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The Association Between HIV-Related Stigma, ART Adherence, and Cardiovascular Disease Risk in People Living With HIV

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Introduction: HIV/AIDS continues to be a significant health issue in sub-Saharan Africa, with stigma likely affecting ART adherence, and subsequently viremia, inflammation, and cardiovascular disease (CVD). We investigated the association between stigma, ART adherence, and CVD risk among people living with HIV (PLWH).

Setting: A longitudinal study was conducted among 325 PLWH from the Ndlovu Cohort Study, South Africa.

Methods: Stigma was assessed using a 12-item questionnaire (range: 0–44; higher scores indicate greater stigma). Pulse wave velocity (PWV, CVD surrogate marker) and viral load (VL) were assessed at 12 and 36 months. VL was considered a surrogate marker of ART adherence: VL > 1000 copies indicating poor/no adherence, VL 50–1000 copies suboptimal, and VL < 50 copies good adherence. The relationship between stigma, VL, and PWV was assessed by linear regression and changes in PWV overtime by mixed linear models.

Results: At baseline, PLWH (n = 325, mean age (SD) = 41.1 (10.2) years, 67% female) had mean PWV of 7.3 min/s. Good, suboptimal, and poor adherence were 78%, 15%, and 7%, respectively. The mean (SD) stigma score was 16.9 (1.4) and was not associated with VL and PWV. Suboptimal and poor adherence were associated with higher PWV [beta = 4.18 (95% confidence interval (CI): 1.79 to 6.57)] at 12 months and between 12 and 36 months [beta = 1.30 (95% CI: 0.06 to 2.55)] in mixed model analyses in PLWH older than 49 years, respectively. PWV increased by 0.21 min/s (95% CI: 0.02 to 0.40; $P = 0.03$) between 12 and 36 months overall.

Conclusions: In this study, poor ART adherence was associated with higher PWV. The stigma score was low and not associated with ART adherence and PWV.

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INTRODUCTION

Recent statistics indicate that more than 26 million (70%) people living with HIV (PLWH), are from sub-Saharan Africa (SSA), with South Africa (SA) accounting for approximately 8.45 million cases.[1] Approximately 75% of PLWH in SA are receiving antiretroviral therapy (ART), contributing to a reduction in disease progression and a great improvement in life expectancy.[1,2] Consequently, the focus of chronic care for PLWH has shifted toward age-related noncommunicable diseases, particularly cardiovascular diseases (CVDs).[3,4] This shift poses a significant public health challenge, especially for PLWH on ART, who face a 2-fold increased risk of CVD compared with age- and sex-matched people living without HIV.[3,5,6] Despite this heightened CVD risk among PLWH, the exact HIV–CVD pathogenesis remains unclear.[3,7] HIV, coupled with other factors, is suspected to be involved in the development of CVD in

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Ethical approval was obtained from the Ethics Committee of the University of Pretoria (NO: 227/2014) and from the University of Witwatersrand (M230850). Informed consent was obtained from each of the participants before study inclusion. The questionnaires were anonymous, and participation was voluntary.

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PLWH with HIV-associated chronic inflammation as a primary determinant.[8]

Despite HIV/AIDS awareness since the 1980s, persistent misconceptions contribute to stigma and discrimination against PLWH. Individuals with limited or no knowledge of HIV often exhibit fears of infection through casual contact with PLWH, which contributes to HIV stigma.[9,10] Studies showed that stigma and discrimination hinder HIV testing and public health efforts whose objective is to prevent further infections.[11] These barriers prevent PLWH from obtaining essential health care, affecting ART adherence.[12–14] In SA, despite the availability of ART in local health care centers, PLWH have been reported to avoid these nearby facilities to maintain their HIV status undisclosed and to minimize stigma within their families and communities.[15] Achieving at least 95% ART adherence is crucial for successful control of the HIV pandemic,[16,17] yet HIV stigma and discrimination limit disease management.[14,15] In addition, HIV-related stigma causes anxiety and depression in PLWH.[14]

Research on adherence to ART showed that individuals with noncompliance have mortality rates up to 4 times higher than those who adhere to the same treatment.[7,16] Both short and prolonged interruptions of ARTs can lead to reduced $CD4^+$ count, heightened HIV replication, increased vulnerability to opportunistic infections, and an elevated risk of developing ART resistance.[18] Furthermore, discontinuation of ART is associated with heightened immune activation, inflammation, and an increased risk of CVD and other HIV-related diseases.[12,15]

