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ORIGINAL ARTICLE

People living with HIV on modern antiretrovirals do not display a pro-atherogenic lipid profile and have similar body composition compared to healthy controls

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Abstract

Objectives: Alterations in lipids and apolipoproteins contribute to cardiovascular disease (CVD) and are common in people with HIV. The aim of our study was to compare lipid profiles and body composition between people with and without HIV and to explore whether any associations with HIV could be explained by socio-demographic, clinical characteristics and body composition.

Methods: Cross-sectional analysis of a cohort study enrolling people with HIV and HIV-negative controls. Apolipoproteins [ApoB-100, ApoA1, Lp(a)] were analysed by immunoturbidimetry. Lipids (total cholesterol [TC], low-density lipoprotein [LDL], high-density lipoprotein [HDL]), clinical/demographic data and dual-energy X-ray absorptiometry (DXA)-measured body composition parameters were collected. Between-group differences were assessed with Student's T-test. Linear regression models assessed associations of lipids and apolipoproteins with HIV status and associations with socio-demographic, clinical characteristics and body composition.

Results: We included 108 people with HIV on treatment (93.5% with viral suppression) and 96 controls. People with HIV were younger, more likely to be male, with obesity, of African ethnicity, smokers and with a higher representation of CVD, hypertension, diabetes and statin use. ApoB-100, TC, HDL and LDL were significantly lower in people with HIV, with no between-group difference in ApoA, Lp(a) and body composition. HIV infection remained independently associated with lower TC and LDL after adjustment for possible confounders.

Conclusions: People with HIV from a contemporary cohort had lower pro-atherogenic lipid parameters compared to controls, and no differences in body composition between people with HIV and controls were observed. Traditional

risk factors for CVD and chronic inflammation might have a greater impact than dyslipidaemia itself on the increased CVD risk in people with HIV.

KEYWORDS

apolipoprotein, body composition, HIV, lipids, metabolic diseases

INTRODUCTION

Dyslipidaemia is common in people with HIV in most geographic settings [1, 2]. In addition to traditional risk factors like cigarette smoking, type 2 diabetes (T2DM) and hypertension (HTN), virus-specific factors, chronic inflammation and antiretroviral treatment (ART) contribute to dyslipidaemia in people with HIV [3].

Untreated HIV infection is associated with alterations in plasma lipids, particularly reductions in total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), apolipoprotein A1 (ApoA-1) and apolipoprotein B-100 (ApoB-100). In contrast, triglycerides (TG) are increased, especially in people with acquired immunodeficiency syndrome (AIDS) [4].

Initiation of ART has a variable impact on lipid abnormalities, with older protease inhibitors (PI) associated with a pro-atherogenic lipid profile (high TG, LDL and non-HDL cholesterol), as compared to non-nucleoside reverse-transcriptase inhibitors (NNRTI) [5–8]. Pro-atherogenic lipids infiltrate the subendothelial space of the arterial walls, contributing to the formation of atherosclerotic plaques [9]. Older ART, predominantly thymidine analogue nucleoside reverse-transcriptase inhibitors (NRTI), have also been associated with reductions in lean mass and limb fat and an increase in visceral adiposity [10, 11].

Alterations in lipids, body composition and weight gain have been described with the use of modern ART, including integrase strand transfer inhibitors (InSTI) and tenofovir alafenamide (TAF), which also contribute to overweight and obesity in people with HIV [12–15]. All these represent risk factors for cardiovascular disease (CVD) [16, 17]. CVD risk is increased in people with HIV compared to the general population [18], but existing CVD risk predictors tend to underestimate the actual risk in this group [19]. These risk scores generally use routinely measured plasma lipids, including TC, LDL and HDL. ApoA1 and ApoB have outperformed conventional lipid measures in some studies looking at the prediction of the risk of myocardial infarction in the general population [20]. Most studies comparing lipid parameters in people with HIV and controls either enrolled participants on older PI and NNRTI [21, 22], or were limited to the assessment of specific parameters, like ApoB or lipoprotein a (Lp(a)) [23, 24]. The aim of our study was to compare differences in plasma lipids, apolipoproteins and body composition between a contemporary cohort of ART-treated people with HIV and controls and to explore whether any associations seen could be explained by socio-demographic and clinical characteristics or body composition.

