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An Assessment of the Effect of HIV and ART on Cardiovascular Risk Factors to Predict Retinal Microvascular Impairment in Pregnant Women: A Pilot Study in a South African Population

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Abstract

Background: Human immunodeficiency virus (HIV) and antiretroviral therapy (ART) are known to be involved in cardiovascular disease development. They act alongside systemic risk factors, which interact with both macrovascular and microvascular vessels to accelerate vascular damage. Therefore, the aim of this study was to investigate the cardiovascular risk factors and their relationship with retinal microvascular function in HIV-positive pregnant women on ART in Mthatha, South Africa. **Methods:** A cross-sectional study was carried out among 78 pregnant women (25 HIV-positive and 53 HIV-negative) in Mthatha, South Africa. Blood pressure (BP) parameters, including systolic BP (SBP), diastolic BP (DBP), and heart rate (HR), were measured, and mean arterial pressure (MAP) was calculated. Lipid profile parameters and fasting blood glucose were assessed. Markers for kidney function, such as albuminuria, were determined. Vascular biomarkers including asymmetric dimethyl arginine (ADMA) and human endothelial specific molecule-1 were quantified. Non-invasive vascular function parameters such as flow-mediated slowing (FMS), carotid-femoral pulse wave velocity (cfPWV), ankle-brachial index, central retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE), arteriolar venular ratio (AVR), uterine artery pulsatile index (UtA PI) were determined. **Results:** Diastolic BP, MAP, cfPWV, ADMA, low density lipoprotein (LDL-c) and UtA PI were higher in the HIV-positive group ($p \leq 0.05$) compared to the HIV-negative group. The prevalence of prehypertension/hypertension was higher in the HIV-positive group ($p \leq 0.05$). DBP, MAP, and cfPWV correlated positively with CRVE in the HIV-positive group ($p \leq 0.05$), while AVR negatively correlated with the urinary creatinine (uCr) in the same group ($p \leq 0.05$). Linear regression results demonstrated that DBP, cfPWV, ABI, and LDL-c were predictors of reduced AVR in the HIV-positive group. **Conclusions:** Increased cardiovascular risk was observed in HIV-positive pregnant women on ART. Further, increased cardiovascular risk

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such as hypertension and endothelial dysfunction due to ART predicted retinal microvascular dysfunction in the HIV-positive population. This implies a potential mechanistic link between macrovascular dysfunction due to cardiovascular risk factors and retinal microvascular impairment, highlighting the importance of assessing cardiovascular risk early and preserving overall vascular health in HIV-positive population.

Keywords: retinal microvascular impairment; cardiovascular risk; macrovascular dysfunction; human immunodeficiency virus; antiretroviral therapy; pregnancy

1. Introduction

Human immunodeficiency virus (HIV) is a global health challenge. An estimated global population of 40.8 million was documented to be HIV-positive at the end of 2024, with 65% in the African region [1]. South Africa ranks among the countries with the highest prevalence, with a national prevalence of 18.8% among adults aged 15–45 years old [2]. Before the era of antiretroviral therapy (ART), HIV reduced the quality of life and was associated with high morbidity and mortality worldwide [3]. The widespread access to ART has significantly improved the quality of life, allowing HIV-positive individuals to live longer [4].

In South Africa, ART was introduced in 2004 and improved the quality of life and life span of those infected [5]. Women were previously discouraged from having children due to safety concerns about the transmission of HIV to their offspring [6]. However, with ART widely available, they can now bear children with minimal risk to themselves and offspring [7]. Although ART has reduced the prevalence of vertical transmission, there are concerns of it contributing to cardiovascular diseases through the promotion of cardiovascular risk factors [8].

Cardiovascular risk factors such as obesity, dyslipidaemia, hypertension, insulin resistance, and renal dysfunction are major contributors to systemic endothelial dysfunction, a central driver of vascular complications [9]. Obesity and insulin resistance increase the release of pro-inflammatory cytokines and plasma fatty acids, inducing oxidative stress and endothelial activation [10]. Dyslipidaemia, in particular elevated low density lipoprotein cholesterol (LDL-c) and reduced high density lipoprotein cholesterol (HDL-c) contribute to the oxidation of lipids, directly injuring endothelial cells [11]. Chronic hypertension places mechanical strain on vessel walls that disrupts the endothelial integrity, while renal dysfunction results in increased levels of uremic toxins, known to be strongly associated with vascular damage [12,13]. Together, these factors impair the synthesis of nitric oxide (NO), shifting endothelium to prothrombotic and pro-inflammatory state, increasing the susceptibility of macrovascular and microvascular damage [14].