Cultural or social factors, such as stigma, are suspected to contribute to CVD risk, but their impact remains unclear.[7] A possible explanation might be that HIV stigma leads to insufficient ART adherence, and this in turn increases CVD risk through increased viremia and subsequent immune activation.[19] The resultant inflammation promotes the development of atherosclerosis and arterial stiffness, endothelial dysfunction, and platelet and coagulation cascade activation by altering the vascular smooth muscle phenotype.[19,20] Elevated arterial stiffness results in higher pulse pressure and pulse wave velocity (PWV) (the rate with which the pressure waves circulate through the cardiovascular system).[20,21] Consequently, arterial stiffness results in increased left ventricular afterload, causing left ventricular impairment, myocardial infarction, and heart failure.[19,20] PWV has been established as a gold-standard CVD risk predictor in multiple populations.[22–25] Its reliability and ability to predict future cardiovascular events make it particularly valuable in resource-constrained settings such as SSA, where alternative methods may be less accessible. In addition, 1 meter per second (min/s) increase in PWV is associated with 1.14 CVD risk.[26]

In SSA, the relationship between stigma and ART adherence has not yet been examined for CVD risk. Therefore, this study aimed to investigate this association among middle-aged PLWH in rural SA. We hypothesized that stigma is associated with suboptimal ART adherence, and this in turn results in a higher CVD risk measured by PWV.

METHODS

Study Setting

This study formed part of the Ndlovu Cohort Study (NCS), conducted in Elandsdoorn, a rural area within the Moutse area, in the Limpopo province, South Africa.

Study Population

The NCS is a longitudinal study that commenced in 2014 with follow-ups at 12, 24, 36, and 48 months.[27] The study population was enrolled from December 2014 to May 2017 and included 887 PLWH [529 women (60%)]. All recruited participants provided informed consent, were 18 years or older, and committed to long-term follow-up. The NCS exclusively includes participants from a rural Black population in SA. A total of 690 PLWH (78%) were on ART, with 89% of those on first-line and 11% on second-line therapy[28] while 197 (22%) were ART-naïve at baseline. Those who were ART-naïve at baseline (recruitment) were immediately offered ART initiation on testing HIV positive. By the 12-month follow-up, these participants were no longer naïve, having been on treatment for a minimum of 12 months. HIV viral load (VL) was measured at baseline, 12, 24, and 36 months by the realtime PCR (qPCR) at the TOGA laboratory. In addition, PWV was assessed at 12 and 36 months. In this study, PLWH with full PWV data at both 12 and 36 months were included (see Supplementary Fig. 1, Supplemental Digital Content, http://links.lww.com/QAI/C455).

Data Collection

Sociodemographic and Clinical Characteristics

Questionnaires were used to capture information about stigma[29] and lifestyle (smoking and alcohol usage). The stigma questionnaire was only assessed at baseline.[27,28]

Physical Measurements

Trained staff recorded all the physical measurements (blood pressure, pulse rate, and anthropometric information) at baseline and follow-up visits. Height, weight, and hip and waist circumference measurements were taken in a standing position as per the standardized procedure. Blood pressure was measured in a sitting position after 5 minutes of rest with a sphygmomanometric device on both arms and repeated on the side with the highest values. The mean of all measurements was used in the analysis. For 12–6 months follow-up, all participants were invited for a physical visit.

Lipid and Glucose Measurements

Blood samples to measure lipid profiles and random glucose were taken at each clinic visit. They were only assayed at the study baseline.

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Pulse Wave Velocity

PWV, a surrogate marker of arterial stiffness and function,[22] was assessed from 12- to 36-month data to investigate CVD risk. All the participants whose 12-month follow-up visit was scheduled before 2016 were not assessed for PWV because this measurement was only introduced into the study in 2016. The participants were in a supine position for the PWV test. Three electrodes were attached to record the heart rhythm. Subsequently, the carotid–femoral distance was measured with a measuring tape. The value was then multiplied by 0.8.[30–32] Quality was based on operator index (%SD), ECG tracing, and SD <10%. The tonometer was used to obtain a stable pulse waveform for 12 heartbeats on the right common carotid artery. The same procedure was performed on the right femoral artery. The results of pulse waveforms that satisfied the quality requirements were stored on the sphygmocor software (SphygmoCor XCEL, AtCor Medical PTY.Ltd., Sydney Australia).[33–35] In this study, PWV was treated as a continuous variable where higher values indicate greater arterial stiffness. Published normal values for PWV are: 6.6 min/s for those aged 18-29 years, 6.8 min/s for those aged 30–39 years, 7 min/s for those 40–49 years, 7.6 min/s for 50–59 years, and 9-10 min/s for those older than 60 years.[36] Overall, a PWV above 10 min/s was confirmed in a meta-analysis as a reliable marker of risk for cardiovascular mortality.[37]

