Cardiovascular Topics

The temporal relationship between body composition and cardiometabolic profiles in an HIV-infected (on ART) and HIV-free Western Cape study population

Yushra Dinnie, Frans Everson, Festus M Kamau, Ingrid Webster, Boipelo Kgokane, Patrick De Boever, Nandu Goswami, Hans Strijdom

Abstract

Aim: Cardiovascular risk is a health concern in people living with HIV/AIDS (PLWH). This longitudinal study (baseline vs 36 months) aimed to investigate the relationship between body composition and markers of cardiovascular risk in a South African study population [HIV-free, $n = 22$ vs HIV-positive on antiretroviral therapy (HIV+ART), $n = 73$].

Methods: Health questionnaires, anthropometric measurements, biochemical analyses and flow-mediated dilation were performed. Linear mixed-model statistical analyses were applied.

Results: HIV+ART vs HIV-free groups were independently associated with body mass index (BMI) [–4.92 (–7.99 to –1.84) kg/m^2, $p = 0.002$] and waist circumference [–10.48 (–17.19 to –3.77) cm, $p = 0.003$]. ART duration was associated with BMI [2.60 (0.57 to 4.62) kg/m^2, $p = 0.013$], waist circumference [3.83 (0.03 to 7.63] cm, $p = 0.048$] and high-density lipoprotein cholesterol levels [20.18 (2.37 to 41.09) %, $p = 0.025$].

Conclusion: The data showed that intricate relationships existed in this study population between HIV, ART, body composition and cardiometabolic variables. There is a need for more research investigating cardiovascular risk in PLWH, particularly in the context of changes in body composition.

Keywords: body composition, body mass index, waist circumference, HIV/AIDS, cardiovascular risk, antiretroviral therapy

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In 2020, 37.6 million people were living with HIV/AIDS (PLWH) with 73% of PLWH on antiretroviral therapy (ART).[1] Sub-Saharan Africa (SSA) represents approximately 71% of the global HIV population.[2,3] During the pre-ART era, HIV/AIDS was characterised by severe wasting and high mortality rates.[4,5] In the post-ART era, these effects have been reversed.[6] Despite the success of ART, various non-AIDS-related co-morbidities such as cardiovascular disease (CVD) have emerged.[7]

Increasing rates of overweight/obesity have been observed in PLWH.[8-10] ART-associated effects, such as increased appetite, lethargy and a rapid decline in viral load have been associated with a change in body composition in PLWH.[10] Additionally, HIV- and/or ART-associated cardiometabolic risk factors such as visceral adiposity and dyslipidaemia predispose PLWH to cardiovascular risk factors such as hypertension, atherosclerosis and endothelial dysfunction, which place PLWH at an increased risk for developing CVD compared to the general population.[7-9,11]

Despite representing the vast majority of the global HIV/AIDS population, cardiovascular risk in PLWH from SSA is not well described, even more so in the context of body composition.[12] Considering the paucity of data from SSA, this longitudinal study aimed to investigate the putative temporal changes in body composition and their associated cardiometabolic risk factors in HIV-free versus HIV+ART study groups from the Western Cape, South Africa.

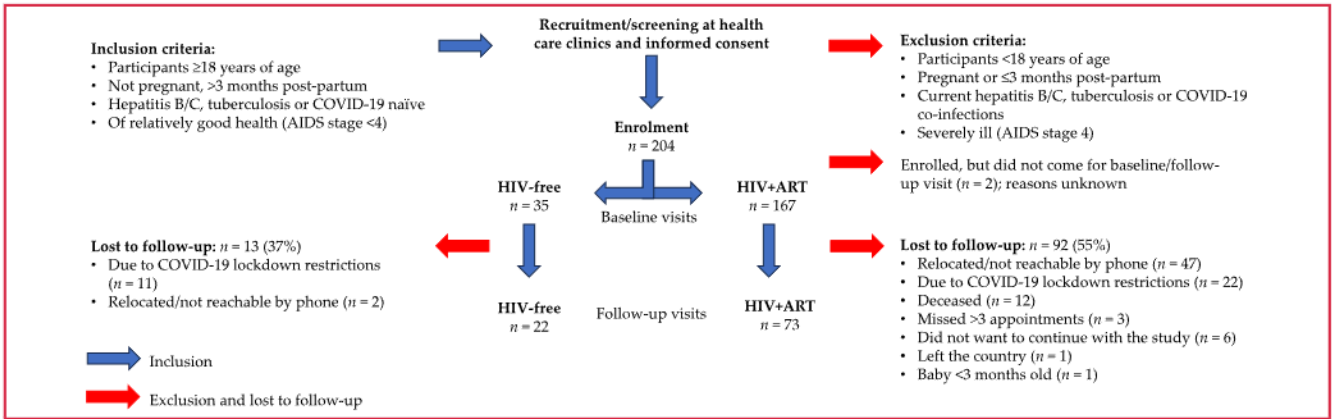

Fig. 1 Consort diagram showing study groups, inclusion/exclusion criteria and loss to follow up of the current study. COVID-19, coronavirus-19 disease; ART, antiretroviral therapy.