METHODS

Study design and participants

Cross-sectional analysis of participants enrolled in the Understanding the Pathology of Bone Disease in HIV-infected Individuals (HIV-UPBEAT) study, a prospective, observational cohort study enrolling people with HIV aged ≥18 years attending the Mater Misericordiae University Hospital in Dublin, Ireland, and HIV-negative controls recruited through advertisement in public areas within the hospital catchment region (i.e., GP practices, public library) [25]. All people with and without (controls) HIV attending for their study visit between October 2016 and November 2017 who had stored blood samples were included in the analysis.

Data collection

Socio-demographic and clinical characteristics were collected by trained staff using a specific proforma. History of CVD, HTN, T2DM, chronic kidney disease (CKD), chronic hepatitis B (positive HBsAg) and hepatitis C virus (HCV, positive HCV-Ag or Ab) infection was confirmed after review of medical records. Smoking status (non-smoker vs current/past smoker), alcohol use (yes vs no) and statin use (yes vs no) were collected at interview and confirmed with medical records. Obesity, overweight and normal weight were defined as a body mass index (BMI) ≥30, 25–29.9 and 18.5–24.9 kg/m^2, respectively. The following HIV-specific factors were collected from medical records: HIV acquisition risk (sex between men, sex between men and women, injecting drug use); duration of HIV treatment (years); nadir CD4 count (cells/μL); current CD4; current CD4/CD8; current HIV

viral load (HIV-VL) (copies/mL); NRTI backbone (tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC), TAF/FTC, abacavir (ABC)/lamivudine (3TC), NRTI-sparing regimen); third agent (NNRTI, PI, InSTI). HIV-VL was considered undetectable if <40 copies/mL. Values of plasma lipids (TC, LDL, HDL) were collected from the laboratory system, based on fasting blood samples collected on the day of the visit. Information on the use of lipid-lowering agents was collected during the study visit and confirmed after review of medical records.

Analysis of apolipoproteins and body composition

Plasma samples were obtained from whole blood S-Monovette® K3 EDTA tubes (SARSTEDT AG & Co. Germany) and were processed between 4 and 6 h after collection by centrifugation at 1500 G (room temperature), and single-use aliquots were immediately frozen at −80°C until apolipoprotein analysis. All apolipoprotein measurements were performed using the Cobas c501 chemistry analyser (Roche Diagnostics, Switzerland) in the Clinical Biochemistry and Diagnostic Endocrinology Laboratory (Accredited to ISO 15189:2012) at Mater Misericordiae University Hospital Dublin.

ApoA-1 (Roche Tina-quant Apolipoprotein A-1 ver.2) and ApoB-100 (Roche Tina-quant Apolipoprotein B ver.2) were analysed by immunoturbidimetric assays, where a complex is formed between the Apolipoprotein (Plasma) and the antigen–antibody (Kit), and the turbidity of the sample is quantified and expressed as concentration, with an analytical measurement range (AMR) of 20–400 mg/dL.

Lipoprotein (a) (Lp(a)) was measured using the Roche Tina-quant Lp(a) Gen 2 Kit, a particle-enhanced immunoturbidimetric assay where Lp(a) in the plasma binds to specific anti-Lp(a) antibodies that are coated on latex particles causing agglutination. Agglutination is then measured optically via turbidity and is directly proportional to the amount of Lp(a) in the sample, with an AMR of 6–80 mg/dL.

Total body composition was assessed by dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy, GE Medical Systems, Madison, Wisconsin, USA). All scans were performed on the day of the visit. Only total body fat (TBF), trunk fat (TF), limb fat (LF), total body lean mass (TLM) and limb/trunk fat ratio (L/T) were collected for the analysis, given that alterations in the fat distribution between limbs and trunk have been previously associated with CVD risk in people with HIV [26].

Statistical analysis

Participant characteristics were summarized using descriptive statistics: median/interquartile range (IQR) for continuous variables, frequencies/percentages for categorical variables. Between-group differences in apolipoproteins (ApoA-1, ApoB-100, Lp(a)), lipids (TC, LDL, HDL) and body composition (TBF, TF, LF, TLM, L/T) were assessed using Student's T-test.