HIV-Related Stigma

A 12-item HIV/AIDS stigma questionnaire was used at enrolment (baseline visit) to assess thoughts and feelings of being stigmatized.[29] The 12 questions were used to grade HIV-related stigma on a 4-point Likert scale (never = 1, sometimes = 2, often = 3, and always = 4). In this study, question 6 was excluded because it was worded with a double-negative statement, which seemed to confuse the participants. The scale response was transformed into 44 points of overall stigma from the remaining 11 questions and considered as a continuous variable. A higher score indicated a stronger HIV stigma. This questionnaire was only given at baseline.

Viral Load

Viral load (VL) was measured at baseline (0 months) and 2 key time points of interest, 12 and 36 months after the baseline visit. The VL category was used as a surrogate marker of ART adherence, where a VL >1000 copies was regarded as no adherence, low-level viremia (between 50 and 1000 copies) as suboptimal adherence, and undetectable VL (<50 copies/mL) as good adherence. At baseline, participants who were newly diagnosed with HIV were immediately put on treatment. Thus, at 12 months, all these participants had been started on treatment for at least 12 months, and the same applied at the 36-month time point. Notably, previous studies have shown that low-level viremia predominantly associated with suboptimal adherence.[38]

Ethical Considerations

Data Analysis

Statistical data analysis was performed using the R studio programme (R.4.2.2, Posit, PBC, Boston, MA).[39,40] All possible covariates (sex, age, duration of diagnosed HIV, time on ART, body mass index (BMI), alcohol and tobacco use, and systolic and diastolic BP) and stigma included in this study were collected at baseline. VL and PWV data included in this study were measured at 12 and 36 months. Basic descriptive statistics for the categorical variables (VL, sex, ART, duration of diagnosed HIV infection, and alcohol and tobacco use) included frequency and percentage; and for continuous variables [age, PWV, stigma, and diastolic and systolic blood pressure (SBP)] mean; and SD for normally distributed data. For skewed distribution, median and interquartile ranges were included.

For 325 PLWH, PWV data at both 12- and 36-month follow-up were available (see Supplementary Fig. 1, Supplemental Digital Content, http://links.lww.com/QAI/C455). Of the 325 included participants in the study, the missingness on the variables varied from 0.6%–8.9%: namely BMI, glucose, LDL, duration of diagnosed HIV infection, and VL. There was 8.9% missingness for VL at 12 months, and only 1.5% of the participants did not have VL at 36 months. Missing data in the covariates were regarded as missing at random, and multiple imputation was performed using multivariate imputation by chained equations to generate 10 imputations and 10 iterations. Subsequently, imputation checks (convergence) were performed to inspect the imputed data set. The imputed data set was then analyzed and combined using Rubin[41]'s rules. PWV, VL, BMI, glucose, LDL, waist circumference, systolic and diastolic blood pressure, age, sex, alcohol and tobacco use, 12-item stigma questionnaire, HIV, and time on ART were included in the imputation model.

To assess the relationship between stigma and ART adherence, one-way ANOVA was performed with the independent variable of interest being baseline overall stigma score and VL status (measured at 12 and 36 months) as the 3 groups (VL < 50, 51–1000, and >1000 copies/mL). Bivariable models were run on possible baseline covariates and follow-up PWV data at 12 and 36 months. Multicollinearity was assessed using a correlation matrix and a variance inflation factor between the independent variables. Subsequently, baseline covariates significantly associated with PWV and not highly correlated with each other (low VIF) were included in successive models. Multiple linear regression was used to assess the association between the independent variables (stigma and ART adherence) and the dependent variable, PWV. Age, sex, SBP, time on ART, smoking, and BMI were included as confounders/covariates in the multiple linear models. Beta coefficients (95% confidence interval) were used to determine the strength and direction of the association. Model 1 had overall stigma, and then, we added VL as a categorical variable in model 2, with a VL of <50 copies/mL as a reference. In model 3, we added age category (reference = 18–29 yrs. vs. 30–49 yrs. and >49) and sex (reference = female). In model 4, we then added SBP, time on ART, smoking (reference=never

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smoked), BMI, and triglycerides. Finally, model 5 consisted of the independent variables of interest, covariates, and interaction terms between VL and age, where having a VL <50 copies/mL and being in the age category18–29 years was considered as a reference. To respect the rule of parsimony in multilinear regression, we did not include in those models' variables which were $P > 0.05$ in the 12-month bivariate analyses or collinear with other variables.

