P-745

LOW DENSITY LIPOPROTEIN SUBFRACTION PHENOTYPE AND LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 IN NAIVE HIV-INFECTED PATIENTS RANDOMIZED TO DRV/r VS ATV/r.

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BACKGROUND

Both darunavir/r (DRV/r) and atazanavir/r (ATV/r) are first-line recommended regimens for the treatment of HIV infection. Whether lipid effects may differ between them is unclear.

OBJECTIVE

The aim of this study was to obtain further insight on lipid effects due to DRV/r or ATV/r by assessing changes in LDL subfraction phenotype and lipoprotein-associated phospholipase A2 (Lp-PLA2) at 48 weeks in HIV-infected antiretroviral (ART) naive patients randomized to DRV/r or ATV/r.

PATIENTS AND METHODS

Design: Substudy of a multicenter, randomized and open label study (Atadar, NCT01274780). Patients were randomized to receive either DRV/r (800/100 mg/day) or ATV/r (300/100 mg/day) plus tenofovir/emtricitabine.
Setting: 5 hospitals located in Barcelona Metropolitan Area
Inclusion criteria: >18 years, clinically stable, never received any ART and a plasma HIV RNA ≥ 1000 copies/mL.
Primary endpoint: Change in LDL subfraction phenotype and Lp-PLA2 in the two arms after 48 weeks of treatment.
Variables analyzed and methods: Clinical assessment and laboratory were performed at baseline, week 24 and 48. Total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-c), high density lipoprotein-cholesterol (HDL-c) and apolipoproteins A-I (apo A-I) and B (apo B), were analyzed. LDL size was measured by gel electrophoresis in 3% polyacrylamide using a commercial system (Lipoprint, Quantimetrix Co., Redondo Beach, CA). We separate 9 LDL subfractions (LDL1 to 9) and evaluate their respective cholesterol content. LDL subfractions were divided into 2 main subgroups: LDL 1,2,3 (large and buoyant LDL), and LDL 4,5,6 smaller and denser LDL (sd-LDL). Total Lp-PLA2 activity was measured in serum and in lipoproteins using 2-thio-platelet-activating factor sustrate. The distribution of Lp-PLA2 between lipoprotein fractions was assessed.
Statistical analysis: Continuous variables are expressed as the median and interquartile range (IQR). The univariate and multivariate analyses was done by regression analysis.

RESULTS

BASELINE CHARACTERISTICS

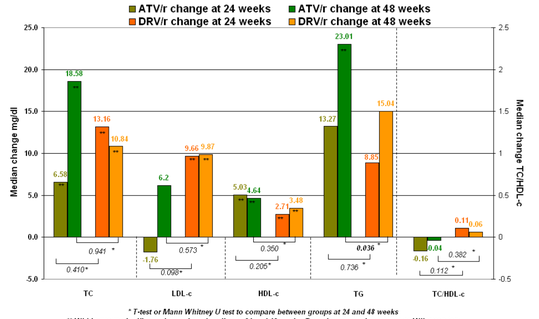
Variables	Atazanavir/r, n=45	Darunavir/r, n=41	p-value	All patients, n=86
Age, years	35 (31-41)	36 (31-41)	0.942	36 (31-41)
Sex, male, n (%)	40 (88.9)	37 (90.2)	1	77 (89.5)
Risk group, n (%)				
- Homosexual men	23 (51.1)	22 (53.7)	0.813	45 (52.3)
- Heterosexual	17 (37.8)	16 (39)	0.905	33 (38.4)
- Intravenous drug user	3 (6.7)	5 (12.2)	0.378	8 (9.3)
- Other/unknown	3 (6.7)	1 (2.4)	0.352	4 (4.6)
AIDS, C stage, n (%)	4 (9.3)	1 (2.6)	0.360	5 (5.8)
CD4 count, cells/µL	285 (144-420)	362 (247-429)	0.118	319 (183-425)
Weight, kg	70 (64.7-77.9)	67.5 (63.5-70)	0.133	68.5 (63.8-76.7)
Body mass index, Kg/m²	23.2 (22.1-25.3)	22.7 (21.6-24.5)	0.287	23.1 (21.7-24.7)
Waist, cm	83 (78-87)	81 (76.5-85.5)	0.383	82 (77-86)
Waist-to-hip ratio	0.89 (0.86-0.93)	0.87 (0.84-0.92)	0.394	0.88 (0.85-0.93)
Systolic blood pressure	119 (110-129)	114 (109-123)	0.188	116 (109-125)
Diastolic blood pressure	72 (66-79)	70 (65-75)	0.178	70 (65-78)
Cardiovascular risk factors, n (%)				
- Smoking	21 (46.7)	23 (56.1)	0.382	44 (51.2)
- Hypertension	4 (8.9)	0	0.118	4 (4.6)
- Diabetes	0	0	-	0
- Personal history of CHD	0	0	-	0
- Family history of premature CHD	3 (6.7)	7 (17.1)	0.183	10 (11.6)
Cardiovascular risk estimation, (FE)	0 (0-3)	1 (0-2)	0.244	1 (0-2)
Lipid lowering therapy, n (%)	0	0	0.424	0

