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Abstract # 742

Antiretroviral Therapy is Associated with Significant Changes in Plasma Lipidome

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Abstract *

Background: Targeted measurement of over 400 plasma lipid species by mass spectrometry can sensitively identify changes in the plasma lipidome associated with the development of atherosclerosis and stratify patients into levels of future cardiovascular risk. Some of the HIV and ART-associated cardiovascular risk that persists despite correction for fasting lipids may be explained by changes in plasma lipidome. This study was performed to determine the change in lipidome associated with initiation of different antiretroviral regimens.

Methods: Plasma lipid profiling (by liquid chromatography, electrospray isonisation-tandem mass spectrometry) was performed on 345 samples from the ALTAIR study which randomised ART-naïve HIV positive participants to one of three initial regiments, tenofovir/emtricitabine with efavirenz (EFV), ritonavir-boosted atazanavir (ATZr) or zidovudine/abacavir (ZDV/ABC). Participants (n = 115) who remained on the randomised regimen with complete samples available at baseline, week 12 and 48 were included. 306 lipid species were detected in significant abundance for inclusion.

Results: Baseline characteristics and lipid profile (including lipid classes and species) were similar between the arms. Lower total and LDL cholesterol was seen with ZDV/ABC at week 48 compared with EFV or ATZ/r. In the EFV and ATZr arms there were significant changes in a number of lipid species from baseline to week 48 (42 and 35 respectively), some of which (11 and 7 respectively) have been previously identified to be associated with cardiovascular events in HIV. There were no significant changes from baseline seen with ZDV/ABC. At week 48 significant differences in lipid species and classes by treatment regimen were detected; including increased trihexosylceramide (1.21 nM vs 0.99 nM, p = 0.001), monohexosylceramide (9.55 nM vs 6.67 nM, p =0.002) and ceramide (8.45 nM vs 6.97 nM, p = 0.024) classes with EFV compared with ATZr. The same pattern of results was seen when comparing EFV with ZDV/ABC. Baseline HIV and metabolic characteristics did not predict changes in lipid species. The total and percent change in lipid species from baseline to week 48 was not statistically different between arms. Early change in HIV viral load was predictive of change in 3 lipid species at 12 weeks; independent of treatment arm.

Conclusions: ART with EFV or ATVr induces significant changes in plasma lipidome which may be associated with future cardiovascular risk.

* Modified abstract from initial submission following inclusion of additional participants

Background

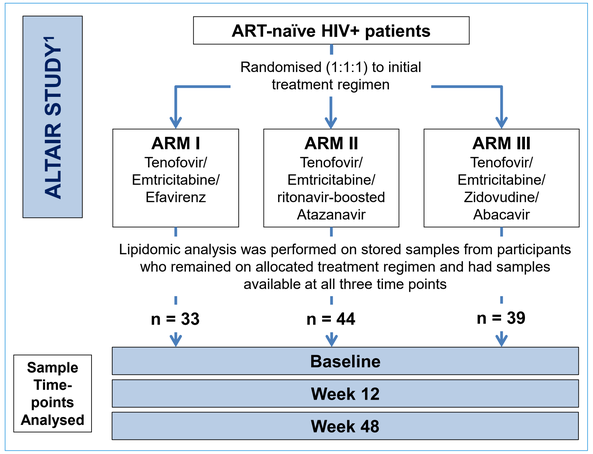
- HIV and ART have been associated with an increased risk of cardiovascular disease in large HIV+ cohorts.
- Plasma lipid profiling, where several hundred lipid species are measured using mass spectrometry, has detected associations between individual lipid species and the development of atherosclerosis in the general population.
- Our group have described the possible utility of plasma lipid profiling to stratify HIV+ patients into levels of future cardiovascular risk (see abstract 1005).
- Alterations in the plasma lipidome may explain some of the HIV and ART-associated cardiovascular risk that persists despite correction for fasting lipids.
- Whether specific antiretroviral regimens have differing effects on the plasma lipidome is not yet known.

AIMs:

1. To determine the change in lipidomic profile 48 weeks after initiation of ART and compare the difference between three antiretroviral regimens.
2. To determine the associations between patient and biochemical characteristics and lipidomic profile in antiretroviral-naïve HIV+ participants.
3. To determine if baseline patient or biochemical characteristics predict change in profile following commencement of ART

Methods

Figure 1: Study design



Laboratory Methods:

- Total lipid extraction from a 10µl aliquot of plasma was performed by a single phase chloroform:methanol (2:1) extraction
- Lipid analysis was performed by liquid chromatography, electrospray ionisation-tandem mass spectrometry using a Agilent 1200 liquid chromatography system combined with an Applied Biosystems API 4000 Q/TRAP mass spectrometer with a turbo-ionspray source (350°C) and Analyst 1.5 data system[2].
- 306 individual lipid species from 22 lipid classes were detected in significant abundance from all arms for inclusion

Statistical Methods:

- Corrections for multiple comparisons was performed using the Benjamini-Hochberg method.
- Logistic and linear regression was performed to identify associations between patient characteristics and lipid species and classes

References:

1. Puls RL, Srasuebkul P, Petoumenos K, et al. Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, HIV-infected subjects: week 48 data from the Altair study. Clin Infect Dis 2010;51:855-64.
2. Weir JM, Wong G, Barlow CK, et al. Plasma lipid profiling in a large population-based cohort. J Lipid Res 2013;54:2898-908.