To assess trends in PWV over time, linear mixed models using the restricted maximum likelihood method (REML) were fitted. Clinic visits at 12 and 36 months (time), baseline overall stigma, and VL category (a surrogate marker of ART adherence, measured at 12 and 36 months) were specified as fixed effects in model 1. Subsequently, potential covariates such as age, sex, SBP, time on ART, smoking, and BMI were included (mixed models 2, 3, and 4). In addition, interaction terms between age and VL categories were added (mixed model 5).

RESULTS

Table 1 summarizes the characteristics of the participants at baseline, as well as VL and PWV at 12 and 36 months. Of the 325 study participants, 33% (108) were males. At baseline, the mean age was 41.1 (10.2) years, median systolic and diastolic blood pressure were 114.4 (19.1) mm Hg and 73.6 (12.2) mm Hg, respectively, and the median BMI was 24.0 (5.9) kg/m^2. Most participants had never used tobacco and less than half had used alcohol. Percentage difference of undetectable viremia (good adherence) between the 2 time points (12 and 36 months) was 1%. Approximately 5% transitioned from high viremia to low VL (suboptimal ART adherence) at 36 months. The percentage of people with high VL (poor adherence) decreased from 15% at 12 months to 10% at 36 months. Overall stigma was low with a mean (SD) score of 16.9 (1.4), with approximately 79.6%–100% of the participants indicating no or low stigma on the 11 questions used for this analysis (see Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/QAI/C455). The overall percentage for no or low stigma was 87%. The PWV median at 12 and 36 months was 7.3 (6.3–8.5) and 7.6 (6.7–8.4) m/s, respectively (Table 1). There was no significant association between overall stigma and ART adherence (as represented by the 3 VL categories) [one-way ANOVA test statistic, F (2, 322) = 0.59, $P = 0.55$]. Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/QAI/C455 summarizes the results of the bivariate analysis at 12 and 36 months. Stigma was not associated with PWV (index of CVD risk) in the crude models [at 12 months −0.10 min/s ($P = 0.26$) and 36 months −0.09 min/s ($P = 0.24$)] nor in the multivariable regression analyses ($\beta = 0.01$, $P = 0.88$).

To examine the nonlinear associations between PWV and VL, regression models were estimated using dummy-coded variables for VL, where undetectable VL was used as a reference. Low viremia (VL = 50–1000) showed a significant positive association with PWV as compared with the undetectable viremia (VL < 50) in models 2–4. High viremia was not significantly associated with PWV as compared with the undetectable viremia. In model 5, we added interactions between VL categories and age groups to explore potential age-specific effects. Being 49 years or older with low viremia was associated with an additional 4 min/s increase in PWV when compared with the reference group (18–29 years) with undetectable viremia (VL < 50) ($\beta = 4.18$, $P = 0.001$). In that model with interaction terms, low viremia was not significantly associated with PWV as a main effect, whereas high

TABLE 1. Demographics and Clinical Characteristics of the 325 Participants Living With HIV From the NCS With Full Case PWV Data at 12 and 36 Months

Characteristics	Baseline (n = 325)	
Age, mean (SD), years	41.1 (10.2)	
Men (n, %)	108 (33)	
Women (n, %)	217 (67)	
Cardiovascular measurements		
SBP (mm Hg)	112.8 (101.0–126.0)	
DBP (mm Hg)	72.2 (65.6–81.0)	
Pulse rate per minute (bpm)	76.0 (67.0–85.0)	
Anthropometric measurements		
BMI (kg/m^2)*	23.1 (19.8–26.9)	
Waist circumference (cm)	84.2 (76.0–92.0)	
Lifestyle factors		
Alcohol use (n, %)		
Never	182 (56)	
Ever	143 (44)	
Tobacco use (n, %)		
Never	255 (78)	
Current	70 (22)	
Other CVD risk factors		
Glucose (mmol/L)*	4.7 (4.3–5.2)	
LDL (mmol/L))*	2.1 (1.7–2.7)	
HDL (mmol/L)*	1.4 (1.2–1.7)	
Triglycerides (mmol/L)*	1.0 (0.7–1.40)	
Clinical characteristics		
HIV-related factors		
Duration of diagnosed HIV infection*		
In months (median, IQR)	60.0 (14.0–101.0)	
Time on ART		
In months (median, IQR)	43.0 (3.0–94.0)	
ART status (n, %)		
ART naïve (at baseline)	62 (19)	
On ART	263 (81)	
Overall stigma		
Mean (SD)	16.9 (1.4)	
	12 mo	36 mo
Viral load (copies/mL) n (%)		
<50	254 (78)	256 (79)
50–1000	23 (7)	37 (11)
>1000	48 (15)	32 (10)
Cardiovascular measurements (pulse wave velocity)		
Median (IQR)	7.3 (6.3–8.5)	7.6 (6.7–8.4)

Data are expressed as median (IQR) and count (%) unless stated otherwise.