Methods

Ethics approval was granted by the Health Research Ethics Committee of Stellenbosch University (ethics reference number: N19/02/029). This study was embedded in a larger parent study named EndoAfrica.[12]

Study participants were mostly of self-identified mixed ancestry and gave written, informed consent before being enrolled in this study, as previously described.[12] The study followed a longitudinal, repeated-measures design (baseline and 36-month follow up). Volunteering study participants were recruited from healthcare clinics in the Worcester area, Western Cape, South Africa.

HIV-negative control (HIV-free) and HIV-positive participants on ART (HIV+ART) receiving either first-line [emtricitabine, tenofovir and efavirenz at baseline, or dolutegravir 3 (DTG) based at 36 months] or second-line (lopinavir/ritonavir based) ART were recruited for the study. Therefore, the type of ART was not an inclusion or exclusion criterion.

All participants fasted for eight hours or longer before clinical assessments. A total number of 105 participants (55%) of the study population were lost to follow up. The 36-month follow up happened during the height of the COVID-19 pandemic. Also, a large number of participants relocated or could not be traced during this period. Only participants who completed baseline and 36-month follow-up visits were included in the study. Therefore, 95 study participants (HIV-free: $n = 22$ and HIV+ART: $n = 73$) were included in this study. A consort diagram of the participant selection process is shown in Fig. 1.

Demographic, lifestyle, number of meals per day, level of physical activity and socio-economic data were collected using a comprehensive health questionnaire. Information about the period of HIV infection and ART treatment were collected from patient files.

A qualified research nurse conducted anthropometric measurements, which included weight, height, and waist and hip circumferences. Weight was measured using an electronic scale (Omron, Kyoto, Japan), height was measured using a stadiometer (SECA, Hamburg, Germany) and waist and hip circumferences were measured using a measuring tape. Additionally, waist-to-hip ratio and body mass index (BMI) were calculated. BMI was sub-categorised as underweight (< 18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2) and obese (> 30 kg/m^2), according to World Health Organisation (WHO) guidelines.[13] Elevated waist-to-hip ratio was defined as > 0.85 and > 0.90 for women and men, respectively, according to WHO guidelines.[14]

Following anthropometry, brachial systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) were measured using an Omron M6 (Omron, Kyoto, Japan) according to American Heart Association standards.[15] Participants were seated and asked to rest for five minutes before blood pressure measurements were performed. Three blood pressure measurements were taken at five-minute intervals and the mean SBP, DBP and HR were calculated, respectively. Hypertension was defined as SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg.[16]

The HIV statuses of all HIV-free participants were confirmed with an HIV rapid test (SD Bioline HIV 1/2 3.0 immunochromatographic test kit, Standard Diagnostics, Republic of Korea). Blood samples were collected from all study participants and sent to the National Health Laboratory Service (NHLS), Tygerberg Hospital (Western Cape, South Africa) for biochemical analysis, using standardised laboratory techniques.

Biochemical analyses included the quantification of plasma lipids [total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides], high-sensitivity C-reactive protein, liver gamma-glutamyl transferase (GGT), fasting glucose concentration, haemoglobin (Hb) and glycated haemoglobin levels (HbA_{1c}). Estimated glomerular filtration rate (eGFR) was calculated as previously described.[17] Additional blood samples were taken from the HIV+ART participants and sent to the NHLS for the quantification of viral loads and CD4 counts.

The flow-mediated dilation (FMD) procedure was based on a previously described protocol.[18] FMD was performed with the subject in the supine position by ultrasound-directed visualisation of the right brachial artery, 3–4 cm proximal to the elbow [Esaote MyLab™ Five portable ultrasound (Genoa, Italy)] with an Esaote Doppler probe (LA523, 12 MHz, Italy) connected to computerised software with edge-detection technology (Quipu Cardiovascular Suite™; Pisa, Italy).

The mean baseline brachial artery lumen diameter was determined over a 60-second period. Ischaemic occlusion (hyperinflation of a blood pressure cuff around the forearm at 50 mmHg supra-systolic pressure for five minutes) was followed by inducing reactive hyperaemia (deflating the blood pressure cuff) via release of the ischaemic occlusion. The maximum displacement of lumen diameter during reactive hyperaemia from the mean baseline brachial diameter was expressed as a percentage of FMD (%FMD).

Statistical analysis

Study data were collected and managed using Research Electronic Data Capture (REDCap; Stellenbosch University, South Africa). REDCap is a secure, web-based software platform designed to support data capture for research studies.[19]

All statistical analyses were performed using IBM® SPSS® software (version 25, NY, USA). The data distribution of each variable was assessed using Q-Q plots, histograms and Shapiro–Wilk tests. Categorical variables are presented as an *n*-value (% of the study group). Continuous variables are presented as median (range) and mean ± standard deviation (SD) for non-parametric and parametric variables, respectively. Two-way repeated measures ANOVA or Kruskal–Wallis analyses were used to determine significant differences between the groups.

