

Increased Adiposity and Dyslipidemia in Young Men Living with HIV Compared to Matched PrEP Users: a cross-sectional study

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Supplementary Methods

Study population

Exclusion criteria: included ongoing or recent (within 12 weeks) AIDS-defining or acute non-AIDS events; other chronic liver diseases besides MASLD, such as alcoholic liver disease (alcohol intake >140/210 g/week), active hepatitis B or C co-infection (HBsAg positivity or anti-HCV positivity prior to direct-acting antiviral therapy), autoimmune liver diseases, cholestatic liver diseases, hemochromatosis, Wilson's disease, or alpha-1-antitrypsin deficiency; chronic inflammatory conditions; use of immunosuppressive, immunomodulatory, or steroid therapies; and active substance use disorders; congestive heart failure or other contraindication to Fibroscan assessment.

Assessment of past medical history and lifestyle factors

Dietary intake was assessed via a semi-quantitative Food Diary covering key food groups and including cereals, fresh and processed meats, fish, dairy products, fruits, vegetables, legumes, and beverages such as soft drinks and alcohol, over the past week. The Mediterranean diet adherence score was calculated by assigning 1 point for each dietary component that met predefined cut-offs based on Mediterranean diet guidelines and previous studies [1]: cereals (≥ 7 times/week), fresh meat (≤ 3 times/week), processed meats (≤ 1 time/week), fish (≥ 2 times/week), dairy products (2–7 times/week), cheese (≤ 3 times/week), fresh fruits (≥ 7 times/week), dry fruits (≥ 2 times/week), vegetables (≥ 7 times/week), legumes (≥ 2 times/week), eggs (2–4 times/week), sweets (≤ 2 times/week), and sugar-sweetened beverages (≤ 1 time/week). The total score (0–13) indicated adherence, with participants categorized into low (0–4 points), moderate (5–8 points), and high (9–13 points) adherence levels.

Physical activity was assessed using the long-form International Physical Activity Questionnaire (IPAQ), which quantified total activity in metabolic equivalents of tasks-minutes (METs-minutes) per week across various domains (work, transportation, household, and leisure) and classified participants as having low (≤ 600 METs), moderate (700–2999 METs) or high activity levels (≥ 3000 METs) based on the IPAQ scoring system, with vigorous activity specifically assessed as part of the questionnaire [2].

Assessment of metabolic comorbidities, anthropometric features and bioimpedance analysis

Fasting venous blood samples were collected to assess glycemic parameters (glucose, insulin and glycated hemoglobin [HbA1c]), lipid profile (total cholesterol, high density lipoprotein [HDL] cholesterol, triglycerides, low density lipoprotein [LDL] cholesterol), kidney function (creatinine levels). Dyslipidemia was defined as plasma triglycerides ≥ 150 mg/dL and/or HDL cholesterol ≤ 40 mg/dL, or the use of lipid-lowering therapy [3]. Elevated LDL cholesterol was defined based on the following thresholds according to the Systematic Coronary Risk Evaluation 2 (SCORE2): >100 mg/dL for individuals with low-to-intermediate cardiovascular risk, >70 mg/dL for those with high risk, and >55 mg/dL for those with very high risk [4]. Insulin resistance was diagnosed with a homeostatic model assessment of insulin resistance (HOMA-IR) >2.5 [5]. Type 2 diabetes mellitus was defined by ongoing hypoglycemic therapy or the presence of at least one of the following criteria: (1) HbA1c $\geq 6.5\%$ (48 mmol/mol); (2) fasting glucose ≥ 126 mg/dL; (3) 2-hour post-oral glucose tolerance test (OGTT, 75 g) glucose ≥ 200 mg/dL; or (4) random glucose ≥ 200 mg/dL with symptoms of hyperglycemia or during a hyperglycemic crisis [6]. Hypertension was defined as an in-office systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or a home systolic blood pressure >135 mmHg and/or diastolic blood pressure >85 mmHg, a history of hypertension, or ongoing antihypertensive therapy [7].

