mean baseline diameter) and other related measurements were automatically calculated by the Cardiovascular Suite™ ultrasound edition version 2.8 (Quipu, Italy) software.

Duplicate brachial blood pressure measurements of the left arm were obtained five minutes apart using the OMRON M6 automatic digital blood pressure monitor (Omron Healthcare, Kyoto, Japan) with participants in the seated position. Hypertension classification was according to the 2021 European guidelines for managing arterial hypertension[38] as an office systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg and/or receiving anti-hypertensive treatment.

Biochemical analyses: A nurse drew blood from each participant with a sterile winged infusion set. Standardised methods were followed for preparing all samples, which were stored at –80°C until analysis. EDTA samples were sent to the National Health Laboratory services (NHLS) to determine viral load (Cobas® AmpliPrep/COBAS® TaqMan® HIV-1 test, version 2.0) and CD4 count (Beckman Coulter FC500 MPL/CellMek, Miami, FL). Further analyses for the North West leg of the study were performed at the on-site laboratory of the North-West University, while all analyses in the Western Cape were performed at the NHLS. The procedures and equipment used for all biochemical analyses were described previously.[30,31]

Statistical analyses

IBM® SPSS® version 25.0 (IBM Corporation, Armonk, New York) software was used for statistical analyses. Differences were determined with independent t-tests for continuous data and with χ^2 tests for categorical data. Analyses of covariance determined

Table 1. Characteristics of PLWH compared to HIV-free participants of the Western Cape and North West regions combined

Characteristics	*PLWH* (n = *200*)	*HIV-free* (n = *100*)	p-*value*
Age (years)	43 ± 7.32	39 ± 9.79	0.001
Gender, men, *n* (%)	50 (25)	32 (32)	0.20
HIV-related data			
HIV duration > 5 years, *n* (%)	119 (59.5)	–	
ART duration (weeks)	273 ± 410	–	
Viral load (copies/1 000 cells)	12609 (10.0; 55612)	–	
CD4 count (cells/mm^3)	525 (91.4; 1084)	–	
Anthropometric measurements			
Body mass index (kg/m^2)	24.8 ± 6.96	28.2 ± 8.13	< 0.001
Waist circumference (cm)	86.3 ± 14.5	90.9 ± 16.4	0.016
Cardiovascular measurements			
Flow-mediated dilation (%)	7.70 ± 5.79	6.67 ± 5.55	0.14
Baseline diameter (mm)	3.37 ± 0.60	3.40 ± 0.57	0.68
Diameter change (mm)	0.23 ± 0.22	0.22 ± 0.19	0.56
Systolic blood pressure (mmHg)	121 ± 18.8	121 ± 14.0	0.99
Diastolic blood pressure (mmHg)	84 ± 11.9	85 ± 11.8	0.71
Mean arterial pressure (mmHg)	96 ± 13.7	97 ± 11.9	0.82
Hypertensive, *n* (%)	77 (38.5)	46 (46)	0.21
Antihypertensive medication, *n* (%)	31 (15)	21 (21)	0.24
Biochemical markers			
Glycated haemoglobin (%)	5.36 (4.70; 6.10)	5.52 (4.50; 6.78)	0.21
Total cholesterol (mmol/l)	3.79 ± 1.16	3.59 ± 1.19	0.17
HDL cholesterol (mmol/l)	1.29 (0.61; 2.20)	1.14 (0.56; 2.35)	0.005
LDL cholesterol (mmol/l)	2.15 ± 0.80	2.13 ± 0.81	0.84
Triglycerides (mmol/l)	1.06 (0.41; 2.14)	0.93 (0.36; 2.10)	0.75
C-reactive protein (mg/l)	7.62 (0.30; 26.7)	6.17 (0.20; 20.4)	0.15
Lifestyle factors			
Tobacco use, *n* (%)	123 (62)	59 (59)	0.68
Alcohol use, *n* (%)	106 (53)	53 (53)	1.00

Data are expressed as arithmetic mean ± SD, geometric mean (5th and 95th percentile boundaries), or % of *n*. *p*-values for comparison between groups were obtained with independent *t*-tests and χ^2 tests.
ART, anti-retroviral therapy; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2. Characteristics of people living with and without HIV from two distinct regions in South Africa