To explore whether HIV was independently associated with those parameters for which a significant difference between the two groups was observed, a series of linear regression models was fitted using each lipid parameter/apolipoprotein as the dependent variable and HIV status (positive/negative) as the main explanatory variable, using propensity scores, body composition parameters and BMI to adjust for potential confounders. Propensity scores were calculated using a logistic regression model including HIV status as a binary dependent variable (yes/no) and socio-demographic and clinical characteristics that were different between the two groups as independent variables. These included the following: age in years, sex at birth, ethnicity, smoking status, alcohol use, HCV status, history of CVD, history of HTN, history of type 2 diabetes mellitus and statin use.

Next, to explore the contribution of other factors to the levels of lipids/apolipoproteins, additional linear regression models were fitted using each lipid parameter/apolipoprotein as dependent variables, and HIV status, socio-demographic, clinical characteristics and body composition as covariates. Factors determined a priori to be associated with CVD risk [19] were included in these models irrespective of their level of significance. These included age (in years), sex (male vs. female), ethnicity (African vs. non-African) and smoking status. HIV status was included if an independent association had been demonstrated after adjustment for the propensity score. Other variables were included in the multivariable model if the p value for their association with lipid parameters in univariable analyses was <0.1. Values of body composition parameters were log-transformed to account for non-linear effects. Unadjusted and adjusted B coefficients and 95% confidence intervals (CIs) are reported in the text. All analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, N.Y., USA).

RESULTS

Study population

A total of 108 people with HIV and 96 controls with stored plasma samples were included. People with HIV were younger and were more likely to be male, of African

ethnicity, current smokers and to have a history of HCV infection, co-morbidities (CVD, HTN, T2DM, CKD) and statin use (Table 1). Of note, statins were the only lipid-lowering agents used in the study population. In contrast, controls were more likely to report alcohol use and to be overweight. Almost all people with HIV had acquired HIV through a sexual route (38.9% sex between men, 46.3% sex between men and women); the median duration of HIV treatment was 8.9 years; 93.5% were virologically suppressed and the group had good immunological status overall (median CD4 count: 693 cells/μL) (Table 2).

Associations of HIV status with lipids, apolipoproteins and body composition

Values of TC, LDL, HDL and ApoB-100 were each lower in people with versus without HIV, while levels of Lp(a) were higher in people with HIV (Table 3). There was no difference in ApoA-1 between the two groups, nor in body composition parameters (TBF, TF, LF, TLM, L/T). Given the higher use of statins among people with HIV, a sensitivity analysis excluding people on statin treatment was performed, with similar conclusions, except for levels of Lp(a), which were no longer significantly different between the two groups (Supplementary Table S1).

In an unadjusted linear regression model, HIV status was associated with a mean reduction in TC of 0.61 (mean reduction −0.61, 95% CI [−0.88, −0.34]); after adjusting for potential confounders via the propensity score, the association changed only slightly (−0.46 [−0.84, −0.08]) (Table 4). The association of HIV status with LDL also remained (before adjustment: −0.41 [−0.63, −0.19]; after adjustment: −0.44 [−0.76, −0.19]). In contrast, associations with HDL, ApoB-100 and Lp(a) were all reduced and became non-significant after adjustment for the propensity

TABLE 1 Participant characteristics.

Participant characteristics Median [IQR]; *n* (%)	People with HIV (*N* = 108)	People without HIV (*N* = 96)	Overall (*N* = 204)	*p* value
Age (years)	47 [41, 54]	51 [44, 57]	48 [42, 56]	0.008
Sex				
Male	78 (72.2%)	49 (51%)	127 (62.3%)	0.002
Female	30 (27.8%)	47 (49%)	77 (37.7%)	
BMI (kg/m^2)	26.4 [23.9, 31.1]	27.1 [24.7, 30.4]	27.0 [24.1, 30.7]	0.685
BMI category				
Normal weight	44 (40.7%)	27 (28.1%)	71 (34.8%)	0.034
Obesity	30 (27.8%)	43 (44.8%)	73 (35.8%)	
Overweight	34 (31.5%)	26 (27.1%)	60 (29.4%)	
Ethnicity				
White	75 (69.4%)	87 (90.6%)	162 (79.4%)	<0.001
African	33 (30.6%)	9 (9.4%)	42 (20.6%)	
Smoking status				
Non-smoker	52 (48.1%)	59 (61.5%)	111 (54.4%)	0.006
Ex-smoker	24 (22.2%)	26 (27.1%)	50 (24.5%)	
Current smoker	32 (29.6%)	11 (11.5%)	43 (21.1%)	
Alcohol use	76 (70.4%)	86 (89.6%)	162 (79.4%)	<0.001
HCV-Ag/Ab+	10 (9.3%)	2 (2.1%)	12 (5.9%)	0.030
HBsAg+	1 (0.9%)	0 (0%)	1 (0.5%)	0.345
History of CVD	5 (4.6%)	0 (0%)	5 (2.5%)	0.033
History of HTN	32 (29.6%)	7 (7.3%)	39 (19.1%)	<0.001
History of T2DM	12 (11.1%)	3 (3.1%)	15 (7.4%)	0.029
History of CKD	3 (2.8%)	0 (0%)	3 (1.5%)	0.100
Statin use	43 (39.8%)	5 (5.2%)	48 (23.5%)	<0.001