*Indicates the imputed value. Missingness ranged from 0.6% to 8.9% (details included in the data analysis section).

DBP, diastolic blood pressure; HDL, high-density lipoproteins; IQR, interquartile range; SBP, systolic blood pressure; LDL, low-density lipoproteins.

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viremia became significantly negatively associated with PWV (Table 2, model 5). An interaction term between high viremia (VL >1000) and being 30–49 years old was significantly associated with PWV (β = 1.67, $P = 0.03$) when compared with the reference group (18–29 years × VL < 50); when adding to the main effect of high viremia (β = −1.66), this meant a weak positive association between high viremia and PWV in the 30–49 year old group. The distribution of participants across VL categories showed small sample sizes for VL = 50–1000 in the 18–29 (n = 5) and older than 49 (n = 4) age groups, as well as VL > 1000 in the 18–29 (n = 9) and older than 49 (n = 9) age groups.

A mixed linear model was used to assess changes in PWV overtime. There was a significant increase in PWV of 0.21 min/s ($P = 0.04$) between 12 and 36 months in a model with only overall stigma, and VL. Overall stigma and low viremia were not associated with a change in PWV (Table 3). Clinic visit (time) was significantly and positively associated with PWV in crude and adjusted models. Being 49 years or older was independently associated with higher PWV compared with the reference group. In model 4, including an interaction term between age and viral load, VL >1000 became significantly associated with higher PWV. Moreover, having a VL >1000 and being 49 years or older showed a significant association with an accelerated increase in PWV (Table 3). For those aged 30–49 years, a significant positive association with PWV in models 2 and 3 ($P < 0.05$) (Table 3) was observed, while male sex showed a significant positive association with PWV only in model 2 ($P < 0.001$).

DISCUSSIONS

This study aimed to investigate the association of stigma and ART adherence at baseline with arterial stiffness among PLWH at 12 months follow-up and changes in arterial stiffness (as measured by PWV) from 12 to 36 months. Our findings showed that HIV-related stigma was low and not associated with ART adherence or PWV. However, high viremia (>1000 copies/mL) showed contrasting effects across age groups: an inverse association with PWV in younger individuals suggests that elevated VL may not significantly affect arterial stiffness at younger age, whereas a weakly positive association in the 30–49 age group indicates that prolonged high VL may contribute to arterial stiffness as individuals age. High viremia may reflect active uncontrolled HIV infection, including wasting, and thus a lower contribution of traditional cardiovascular risk factors to PWV, which may outweigh any possible impact of immune activation on PWV. Low viremia in the age group older than 49 years was independently associated with higher PWV at 12 months. In addition, PWV increased significantly over time with high viremia significantly associated with an increase in PWV in the age group older than 49 years. Although the observed PWV increase of 0.21 min/s over time

TABLE 2. Association Between HIV-Related Stigma and ART Adherence on CVD Risk (Outcome = PWV) at 12 Months