	PLWH			*HIV free*		
Characteristics	*Western Cape* (n = *100*)	*North West* (n = *100*)	p-*value*	*Western Cape* (n = *50*)	*North West* (n = *50*)	p-*value*
Age (years)	43 ± 7.24	43 ± 7.41	1.00	39 ± 9.77	39 ± 9.92	0.98
Gender, men, *n* (%)	25 (25)	25 (25)	1.00	16 (32)	16 (32)	1.00
HIV-related data						
HIV duration > 5 years, *n* (%)	52 (52)	67 (67)	0.031	-	-	
ART duration (weeks)	234 ± 532	311 ± 227	0.18	-	-	
Viral load (copies/1 000 cells)	10623 (10; 86435)	313184 (10; 166443)	0.57	-	-	
CD4 count (cells/mm^3)	499 (93; 1009)	558 (79.7; 1153)	0.47	-	-	
Anthropometric measurements						
Body mass index (kg/m^2)	22.7 ± 5.54	26.8 ± 7.61	< 0.001	26.0 ± 7.58	30.4 ± 8.15	0.007
Waist circumference (cm)	87.3 ± 15.1	85.3 ± 13.9	0.33	91.3 ± 16.6	90.6 ± 16.3	0.84
Cardiovascular measurements						
Flow-mediated dilation (%)	8.51 ± 6.64	6.89 ± 4.68	0.047	6.24 ± 4.41	7.10 ± 6.52	0.44
Baseline diameter (mm)	3.33 ± 0.60	3.40 ± 0.61	0.40	3.45 ± 0.61	3.34 ± 0.53	0.35
Diameter change (mm)	0.26 ± 0.18	0.20 ± 0.25	0.049	0.21 ± 0.14	0.23 ± 0.22	0.48
Systolic blood pressure (mmHg)	123 ± 17.8	119 ± 19.8	0.17	121 ± 14.0	121 ± 14.1	0.95
Diastolic blood pressure (mmHg)	85 ± 11.7	83 ± 12.0	0.14	83 ± 10.4	86 ± 12.9	0.24
Mean arterial pressure (mmHg)	98 ± 13.2	95 ± 14.1	0.14	96 ± 11.1	98 ± 12.6	0.45
Hypertensive, *n* (%)	37 (37)	40 (40)	0.66	19 (38)	27 (54)	0.11
Antihypertensive medication, *n* (%)	7 (7)	45 (45)	< 0.001	4 (8)	17 (34)	0.001
Biochemical markers						
Glycated haemoglobin (%)	5.23 (4.41; 6.10)	5.46 (4.88; 6.25)	0.012	5.21 (4.40; 5.95)	5.84 (4.95; 11.0)	0.001
Total cholesterol (mmol/l)	4.61 ± 0.92	2.97 ± 0.69	< 0.001	4.41 ± 0.93	2.77 ± 0.77	< 0.001
HDL cholesterol (mmol/l)	1.52 (0.75; 2.58)	1.06 (0.50; 1.80)	< 0.001	1.46 (0.86; 2.89)	0.82 (0.47; 1.16)	< 0.001
LDL cholesterol (mmol/l)	2.52 ± 0.81	1.78 ± 0.61	< 0.001	2.44 ± 0.80	1.81 ± 0.69	< 0.001
Triglycerides (mmol/l)	1.29 (0.57; 2.48)	0.82 (0.37; 1.77)	< 0.001	1.11 (0.50; 2.36)	0.74 (0.31; 1.95)	< 0.001
C-reactive protein (mg/l)	9.70 (0.40; 42.0)	5.53 (0.20; 18.0)	0.004	7.33 (0.35; 29.9)	5.06 (0.08; 20.4)	0.11
Lifestyle factors						
Tobacco use, *n* (%)	71 (71)	52 (52)	0.006	39 (78)	20 (40)	< 0.001
Alcohol use, *n* (%)	46 (46)	59 (59)	0.66	26 (52)	27 (54)	0.84

Data are expressed as arithmetic mean ± SD, geometric mean (5th and 95th percentile boundaries), or % of *n*.
p-values for comparison between groups were obtained with independent *t*-tests and χ^2 tests.
ART, anti-retroviral therapy; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

the mean of FMD between groups while adjusting for age, gender, body mass index and baseline diameter, and stratified by median split of CD4 count and viral load, respectively. Multiple linear regression analyses were performed to determine independent relationships between FMD and cardiometabolic markers.