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; HBsAg, hepatitis B surface antigen; HCV-Ag/Ab, hepatitis C virus antigen/antibody; HD, HIV-negative controls; HTN, hypertension; PLWH, people living with HIV; T2DM, type 2 diabetes.

TABLE 2 HIV-specific characteristics.

HIV-specific characteristics ($n = 108$)	Median [IQR]; n (%)
HIV transmission risk	
Sex between men	42 (38.9%)
Sex between men and women	50 (46.3%)
Injecting drugs	16 (14.8%)
Duration of HIV treatment (years)	8.9 [6.5, 11.1]
Nadir CD4 count (cells/μL)	299 [211, 408]
Current CD4 count (cells/μL)	693 [514, 891]
Current CD4/CD8 ratio	0.84 [0.67, 1.19]
Detectable Viral load	7 (6.5%)
Viral load level in those with a detectable viral load	200 [200, 290]
NRTI backbone	
TDF	52 (48.1%)
TAF	40 (37%)
ABC	11 (10.1%)
NRTI sparing	5 (4.6%)
Use of PI	
Total	23 (21.3%)
DRV/r	18 (16.7%)
ATV/r	5 (4.6%)
Use of NNRTI	
Total	37 (34.3%):
EFV	23 (21.3%)
RPV	14 (13%)
Use of InSTI	
Total	48 (44.4%)
EVG/c	30 (27.8%)
DTG	16 (14.8%)
RAL	2 (1.8%)

Abbreviations: ABC, abacavir; ATV/r, Atazanavir/ritonavir; DRV/r, Darunavir/ritonavir; DTG, dolutegravir; EFV, Efavirenz; EVG/c, Elvitegravir/cobicistat; InSTI, integrase strand transfer inhibitors; NNRTI, non-nucleoside reverse-transcriptase inhibitors; NRTI, nucleoside reverse-transcriptase inhibitors; PI, protease inhibitors; RAL, raltegravir; RPV, Rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

score. Similar results were obtained after excluding participants on statins (Supplementary Table S2).

Associations of socio-demographic, clinical characteristics and body composition with lipids and apolipoproteins

In further adjusted analyses, TC levels were lower in those with obesity, T2DM and higher TLM, while they were higher in females (Supplementary Table S3). LDL levels were also lower in those with obesity, T2DM and higher TLM, whereas levels were higher in females (Supplementary Table S4). Lower HDL levels were seen in those with obesity, T2DM, in those receiving statins and in those with higher TBF, TF, LF and TLM, whereas higher HDL levels were seen in females, in those reporting alcohol use, and in those with higher L/T ratio (Supplementary Table S5). Higher Apo-B100 levels were significantly associated with female sex and higher L/T ratio (Supplementary Table S6). Finally, higher levels of Lp(a) were seen in older people, those of African ethnicity, those on statins and those with a history of CVD and HTN (Supplementary Table S7).

Conclusions were broadly similar in sensitivity analyses excluding people on treatment with statins, except for Lp(a), where higher plasma levels remained associated only with African ethnicity in adjusted analyses (Supplementary Tables S8–S12).

TABLE 3 Between-group differences in lipids, apolipoproteins and body composition.