To determine independent associations, linear mixed-model regression analyses were performed. All models included participants nested in each visit as a random-effects factor variable with random intercept. Non-parametric variables were $\log_{10}$-transformed. Various models were adjusted for in the regression analyses.

Model A: Timepoint (36 months vs baseline), total monthly household income [monthly income (≥ R5 000 vs < R5 000)], GGT, HIV status in the total study population (HIV+ART vs HIV-free) or in HIV+ART only (markers of HIV and ART: viral load, CD4 cell count, ART type, HIV duration and ART duration). Model B: Model A plus BMI and waist circumference. Model C: Model B without GGT. Model D: Model B plus hypertension (yes vs no). Model E: Model D plus mean brachial artery diameter.

Estimates are presented as a change or % change in dependent variables for each incremental change in independent variables. Only significant confounding factors are reported. Specific models are indicated below the results table. The significant threshold for all statistical analyses was set at $p < 0.05$.

Results

A total of 95 study participants (HIV-free: $n = 22$ and HIV+ART: $n = 73$) were included in this study (Table 1). The mean age was relatively young for both study groups. Total monthly household income (≥ R5 000 vs < R5 000) was significantly lower in the HIV+ART vs the HIV-free subjects. No other significant differences in demographic, lifestyle and socio-economic characteristics were observed.

The mean BMI was significantly higher in the HIV-free vs HIV+ART subjects. Most participants were obese in the HIV-free patients, and in HIV+ART subjects, most participants were of normal weight.

Waist circumference was significantly higher in the HIV-free vs HIV+ART participants, but waist-to-hip ratio did not differ between the study groups. The proportions of study participants (men and women, respectively) with elevated waist circumference and waist-to-hip ratio were high in both study groups (Table 1).

In the HIV+ART group, the median viral load and CD4 cell counts were within acceptable ranges (< 1 000 copies mRNA/ml and > 200 cells/mm^3).[20] The median ART duration was approximately two years with about half of the study population being HIV positive for five or more years. Only 10 participants in the HIV+ART study group were using second-line ART at the baseline clinical visit (Table 1).

The median GGT level in HIV+ART participants was significantly higher in the HIV+ART vs HIV-free subjects. No other significant differences in biochemical variable outcomes were observed between the study groups.

The mean DBP and SBP were in the normal range for both study groups, with significantly more study participants in the HIV-free study group clinically hypertensive vs the HIV+ART subjects. Only one participant in the total study population reported being on antihypertensive medication. No other significant differences in cardiovascular variable outcomes were observed between study groups (Table 1).

BMI and waist circumference were significantly lower in the HIV+ART compared to HIV-free participants at baseline and the 36-month follow up, but no temporal changes were observed. HbA_{1c} level was significantly lower in the HIV+ART compared to HIV-free participants at 36 months.

GGT was significantly higher at baseline and 36 months in the HIV+ART compared to HIV-free participants. Temporal decreases in eGFR in the HIV-free and HIV+ART participants were observed. %FMD significantly decreased in the HIV+ART participants over a 36-month period (Fig. 2).

In the total study population, HIV+ART vs HIV-free status was independently associated with a 4.9-kg/m^2 decrease in BMI, a 10.5-cm decrease in waist circumference and an 88.5% increase in GGT. For the total study population, each 2.0-kg/m^2 increase in BMI was associated with a 1.8- and 1.3-mmHg increase in SBP and DBP, respectively. In contrast, each 5-cm increment increase in waist circumference was associated with a 4.2% decrease in HDL-C. Each 25-U/l increment increase in GGT level was associated with an increase in HDL-C (57.4%), total cholesterol (1.7 mmol/l) and fasting glucose (0.9 mmol/l) levels, DBP (12.1 mmHg) and heart rate (10 bpm).

In the HIV+ART study group, each 1 000 copies of mRNA/ml increment increase in viral load was associated with a 2.2-kg/m^2 increase in BMI. Each 250 cells/mm^3 increment increase in CD4 cell count was associated with a 7.1% increase in %FMD. Each year (52 weeks) on ART treatment was associated with an increase in BMI (2.6 kg/m^2), waist circumference (3.8 cm), HDL-C level (20.2%) and Hb (0.7 g/dl). An HIV duration of ≥ 5 years vs < 5 years was associated with a 4.0-mmHg decrease in DBP (Table 2). Fig. 3 is a schematic illustration summarising all the regression results.

