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Comparison of Oxidative Stress Markers in HIV-infected Patients on Efavirenz or Atazanavir/ritonavir-Based Therapy.

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Background:
Oxidative stress (OS) may be the result of an imbalance between the production of reactive oxygen species (ROS) and the ability to detoxify oxygen reactive intermediates or repair the resulting damage. A substantial body of evidence now implicates OS in the pathogenesis of atherosclerosis . ROS generated during cellular metabolic pathways modifies polyunsaturated fatty acids and lipoproteins, resulting in proinflammatory and atherogenic particles such as oxidized LDL (OxLDL). Cardiovascular disease (CVD) is one of the main causes of death in the general population and represents a significant morbi-mortality in HIV-infected patients. There is increased evidence suggesting that bilirubin, the metabolic end product of heme catabolism, may have anti-inflammatory properties as well as a beneficial potent antioxidant role by inhibiting the oxidation of LDL, scavenging oxygen radicals, and counteracting OS Epidemiological studies have shown an inverse relationship between serum bilirubin and CVD. Gilbert syndrome (GS), a genetic disorder that affect the enzyme responsible for bilirubin metabolism the UDP-glucuronosyl-transferase 1A1 (UGT1A1), is associated with a low prevalence of ischemic heart disease. Atazanavir (ATV) is a potent HIV protease inhibitor (PI). Hyperbilirubinemia is a common adverse event because ATV is an inhibitor of the UGT1A1. **The main hypothesis** of our study is that HIV patients on ATV-based therapy would show reduced OS associated with increased plasma bilirubin levels.

Methods
The study was conducted with patients from the cohort of the Spanish AIDS Research Network (CoRIS) (Annex). This is an open, multicentre, prospective cohort of HIV- infected patients over 13 years of age with confirmed HIV infection and naïve to ART at entry, seen for the first time from 1 January 2004 to 31 May 2012 in any of the 32 participating centers. Patients are followed periodically in accordance with routine clinical practice. The cohort is associated with a central Biobank where baseline and follow-up blood samples are stored. We selected previously ART-naïve patients from CoRIS who started first-line ART with either ATV/r or EFV-based regimen plus a combination of Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTI), who had a baseline Biobank sample within 6 months before ART initiation and a follow-up sample after at least 9 months of ART while maintaining initial regimen and being virologically suppressed. Positive serologies for either hepatitis C or B virus were exclusion criteria. Sample size was calculated for a difference of 50% between groups, 80% power and a 1:2 ratio, resulting in 48 patients for ATV and 96 for EFV group. Markers of OS: Lipoprotein-Associated Phospholipase A2 (Lp-PLA2), Myeloperoxidase (MPO) and Oxidized LDL (OxLDL), were measured in paired samples with commercial enzyme-linked immunosorbent assay (ELISA) at baseline and follow-up.

Baseline characteristics according to treatment group

		EFAVIRENZ (N=97)	ATAZANAVIR (N=48)	p
		n (%)	n (%)	
Age	Me[IQR]	35.9 [29.9-41.6]	37.0 [29.4-42.9]	0.98
Gender	Male	83 (85.5)	37 (77.1)	0.20
	Female	14 (14.4)	11 (22.9)	
Transmission category	MSM	64 (65.9)	27 (56.2)	0.48
	HTX	28 (28.8)	17 (35.4)	
	OT/UNK	5 (5.1)	4 (8.3)	
Nationality	Spain	67 (69.1)	35 (72.9)	0.63
	Other	30 (30.9)	13 (27.1)	
Educational level	Low	54 (55.6)	34 (70.8)	0.11
	Higher	41 (42.2)	12 (25.0)	
	NC	2 (2.1)	2 (4.1)	
AIDS diagnosis	Yes	18 (18.5)	6 (12.5)	0.36
	No	79 (81.4)	42 (87.5)	
CD4 count (cel/ml)	Me[IQR]	263 [160-355]	289.5 [189.5-399]	0.31
	≥350	25 (25.7)	19 (39.5)	0.21
	100-350	58 (59.7)	22 (45.8)	
	<100	14 (14.4)	7 (14.5)	
HIV1 VL (log cop/µl)	Me[IQR]	4.68 [3.9-5.2]	4.69 [3.9-5.2]	0.73
	<4	26 (26.8)	13 (27.1)	0.43
	4-5	40 (41.2)	15 (31.2)	
	>5	31 (31.9)	20 (41.6)	
BMI	Me[IQR]*	23.4 [21.8-25.2]	23.3 [21.2-25.5]	0.88
	<20	9 (9.2)	8 (16.6)	0.54
	20-25	60 (61.8)	27 (56.2)	
	>25	27 (27.8)	13 (27.1)	
	NC	1 (1.03)	0 (0.0)	
Smoking	Yes	38 (39.1)	24 (50.0)	0.46
	No	57 (58.7)	23 (47.9)	
	NC	2 (2.1)	1 (2.1)	
Hypertension	Yes	8 (8.2)	7 (14.5)	0.24
	No	89 (91.7)	41 (85.4)	
DM2	Yes	6 (6.1)	2 (4.1)	0.62
	No	91 (93.8)	46 (95.8)	
Cholesterol Total	Me[IQR]†	163 [133-192]	157.5 [137.5-183]	0.48
HDL	Me[IQR]†	41 [31-45]	39.5 [31-44.5]	0.62
LDL	Me[IQR]†	101.5 [80-127]	96 [72.5-109.5]	0.09
Lipid lowering-therapy	Yes	4 (4.1)	3 (6.2)	0.57
	No	93 (95.8)	45 (93.7)	
Baseline BLR (total;mg/dl)	M(SD)	0.53 (0.2)	0.45 (0.1)	0.03
LpPLA2 (ng/mL)	M(SD)	142.2 (72.8)	150.1 (92.8)	0.93
MPO (µg/L)	M(SD)	74.3 (48.2)	93.9 (64.3)	0.02
LDLOX (U/L)	M(SD)	76.3 (52.3)	82.2 (54.4)	0.40
Follow-up (Days)	Me[IQR]	390 [357-495]	429.5 [355.5-669]	<0.01