Abdominal circumference was measured in the standing position at the umbilical level, with values exceeding 94 cm in men considered above normal limits [8].

Additional anthropometric measurements, including dominant arm and wrist circumference, as well as waist, hip, and thigh circumference at the root of the dominant leg, were taken to perform bioelectrical impedance analysis (BIA) [9]. BIA, by using body resistance and reactance values, is able to calculate total and regional lean and fat mass (in kilograms and percentages), segmented into trunk and appendicular regions.

Assessment of liver disease

Fasting morning blood samples were collected to measure hepatic and cholestasis enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyltransferase

[GGT]), liver synthesis indices (albumin levels), and platelets. Elevated levels were defined according to local laboratory cut-offs as follows: AST ≥ 39 U/L, ALT ≥ 41 U/L, and GGT ≥ 61 U/L. Hepatic steatosis was further evaluated using FibroScan® with controlled attenuation parameter (CAP) [10-11]. MASLD was defined by the presence of hepatic steatosis with at least one cardiometabolic risk factor among (i) overweight or waist circumference >94 cm for men and >80 cm for women; (ii) fasting serum glucose ≥ 100 mg/dl, 2-hour post-load glucose ≥ 140 mg/dl, hemoglobin A1c ≥ 39 mmol/mol, type 2 diabetes, or diabetes treatment; (iii) blood pressure $\geq 130/85$ mmHg or antihypertensive treatment; (iv) plasma triglycerides ≥ 150 mg/dl or lipid-lowering treatment; or (v) high-density lipoprotein cholesterol ≤ 39 mg/dl in men and ≤ 50 mg/dl in women, or lipid-lowering treatment, in the absence of other causes of SLD [12]. Hepatic fibrosis was assessed by liver stiffness measurement (LSM) using Fibroscan, with advanced fibrosis defined as LSM ≥ 8 kPa [13]. Non-invasive fibrosis tests were also employed: Fibrosis-4 (FIB-4) values <1.3 ruled out advanced fibrosis, while FIB-4 values >2.67 ruled in advanced fibrosis [14]. The FibroScan-AST (FAST) score, which combines AST, LSM and CAP values, was applied to identify at-risk MASH with advanced fibrosis, using thresholds of <0.35 to exclude and >0.67 to confirm its presence [15].

Assessment of cardiovascular damage

Clinical records were reviewed for previous cardiovascular events, including myocardial infarction, angina, stroke, or peripheral arterial disease. For patients aged 40 years and older, the SCORE2 cardiovascular risk score was calculated according to ESC guidelines, using age, sex, systolic blood pressure, total cholesterol, and smoking status to classify patients into low-to-intermediate, high, and very high risk categories [4]. Eco-Color Doppler of the supra-aortic trunks was performed using a high-resolution B-mode ultrasound with a 7.5 MHz probe to evaluate elevated intima-media thickness (IMT) >0.9 mm [7], and carotid plaques, defined as defined as focal thickening >1.2 mm or ≥ 0.5 mm (or $>50\%$) above adjacent IMT [7,16]. Carotid stiffness was evaluated using the Quality Assessment Stiffness system by Esaote, which is based on radiofrequency technology [17], with vascular stiffness, measured as Pulse Wave Velocity (PWV), classified as pathological at values exceeding 10 m/s [7]. Transthoracic echocardiography evaluated cardiac anatomy and function. Echocardiographic parameters included interventricular septal and posterior wall thickness during

diastole, left ventricular mass, end-diastolic and end-systolic volumes, ejection fraction (EF), and diastolic function, assessed per American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines [18]. Threshold values for interventricular septal thickness were defined as <11 mm in women and <12 mm in men [18]. Epicardial fat thickness was also measured and considered normal if <9.5 mm [19].