Discussion

The current study investigated the putative temporal (36 months) changes in body composition and their associations with cardiometabolic risk factors in an HIV-free vs HIV+ART study population residing in the Western Cape of South Africa. The main findings in the current study are (1) an inverse association

Table 1. Baseline characteristics for HIV-free participants and PLWH in the Western Cape, South Africa

Variables[a]	*HIV-free*	*HIV+ART*	p-*value*
Demographic, lifestyle and socio-economic factors			
Age, years	41.73 ± 9.09	39.97 ± 9.00	0.855
Gender, women, *n* (%)	16 (73)	43 (59)	0.165
Ethnicity,[b] mixed ancestry, *n* (%)	20 (91)	59 (81)	0.322
Smoking status,[c] actively smoking, *n* (%)	11 (50)	37 (51)	0.955
Alcohol consumption,[d] *n* (%)	12 (55)	34 (47)	0.512
Monthly household income, ≥ R5 000, *n* (%)	13 (59)	17 (23)	0.016
Meals per day, ≥ 3 meals,[e] *n* (%)	13 (59)	50 (69)	0.171
Physically active,[f] *n* (%)	17 (77)	45 (62)	0.177
Body composition			
Body mass index, kg/m^2	28.68 ± 8.67	23.22 ± 5.97	0.004
Underweight, *n* (%)	2 (9)	13 (18)	0.015
Normal weight, *n* (%)	8 (36)	35 (48)	
Overweight, *n* (%)	2 (9)	14 (19)	
Obese, *n* (%)	10 (46)	11 (15)	
Waist circumference, cm			
Elevated[g]	102.05 ± 19.84	90.15 ± 11.67	0.001
Men, *n* (%)	3 (50)	6 (19)	0.098
Women, *n* (%)	13 (81)	31 (76)	0.648
Waist-to-hip ratio			
Elevated	0.93 ± 0.07	0.93 ± 0.06	0.774
Men, *n* (%)	4 (67)	24 (75)	0.671
Women, *n* (%)	14 (88)	37 (90)	0.762
Biochemical analyses			
Total cholesterol, mmol/l	5.01 ± 1.03	4.85 ± 1.02	0.331
High-density lipoprotein, mmol/l	1.44 (0.8–3.5)	1.37 (0.7–8.2)	0.898
Low-density lipoprotein, mmol/l	2.81 ± 0.90	2.67 ± 0.74	0.099
Triglycerides, mmol/l	0.99 (0.5–3.9)	1.18 (0.4–9.6)	0.747
Fasting glucose, mmol/l	4.99 ± 1.16	4.82 ± 0.62	0.014
Glycated haemoglobin, %	5.46 ± 0.56	5.26 ± 0.422	0.257
Haemoglobin, g/dl	14.03 ± 1.34	13.93 ± 1.43	0.903
Gamma-glutamyl transferase, U/l	25.0 (11–1058)	56.0 (14–327)	< 0.001
High-sensitivity C-reactive protein, mg/l	5.60 (0.20–49.0)	5.80 (0.20–200)	0.900
Estimated glomerular filtration rate,[h] ml/min/1.73 m^3	112.55 ± 10.28	117.19 ± 16.02	0.138
HIV and ART characteristics			
Viral load, copies mRNA/ml	–	50 (10–187073)	–
CD4 count, cells/mm^3	–	513 (49–1434)	–
ART duration, weeks	–	117.0 (1.0–630.0)	–
ART type, 2nd line, *n* (%)	–	10 (14)	–
HIV duration,[i] ≥ 5 years, *n* (%)	–	38 (52)	–
Cardiovascular variable outcomes			
Systolic blood pressure, mmHg	129.00 ± 20.85	122.04 ± 16.91	0.144
Diastolic blood pressure, mmHg	88.05 ± 12.85	84.50 ± 11.13	0.334
Hypertension, *n* (%)	12 (55)	23 (32)	0.049
History of hypertension, *n* (%)	5 (23)	10 (14)	0.538
On hypertensive medication, *n* (%)	0	1 (1)	–
Heart rate, bpm	73.06 ± 13.12	74.10 ± 14.62	0.813
Baseline brachial artery diameter, mm	3.39 ± 0.68	3.43 ± 0.65	0.584
Flow-mediated dilation, %	6.5 (0–18.5)	7.2 (0.5–35.9)	0.374

[a]Data presented as mean ± SD, or *n* (% of the study group). [b]Defined as self-identified mixed ancestry or African. [c]Defined as currently an active smoker or a non-smoker. [d]Alcohol consumption within the last 12 months. [e]Defined as < 3 or ≥ 3 meals daily. [f]Defined as rigorous exercise < 3 or > 3 times a week. [g]Defined as < 0.90 cm for men and < 0.85 cm for women.[15] [h]Calculated according to the CKD-EPI formula.[18] [i]Defined as < 5 years or ≥ 5 years. ART, antiretroviral therapy; bpm, beats per minute.

between HIV+ART status (vs HIV-free) and body composition (BMI and waist circumference), and a positive association between HIV+ART and GGT. In the HIV+ART population alone, (2) ART duration was positively associated with BMI and waist circumference. Body composition (BMI and waist circumference) was associated with multiple cardiometabolic variables in the total study population and HIV+ART alone (Fig. 3, Table 2).