Parameters Mean (SD)	People with HIV ($N = 108$)	People without HIV ($N = 96$)	p value
Lipids			
TC (mmol/L)	4.73 [0.98]	5.34 [0.95]	<0.001
LDL (mmol/L)	2.88 [0.82]	3.29 [0.78]	<0.001
HDL (mmol/L)	1.26 [0.31]	1.47 [0.40]	<0.001
Apolipoproteins			
ApoB-100 (g/L)	1.19 [0.34]	1.35 [0.43]	0.004
ApoA-1 (g/L)	1.12 [0.35]	1.17 [0.37]	0.309
LP(a) (nmol/L)	77.42 [98.14]	49.95 [64.85]	0.018
Body composition			
TBF (kg)	26.22 [12.50]	27.0 [9.54]	0.648
TF (kg)	15.03 [7.38]	15.30 [6.12]	0.799
LF (kg)	10.40 [5.70]	11.0 [4.24]	0.509
TLM (kg)	52.95 [11.07]	50.56 [12.0]	0.161
L/T	0.76 [0.43]	0.82 [0.79]	0.499

Note: Values are mean and standard deviation [SD].
Abbreviations: ApoA-1, apolipoprotein A-1; ApoB-100, apolipoprotein B-100; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LF, limb fat mass; LP(a), lipoprotein a; L/T, limb fat/trunk fat mass ratio; TBF, total body fat mass; TF, trunk fat mass; TLM, total body lean mass.

DISCUSSION

Our study showed the presence of significantly lower values of plasma TC, LDL, HDL and ApoB-100 in a

TABLE 4 Linear regression: association between lipids/apolipoproteins and HIV status, before and after adjustment for the propensity score, BMI and body composition parameters.

	Unadjusted		Propensity score adjusted	
Lipid or apolipoprotein	**B (95% CI)**	***p* value**	**B (95% CI)**	***p* value**
TC	−0.61 (−0.88, −0.34)	<0.001	−0.46 (−0.84, −0.08)	0.017
LDL	−0.41 (−0.63, −0.19)	<0.001	−0.44 (−0.76, −0.19)	0.008
HDL	−0.21 (−0.31, −0.11)	<0.001	−0.10 (−0.22, 0.03)	0.123
ApoB-100	−0.16 (−0.27, −0.05)	0.003	−0.12 (−0.27, 0.03)	0.115
Lp(a)	27.47 (4.20, 50.74)	0.021	−6.51 (−39.8, 26.7)	0.700

Note: Values reported are B coefficient and 95% confidence intervals (CI).
Abbreviations: ApoB-100, Apolipoprotein B-100; BMI, body mass index; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); TC, total cholesterol.

contemporary cohort of people with HIV on ART, compared to controls, but no difference in levels of ApoA-1 between groups, or Lp(a) after exclusion of people on statins. HIV infection remained independently associated with lower values of TC and LDL after adjustment for CVD risk factors and statin use. These findings point towards the absence of a pro-atherogenic lipid profile in a contemporary cohort of mostly virologically suppressed people with HIV, compared to controls, even after controlling for statin use, although persistently lower levels of HDL in people with HIV might still represent a risk factor for CVD. In addition, body fat distribution and body composition parameters did not differ between the two groups.

Most of the studies of lipid composition in people with HIV were conducted in the early years of the HIV epidemic when older ART regimens were in use. Historically, ART-naïve people with HIV have been shown to have lower levels of TC, LDL, HDL, ApoA-1, ApoB-100 and higher levels of TG, compared to controls [4]. While the observation of low HDL in HIV is consistent across studies, levels of LDL were comparable between people with HIV and controls in some studies [21], and others have described a variable degree of dyslipidaemia based on CD4 count (lower TC and LDL in patients with CD4 count <200 cells/μL) [27].

The effect of ART on lipid changes in people with HIV has been widely studied. TC, LDL, HDL and non-HDL cholesterol are significantly increased 6 months after initiation of treatment, reaching a peak at 2–3 years and persisting at 7 years follow-up [28]. HDL levels tend to remain lower than in the general population. PI have been associated with a more pro-atherogenic lipid profile, characterized by higher levels of TC, TG, small dense LDL and Lp(a), compared to NNRTI [5, 7, 8, 21]. NRTI impact on lipids varies widely among different agents, with TDF use resulting in lower levels of pro-atherogenic lipids compared to thymidine analogues, ABC and TAF, possibly due to a lipid-lowering effect of TDF [6, 13, 29, 30].

More recent studies have shown a more favourable lipid profile for InSTIs compared with PI, but higher rates of dyslipidaemia compared to NNRTI, especially rilpivirine [31, 32]. Of note, our cohort had a high proportion of InSTI use (41.7%), while use of PI was mostly limited to darunavir (DRV) and atazanavir (ATV), which might have influenced our results.