CHD: coronary heart disease; FE: Framingham equation. Variables are expressed as median (interquartile range) 1

Variables	Atazanavir/r, n=45	Darunavir/r, n=41	p-value	All patients, n=86
Lipid measurements,				
- Total cholesterol, mg/dL	146.3 (129.3-163.3)	145.5 (133.1-169.5)	0.817	145.9 (131.2-169.5)
- LDL-c, mg/dL	85.2 (71.8-107.8)	91.2 (74.6-110.3)	0.638	89.0 (073.2-107.8)
- HDL-c, mg/dL	35.6 (29.4-41.8)	35.9 (31.7-41.8)	0.663	35.8 (31.3-41.8)
- Triglycerides, mmol/L	101.8 (72.6-133.6)	85.8 (65.5-120.4)	0.689	97.3 (69.9-129.2)
- TC/HDL-c	4.17 (3.3-5.1)	3.9 (3.5-5.2)	0.625	4.1 (3.3-5.2)
- Apo A1, g/L	1.2 (1.0-1.4)	1.2 (1.1-1.3)	0.813	1.18 (1.1-1.3)
- Apo B, g/L	0.8 (0.6-0.9)	0.8 (0.7-0.9)	0.877	0.8 (0.7-0.9)
- ApoA1/Apo B	1.6 (1.2-1.9)	1.5 (1.2-1.7)	0.976	1.6 (1.2-1.8)
LDL particles				
- LDL size, Angstroms	271.6 (268.4-273.4)	271 (268.9-272.1)	0.375	271.1 (268.4-272.8)
- sdLDL, mg/dL	20.1 (11.2-28.1)	24.7 (18.1-34.4)	0.343	24.3 (12.7-34.4)
- LDL particles phenotype, n (%)				
A	33 (73.3)	33 (80.5)		66 (78.6)
Intermediate	10 (22)	7 (17.1)	0.341	17 (20.2)
B	0	1 (2.4)		1 (1.2)
Lp-PLA2 activity (µmol/min-1*mL)				
Total	21.4 (19-26.2)	22.2 (17.1-27.2)	0.729	21.4 (18.3-26.7)
LDL-Lp-PLA2	14.1 (10.7-18.8)	14.7 (10.8-19.6)	0.811	14.5 (10.8-19.4)
HDL-Lp-PLA2	7.0 (5.9-7.7)	6.75 (5.8-8)	0.660	6.9 (5.9-7.8)
Lp-PLA2 distribution , %				
LDL-Lp-PLA2	67.6 (60.2-72.5)	69.5 (60.4-73.5)	0.676	69.1 (60.4-73.1)
HDL-Lp-PLA2	32.4 (27.5-39.7)	30.5 (26.5-39.6)	0.671	30.9 (26.9-39.6)

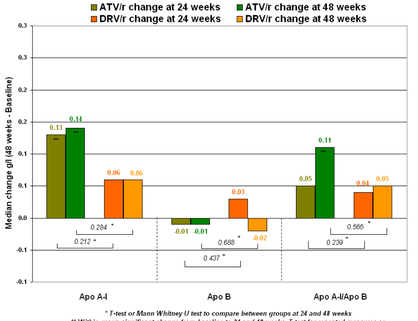
LDL-c: low density lipoprotein-cholesterol; HDL-c: high density lipoprotein-cholesterol; TC: total cholesterol; Lp-PLA2: lipoprotein-associated phodholipase A2. Variables are expressed as median (interquartile range) 2

CHANGE OF LIPID VARIABLES AT WEEK 24 AND 48



* T-test or Mann Whitney U test to compare between groups at 24 and 48 weeks
** Within-group significant change from baseline to 24 and 48 weeks, T-test for repeated measures or Wilcoxon test

LDL-c: low density lipoprotein-cholesterol; HDL-c: high density lipoprotein-cholesterol; TC: total cholesterol; TG: triglycerides 3