Our results indicate that body composition did not change over 36 months. These findings contrast with previous evidence that showed increased body composition in ART-treated participants over time.[21,22] Factors associated with body composition in PLWH may include increased appetite, a reduction in opportunistic infections, and a rapid decline in viral load/activity.[10] We did not observe a significant difference in meals per day or activity level between HIV-free and HIV+ART subjects. Participants with co-infections were excluded from the current study and viral load and CD4 cell count did not significantly change. These results may explain why no significant temporal changes were observed in this HIV+ART study population.

Menard *et al.* observed an increase in body weight over time (276 ± 79 days from baseline) in HIV-infected patients receiving dolutegravir- and abacavir/lamivudine-based ART.[8] However, the study by Menard *et al.* mainly consisted of men (65%), while our study consisted mainly of women (72.7% HIV-free and 58.9%

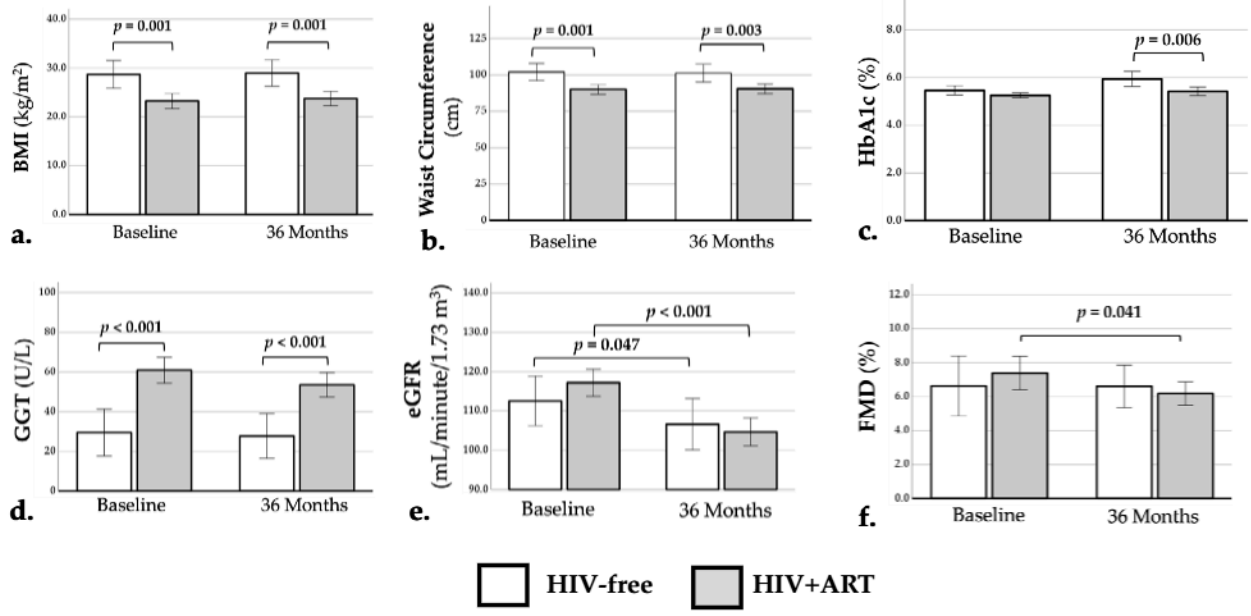

Fig. 2 Variables with significant within- and/or between-subject effect [mean (95% CI)] in an HIV-free and HIV+ART population from the Western Cape, South Africa. BMI: body mass index; eGRF, estimated glomeration filtration rate; FMD, flow-mediated dilation; GGT, gamma-glutamyl transferase; HbA_{1c}, glycated haemoglobin.

HIV+ART, Table 1). Therefore, gender differences may explain the discrepancy between the studies.[23] Additionally, the baseline CD4 count in the present study (513, 49–1439) is higher than the baseline CD4 count observed in other studies, indicating a slightly healthier study population. For example, in the study by Kouanfack *et al.*, most participants (31.3%) had a baseline CD4 count of < 200 cells/mm^3.[22]

After adjusting for confounding factors, ART duration was positively associated with waist circumference and BMI in the HIV+ART study group. These findings align with previous