Endothelial dysfunction plays an important role in the development of retinal microvasculature impairment. Damaged endothelial cells in the retina diminish NO synthesis, limiting vasodilation and impairing autoregulation of retinal blood flow, thereby promoting retinal microvascular dysfunction and localised ischaemia and the development of cardiovascular diseases [15,16]. The standardised parameters of retinal vessel calibre include central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) derived from fundus photographs. CRAE and CRVE reflect the average diameter of retinal arterioles and the average of retinal venules, respectively [17]. These indices are used as non-invasive markers of systemic microvascular health. The ratio of CRAE to CRVE, which is the arteriolar venular ratio (AVR), integrates both into a single indicator of retinal microvascular status, with lower values indicating the narrowing of arterioles or the

widening of venules, which may indicate retinal microvascular dysfunction and potential risk for the development of cardiovascular diseases [18].

Although cardiovascular risk factors such as hypertension, dyslipidemia, obesity, and insulin resistance are well-known contributors to vascular dysfunction, there is little evidence on their predictive potential for impaired retinal microvascular health, especially in pregnant women infected with HIV on ART. Therefore, this study aimed to assess the effect of ART and HIV on cardiovascular risk factors in predicting retinal microvascular impairment in HIV-positive pregnant women in Mthatha, South Africa.

2. Materials and Methods

2.1. Study Setting and Population

A cross-sectional study was carried out among HIV-positive pregnant women and HIV-negative pregnant women. Clinic charts were used to confirm that HIV-positive pregnant women were on ART for four months or longer. Participants were recruited from peripheral clinics, including the Ngangelizwe clinic and the Gateway clinic, and Nelson Mandela Academic Hospital, Mthatha, Eastern Cape Province, South Africa. This is part of the ARTMOMSBABES study with Protocol ClinicalTrials.gov Identifier: https://clinicaltrials.gov/ct2/show/NCT04763668 (accessed on 12 March 2025)

2.2. Ethical Clearance

This study was carried out in accordance with the 2008 Helsinki Declaration, amended version, as well as in line with the South African national and local laws. The ethical clearance (072/2022) was sought and obtained from Walter Sisulu University, Health Research Ethics Committee. The Eastern Cape Department of Health granted permission to carry out the study in selected health facilities.

2.3. Inclusion and Exclusion Criteria

Women at 11–16 weeks of singleton pregnancy with a minimum age of 18 years without confirmed diabetes, or hypertension, kidney diseases, or cardiovascular diseases, and confirmed to be on ART for more than 4 months for the HIV-positive pregnant women were enrolled into the study. Pregnant women on medications besides ART, women who exhibited COVID-19 symptoms and those with multiple pregnancies were excluded from the study.

2.4. Data Collection

2.4.1. Anthropometry

The participant's height was measured using a wall-mounted Harpenden stadiometer, and the reading was documented to the nearest 0.1 cm. Weight was measured in kilograms (kg) using a Tanita weight scale (BC1000, Tanita Corporation, Tokyo, Japan). Waist circumference (WC) and hip circumference (hip C) were measured using a non-stretchable tape.

2.4.2. Blood Pressure

Blood pressure (BP) parameters, including systolic BP (SBP), diastolic BP (DBP), and heart (HR), were measured using an automated sphygmomanometer connected to a cuff (CARESSCAPE V100 Dinamap vital signs monitor, GE Healthcare, Buckinghamshire, United Kingdom). Participants were required to sit up straight with their bare left arms on the table. The readings were taken three times, with the first reading taken following 5 min of rest, while readings two and three were taken at 2 min intervals. The average of 3 blood pressure readings was calculated. The mean arterial pressure (MAP) was computed using the following calculation: MAP = (DBP + (1/3 × (SBP − DBP))).

2.4.3. Non-Invasive Measure for Vascular Function Assessment

A Vicorder (SMT medical GmbH & Co. KG, Berlin, Germany) was used to determine flow-mediated slowing (FMS), ankle brachial index (ABI) and carotid femoral pulse wave velocity (cfPWV). Details of the participants such as study ID, date of birth and anthropometry data were computed into the Vicorder software version 4 in a laptop connected to the Vicorder device to perform various tests. Participants were in supine position and the tests were done as follows;

2.4.4. Flow Mediated Slowing

To assess flow-mediated slowing (FMS), the bare right arm of the participant was abducted at an angle of 45°, the upper arm and wrist of the same hand were wrapped with a 10 cm blood pressure cuff and a 7 cm blood pressure cuff, respectively. The Vicorder, which was connected to the laptop, was in turn connected to the 10 cm blood pressure cuff and 7 cm blood pressure cuffs using red and blue coloured pressure lines. The readings were taken according to the manual's instructions.