* T-test or Mann Whitney U test to compare between groups at 24 and 48 weeks
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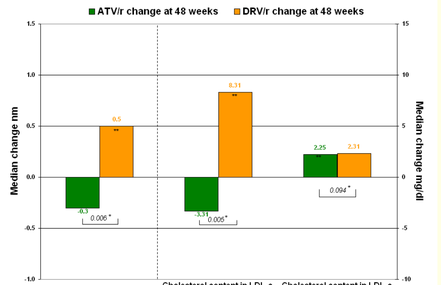
Apo A-I: apolipoprotein A-I; Apo B: apolipoprotein B 4

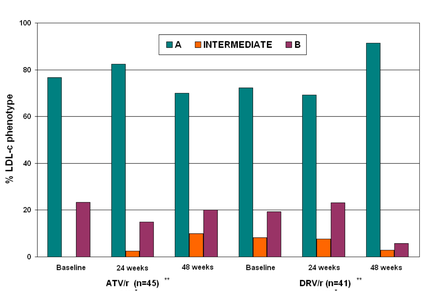
CHANGE IN LDL SUBFRACTION PHENOTYPE AT WEEK 48



* T-test or Mann Whitney U test to compare between groups at 24 and 48 weeks
** Within-group significant change from baseline to 24 and 48 weeks, T-test for repeated measures or Wilcoxon test

LDL: low density lipoprotein; sd-LDL: small and dense low density lipoprotein 5

CHANGE IN LDL PHENOTYPE AT WEEK 48



* Homogeneity marginal test to compare proportions at baseline, 24 and 48 weeks in each arm
** No statistically significant differences were found between arms at baseline, 24 and 48 weeks (Pearson Chi-square or Fisher exact test)

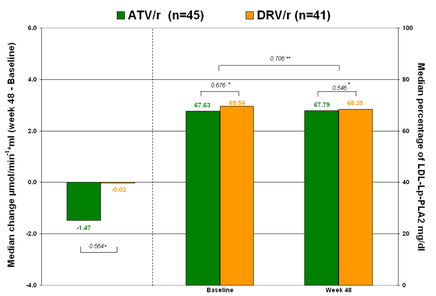
ATZ/r: ATV/ritonavir; DRV/r: DRV/ritonavir.
Phenotype A: LDL size >26.8 nm with predominance of large buoyant LDL subfractions,
Phenotype intermediate: LDL size 26.0-26.8 nm
Phenotype B: LDL size <26.0 nm with a predominance of small and dense LDL subfractions (sd-LDL) 6

UNI AND MULTIVARIATE ANALYSIS OF LDL SIZE CHANGE AT WEEK 48

Variables	Univariate analysis β (95% CI); p-value	Multivariate analysis β (95% CI); p-value
Basal body mass index	-0.25 (-0.48;-0.01); p= 0.041	
Basal waist	-0.08 (-0.16;0.0); p=0.047	
Basal diastolic blood pressure	-0.09 (-0.15;-0.02); p=0.013	
Basal LDL size	-0.34 (-0.56;-0.11); p=0.004	
Arm treatment	1.91 (0.58;3.24); p=0.006	
Basal cholesterol content in sd-LDL	0.27 (0.3;3.7); p<0.001	
Basal CD4 cell count	0.01 (0.0;0.01); p=0.0015	
Change at w 48 body mass index	-0.56 (-0.95;-0.17); p=0.006	
Change at w 48 waist	-0.13 (-0.26;-0); p=0.053	
Change at w 48 total cholesterol	-0.02 (-0.04;0);p=0.043	
Change at w 48 triglycerides	-0.02 (-0.03;-0.01); p<0.0001	-0.02 (0.03;0.01); p<0.001
Change at w 48 Apo A1	-3.3 (-6.37;-0.22); p=0.036	
Change at w 48 Apo B	-5.7 (-9.85;-1.71); p=0.006	
Change at w 48 in cholesterol content in LDL 1,2,3	0.07 (0.04;0.1); p<0.001	0.06 (0.04;0.09); p<0.001

Sd-LDL: small dense low density lipoprotein; w: week 7

CHANGE IN LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 AT WEEK 48



* T-test or Mann Whitney U test to compare between groups
**T-test or Mann Whitney U test to compare change at week 48 between groups

Lp-PLA2: lipoprotein-associated phospholipase A2; HDL-Lp-PLA2: high-density lipoprotein-associated phospholipase A2; LDL-Lp-PLA2: low-density lipoprotein-associated phospholipase A2 8

CONCLUSIONS

- **There were small and non-significant changes between arms in most lipid parameters assessed.**
- **However, patients assigned to ATV/r had higher triglyceride elevations and more atherogenic LDL subfraction phenotype than patients assigned to DRV/r.**
- **Total lipoprotein-associated phospholipase A2 as well as the distribution of the enzyme between LDL and HDL particles did not change in any arm.**

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