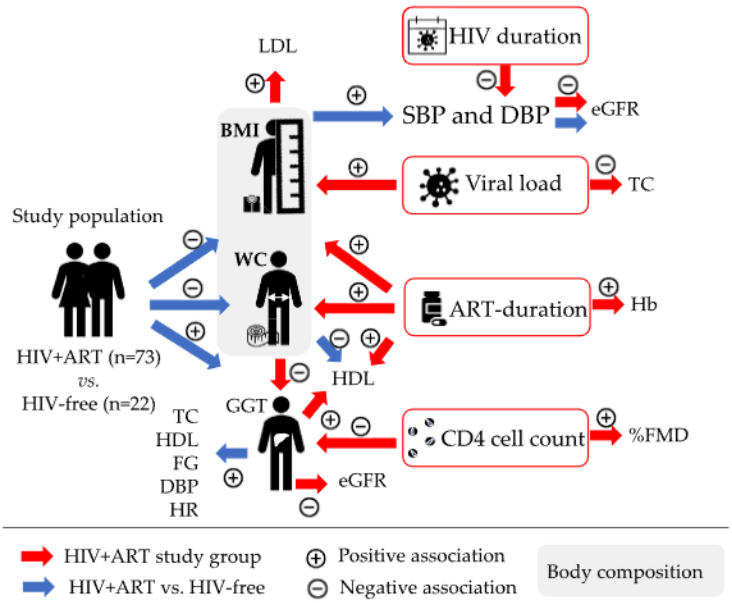

Fig. 3 Summary of the main findings. To view the comprehensive data of all the findings, please refer to Table 2. %FMD, % flow-mediated dilation; ART, antiretroviral therapy; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerulation filtration rate; FG, fasting glucose; GGT, gamma-glutamyl transferase; Hb, haemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; WC, waist circumference.

Table 2. Estimated effects of significant confounding factors in an HIV-free and HIV+ART population from the Western Cape, South Africa

				95% CI		
Study population	*Significant independent variables*	*Dependent variables*	*Change/% change*[a]	*Lower*	*Upper*	p-*values*
Total study population						
	HIV+ART vs HIV-free [b]	BMI, kg/m^2 [b]	–4.92	–7.99	–1.84	0.002
		Waist circumference, cm [b]	–10.5	–17.2	–3.77	0.003
		GGT, % [d]	88.5	37.7	157.9	< 0.001
	Monthly income, ≥ R5 000 vs < R5 000	HbA_{1c}, % [c]	0.195	0.024	0.366	0.025
	BMI, kg/m^2	SBP, mmHg [c]	1.82	0.405	3.23	0.012
		DBP, mmHg [c]	1.33	0.356	2.31	0.008
	Waist circumference, cm	HDL-C, % [c]	–4.17	–7.40	–0.836	0.015
	GGT, U/l	Total cholesterol, mmol/l [c]	1.67	0.999	2.34	< 0.001
		HDL-C, % [c]	57.4	24.3	99.3	< 0.001
		Fasting glucose, mmol/l [c]	0.884	0.375	1.39	0.001
		DBP, mmHg [c]	12.1	4.72	19.5	0.001
		Heart rate, bpm [c]	9.93	0.733	19.1	0.034
	Hypertension, yes vs no	eGFR, ml/min/1.73 m^3 [c]	–6.27	–10.8	–1.74	0.007
	Timepoint, 36 months vs baseline	Fasting glucose, mmol/l [c]	0.227	0.024	0.429	0.028
		HbA_{1c}, % [c]	0.336	0.180	0.492	< 0.001
		GGT, % [d]	–14.9	–27.0	–0.624	0.042
		eGFR, ml/min/1.73 m^3 [c]	–10.2	–13.8	–6.51	< 0.001
HIV+ART						
	Viral load, copies mRNA/ml	BMI, kg/m^2 [b]	2.21	0.472	3.94	0.013
		Total cholesterol, mmol/l [c]	–0.394	–0.742	–0.047	0.027
	CD4 count, cells/mm^3	GGT, % [d]	–85.6	–95.8	–51.2	0.002
		%FMD, % [f]	7.09	0.445	13.7	0.037
	ART type, 2nd- vs 1st-line ART	–				
	ART duration, weeks	BMI, kg/m^2 [b]	2.60	0.57	4.62	0.013
		Waist circumference, cm [b]	3.83	0.03	7.63	0.048
		HDL-C, % [c]	20.18	2.37	41.09	0.025
		Hb, g/dl [c]	0.69	0.01	1.37	0.047
	HIV duration, ≥ 5 years vs < 5 years	DBP, mmHg [c]	–4.01	–7.83	–0.184	0.040
	BMI, kg/m^2	LDL-C, mmol/l [c]	0.079	0.003	0.155	0.040
		Heart rate, bpm [c]	–1.98	–3.51	–0.451	0.012
	Waist circumference, cm	GGT, % [d]	–8.21	–15.4	–0.441	0.039
	GGT, U/l	Waist circumference, cm [b]	–11.1	–18.6	–3.50	0.004
		Total cholesterol, mmol/l [c]	1.09	0.365	1.81	0.004
		HDL-C, % [c]	52.2	14.9	101.8	0.004
	Hypertension, yes vs no	eGFR, ml/min/1.73 m^3 [c]	–7.70	–13.4	–1.94	0.009
	Timepoint, 36 months vs baseline	HbA_{1c}, % [c]	0.210	0.033	0.387	0.021
		GGT, % [d]	–22.3	–37.6	–3.26	0.024
		eGFR, ml/min/1.73 m^3 [c]	–12.6	–18.3	–6.85	< 0.001
		Heart rate, bpm [c]	5.65	0.712	10.6	0.025