	Pulse Wave Velocity				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
	β (95% CI)	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
Overall stigma	−0.10 (−0.21 to 0.01)	−0.09 (−0.25 to 0.07)	0.03 (−0.11 to 0.16)	0.02 (−0.12 to 0.15)	0.01 (−0.12 to 0.14)
VL <50 copies/mL reference					
VL 50–1000 copies/mL		**1.17 (0.30 to 2.04)**	**1.28 (0.55 to 2.01)**	**1.06 (0.32 to 1.80)**	0.22 (−1.49 **to** 1.94)
VL >1000 copies/mL		−0.48 (−1.12 to 0.17)	−0.32 (−0.86 to 0.22)	−0.32 (−0.87 to 0.22)	**−1.66 (-2.96 to −0.36)**
18-29 (in yrs.) reference					
30–49 (in yrs.)			**0.97 (0.36 to 1.57)**	**0.74 (0.11 to 1.37)**	0.35 (−0.37 to 1.08)
>49 (in yrs.)			2.98 (2.27 to 3.68)	**2.42 (1.62 to 3.23)**	**1.87 (1.00 to 2.74)**
Female reference					
Sex (male)			**0.89 (0.48 to 1.30)**	**0.57 (0.07 to 1.06)**	**0.50 (0.01 to 0.98)**
Systolic BP (mm Hg)				**0.02 (0.005 to 0.03)**	**0.01 (0.003 to 0.03)**
Time on ART				0.004 (−0.004 to 0.01)	0.004 (−0.001 to 0.01)
Never smoked reference					
Ever smoked				0.11 (−0.42 to 0.65)	−0.01 (−0.53 to 0.51)
BMI				**−0.04 (−0.07 to -0.01)**	**−0.05 (-0.08 to −0.01)**
Triglycerides				0.10 (−0.14 to 0.34)	0.15 (−0.09 to 0.38)
VL <50:18–29 yrs. Reference					
VL 50–1000: Age 30–49 yrs					0.08 (−1.85 to 2.02)
VL >1000: age 30–49 yrs					**1.67 (0.21 to 3.14)**
VL 50–1000: age>49 yrs					**4.18 (1.79 to 6.57)**
VL >1000: age >49					1.39 (−0.39 to 3.17)

Bolded values indicate statistically significant associatios with PWV ($p < 0.05$)

Multivariable models at 12 months, outcome = PWV (CVD risk predictor). Model 3: Independent variables of interest (overall stigma and VL) and covariates (sex and age). Model 4: adjusted for sex, age, systolic BP, time on ART, smoking, BMI, and triglycerides. Model 5: covariates in model 4, and interaction term between age and VL.

ART, antiretroviral therapy; BP, blood pressure.

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TABLE 3. Estimates of the Fixed Effects for the Association of HIV-Related Stigma, ART Adherence, and CVD Risk Between 12 and 36 Months

	Pulse Wave Velocity	
	β (95% CI)	***P***
Model 1: unadjusted		
Clinic visit		
12 mo	Ref	REF
36 mo	**0.21 (0.01 to 0.40)**	**0.04**
Overall stigma	−0.08 (−0.20 to 0.05)	0.21
Viral load		
VL <50 copies/mL	Ref	Ref
VL 50–1000 copies/mL	0.25 (−0.19 to 0.69)	0.27
VL >1000 copies/mL	−0.33 (−0.74 to 0.07)	0.11
Model 2: adjusted (age and sex)		
Clinic visit		
12 mo	Ref	Ref
36 mo	**0.21 (0.02 to 0.40)**	**0.03**
Overall stigma	0.02 (−0.08 to 0.12)	0.73
Viral load		
VL <50 copies/mL	Ref	Ref
VL 50–1000 copies/mL	0.35 (−0.06 to 0.76)	0.10
VL >1000 copies/mL	−0.20 (−0.57 to 0.17)	0.29
Age		
18–29 yrs	Ref	Ref
30–49 yrs	**0.99 (0.54 to 1.43)**	**<0.001**
>49	**2.61 (2.09 to 3.12)**	**<0.001**
Sex		
Female	Ref	Ref
Male	**0.72 (0.41 to 1.03)**	**<0.001**
Model 3: adjusted (age, sex, SBP, time on ART, smoking, BMI, and triglycerides		
Clinic visit		
12 mo	Ref	Ref
36 mo	**0.21 (0.02 to 0.40)**	**0.03**
Overall stigma	−0.003 (−0.10 to 0.10)	0.95
Viral load		
VL <50	Ref	Ref
VL 50–1000	0.23 (−0.17 to 0.64)	0.26
VL >1000	−0.25 (−0.62 to 0.12)	0.19
Age		
18–29 yrs	Ref	Ref
30–49 yrs	**0.71 (0.26 to 1.16)**	**0.003**
>49	**1.95 (1.39 to 2.52)**	**<0.001**
Sex		
Female	Ref	Ref
Male	0.33 (−0.02 to 0.68)	0.07
Systolic BP	**0.02 (0.01 to 0.02)**	**<0.001**
Time on ART	**0.005 (0.002 to 0.01)**	**0.001**
Smoking		
Never	Ref	Ref
Ever	−0.28 (−0.06 to 0.62)	0.11
BMI	**−0.04 (−0.07 to −0.02)**	**0.003**
Triglycerides	0.12 (−0.06 to 0.30)	0.22
Model 4: adjusted (age, sex, SBP, time on ART, smoking, BMI, and triglycerides), and interaction term between age and viral loads		
Clinic visit		
12 mo	Ref	Ref
36 mo	**0.21 (0.02 to 0.40)**	**0.03**
Overall stigma	−0.004 (−0.02 to 0.40)	0.93
Viral load		
VL <50	Ref	Ref
VL 50–1000	−0.18 (−1.30 to 0.95)	0.75
VL >1000	**−1.06 (−1.94 to −0.17)**	**0.02**
Age		
18–29 yrs	Ref	Ref
30–49 yrs	0.50 (−0.01 to 1.01)	0.06
>49	**1.64 (1.02 to 2.26)**	**<0.001**
Sex		
Female	Ref	Ref
Male	0.31 (−0.04 to 0.65)	0.09
Systolic BP	**0.02 (0.01 to 0.02)**	**<0.001**
Time on ART	**0.004 (0.002 to 0.01)**	**0.001**
Smoking		
Never	Ref	Ref
Ever	0.26 (−0.08 to 0.60)	0.14
BMI	**−0.04 (-0.07 to −0.02)**	**0.001**
Triglycerides	0.11 (−0.06 to 0.29)	0.22
Interaction term		
VL <50:18–29 yrs	Ref	Ref
VL 50–1000: Age 30–49 yrs	0.24 (−0.99 to 1.48)	0.70
VL >1000: Age 30–49 yrs	0.88 (−0.11 to 1.88)	0.09
VL 50–1000: age >49 yrs	1.13 (−0.27 to 2.56)	0.12
VL >1000: age >49	**1.30 (0.06 to 2.55)**	**0.04**