Inflammatory panel with cytokines and adipokines pool

For the analysis of the inflammatory and adipokine profile, sera samples were collected and analysed following standardized procedures. In particular, three custom Human Magnetic Luminex Assays (R&D Systems, Minneapolis, USA) were used to evaluate biomarkers: a 7-plex assay for Chemerin, IL-1 β , IL-6, Leptin, PBEF/Visfatin, Resistin, and TNF- α (1:2 dilution); a separate assay for Acrp30 or adiponectin (1:200 dilution); and another for RBP4 (1:4000 dilution). Data acquisition was performed using the LABScanTM 100 flow cytometer (Luminex Corporation, Austin, TX, USA) and analyzed with xPONENT software (ver. 4.2). Analyte levels were expressed in pg/ml or ng/ml, as appropriate, with all standards and samples measured in duplicate.

Supplementary Results

Supplementary Table 1 Comparison of lifestyle factors, dietary habits, and physical activity between PLWH and PrEP users

	PLWH (n=53)	PrEP (n=29)	p-value
Alcohol, g/day	3.2 (0-11)	3.4 (0-5.14)	0.18
Smoking, n (%)	18 (34%)	9 (31%)	0.82
Food questionnaire			
Cereals & derivatives, times/week	11 (7-16)	12 (8-17)	0.44
Fresh meat, times/week	3 (1-4)	3 (2-5)	0.17
Processed meats, times/week	3 (1-4.5)	3 (1-3)	0.82
Fish, times/week	2 (1-3)	2 (1-4)	0.78
Dairy products, times/week	2 (0-7)	4.5 (1.5-7)	0.26
Cheese, times/week	3 (1-5)	3 (2-5)	0.90
Fresh fruits, times/week	7 (4-7)	6 (2-12)	0.82
Dry Fruits, times/week	2 (0-3)	2 (.5-4.5)	0.55
Vegetables, times/week	6 (4-9)	7 (5-11)	0.34
Legumes, times/week	2 (0-3)	1 (.5-3)	0.40
Eggs, times/week	2 (0-3)	2.5 (1-3.5)	0.45
Sweets, times/week	3.5 (2-6)	4 (2-7)	0.78
Sweetened beverages, times/week	1 (0-2)	1 (0-3)	0.72
Alcoholic drinks, times/week	2 (0-4)	2 (0-4)	0.96
Mediterranean diet adherence score	6 (6-8)	6 (5-8)	0.93
Mediterranean diet adherence			
Low	3 (6%)	5 (17%)	0.07
Moderate	43 (81%)	17 (59%)	

High	7 (13%)	7 (24%)	
IPAQ			
Work PA, MET	495 (0-1980)	82.5 (0-3055.5)	0.81
Transport PA, MET	495 (198-660)	363 (198-625.5)	0.49
Domestic PA, MET	360 (90-840)	217.5 (50-555)	0.25
Leisure, MET	1386 (297-2379)	1927.5 (1143-3192)	0.10
Walking PA, MET	990 (495-1881)	973.5 (528-1435.5)	0.61
Moderate PA, MET	840 (340-1560)	660 (180-1942.5)	0.58
Vigorous PA, MET	1120 (0-2448)	1920 (1440-3840)	0.041
Total PA, MET	3366 (1980-5526)	4066.5 (2236.5-6888)	0.30
Intensity of PA			
Low, n (%)	4 (8%)	0 (0%)	0.49
Moderate, n (%)	14 (26%)	9 (31%)	
High, n (%)	25 (47%)	15 (52%)	
Sitting time, minutes/week	2520 (1530-3240)	2560 (1740-2790)	0.98

Abbreviations: PLWH, people living with HIV; PrEP, pre-exposure prophylaxis; PA, physical activity; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent of task.

Supplementary Table 2: Comparison of anthropometric measurements, body composition, and metabolic comorbidities between PLWH and PrEP users.