2.4.5. Ankle Brachial Index

For the ankle brachial index (ABI) test, the red and blue pressure lines connected to the Vicorder were in turn connected to the 10 cm BP cuff and 7 cm BP cuff. The 10 cm BP cuff and 7 cm BP cuff were wrapped around the bare right arm and bare right ankle, respectively. Blood pressure was taken at these two points following instructions from the manual and ABI was automatically computed and recorded.

2.4.6. Carotid Femoral Pulse Wave Velocity

To measure the cfPWV, a neckband was wrapped around the neck of a participant with the cuff bladder part covering the carotid artery and a 10 cm BP was wrapped around the bare right thigh. The neckband was connected to a red pressure line, and the 10 cm BP was connected to the blue pressure line. Reading was taken based on the manufacturer's manual and recorded.

2.4.7. Uterine Artery Pulsatile Index

The participant was requested to lie in supine position. Obstetric mode was activated on the ultrasound machine (HS60 Samsung Medison Co., Ltd., 3366, Seoul, Republic of Korea). The participant's abdomen was exposed, and the gel was applied to the abdomen. The transducer was placed on both sides of the lower abdomen, just above the groin area. The iliac artery was detected, and the uterine artery was tracked as it branched to the uterus. The Doppler mode was turned on, and the reading was documented. The average uterine artery pulsatile index (UtA PI) of both the left and right uterine artery was computed and recorded.

2.4.8. Retinal Imaging

A portable fundus Optomed Aurora camera (Optomed, Oy, Oulu, Finland), was used by trained personnel to capture retinal images of the right eye of each participant [19]. The participant was required to sit up straight with their left eye covered with the left hand in a dim room. The device was positioned in line with the participant's right eye, and the picture was taken by focusing the camera on the retina. The retinal images were analysed using MONA REVA software version 2.1.1 (VITO, Mol, Belgium) and the details of the analysis are described elsewhere [20]. The Parr–Hubbard–Knudson formula was used to obtain the mean diameter of the 6 largest venules which represented the CRVE, while the mean diameter of 6 arterioles represented the CRAE. The results were reported in micrometre (μm). The AVR was computed using CRAE and CRVE [21,22].

2.4.9. ART Information

Twenty (86.96%) HIV-positive pregnant women were on Tenofovir disoproxil, lamivudine and dolutegravir, which is the first preferred first line regimen in South Africa. While the remaining three (13.04%) in the HIV-positive group were on Tenofovir, efavirenz, emtricitabine (TEE).

2.4.10. Biochemical Analysis

A total volume of 7 mL fasting venous blood was collected from each participant into three blood collecting tubes (1.5 mL K2 EDTA lavender top, 2 × 2 mL ACD yellow top, and 1.5 mL potassium oxalate grey top). Serum was collected into the Eppendorf tubes after centrifugation of venous blood and quantified for asymmetric dimethyl arginine (ADMA), and human endothelial specific molecule-1 (HESM-1) (Elabscience, Houston, TX, USA) as described in the manufacturer's protocol. Serum was further used for the quantification of glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c) and low density lipoprotein cholesterol (LDL-c) using COBAS 501/502 panel/system (Roche Diagnostics, Indianapolis, IN USA). Mid-stream urine was collected for the determination of urinary creatinine (uCr) and urinary albumin (uALB) on the Cobas c502 module® (Roche Diagnostics, Mannheim, Germany). The urinary albumin to creatinine (uACR) ratio was calculated and documented.

The cut-off values for clinical and biochemical parameters are shown in Table 1.

Table 1. Cut-off values for clinical and biochemical parameters.