Results

Table 1: Baseline Characteristics

	Arm I (TDF/3TC/EFV)	Arm II (TDF/3TC/ATZ/r)	Arm II (TDF/3TC/ZDV/ABC)
n	32	44	39
Male, n(%)	26 (81.2)	36 (81.8)	33 (84.6)
Age (years)	38.4 (32.0 – 42.6)	37.1 (28.4 – 41.3)	34.9 (29.1 – 43.3)
Current Smoker, n(%)	17 (53.1)	16 (36.3)	20 (51.2)
Systolic Blood Pressure (mmHg)	120 (111-126)	120 (111-125)	120 (110-120)
BMI (kg/m²)	23.3 (21.1-25.4)	23.4 (21.1-25.6)	23.2 (21.1-25.0)
Glucose (mmol/l)	4.84 (4.68-5.11)	4.76 (4.57-5.21)	4.77 (4.40-5.40)
Cholesterol (mmol/l)	4.43 (3.69-4.90)	3.77 (3.15-4.45)	3.76 (3.30-4.32)
HDL (mmol/l)	0.89 (0.80-1.04)	0.85 (0.70-1.00)	0.90 (0.73-1.04)
LDL (mmol/l)	2.54 (2.21-3.28)	2.15 (1.71-2.71)	2.33 (1.90-2.87)
Triglycerides (mmol/l)	1.31 (1.00-2.04)	1.18 (0.92-1.95)	1.02 (0.90-1.40)
HIV Duration (years)	1.3 (0.9-3.0)	1.7 (0.8-4.1)	2.1 (0.6-3.7)
HIV Viral load (copies/ml)	36,800 (12,111-100,000)	92,637 (30,100-100,000)	56,100 (11,707-100,000)
CD4 T cell count	217 (173-265)	210 (126-318)	206 (132-268)
CD4 Nadir	206 (149-243)	174 (119-260)	179 (116-220)

Median (inter-quartile range) unless otherwise stated

- There were no significant differences between baseline lipid measurements (including lipid classes and species) between arms.
- Following adjustment for age and gender, a number of lipid species at baseline were correlated with total cholesterol, low-density-lipoprotein cholesterol (LDL) , triglycerides and to a lesser degree body mass index.
- There was no correlation between baseline lipid species and CD4+ T cell count or duration of known HIV infection.
- 2 lipid species at baseline (phosphatidylethanolamine [PE] 40:6 (beta-coefficient 194313.13 (95% CI 93138.73 - 295487.54) p value = 0.041) and diacylglycerol [DG]16:0/22:6 (beta-coefficient 62375.27 (95% CI 89713.2 - 235037.34) p value = 0.008) were correlated with HIV viral load.
- Baseline HIV and metabolic characteristics did not predict changes in lipid species at 12 or 48 weeks.
- Early change in HIV viral load was predictive of change in 3 lipid species at 12 weeks, independent of treatment arm (see table 2).
- In the EFV and ATZ/r arms there were significant changes in a number of lipid species from baseline to week 48 (42 and 35 respectively). Of these 11 and 7 lipid species (respectively) have been previously identified by our group to be associated with coronary artery disease in HIV patients
- There were no significant changes in lipid species or classes from baseline seen with ZDV/ABC.

Results

Table 2: Lipid species correlated with early change in HIV Viral Load

Lipid Species	Beta-coefficient [95% CI]	p value
Phosphatidylinositol (PI) 34:0	11.66 [6.11 – 17.22]	0.008
Diacylglycerol (DG) 16:0/20:4	51.32 [I 32.22 - 70.31]	0.0002
Diacylglycerol (DG) 16:0/ 22:6	25.09 [CI 14.91 – 35.28]	0.0007

- At week 48 significant differences in 73 lipid species and 7 lipid classes by treatment regimen were detected (see Figure 2).
- The total and percentage change in lipid species from baseline to week 48 was not statistically different between arms.

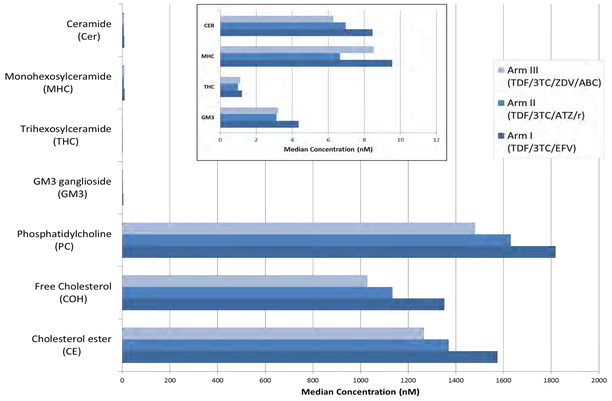


Figure 2: Lipid classes displaying significant differences in concentration between treatment regimens at week 48 [Insert – Magnification of concentrations for Cer, MHC, THC and GM3 classes]

Conclusions

- Initiation of antiretroviral therapy with an efavirenz or ritonavir-boosted atazanavir based regimen was associated with significant changes in plasma lipidome, particularly pronounced in the efavirenz arm.
- These changes may explain some of the cardiovascular risk associated with antiretroviral therapy.
- No significant change in plasma lipidome was seen with zidovudine/abacavir

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