<i>Anthropometric measurements and Bioimpedance analysis</i>			
	PLWH (n=53)	PrEP (n=29)	p-value
BMI, Kg/m ² median (range)	24.6 (22.5-27.8)	22.9 (20.9-24.7)	0.015
WC, cm	90 (86-102)	87 (80-91.5)	0.011
High WC, n (%)	20 (38%)	6 (21%)	0.081

FAT	22.2 (15.3-32.1)	15.15 (12.95-21.25)	0.009
FFM	77.8 (67.9-84.7)	83.9 (78.2-86.2)	0.033
Basal metabolism, cal	1697 (1606-1777)	1669 (1592-1766.5)	0.75
SM, Kg	32.9 (30.1-35.4)	32.75 (30.4-34.6)	0.90
SMI (SM/h ²)	10.26 (9.72-11.01)	10.29 (9.58-10.70)	0.47
Arm Skeletal Muscle, Kg	4.5 (3.9-4.9)	4.4 (4.05-5.15)	0.86
Trunk Skeletal Muscle, Kg	12.85 (12.1-14)	12.95 (12.25-14.25)	0.61
Leg Skeletal Muscle, Kg	15.25 (13.6-16.8)	15.1 (13.55-16.4)	0.75
Trunk Fat Mass, Kg	8.2 (4.9-11.8)	5.05 (3.65-7.55)	0.016
Arm Fat Mass, Kg	2.3 (1.3-3.5)	1.7 (1.15-2.6)	0.086
Leg Fat Mass, Kg	6.9 (4.1-11.2)	4.55 (3.75-6.75)	0.040
<i>Metabolic comorbidities and related therapies</i>			
Obesity, n (%)	8 (15%)	2 (7%)	0.15
Overweight, n (%)	23 (43%)	7 (24%)	0.041
Hypertension, n (%)	2 (4%)	1 (3%)	0.23
Dyslipidemia, n (%)	17 (32%)	11 (38%)	0.12
Statin, n (%)	2 (4%)	0 (0%)	0.088
Total Cholesterol, md/dl	173 (157-200)	154.5 (135.5-180.5)	0.014
HDL, mg/dl	47 (40-54)	49 (36.5-55)	0.91
Low HDL, n (%)	13 (25%)	10 (34%)	0.23
Triglycerides, mg/dl	89 (66-135)	77.5 (56.5-96.5)	0.044
High Triglycerides, n (%)	8 (15%)	3 (10%)	0.79
LDL, mg/dl	111.8 (89.8-136)	89.2 (71-111.8)	0.004
High LDL, n (%)	33 (62%)	10 (34%)	0.016
Type 2 Diabetes, n (%)	1 (2%)	0 (0%)	0.45
Glucose, mg/dl	87 (80-91)	85 (81.5-92)	0.92
Insulin, µg/L	7.6 (4.8-11.7)	6.25 (4.9-8.3)	0.18

HbA1C, mmol/l	34 (32-36)	33 (31-36)	0.32
HOMA index	1.6 (0.99-2.3)	1.4 (0.9-1.69)	0.15
Insulin Resistance, n (%)	10 (19%)	2 (7%)	0.23

Abbreviations: BMI, body mass index; WC, waist circumference; FAT, fat mass; FFM, fat-free mass; SM, skeletal muscle; SMI, skeletal muscle mass index; HDL, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; HOMA, homeostasis model assessment.

Supplementary Table 3: Comparison of liver and cardiovascular features between PLWH and PrEP users.