[a]Estimates are presented as a change (parametric) or % change (non-parametric data); 95% CI, *p*-value in the independent variables for each increment change in the independent variables (BMI: 2 kg/m^2, waist circumference: 5 cm, GGT: 25 U/l, SBP: 10 mmHg, DBP: 10 mmHg, mean brachial artery diameter: 0.5 mm, CD4 cell count: 250 cells/mm^3, viral load: 1 000 copies mRNA/ml and ART duration: 52 weeks).
[b]Model A: Adjusted for: timepoint (36 months vs baseline), total monthly household income [monthly income (≥ R5 000 vs < R5 000)], gamma-glutamyl transferase (GGT, U/l), HIV status in the total study population (HIV+ART vs HIV negative) or in HIV+ART only (markers of HIV and ART: viral load, CD4 cell count, ART type, HIV duration and ART duration).
[c]Model B: Model A additionally adjusted for BMI and waist circumference.
[d]Model C: Model B without gamma-glutamyl transferase (GGT, U/L).
[e]Model D: Model B additionally adjusted for hypertension (Yes vs No).
[f]Model E: Model D additionally adjusted for mean brachial artery diameter.
ART, antiretroviral therapy; BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; eGFR, estimated glomeration filtration rate; FMD, flow-mediated dilation; GGT, gamma-glutamyl transferase; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

reports, which showed that HIV disease regression and ART use are associated with an increase in body composition.[8-10] Our results support the findings of a 2016 cross-sectional study showing that the use of ART was positively associated with waist circumference.[24] It is well known that the use of ART is associated with the reversal of HIV-associated weight loss. However, this was not observed in our study population. The non-significant changes in viral load and CD4 cell count could account for no changes in BMI over time.[25]

Interestingly, CD4 cell count was positively associated with %FMD, which indicates improvement in endothelial function. The positive associations between CD4 cell count and %FMD may also indicate a relationship between immune status and endothelial function. The cardioprotective effects observed in the current study may also be attributed to the use of ART. It has previously been shown that ART use is associated with the upregulation of endothelial nitric oxide synthase (eNOS) in an animal model.[26]

Viral load was independently associated with BMI, while CD4 count was not associated with body composition variables. Furthermore, our findings suggest that the restoration of immune function, as indicated by CD4 cell count,

may be closely related to body composition in our study population.

Although an increase in body composition often indicates an improved health status in PLWH, an increase in body composition beyond that of the normal range is also associated with an increased cardiovascular risk profile through possible increases in systemic inflammation[27] and dyslipidaemia.[28] We have reported positive and negative associations between body composition, cardiometabolic and cardiovascular variable outcomes. BMI was positively associated with DBP and SBP in the total population and positively related to LDL-C in the HIV+ART population. These effects are well-known cardiovascular risk factors and may have adverse cardiovascular outcomes.[29] These results suggest that the current HIV+ART study population may have had less cardiovascular risk than their HIV-free counterparts, but this needs to be further investigated.

The HIV+ART study group presented with higher GGT levels than the HIV-free group. The hepatotoxic effect of ART is well-known as ART is metabolised by the liver.[30] GGT is a non-specific marker of liver function, often associated with dyslipidaemia due to its central role in lipid metabolism. Elevated GGT levels and associated dyslipidaemia may therefore contribute to a pro-atherosclerotic profile[31,32] and increased cardiovascular risk in PLWH.[33]

Furthermore, GGT was positively associated with total cholesterol, fasting glucose and heart rate, while inversely associated with eGFR. These findings align with the 2020 Tehran Lipid and Glucose Study,[34] whereby liver enzymes such as GGT are associated with diabetes, hypertension and dyslipidaemia. Increased liver enzyme levels may also contribute to obesity due to decreased anti-inflammatory adiponectin levels and increased pro-inflammatory adipocytokines.[34] However, we did not observe significant temporal changes in GGT level and weight in our HIV+ART subjects. The complex interplay between liver function, ART toxicity and body composition in the current study population needs further investigation.

A significant temporal decrease in eGFR was observed in the HIV+ART and HIV-free groups. It was previously established that HIV and ART may be associated with kidney dysfunction, as indicated by a lower eGFR.[35,36] HIV can infect kidney cells such as tubular and glomerular epithelium cells and cause focal segmental glomerulosclerosis and an increase in eGFR.[37,38] Although ART may reduce/reverse the effects of HIV on kidney function, ART-associated toxicity may contribute to an increased risk for kidney disease and an increased risk of CVD.[39-41] Furthermore, obesity has also been linked to reduced eGFR levels.[42-44] The temporal decrease in eGFR observed in HIV-free participants could possibly be explained, in part at least, by the higher proportion of obese participants in the HIV-free group (mostly obese) compared to HIV+ART group (mostly normal weight).