Parameters	Level	Cut-Off	Citation
Lipid profile parameters	High	TC > 5 mmol/L	[23]
		LDL-c > 3 mmol/L	
		TG > 1.7	
	Low	HDL-c < 1.20 mmol/L	
albuminuria		uACR > 3 mg/mmol	[24]
FG	High	≥7 mmol/L	[25]
Blood pressure	Normal	<120 systolic and <80 mm Hg diastolic	[26]
	Elevated	120–129 systolic and <80 mm Hg diastolic	
	Stage 1 hypertension	130–139 systolic or 80–89 mm Hg diastolic	
FMS	Endothelial dysfunction	FMS < 11.3%	[27]
	Normal	FMS > 11.3%	
cfPWV	High	≥10 m/s	[28]
ABI	Low	<0.9	[29,30]
	High	>1.3	

TC: Total cholesterol; LDL-c: Low density lipoprotein cholesterol; TG: Triglyceride; HDL-c High density lipoprotein cholesterol; uACR: Urine creatinine; FG: Fasting plasma glucose; FMS: Flow mediated slowing; cfPWV: Carotid femoral pulse wave velocity; ABI: ankle brachial index; µmmol: Micromolar; L: Litre; m/s: metre per second; kg/m^2: Kilogram per square metre; mg: Milligram; mmol/L: millimole per litre.

3. Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 29 (IBM Corp., Armonk, NY, USA) was used to analyse the data. Data is expressed as mean ± 95% Confidence interval

(CI). Continuous variables between HIV-infected pregnant women and HIV-uninfected pregnant women were compared using an independent sample T-test. Pearson's Chi-square was used to compare proportions of categorical variable between the HIV-infected pregnant women and HIV-uninfected pregnant women. The relationship between macrovascular and retinal microvascular function was determined using Spearman correlation. Linear regression was done to determine the strength of the relationship between macrovascular and retinal microvascular function. A p-value of $p \leq 0.05$ was considered statistically significant.

4. Results

A total of 78 pregnant women (25 HIV-positive and 53 HIV-negative) were recruited into the study. Pregnant women from the HIV-positive group were older ($p < 0.05$) than their HIV-negative counterparts. Weight, height and WC were similar ($p > 0.05$) between the two groups (Table 2).

Table 2. General characteristics of participants.

	HIV-Negative	HIV-Positive	*p*-Value
N	53	25	
	Mean (95%CI)	Mean (95%CI)	
Age (y)	27.53 (26.03–29.02)	32.04 (29.52–34.56)	0.001
Weight (kg)	76.64 (72.08–81.20)	73.14 (66.52–79.76)	0.191
Height (cm)	161.38 (159.60–163.15)	160.04 (156.80–163.28)	0.214
WC (cm)	95.81 (91.39–100.23)	93.98 (87.60–100.36)	0.327

HIV = human immunodeficiency virus; y = years; kg = kilogram; cm = centimetre; WC = waist circumference. N = number of participants.

SBP and HR were similar between the HIV-positive group and the HIV-negative group ($p \geq 0.05$), while DBP and MAP were higher in the HIV-positive group ($p \leq 0.05$). Moreover, HIV-positive pregnant women had increased cfPWV ($p \leq 0.05$) compared to their HIV-negative counterparts, whereas FMS and ABI were comparable ($p > 0.05$) between the two groups. The UtA was higher in the HIV-positive group ($p \leq 0.05$). The HIV-positive group had increased levels of ADMA, whereas HEMS1 was similar between the HIV-positive and HIV-negative groups. The uCr, uALB and uACR were similar between the two groups ($p > 0.05$). Lipid parameters such as TC, TG and HDL-c were comparable between the HIV-positive group and HIV-negative group ($p > 0.05$). However, LDL-c was higher in the HIV-positive group ($p \leq 0.05$) (Table 3).

Table 3. Macrovascular function characteristics.

	HIV-Negative	HIV-Positive	*p*-Value
SBP (mm Hg)	109 (107–111)	111 (106–116)	0.232
DBP (mm Hg)	66 (63–68)	69 (67–72)	0.019
HR (bpm)	84 (81–87)	84 (79–89)	0.495
MAP (mm Hg)	80 (78–82)	83 (80–86)	0.041
FBG	4.22 (4.11–4.34)	4.15 (3.86–4.44)	0.580
uCr	16.63 (13.35–19.92)	12.96 (9.52–16.39)	0.209
uALB	10.84 (7.33–14.36)	8.05 (4.04–12.06)	0.381
uACR	0.6180 (0.47–0.76)	0.62 (0.39–0.84)	0.989
TC	4.05 (3.77–4.34)	4.33 (3.84–4.81)	0.320
TG	1.04 (0.95–1.137)	1.07 (0.88–1.26)	0.772
HDL-c	1.51 (1.41–1.61)	1.51 (1.38–1.64)	0.990
LDL-c	2.00 (1.76–2.24)	2.45 (2.04–2.87)	0.046