Only a few studies have compared lipids and apolipoprotein parameters between people with and without HIV in the modern ART era. Older studies on people with HIV treated with PI or NNRTI showed no differences in the levels of TC and LDL, but lower HDL in ART-treated people with HIV compared to controls [21, 22]. In a more recent prospective observational study, following people with and without HIV for 3 years, TC, LDL and ApoB increased more in controls than in people with HIV on ART, while no significant differences were found in HDL [23]. Unlike our cohort, people enrolled in this study were relatively young (18–60 years), only using NNRTI, and people on statins were not included.

In the largest longitudinal observational study to date (COCOMO, Denmark) comparing people with and without HIV, those with HIV had lower levels of LDL, but also a higher prevalence of lipid-lowering agents' use [33]. Interestingly, HIV infection was associated with elevated LDL levels after adjustment for BMI, sex, age, physical activity levels, origin, education level, abdominal obesity and smoking status. Older age was also associated with higher LDL levels in people with HIV. This is in contrast with the findings in our study, where lower LDL values continued to be seen in those with HIV after adjustment for age, sex, ethnicity and smoking. However, we did not have information on physical activity levels

and abdominal obesity, and ethnic differences between the two studies could also explain the different results.

Our study also considered the influence of demographic and clinical factors on dyslipidaemia in people with HIV. Female sex and African American ancestry have been associated with higher levels of HDL, while older age has been associated with higher TC [34]. In our study, female sex was independently associated with higher levels of lipids and ApoB. This association might be particularly relevant in HIV, given recent evidence from multiple observational studies showing a 1.5- to 2-fold higher risk of CVD in women compared to men with HIV [35]. While age is generally considered as a risk factor both for dyslipidaemia and CVD in the general population and in people with HIV [36], we did not observe this association in our cohort, except for Lp(a). This could have been influenced by the characteristics of our cohort, which mostly comprised middle-aged people.

Among clinical factors, we observed an association between T2DM and lower levels of TC and LDL, which was no longer significant after excluding people taking statins. This is quite unusual, given dyslipidaemia is frequently seen in people with T2DM [37], but most likely explained by the high frequency of statin use in our cohort.

Our study is one of the few to compare differences in DXA-assessed body composition between people with and without HIV in the modern ART era. A previous study comparing body composition changes between people with HIV and controls showed that after 96 weeks of ART people with HIV lost more lean mass compared to controls and gained more total, trunk and limb fat [14]. People with HIV in this study were randomized to receive either atazanavir/ritonavir or efavirenz, combined with either TDF/FTC or ABC/3TC, while participants in our study received a wider range of ART. Other studies on body composition in people with HIV mostly focused on lipoatrophy caused by thymidine analogues (didanosine, stavudine) [10], and lipodystrophy caused by older PI [38]. Although we did not find any differences in body composition between the two groups, this might reflect the characteristics of people with HIV included in the study, who mostly had undetectable HIV-RNA on stable ART. Older age and Black ethnicity have been previously associated with loss of lean mass in HIV, while older age and female sex have been associated with smaller increases in TBF [14]. Lower lean mass in our cohort was associated with higher values of TC, LDL, HDL and ApoB-100, suggesting a relatively more unfavourable lipid profile, which is in keeping with studies showing an association between higher muscular skeletal mass and lower TG and cholesterol [39]. However, the association between higher lipid values and higher L/T ratio is quite unusual, given that higher TF and lower limb fat have been previously associated with increased risk of CVD [40], and the opposite relationship between L/T ratio and lipid parameters would have been expected. Therefore, these associations are difficult to interpret and should be explored in future studies.

One of the main strengths of our study was the use of a comprehensive assessment of lipid parameters, including apolipoproteins. Among these, Lp(a) has recently emerged as a pro-atherogenic lipoprotein contributing to CVD risk in the general population [41]. Data in people with HIV are scarce, with some studies showing higher Lp(a) levels in ART-treated versus ART-naïve people with HIV, but no differences with controls [24, 42, 43]. We observed higher levels of Lp(a) in people with HIV, but there was no difference with controls after exclusion of people on statin. It is important to note that circulating levels of Lp(a) are mainly genetically determined, with a substantial variability within the general population, making it hard to assess differences in diverse populations [41]. In addition, statin treatment has been shown to increase levels of Lp(a) in the general population [44], which could have influenced our results, given high rates of statin use in our cohort.

