Cholesterol Metabolism Gene Expression in People Living with HIV is Similar to Risk Factor Matched Uninfected Controls: The HIV UPBEAT CAD Substudy

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Introduction

HIV infection is associated with an increased risk of coronary artery disease (CAD) with dyslipidaemia, a major CAD risk factor, prevalent in treated People Living with HIV (PLWH)[1].

HIV protein Nef may impair the function of ABCA1, a key cell membrane cholesterol efflux transporter leading to intracellular accumulation of cholesterol[2].

Previous studies have suggested a pattern of cholesterol metabolism gene expression consistent with high intracellular cholesterol concentrations in antiretroviral therapy (ART) naïve patients, which improves but does not normalise with treatment initiation[3].

Objectives

Within the UPBEAT CAD sub-study, we aimed to examine the expression of Monocyte cholesterol metabolism genes in a cohort of older, ART treated PLWH and CAD risk factor matched uninfected controls, to assess for differences in cholesterol metabolism despite long term ART.

Methods

The UPBEAT CAD substudy, examining CAD risk in PLWH, enrolled 100 participants matched on HIV status and traditional CADRF.

Quantitative Polymerase Chain Reaction (qPCR) was used to assess expression of 17 cholesterol sensing, synthesis and efflux genes.

Data are reported as median (IQR), and gene expression was reported relative to 3 housekeeping genes (TBP, ACTB, and RPLPO). Between group differences and association with HIV status was assessed using Mann-Whitney-U test and ANCOVA respectively (SPSS vers24).

Results

99 participants were included in the analysis. Median age was 50.81 (46.29, 56.24) years, 71.71% male, 76.76% Caucasian and 48.48% were current smokers.

PLWH had lower HDL cholesterol and more likely to be on statin therapy compared to matched controls. Other demographics and CVD risk factors were similar between groups (see table 1).

46.9% of PLWH were infected through homosexual contact, 36.7% through heterosexual contact, and 16.3% through injecting drug use. The median of current CD4+ cell count was 710 (575.75, 916.00) cells/cm^3. The median duration of ART was 10.0 (7.22,14.27) years. 48.97% were on INSTIs based therapy, while 14.28% were on PI.

	HIV Negative (n=50)	HIV Positive (n=49)	P Value
Age in years	51.5 (46.59,56.2)	50.4 (45.7, 57.9)	0.916
Male gender n (%)	35 (70)	36 (73.5)	0.702
Caucasian n (%)	40 (81.6)	36 (75)	0.442
Current Smoker n (%)	22 (44.9)	26 (53.1)	0.419
Body Mass Index (kg/m^2)	27.96 (24.9,29.6)	28.15 (24.06,32.4)	0.743
CVD Family History n (%)	27 (56.3)	16 (32.7)	0.019
Total Cholesterol (mmol/L)	5.1 (4.2,5.7)	4.9 (4.3, 5.85)	0.518
HDLc (mmol/L)	1.4 (1.1,1.6)	1.27 (1.05,1.34)	0.017
LDLc (mmol/L)	3.0 (2.4,3.7)	3.0 (2.45,3.65)	0.787
Triglycerides (mmol/L)	1.1 (0.85,1.5	1.29 (0.86,2.08)	0.132
Total Chol.: HDL Ratio	1 (0.8,1.14)	1.02 (0.8,1.2)	0.499
Statin Use n (%)	6 (12)	24 (49)	<0.001
Diabetes n (%)	1 (2)	3 (6.1)	0.298
Hypertension n (%)	11 (22.9)	17 (34.7)	0.201

There were no significant between group differences in expression of cholesterol sensing (SCAP, SREBF1/2, MBTPS1/2, PPARA, PPARG, NR1H3, and LPL), cholesterol uptake (LDLR, and CD36), synthesis (HMGCR, PMVK, and ACAT2) or efflux genes (ABCA1, ABCG1, and SCARB1) (see figures 1, and 2).

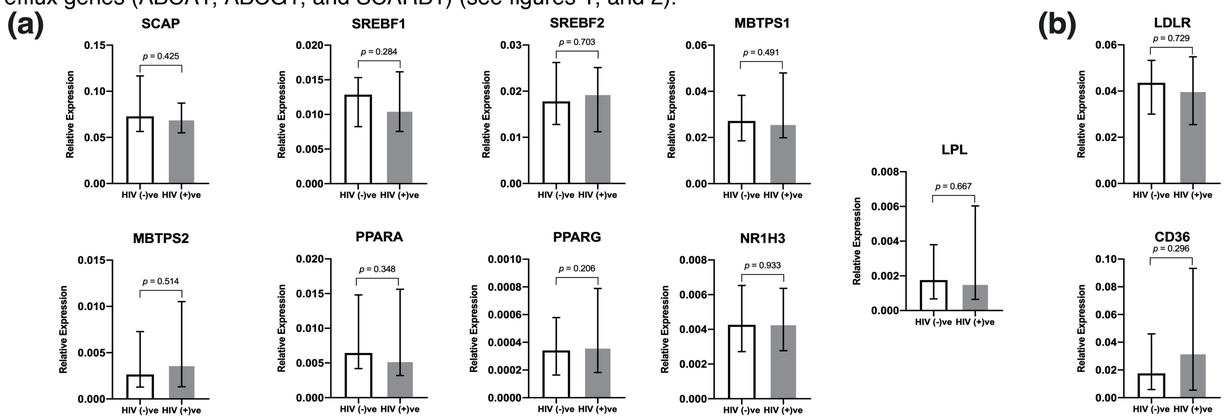

Figure 1. Relative Gene Expression of Cholesterol Sensing (a), and Uptake (b) Genes

Results continued

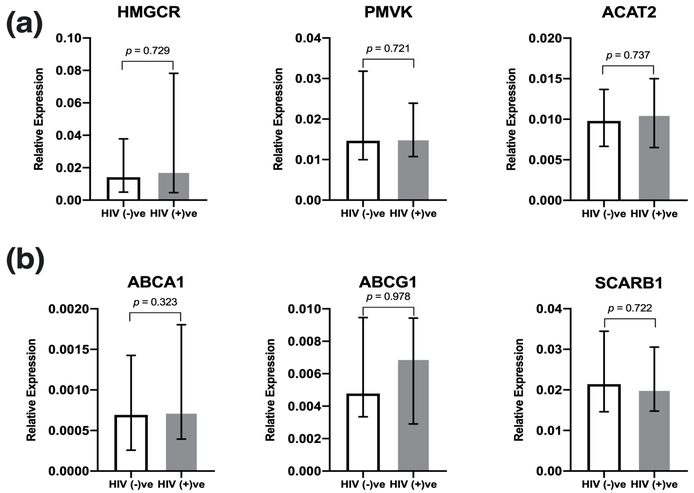

Figure 2. Relative Gene Expression of Cholesterol Synthesis (a), and Efflux (b) Genes

After adjustment for HDL and statin use, there remained no significant association between HIV serostatus and cholesterol metabolism gene expression.

Conclusion

In a cohort of treatment experienced PLWH and CVD risk factor matched controls, there was no significant difference in monocyte cholesterol gene expression suggesting a persistent dysfunctional intracellular cholesterol metabolism may not contribute to the increased risk of CAD observed in stable, ART-treated PLWH.

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