Table 3. *Cont.*

	HIV-Negative	HIV-Positive	*p*-Value
cfPWV (m/s)	6.85 (6.65–7.06)	7.34 (6.84–7.85)	0.015
FMS (%)	22.57 (19.41–25.74)	22.84 (17.24–28.43)	0.465
ABI	1.16 (1.11–1.20)	1.19 (1.10–1.27)	0.249
UtA PI	1.59 (1.44–1.73)	1.80 (1.57–2.02)	0.048
ADMA (ng/mL)	224.48 (137.90–371.06)	378.72 (151.48–605.95)	0.05
HESM-1 (pg/mL)	42.28 (29.94–54.63)	48.03 (38.22–57.85)	0.257

HIV = human immunodeficiency virus; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial pressure; cfPWV = carotid femoral pulse wave velocity; FMS = flow mediated slowing; ABI = ankle brachial index; UtA PI = Uterine artery pulsatile index; ADMA = asymmetric dimethyl arginine; HESM-1 = Human endothelial cell specific molecule-1; uCr = urinary creatinine; uALB = urinary albumin; uACR = urinary albumin creatinine ratio; TC = total cholesterol; TG = triglyceride; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; mm Hg = millimetre of mercury; bpm = beats per minute; m/s = metre per second; ng/mL nanogram per millilitre; pg/mL = picogram per millilitre; % = percentage.

The CRAE and CRVE were similar between the two groups ($p > 0.05$), while AVR was higher in the HIV-negative group ($p \leq 0.05$) (Table 4).

Table 4. Retinal microvascular function characteristics.

	HIV-Negative	HIV-Positive	*p*-Value
CRAE (µm)	134.86 (130.19–138.35)	129.03 (124.67–133.38)	0.063
CRVE (µm)	231.50 (225.84–237.16)	236.25 (227.07–245.45)	0.180
AVR	0.58 (0.57–0.60)	0.55 (0.52–0.58)	0.008

CRAE = central retinal arteriolar equivalent; CRVE = central retinal venular equivalent; AVR = arteriolar venular ratio; µm = micrometre; HIV = human immunodeficiency virus.

The HIV-positive group had a higher prevalence of pre-hypertension/hypertension (pre-HT/HT) compared to the HIV-negative group ($p < 0.05$). Hypercholesterolaemia, Hypertriglyceridaemia and low HDL-c were comparable between the HIV-positive group and the HIV-negative group ($p > 0.05$). However, high LDL-c was prevalent in the HIV-positive compared to the HIV-negative group ($p < 0.05$). The HIV-positive group and HIV-negative group had similar high cfPWV and high FMS ($p > 0.05$). Low ABI was prevalent among the HIV-positive group compared to the HIV-negative group ($p < 0.05$) (Table 5).

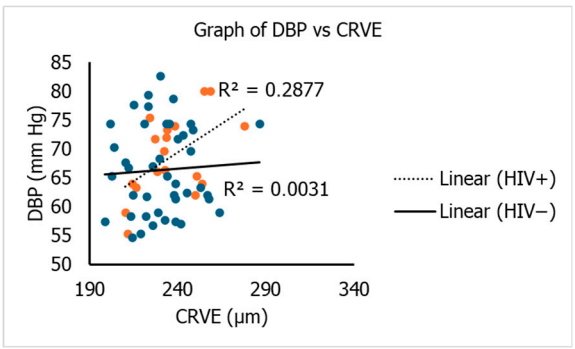
Table 5. Prevalence of macrovascular risk factors.

	HIV-Negative N (%)	HIV-Positive N (%)	χ^2	*p*-Value
N	53	25		
Pre-HT/HT	1 (1.9)	4 (16.0)	4.52	0.033
Hypercholesterolaemia	8 (11.1)	5 (6.9)	1.19	0.275
Hypertriglyceridaemia	3 (4.3)	1 (1.4)	0.014	0.907
Low HDL-c	5 (7.8)	4 (6.2)	1.38	0.240
High LDL-c	4 (6.2)	6 (9.2)	5.409	0.020
High cfPWV	0 (0.0)	1 (1.4)	2.248	0.124
High FMS	4 (5.4)	3 (4.1)	0.501	0.476
Low ABI	0 (0.0)	2 (2.7)	4.282	0.039

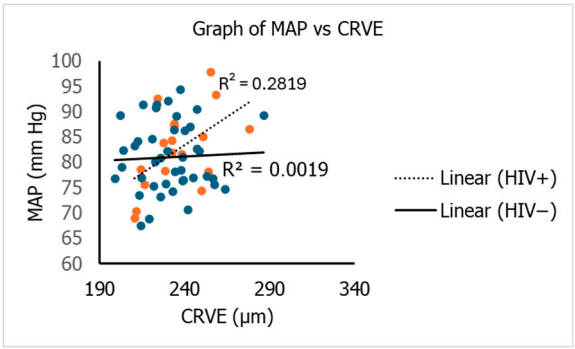
N = number; % = percentage; pre-HT/HT = pre-hypertension or Hypertension; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; cfPWV = carotid femoral pulse wave velocity; FMS = flow mediated slowing; ABI = ankle brachial index; χ^2 = Chi square.