Other strengths of our study include the use of a standardized protocol for the assessment of participants, the use of objective measures (DXA) to assess body composition and the fact that controls were enrolled from the same cohort and included people in the same catchment area who were not under routine hospital care.

Our study has several limitations. Our cohort was relatively small, and the two groups were not matched for age, sex and ethnicity, which are all factors that could influence lipids and body composition [14, 33, 34, 45]. While the use of multivariable models accounts for some confounders, the lack of matching still represents a limitation, as it increases the risk of bias due to unmeasured confounders. In addition, the recruitment of HIV-negative controls through advertisements in the area might have introduced a bias in terms of the selection of people with greater health literacy and higher socioeconomic status, which could have influenced the results. Only participants with available plasma samples were included in the analysis. This could represent an additional selection bias, through the exclusion of people who did not attend for the study visit for multiple reasons (i.e., poor engagement in care). The cross-sectional nature of our study did not allow us to assess the potential clinical implications of the observed differences in terms of CVD risk.

The higher proportion of statin use in people with HIV constitutes another limitation. Interestingly, HIV infection remained independently associated with lower

lipid levels in multivariable linear regression models after excluding people on statin treatment, except for HDL. While statins are highly effective in lowering LDL levels, their effects on HDL are variable and independent from LDL decrease, with some patients experiencing an increase in the levels of HDL, while others experience a paradoxical decrease in HDL [46]. Therefore, the different results obtained with the sensitivity analysis might be potentially related to the pharmacological properties of statins or to unmeasured confounders. It is important to note that people with HIV tend to have more interactions with healthcare professionals and are screened for CVD risk at a younger age compared to the general population, and non-pharmaceutical interventions such as lifestyle changes might have contributed in part to the observed results.

We also did not have any information on previous exposure to thymidine analogues and older ART, although many of our participants were likely exposed to them, given the median duration of HIV treatment of 8.9 years. In addition, we did not have information on levels of TG and HDL and LDL particles. While elevated TG only seems to contribute marginally to the increased CVD risk in HIV [47], alterations in HDL and LDL particles seem to be more specifically associated with the development of CVD in people with HIV [48]. Body composition was assessed with DXA, which tends to underestimate visceral adipose tissue compared to computed tomography (CT) [49]. The lack of matching and the recruitment strategy might also have influenced the results in terms of body composition, as previously discussed for lipid parameters.

Finally, given the lack of information on cardiovascular events and CVD risk scores, we cannot make any assumptions on differences in CVD risk between the two groups in this cohort.

CONCLUSIONS

Our study shows that people with HIV from an urban Irish setting on modern ART have lower levels of pro-atherogenic lipids and lipoproteins and do not have a different body composition compared to controls. This is in line with the recent literature showing that dyslipidaemia is less common with modern ART and that traditional risk factors (i.e., cigarette smoking, older age, male sex) and chronic inflammation might play a greater role in increasing the CVD risk in people with HIV [50]. In fact, data from the REPRIEVE trial showed that the benefit of statins in reducing CVD risk in people with HIV went beyond their lipid-lowering effects and were possibly related to the impact of statins on other aspects of cardiovascular health, like reduced inflammation [51]. However, people with HIV in our study also had lower HDL. While low HDL is considered a risk factor for CVD in the general population, it is still unclear whether isolated low HDL could have a substantial contribution to CVD risk in the presence of normal TG and LDL levels [52], and the impact of isolated low HDL on CVD risk has not been studied in people with HIV. Therefore, the impact of lipid and lipoprotein abnormalities in people with HIV on modern ART should be prospectively explored in larger cohorts, incorporating clinical outcomes such as end-organ damage (i.e., atherosclerosis) and cardiovascular events.

AUTHOR CONTRIBUTIONS

Savinelli S. designed the study protocol, collected and analysed data and wrote the manuscript. Heeney A. contributed to data collection and analysis of data. Tinago W. designed the statistical analysis plan and reviewed the results. Garcia Leon A.A., Walsh I and Fitzgibbon M. contributed to laboratory analysis of samples. Sabin C.A. contributed to the revision of the statistical analysis plan and reviewed the manuscript. McGettrick P., Cotter A.G., Mallon P.W.G. and Feeney E.R. contributed to the recruitment of participants and reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The HIV-UPBEAT study was approved by the Mater Misericordiae University Hospital Research Ethics Committee (Reference: [1]/378/1351). All study participants provided written informed consent prior to enrolment in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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