Mixed models with random intercepts.
Model 1: clinic visit, overall stigma, and VL.
Model 2: clinic visit, overall stigma, VL, age, and sex.
Model 3: Overall stigma, and VL, adjusted for clinic visit and covariates (age, sex, SBP, time on ART, smoking, BMI, and triglycerides.
Bolded values indicate statistically significant associations with PWV ($P < 0.05$).
Interaction terms (age: VL).
BP, blood pressure.

was statistically significant, it falls below the minimal clinically important difference of approximately 1.0–1.1 min/s.[42,43] However, even small changes in PWV may reflect early arterial stiffening trends in longitudinal studies, underscoring the importance of monitoring these changes over time. PWV naturally increases after the age of 40–50 years due to age-related arterial stiffening, making it a more reliable marker of arterial stiffness in older adults compared with younger individuals. These findings may reflect the complex interplay between VL, immune activation, and age-related differences, where low viremia could indicate

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chronic immune activation driving arterial stiffness, while high viremia might show weaker effects in younger individuals.[19,20,42,43] Covariates including age, male sex, SBP, time on ART, and triglycerides were significantly associated with PWV.

Our finding of no association between stigma and PWV is not consistent with previous studies.[7,44] A South Asian study investigating HIV stigma, perceived social support, and risk of premature atherosclerosis in 119 participants cross-sectionally found that PLWH felt lower perceived social support.[7] Furthermore, they observed the presence of high values of carotid intima-media thickness (CIMT, a marker of subclinical cardiovascular disease) in patients living with HIV to be associated with increased HIV stigma. The low stigma in our study might, to a large part, be attributed to the extensive HIV education provided by the Ndlovu Care Group at Elandsdoorn, Limpopo, SA.[45–47] HIV-related stigma has been linked with misinformation about the spread of the disease,[48,49] and increased HIV education has been shown to decrease stigma.[50,51] A cross-sectional study conducted in Zambia and SA,[44] assessing the relation between HIV stigma and ART adherence, is in alignment with our study findings and indicated that the South African population had low stigma and good ART adherence when compared with the Zambian population. The study further explains that HIV stigmatization and its consequent negative impact on ART adherence might have been significantly minimized by a strong history of community-based advocacy and awareness regarding HIV and HIV treatment in the South African context. In our study, stigma was not associated with viremia, which may reflect the low levels of stigma observed in this population. This could also be a result of the successful efforts of the Ndlovu Care Group in promoting ART adherence and HIV education, which have likely minimized the adverse impacts of stigma. A cross-sectional study by Roozen and colleagues[52] that investigated the determinants of CVD risk in a larger sample of the same cohort as ours, observed that suboptimal viral control in elderly people (n = 826 PLWH) was associated with increased CVD when using CIMT. These findings parallel our own, which found that older PLWH with suboptimal ART adherence had an increased CVD risk at baseline. This increased CVD risk in those older than 49 years with suboptimal adherence that may be caused by the higher chronic inflammation and endothelial dysfunction[53] resulting from suboptimal viral control. Others have hypothesized that HIV itself may directly damage vascular endothelium, possibly through negative factor (*nef)* protein.[54,55] Our finding that CVD risk measured by PWV is augmented in people with HIV with suboptimal viral control older than 49 years corroborates those prior results. The small sample sizes of participants with low-level viremia (n = 23) and high viremia (n = 48) at 12 months, particularly when stratified by age groups, may have influenced the stability of estimates and variability of interaction effects. These limitations reduce the statistical power to detect robust associations between viremia and PWV. Therefore, these findings should be interpreted with caution.