The relationship between retinal microvascular function and macrovascular function is presented in Figure 1. The DBP correlated positively ($p \leq 0.05$) with CRVE in the HIV-positive group. Further, MAP had a positive correlation ($p \leq 0.05$) with CRVE in the

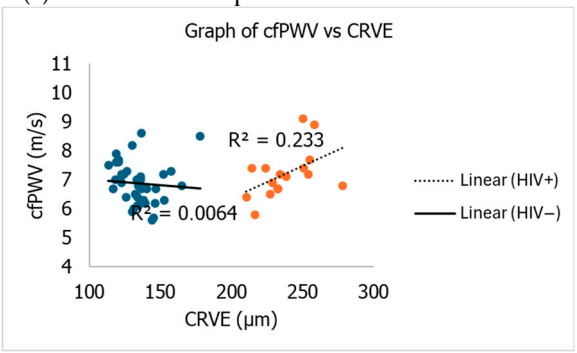
HIV-positive group. A positive correlation ($p \leq 0.05$) was observed between cfPW and CRVE in the HIV-positive group. There was a negative correlation ($p \leq 0.05$) between urinary creatinine and AVR in the HIV-positive group.



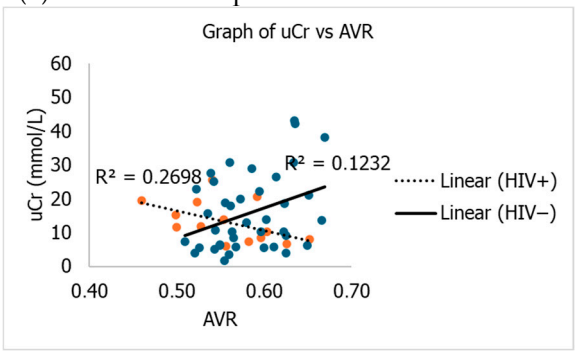
(**a**) The relationship between DBP and CRVE.



(**b**) The relationship between MAP and CRVE.



(**c**) The relationship between cfPWV and CRVE.



(**d**) The relationship between uCr and AVR.

Figure 1. Relationship between cardiovascular risk and retinal microvascular parametre. DBP = diastolic blood pressure; MAP = mean arterial pressure; cfPWV = carotid femoral pulse wave velocity; CRVE = central retinal venular equivalent; AVR = arteriolar venular ratio; uCr = urine creatinine; mm Hg = millimetre of mercury; m/s = meter per second; mmol/L: millimole per litre.

Increased DBP, cfPWV, ABI, and LDL-c were likely to predict significant ($p < 0.05$) reduction in AVR in HIV-positive pregnant women. Moreover, increased HDL-c predicted the likelihood for significant ($p < 0.05$) reduction in AVR in HIV-positive pregnant women (Table 6). These results suggest cardiovascular risk factors to predict microvascular dysfunction defined by reduced AVR in HIV-positive pregnant women on ART.

Table 6. Linear regression analysis for predictors of AVR in HIV-positive pregnant women.

Macrovascular Factors	β	95% CI for β	*p*-Value
SBP (mm Hg)	0.003	0.000–0.006	0.051
DBP (mm Hg)	−0.005	−0.010–0.000	0.048
cfPWV (m/s)	−0.050	−0.084–−0.016	0.012
ABI	−0.168	−0.328–−0.008	0.042
T chol	0.182	−0.026–0.390	0.076
Triglyceride	−0.093	−0.226–0.041	0.140
HDL-c	−0.253	−0.481–−0.026	0.034
LDL-c	−0.224	−0.418–−0.031	0.030

SBP = systolic blood pressure; DBP = Diastolic blood pressure; mm Hg = millimetre of mercury; cfPWV = carotid femoral pulse wave velocity; m/s = metre per second; ABI = ankle brachial index; T chol = Total cholesterol; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; β = Beta.