<i>Liver Features</i>			
	PLWH (n=53)	PrEP (n=29)	p-value
AST, U/L	22 (21-30)	24 (21-29)	0.53
Increased AST, n (%)	1 (2%)	2 (7%)	0.09
ALT, U/L	23 (17-31)	24.5 (18-32)	0.48
Increased ALT, n (%)	3 (6%)	4 (14%)	0.17
GGT, U/L	17.5 (12.5-25.5)	13.5 (12-16)	0.045
Increased GGT, n (%)	2 (4%)	0 (0%)	0.52
FIB4	0.74 (0.58-0.92)	0.72 (0.61-0.84)	0.69
FIB4>2.45, n (%)	4 (8%)	0 (0%)	0.30
LSM, KPa	4.2 (3.6-5.2)	4.1 (3.8-4.9)	0.74
LSM >8 KPa, n (%)	1 (2%)	0 (0%)	0.17
FAST	.07492935 (.05366204-.10778627)	.08055569 (.05855178-.12431263)	0.63
FAST>0.67 n(%)	1 (2%)	0 (0%)	0.70
CAP, dB/m	239 (199-259.5)	213 (205-246)	0.46

CAP>248 dB/m, n(%)	15 (28%)	7 (24%)	0.19
MASLD, n (%)	20 (38%)	7 (24%)	0.067
Cardiovascular features			
History of CVD	0 (0%)	0 (0%)	1
SCORE 2 CV risk	2.3 (1.7-4.3)	2.2 (1.8-2.85)	0.67
CV risk categories (on 26 HIV and 9 PrEP aged >40 years old)	10 (19%)	4 (14%)	0.26
Low-intermediate	15 (28%)	4 (14%)	
High	1 (2%)	0 (0%)	
Very high			
IMT, mm	.67 (.595-.75)	.66 (.58-.71)	0.46
IMT >0.9 mm, n (%)	3 (6%)	1 (3%)	0.20
Carotid Plaques, n (%)	4 (8%)	0 (0%)	0.13
PWV media (m/s)	5.805 (5.315-6.465)	5.72 (5.0475-6.315)	0.33
PWV >10 m/s, n (%)	3 (6%)	0 (0%)	0.031
EAT, mm	6.2 (5.5-8.3)	5.35 (4.25-8)	0.17
EAT >9.5 mm, n (%)	6 (11%)	4 (14%)	0.27
IvsD, mm	9.26 (8.4-10.3)	9.53 (8.19-9.8)	0.78
IvsD >12 mm, n (%)	3 (6%)	1 (3%)	0.15
LVPWd, mm	8.58 (7.93-9.82)	8.69 (7.56-9.98)	0.98
LVIDd, mm	47.8 (43.6-51.2)	48 (44.2-51.1)	0.87
Diastolic Dysfunction	0 (0%)	0 (0%)	1
Systolic Dysfunction	0 (0%)	0 (0%)	1

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; CAP, controlled attenuation parameter; FAST, FibroScan–AST score; MASLD, metabolic dysfunction–associated

steatotic liver disease; CVD, cardiovascular disease; IMT, intima–media thickness; PWV, pulse wave velocity; EAT, epicardial adipose tissue.

Table 4 Univariable and multivariable analysis of factors associated with HIV status

	Univariate analysis			Multivariate analysis		
Variable	OR	95% Confidence Interval	P-Value	OR	95% Confidence Interval	P-Value
BMI	1.137	1.001 - 1.292	0.048	NA		
WC	1.060	1.007 - 1.114	0.025	NA		
FAT	1.063	1.007 - 1.123	0.028	1.015	0.955 - 1.078	0.623
Overweight	2.780	1.004 - 7.702	0.049	NA		
Total Cholesterol	1.021	1.005 - 1.037	0.010	NA		
Triglycerides	1.013	1.000 - 1.026	0.047	NA		
LDLc	1.028	1.009 - 1.049	0.005	1.032	1.004 - 1.061	0.025
Uricemia	1.870	1.060 - 3.299	0.031	NA		
GGT	1.080	1.003 - 1.162	0.042	1.045	0.956 - 1.133	0.35
Vigorous PA	1.023	1.005 - 1.045	0.055	0.999	0.999 - 1.000	0.762
Age	1.030	0.964 - 1.100	0.972	0.388	0.875 - 1.079	0.597

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference; LDLc, low-density lipoprotein cholesterol; GGT, gamma-glutamyl transferase; PA, physical activity; NA, not assessed.

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