A significant decrease in %FMD in the HIV+ART group over time was observed. This may indicate impaired endothelial function. Although no significant association between ART and %FMD was observed in the current study, other studies have reported detrimental effects of ART on endothelial function.[46-49] Possible mechanisms may include ART-associated oxidative stress, HIV-associated down-regulation of eNOS, activation of mitogen-activated protein kinases, and an HIV/ART-associated increase in mitochondrial reactive oxygen species production, leading to cellular dysfunction.[45-48] The possible relationship between HIV/ART and endothelial function and the possible mechanisms involved need further investigation.

The current study did not observe any temporal changes in body composition over the 36-month study period. However, longitudinal studies with larger sample sizes with extended follow-up durations beyond 36 months are warranted. Additionally, the current study population consisted mostly of participants of self-identified mixed ancestry residing in the Western Cape Province of South Africa. The differences in results between the current study and other studies from SSA may be due, in part at least, to demographic differences between study populations.

Limitations and strengths

The current study has various limitations. The study cohort was relatively small (95 participants) and skewed in terms of gender (HIV-free: 73% female; HIV+ART 59% female) and the number of participants in each study group (HIV-free: $n = 22$ vs HIV+ART: $n = 73$). Although the HIV-free group was small, it provided a point of reference to compare with the HIV+ART group. Also, only 14% of the HIV+ART study participants were on second-line ART. A more equal distribution in future studies would allow for more robust correlation analyses between these factors and other variable outcomes.

Due to the small population size, we were furthermore constrained by the number of confounding factors we could adjust for in our regression analyses. Future studies should consider a larger sample size that would allow for a more comprehensive/robust adjustment in regression models.

The study additionally had a large number of study participants that were lost to follow up; mostly due to relocation and COVID-19 lockdown restrictions. The authors speculate that participants were reluctant to attend clinic visits during the COVID-19 pandemic; especially PLWH who were at a reported 38% higher risk of developing severe or fatal COVID-19 compared to people living without HIV infection.[49] Also, co-morbidities associated with HIV/ART such as hypertension, malignancy, tuberculosis and chronic kidney disease have been shown to increase the risk of in-hospital mortality rate in PLWH.[50] Future studies should consider these factors and set possible countermeasures in place to make up or prevent possible loss to follow-up number.

Future studies should also consider greater emphasis on socio-economic, geographical, environmental and lifestyle health risk factors as possible confounding factors. A larger multi-centre study design would allow for the assessment of various population indices. Future studies should also consider the inclusion of a more comprehensive priory of biomarkers, such as markers of oxidative stress and atherosclerosis. This would provide a clearer assessment of possible underlying pathophysiological pathways involved in the results observed.

A study strength is the longitudinal, repeated-measures design of our study, which allowed the temporal assessment of body composition and other variables. It was decided to conduct linear mixed-model analyses due to missing values in the data.

Despite the limitations, this study provides novel findings related to body composition and associated cardiovascular risk in

a study population consisting of PLWH of mostly self-identified mixed ancestry in SSA.

Conclusion

This study set out to investigate the temporal relationship between body composition and cardiometabolic profiles in an HIV-infected (on ART) vs an HIV-free Western Cape study population of mostly mixed ancestry (self-identified). We observed differential outcomes between the HIV-free and HIV+ART participants. This finding is relevant as it indicates that the cardiovascular risk profile between HIV-free subjects and PLWH differs and should be considered in the clinical setting.

We did not observe significant temporal changes in body composition variable outcomes in this study population over a 36-month follow-up period. These results may suggest that the first- and second-line ART regimens in this study population may not have been associated with the reversal of HIV-associated wasting. The effects of ART on body composition beyond 36 months needs further investigation.

Interestingly, the HIV+ART study group presented with a more favourable body composition compared to HIV-free individuals. This may translate into a more favourable cardiometabolic risk profile, but more comprehensive analyses are required to confirm this result. In the total study population, a more favourable BMI was associated with a better blood pressure profile. This finding further underscores the relationship between body composition and cardiovascular risk factors such as blood pressure. Also, various HIV/ART-related factors were independently associated with an improved cardiometabolic profile.

Although ART duration was positively associated with higher body composition, it was also positively associated with higher Hb and HDL-C levels. This indicates that ART may improve the pro-atherosclerotic risk associated with HIV infection, but a more comprehensive panel of biomarkers of cardiovascular risk is needed to confirm this result.

CD4 cell count was positively associated with improved endothelial function in HIV+ART subjects, as indicated by FMD. This result indicates that immune restoration in PLWH may contribute to decreased cardiovascular risk. A panel of markers of vascular function in future studies is needed to confirm this finding.

Overall, our findings indicate that our HIV+ART study population appeared to have a more favourable cardiovascular and cardiometabolic risk profile compared to HIV-free individuals, but more robust investigation is needed to verify these findings. Our findings are clinically relevant as they suggest an intricate interplay among body composition variables, HIV+ART status and cardiometabolic/cardiovascular risk. More robust research related to the relationship between body composition and cardiovascular risk in PLWH, and especially in women and populations of mixed ancestry, is needed.

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