Change at one-year in oxidative stress markers and linear regression analysis for the treatment effect of EFV versus ATV/r.

		LpPLA2 (ng/mL)		MPO (µg/L)		LDLOX (U/L)	
		M/Coef[CI95%]	p	MCoef[CI95%]	p	MCoef[CI95%]	p
On-year change	EFV	-3.7 [-16.0,8.6]	0.55	-0.8 [-9.5,7.9]	0.85	26.1 [14.9,37.3]	<0.01*
	ATZ	-22.6 [-40.4,-4.7]	0.01	-5.4 [-19.4,8.6]	0.44	3.5 [-6.3,13.4]	0.48*
Crude difference	EFV	-		-		-	
	ATZ	-18.9 [-40.2,2.4]	0.08	-4.6 [-20.2,11.1]	0.57	-22.6 [-39.8,-5.3]	0.01
Adjusted for baseline values		-14.6 [-29.7,0.4]	0.06	3.7 [-10.0, 17.5]	0.59	-20.6 [-36.8, -4.4]	0.01
Adjusted for confounders **		-16.3 [-31.4,-1.25]	0.03	1.2 [-14.3,16.7]	0.88	-21.8 [-38.0, -5.6]	<0.01
Adjusted for all baseline variables†		-14.9 [-31.7,2.0]	0.08	1.2 [-14.3,16.7]	0.88	-24.6 [-42.8,-6.3]	<0.01

* p-values for the null hypothesis of mean change equal to zero (Student's T); **LpPLA2: adjusted for basal CD4, transmission category and baseline total cholesterol; MPO: adjusted for basal CD4, transmission category , gender, place of birth, educational level, basal VL, AIDS diagnosis, HTA, DM2, baseline total cholesterol and baseline total and conjugated bilirubin; LDL-OX: adjusted for baseline CD4 basal and smoking; † gender, educational level, age, transmission category place of birth, HTA, DM2, smoking, AIDS, CD4, VL, BMI, total cholesterol, total and conjugated bilirubin. M:Mean (for one-year change); Coef: regression coefficient (for all other estimates); CI95%[confidence interval at 95%].

Variations in Bilirubin levels at one year and linear regression analysis for the effect of Efavirenz versus Atazanavir/R treatment.

		Total BLR (mg/dl)	
		M/Coef[CI95%]	p
One-year change	**EFV**	-0.13 (-0.19,-0.07)	<0.01*
	ATZ	1.25 (0.96,1.54)	<0.01*
Crude differences	**EFV**	-	
	ATZ	1.38 [1.16-1.60]	<0.01
Adjusted for baseline values		1.32 [1.10-1.54]	<0.01
Adjusted for confounders **		1.33 [1.11-1.55]	<0.01
Adjusted for all baseline variables†		1.28 [1.05-1.52]	<0.01

* p-values for the null hypothesis of mean change equal to zero (Student's T); **Baseline CD4 count ; † gender, educational level, age, transmission category place of birth, HTA, DM2, smoking, AIDS, CD4, VL, BMI, total cholesterol, total and conjugated bilirubin. M : Mean (for one-year change); Coef: regression coefficient (for all other estimates); CI95% [confidence interval at 95%].

The present study revealed two main findings. First, OS biomarkers (Lp-PLA2 and Ox-LDL) are significantly reduced after ATV/r initiation. Second, there is a significant correlation between bilirubin levels and changes in OS biomarkers. These data confirm our initial hypothesis that HIV-infected patients on ATV-based therapy could present with reduced OS biomarkers associated with increased plasma bilirubin levels.

Conclusions: In virologically suppressed patients on stable ART, OS was lower in ATV/r-based regimens compared to EFV. We hypothesize these changes could be in part attributable to increased BR plasma levels.

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