Results

The characteristics of the total cohort (North West and Western Cape regions combined) are shown in Table 1. In the total cohort, PLWH were older (p = 0.001), had a lower mean body mass index (p < 0.001) and waist circumference (p = 0.016), and higher high-density lipoprotein (HDL) cholesterol levels

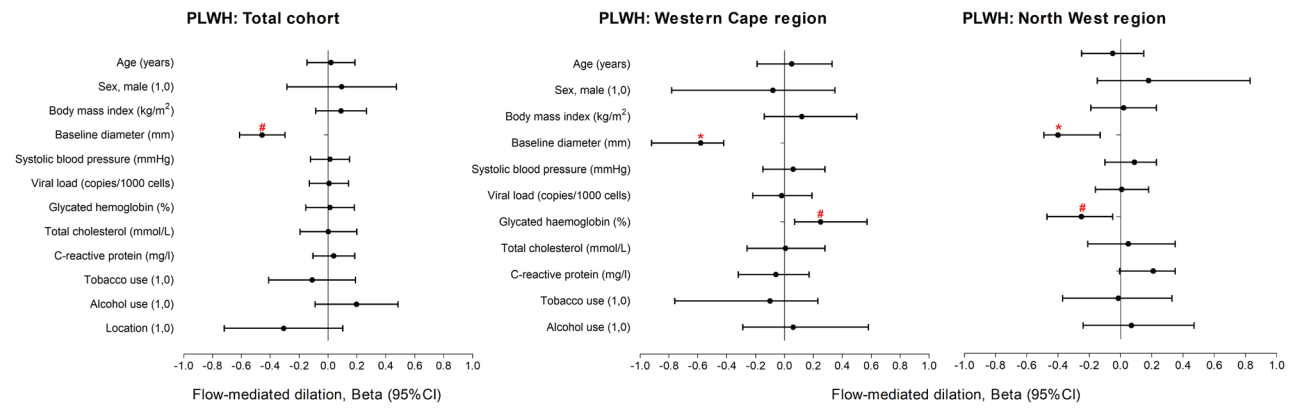

Fig. 1. Multiple regression analyses showing the association between %FMD and cardiometabolic markers in PLWH and receiving ART in the total cohort (two regions combined), as well as in the respective South African regions. *$p \leq 0.050$ and #$p < 0.001$.

(p = 0.005) compared to HIV-free participants. There were no differences in FMD between the groups (p = 0.14).

When comparing PLWH from the two distinct regions (Table 2), we found that the North West cohort had a higher prevalence of individuals who were infected for longer than five years (p = 0.031), more individuals who used anti-hypertensive medication (p < 0.001) and they also had lower FMD (p = 0.047), changes in vessel diameter (p = 0.049) and lower C-reactive protein (CRP) (p = 0.004) levels than the Western Cape cohort. In both the PLWH and HIV free groups, the mean body mass index (HIV positive: p < 0.001, HIV free: p = 0.007) and glycated haemoglobin (HbA_{1c}) (HIV positive: p = 0.012, HIV free: p = 0.004) values were higher, while total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (all p < 0.001) and tobacco use (HIV positive: p = 0.006, HIV free: p < 0.001) were all lower in the North West compared to the Western Cape cohort.

In multiple regression analyses (Fig. 1), we found no associations between FMD and any cardiometabolic variables in PLWH. In the respective regions, FMD was negatively associated with HbA_{1c} in participants from the North West region (β = –0.25; p = 0.016; adjusted R^2 = 0.14) and positively in those from the Western Cape region (β = 0.75; p = 0.013; adjusted R^2 = 0.23). FMD was negatively associated with baseline diameter in PLWH in the total group (β = –0.46; p < 0.001; adjusted R^2 = 0.15), North West (β = –0.40; p < 0.001; adjusted R^2 = 0.14) and Western Cape (β = –0.58; p < 0.001; adjusted R^2 = 0.23) cohorts.

We explored whether FMD decreased in PLWH with lower CD4 counts and higher viral loads in sensitivity analyses. We did this by comparing FMD between groups, stratified by median split of CD4 count and viral load, respectively. However, we found no differences in the total cohort or the individual regions (Table 3).

Discussion

For the first time, we investigated endothelial function and the cardiometabolic profile of PLWH and HIV-free participants from two different geographical regions in South Africa. This study design contributes to an improved generalisability of our findings. Our results reported differences in the endothelial function and cardiometabolic profiles of PLWH between the two regions, while only the metabolic profile of the HIV-free participants differed.

HIV-free participants from the North West region had a higher body mass index and HbA_{1c} level, and higher prevalence of anti-hypertensive medication use. PLWH from the North West region had a lower FMD, even though PLWH of the Western Cape region had higher CRP, total cholesterol, LDL cholesterol and triglyceride levels. The higher levels of CRP found in the Western Cape cohort may in part be explained by the higher prevalence of tobacco use. Several studies that observed higher levels of CRP in smokers compared with non-smokers support this.[39,40]

The discrepancy in the lipid profile between the regions, observed in both PLWH and HIV-free participants, may be because of ethnic, genetic, cultural and socio-economic differences between the North West and Western Cape cohorts. The Heart of Soweto in South Africa study reported that people of African descent in their cohort, albeit HIV free, had overall a more favourable lipid profile (lower total and LDL cholesterol levels) than South Africans of European descent and mixed ancestry.[41] However, studies investigating cardiometabolic variables in terms of regional and ethnic differences in South Africans living with HIV are scarce.