An association (β = 1.43 (95%CI = 0.24:2.63), $p = 0.022$) was observed between DBP and CRVE in the HIV-positive group. The MAP in the HIV-positive group also showed a positive

association (β = 1.26 (95%CI = 0.20:2.33), $p = 0.023$) with CRVE. No significant association was observed between CRVE and cfPWV in both groups (Table 7). These findings suggest DBP and MAP to predict increased CRVE in HIV-positive pregnant women on ART.

Table 7. Independent association by linear regression between retinal microvascular and macrovascular function.

	HIV-Negative		HIV-Positive	
	CRVE		CRVE	
	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value
DBP	0.13 (−0.62:0.88)	0.727	1.43 (0.24:2.63)	0.022
MAP	0.14 (−0.74:0.97)	0.786	1.26 (0.20–2.33)	0.023
cfPWV	−0.12 (−8.47:8.23)	0.977	10.57 (−0.42:21.56)	0.058

β = Beta; DBP = diastolic blood pressure; MAP = mean arterial pressure; cfPWV = carotid femoral pulse wave velocity; CRVE = central retinal venular equivalent.

5. Discussion

The present study investigated the effect of HIV and ART on cardiovascular health to predict retinal microvascular impairment in pregnant women. Macro-cardiovascular riskparameters, including DBP, cfPWV, ABI, HDL and LDL-c were significant predictors of retinal microvascular dysfunction in pregnant women infected with HIV.

Pregnancy is a physiological state characterised by increased cardiovascular demand and endothelial activation [31]. Exposure to HIV and ART before or during pregnancy, both of which have been linked to heightened cardiovascular risk, could accelerate vascular dysfunction in this population [32,33]. The adaptation of the maternal vascular function during pregnancy is important to increase the flow of blood through the uteroplacental unit to meet the requirements for foetal development. The inability of the maternal circulation to adjust can lead to microvascular complications [34]. To better understand the vascular alterations among pregnant women in the present study, vascular function was assessed comprehensively using a combination of circulating biomarkers and hemodynamic techniques.

ART has been reported to cause damage in the endothelium of the placenta and blood vessels, leading to endothelial dysfunction, which may lead to macrovascular damage or dysfunction. ADMA, an inhibitor of NO production has been reported as one of the primary indicators of endothelial dysfunction, demonstrated by its ability to decrease vasodilation [35]. In the present study, HIV-positive pregnant women on ART had significantly higher levels of ADMA compared to HIV-negative pregnant women. Similar finding was observed in a study carried out in Austria that reported high levels of ADMA among HIV-positive patients [36]. A study documented that HIV causes endothelial dysfunction through chronic inflammation and consequent buildup of ADMA [37]. Impaired vasodilatory capacity resulting from endothelial dysfunction reduces the ability of blood vessels to dilate, promoting arterial stiffness [38]. The speed of the pressure wave along the arterial wall, called pulse wave velocity, can be used to assess arterial stiffness [39]. The pulse wave travels at a low speed in a compliant arterial wall. The reflection wave also travels slowly to the aorta, thus augmenting the diastolic blood pressure. However, in arterial stiffness, the pressure wave travels at a higher speed, and the reflected pressure wave also travels to the aorta quickly, augmenting the systolic blood pressure [40]. HIV-positive pregnant women had a higher cfPWV compared to the HIV-negative pregnant women in this study.

Our finding concurs with a study carried out in the United Kingdom, which reported that aortic stiffness was increased among HIV-positive patients [41].

Arterial stiffness impairs the ability of the endothelium to detect and respond to mechanical pressures, thereby compromising the integrity of the endothelial barrier, permitting LDL-c to penetrate the vessel wall. This forms a vicious cycle of stiff arteries and vascular injury [42]. In the present study, HIV-positive pregnant women on ART exhibited increased levels of LDL-c, suggesting vascular damage due to ART. This finding aligns with a study carried out in Turkey that reported significantly increased levels of LDL-c, TC, and triglycerides among the HIV-positive patients compared to the HIV-negative group. ART has been documented to disrupt lipid metabolism, particularly elevating TG levels and decreasing HDL-c [43]. In the present study, a high prevalence of low HDL-c was observed among the HIV-positive group. Certain antiretroviral therapies are linked with endothelial dysfunction and alterations in lipid profiles [44]. Together, these vascular changes increase vascular resistance and eventually lead to the development and progression of hypertension [45]. A study conducted in the Western Cape, South Africa, reported a high prevalence of de novo hypertensive disorders among pregnant women infected with HIV compared to those without HIV [46]. In this study, a high prevalence of pre-hypertension or hypertension was observed among HIV-positive pregnant women compared to HIV-negative pregnant women. This finding suggests that HIV-positive pregnant women are at heightened risk of developing hypertensive complications such as pre-eclampsia. High blood pressure can reduce blood flow to the placenta, elevating the risk of pregnancy outcomes such as foetal growth restriction and preterm birth, among others [47]. Uterine artery Doppler is an accurate method for assessing uteroplacental resistance to blood flow [48]. In this study, the maternal UtA PI was significantly higher in the HIV-positive group. A study reported that some ART could directly contribute to the placental damage, uteroplacental pathology and maternal malperfusion [49,50]. Impaired vascular function can limit blood flow to the tissues and elevate damage to the end organs [51].