Like our study, other factors than HIV-stigma, such as male sex and SBP, were associated with CVD risk in the literature.[7] In men, the risk of CVD increases over time, accompanied by an ongoing progression of the atherosclerotic process.[47,56,57] Conversely, owing to oestrogen's advantageous impact on the cardiovascular system, women of reproductive age may experience protection against atherosclerosis.[58,59] Traditional cardiovascular risk factors were uncommon in our cohort. This aligns with our previous findings[28] emphasizing the potential role of HIV infection and/or ART in increasing CVD risk through nontraditional pathways, including chronic inflammation and immune activation.[19] These pathways may drive arterial stiffness and CVD risk independently of classic risk factors, underscoring the need for research on HIV-associated CVD and the long-term effects of ART on vascular health, even in individuals with low-traditional risk profiles. A longitudinal[60] and cross-sectional study[61] conducted in SA investigating CVD risk using PWV and CIMT in PLWH and controls showed that there was no difference in PWV or CIMT between both groups. The studies further demonstrated that age and male sex were positively associated with a higher PWV.[60,61] Similar to our findings, a cohort study in Namibia found that being on long-term ART was associated with greater arterial stiffness through increased carotid–femoral augmentation index, another marker of arterial stiffness.[62] To date, there are not many longitudinal studies on the topic, especially in SA. In our study, we observed a significant inverse association between BMI and PWV. With a median BMI of 23.0 in our study, this may be an reflection of weight gain associated with consistent adherence to ART regimens.

This study had some limitations. The stigma information was gathered through self-reports by the use of questionnaires, which could have introduced reporting bias, wherein study participants may have provided responses perceived as socially acceptable rather than strictly truthful. Furthermore, stigma data were collected cross-sectionally, therefore may not give precise causal inference. It is also possible that stigma in people with HIV may be of a complex nature and not easily captured in the series of questions used in this specific questionnaire. In particular, this stigma questionnaire did not include enacted or anticipated stigma, which may have decreased the sensitivity of this specific instrument. Our sample size is likely underpowered and may therefore result in underestimation of the causal inference. We adapted our stigma questionnaire from a study by Kalichman and colleagues conducted in SA.[29] However, the validity of the questionnaire was not evaluated in their research, which also involved a limited number of participants. Therefore, our findings may not be generalizable to other sub-Saharan African settings, especially where HIV education is limited. In this study, nonparticipation may have occurred in participants experiencing or in fear of stigma. Selection bias might also arise because PLWH experiencing high levels of stigma may not have enrolled in the NCS; therefore, the exposure–outcome relationship could have been underestimated. In our study, there was a loss to follow-up, which may also have had an impact on the true association.

Although VL serves as a useful and good indirect measure of ART adherence, in our study, it was used as a surrogate marker because it is a robust and widely accepted

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indicator in resource-limited settings, where objective adherence measures are often unavailable. Frequent VL monitoring is essential, as it provides a clear measure of treatment efficacy, with suppressed VL (<50 copies/mL) reflecting good adherence. While low-level viremia (50–1000 copies/mL) often suggests nonadherence, resistance can occasionally contribute.[63,64] No single adherence test fully substitutes for VL monitoring,[65] underscoring its utility in assessing adherence and clinical outcomes. However, it is possible that some individuals with high VL are actually highly adherent, and their viremia results from drug resistance rather than nonadherence. Hence, a limitation of our study is the lack of objective measurements for ART adherence.

CONCLUSIONS AND FUTURE DIRECTION

Our analysis showed low HIV-related stigma in our rural South African study population. HIV-related stigma was not associated with adherence nor risk of CVD. Suboptimal adherence was significantly associated with PWV in people older than 30 years suggesting that with increasing age, the impact of low-grade inflammation triggered by measurable viremia accelerates CVD risk. Besides, the presence of CVD risk was found to be related to well-known risk factors such as sex, age, and hypertension. To further investigate the association between HIV-related stigma and ART adherence on CVD risk, studies should be conducted in settings with high HIV stigma.

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