Further investigations into the relationships between FMD and cardiometabolic markers showed that FMD did not associate with CD4 count, viral load, ART, HIV duration, or traditional risk factors, except for HbA_{1c} level in PLWH in either region. The higher HbA_{1c} levels in the North West region associated inversely with FMD, while the lower HbA_{1c} level in the Western Cape region had a positive association with FMD. The reason for this difference remains unclear and may have been influenced by external factors not measured in this study, such as dietary habits and physical activity, which may have differed between the two regions. Previous studies have shown an association between HbA_{1c} level and endothelial dysfunction in HIV-free individuals from South America,[42,43] and our findings warrant further investigation.

In addition, we found that PLWH did not have a worse endothelial function or cardiometabolic profile compared to HIV-free individuals. Our results support a study where no differences were observed in FMD between PLWH receiving ART and the HIV-free group.[44] In contrast, Blanco *et al.*[21] and Solages *et al.*[20] found that PLWH on treatment had a lower FMD than their uninfected counterparts. These studies were conducted in Western populations where the HIV-1, subtype B virus is predominant, and where the ART regimen includes protease inhibitors. In our South African study cohort, the subtype C virus prevails,[24] and all PLWH were receiving a prescribed, fixed-dose combination ART regime comprising NRTI and NNRTI.

In a case–control study conducted in India,[45] where the HIV1 subtype C virus is also the leading cause of infection, a lower FMD was found in HIV-positive individuals, but these individuals were not receiving ART. Therefore, our result may be attributed to using the specific, fixed-dose combination ART drug (NRTI and NNRTI) and a presumed protective effect of this treatment on our study population. To support this, Torriani and colleagues[46] reported that a fixed-dose combination of ART (NRTI and NNRTI) improved the endothelial function of 82

Table 3. Comparison of %FMD between viral load and CD4 count groups, respectively, stratified by median split

Variables		*Flow-mediated dilation %*	p-*value*
PLWH: total cohort			
Viral load (copies/1 000 cells)	Lower (< 8166)	8.42 ± 5.72	0.34
	Higher (≥ 8166)	7.16 ± 5.85	
CD4 count (cells/mm^3)	Lower (< 1542766)	8.51 ± 6.10	0.99
	Higher (≥ 1542766)	7.69 ± 5.79	
PLWH: Western Cape region			
Viral load (copies/1 000 cells)	Lower (< 8166)	9.11 ± 6.32	0.49
	Higher (≥ 8166)	7.98 ± 6.93	
CD4 count (cells/mm^3)	Lower (< 1542766)	12.3 ± 8.02	0.33
	Higher (≥ 1542766)	8.33 ± 6.58	
PLWH: North West region			
Viral load (copies/1 000 cells)	Lower (< 8166)	7.58 ± 4.82	0.50
	Higher (≥ 8166)	6.43 ± 4.65	
CD4 count (cells/mm^3)	Lower (< 1542766)	5.77 ± 2.08	0.33
	Higher (≥ 1542766)	7.03 ± 4.81	

Data are expressed as arithmetic mean ± SD. p-values for comparison between groups were obtained with analyses of covariance, adjusted for gender, age, body mass index and baseline diameter.

PLWH for 24 weeks. Our study found no significant difference in endothelial function between groups with high and low CD4 counts and viral loads in both regions.

The strength of our study is the inclusion of PLWH from two different regions in South Africa who were on the same first-line ART regimen. We could not compare PLWH receiving ART to those not receiving ART. The South African National Antiretroviral Treatment Guidelines[35] prescribe that PLWH start with ART after diagnosis is confirmed. Therefore, we could not include enough PLWH not receiving ART or individuals who were treated for less than four weeks. Because of voluntary participation, the study population was relatively small, and we did not include extensive sociodemographic data. Nonetheless, our study includes novel data from the country with the highest HIV rate in the world.[30]

Conclusion

The differences in FMD between PLWH from the two distinct regions in South Africa were not explained by the differences in cardiometabolic markers, CD4 count, viral load or duration of infection. This observation warrants further investigation. Furthermore, we found that PLWH on first-line ART did not have a worse endothelial function or cardiometabolic profile than HIV-free individuals. Our results may suggest that the specific ART regimen may have a possible protective effect. Other risk factors such as ethnic, genetic, cultural and socio-economic differences may influence the endothelial function and cardiometabolic profile of South Africans living with HIV.

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