Microcirculation through microvascular vessels plays a role in delivering nutrients and draining blood from all tissues and organs in the body. Because the retina and other end organs, including the brain and kidney, have similar structural characteristics and functional properties, the retinal microvascular vessels provide distinct and easy visualisation to assess human health and disease of the human microcirculation [52]. Mitochondrial toxicity resulting from ART administration may affect the retinal pigment epithelium, resulting in retinal vessel damage or vascular dysfunction [53,54]. ART and viral load have been reported to decrease the tone of the retinal vessels [55]. A study conducted in Cape Town, South Africa, reported that decreased retinal arteriolar diameter was associated with the duration of ART use and viral load [56]. In this study, both the CRAE and CRAE were similar between the two groups. However, AVR was lower in the HIV-positive pregnant women on ART, suggesting that ART could induce vascular damage and dysfunction of the retina. Reduced AVR has been documented to be a predictor of cerebral atrophy, stroke and other cardiovascular complications in adults [57]. A study carried out in Singapore also found decreased AVR among HIV-positive patients [58].

Macrovascular and microvascular dysfunction are both independent but related predictors of cardiovascular events [59]. A study reported that wider retinal venular was independently associated with hypertension [60]. The DBP, MAP and cfPW positively correlated with CRVE among HIV-positive pregnant women on ART in this study. This correlation implies that small microvascular vessels and macrovascular vessels are affected by similar pathophysiological processes in the HIV-positive pregnant women on ART. A negative correlation was observed between uCr and AVR among the HIV-positive group on ART implying increased uCr is associated with reduced AVR. This finding suggests a link

between renal dysfunction and retinal microvascular impairment. Retinal microvascular changes often indicate systemic endothelial impairment, a known effect of both ART and HIV [61].

Cardiovascular risk factors, such as DBP, were shown to predict microvascular dysfunction, revealed by decreased AVR in the HIV-positive pregnant women on ART. These findings support the notion that increased BP contributes to elevated vascular resistance and microvascular impairment [62]. In addition, markers of peripheral resistance and arterial stiffness, ABI and cfPWV, respectively were associated with lower AVR, suggesting that macrovascular alterations related to cardiovascular risk may negatively affect microvascular function [63,64]. High levels of LDL-c, which are known to promote atherosclerosis, emerged as a significant predictor of low AVR in this study. LDL-c has been reported to intensify microvascular damage in HIV-positive individuals [65]. Overall, these findings suggest a potential link between cardiovascular risk factors and microvascular impairment in HIV-positive pregnant women on ART, highlighting the need for comprehensive cardiovascular monitoring to improve pregnancy outcomes in this population.

6. Strengths

To our knowledge, this is the first study to assess the relationship between macrovascular changes due to cardiovascular risk factors and microvascular impairment in HIV-positive pregnant women in the early stages of pregnancy in South Africa. We conducted the study among pregnant women without confirmed cardiovascular disease, thereby reducing possible confounding factors that could affect the validity of the findings. Early microvascular and macrovascular geometrical changes in the present study provide early markers for systemic cardiovascular risk assessment.

7. Limitations

This study is a pilot study limited to a small sample size, indicating a low predictive power of the study and, thus, may limit the reliability of the finding. Also, ART compliance was self-reported and therefore it might have affected the overall outcome of the study. Pregnancy independently triggers vascular alterations and therefore it remains unclear if it affected the outcome of the study. However, our inclusion criteria and exclusion criteria were designed to limit such influences.

8. Conclusions

Our findings demonstrate that increased cardiovascular risks due to ART are significant predictors of retinal microvascular dysfunction among HIV-positive pregnant women. ART may induce macrovascular changes such as hypertension and endothelial dysfunction causing impairment of the retinal microvasculature. Microvascular impairment of the retinal could affect the entire microvasculature and contribute to future cardiovascular adverse events within or after pregnancy. Therefore, there is a need for integrated cardiovascular care to improve maternal-foetal well-being in this population.

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