PE26/10

HIV-DNA LEVELS, HLA-B*27 and HLA-DRB1*13 AMONG LTNPs, ECs and HIV controllers

Arianna Gabrieli[1], Laura Galli[2], Maciej Tarkowski[1], Chiara De Giuli[3], Annalisa Saracino[4], Giulia Marchetti[1], Stefano Bonora[5], Emanuela Lattuada[6], Maurizio Mena[7], Antonella D'Arminio Monforte[1], Antonella Castagna[2], Agostino Riva[1], Stefano Rusconi[1], on behalf of ICONA Foundation and ELVIS cohort

1. University of Milan, Milano; 2. Ospedale San Raffaele, Milano; 3. IRCCS Lazzaro Spallanzani, Rome; 4. University of Bari, Bari; 5. University of Turin, Turin; 6. University of Verona,Verona; 7.Ospedale Civile di Legnano, Italy.

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BACKGROUND

The composition and the development of the HIV-DNA reservoir either in treated or untreated patients is determined by integrated mechanism comprising virological factors, immune system and treatment strategies (1). HLA types have been associated with varying rate of disease progression and different effects have been reported between subtypes of HLA alleles (2). HLA B*27 and HLA B*57 are associated with a slower rate of HIV disease progression, and HLA Class II DRB1*13:03 is associated with a lower plasma viral load in chronic HIV infection.

AIMS

The aim of this study was to determine the association of HLA-B*27 and HLA-DRB1*13:03 with HIV-DNA in *Elite Controllers*, *Long-Term Non-Progressors*, *HIV Controllers, ART-naïve* and *ART treated patients* .

STUDY DESIGN AND METHODS

- We evaluated 231 HIV-1-infected patients from the ICONA and the Elvis Cohorts categorized in 5 distinct groups: 20 *Elite Controllers* (*EC),* 35 *Long-Term Non-Progressors (LTNP)*, 17 *HIV controllers*, *122 ART-naïve* and 37 patients under suppressive ART
- Total HIV-DNA was extracted from PBMCs by droplet digital PCR (ddPCR) and classified as undetectable if below the detection limit
- HLA-B*27 rs4349859 and HLA-DRB1*13:03 rs424232 genotypes were determined by TaqMan Assay

STATISTICAL ANALYSIS

- Statistical analysis was performed using SAS software. The correlations between clinical parameters and molecular data were performed by Spearman correlation test and linear regression analysis. Multivariable linear regression was performed to assess SNPs association with HIV-DNA values.

RESULTS

The characteristics of the patients' cohorts are described in Table 1:

TABLE 1 CHARACTERISTIC	EC (n=20)	HIV-CONTROLLER (n=17)	LTNP (n=35)	NAÏVE (n=122)	ART-TREATED (n=37)	p-value
Age (years)	49 (40-56)	38 (29-48)	47 (38-51)	36 (30-48)	51 (44-55)	***<.0001***
Male gender	13 (65%)	7 (41%)	26 (74%)	86 (71%)	25 (68%)	0.153
Italian nationality	18 (90%)	11 (65%)	29 (83%)	83 (68%)	30 (81%)	0.068
Years since HIV diagnosis	12.7 (5.0-17.00)	1.76 (0.87-4.38)	9.26 (5.00-13.0)	0.20 (0.01-2.0)	17.5 (9.0-22.0)	***<.0001***
CD4+ nadir (cells/µL)	527 (442-844)	472 (423-592)	546 (484-672)	405 (302-513)	220 (74-306)	***<.0001***
CD4+ (cells/µL)	700 (548-1088)	655 (506-717)	739 (626-934)	473 (345-666)	647 (452-891)	***<.0001***
CD8+ (cells/µL)	761 (529-1335)	812 (668-1120)	1040 (783-1464)	865 (659-1258)	681 (449-1200)	0.208
HIV-DNA (log_{10}copies/10^6PBMC)	0 (0-2.09)	2.22 (0-2.54)	2.16 (0-2.97)	2.75 (1.93-3.24)	2.13 (1.80-2.55)	***<.0001***
Undetectable	11 (55%)	6 (35%)	12 (34%)	22 (18%)	7 (19%)	0.003
Detectable	9 (45%)	11 (65%)	23 (66%)	100 (82%)	30 (81%)	
*HLA-B*27 rs4349859*						0.819
AA	1/19 (5%)	0/17 (0%)	1/35 (3%)	7/116 (6%)	1/35 (3%)	
AG	15 (79%)	16 (94%)	29 (83%)	100 (86%)	31 (89%)	
GG	3 (16%)	1 (6%)	5 (14%)	9 (8%)	3 (9%)	
*HLA DR-B1*13:03 rs424232*						0.495
CC	5/16 (31%)	3/16 (19%)	10/31 (32%)	37/105 (35%)	8/30 (27%)	
CT	11 (69%)	12 (75%)	16 (52%)	59 (56%)	17 (57%)	
TT	0	1 (6%)	5 (16%)	9 (9%)	5 (17%)	

rs 4349859 GG genotype was found in 16%, 6%, 14%, 8% and 9% of EC, HIV-controllers, LTNP, ART-naïve and ART-treated patients, respectively (p=0.819; Table 1).

Undetectable HIV-DNA was found in 60%, 31%, 35%, 17% and 19% EC, HIV-controllers, LTNP, ART-naïve and ART-treated pts with rs4349859 AG genotype, respectively (p=.004) and in 67%, 100%, 40%, 22% and 0% of EC, HIV-controllers, LTNP, ART-naïve and ART-treated pts with GG genotype(p=.231).

TABLE 2 CHARACTERISTIC	CATEGORY	ADJUSTED MEAN HIV-DNA (95%CI) (LOG_{10}COPIES/10^6PBMC)	SLOPE OF HIV-DNA (95%CI)	P-VALUE
Age	Per 1-year older		-0.005 (-0.027, 0.017)	0.674
Gender				
	F	1.828 (1.042, 2.614)	0.444 (-0.110, 0.997)	0.115
	M	1.384 (0.768, 2.000)	Ref	-
Patients' group				0.244
	EC	1.070 (-0.357, 2.496)	-0.784 (-2.219, 0.651)	0.280
	HIV-CONTROLLER	1.954 (0.976, 2.932)	0.100 (-0.917, 1.116)	0.846
	LTNP	2.227 (1.232, 3.221)	0.373 (-0.666, 1.411)	0.477
	NAIVE	1.854 (1.274, 2.434)	Ref	Ref
	ART-TREATED	0.926 (-0.329, 2.181)	-0.928 (-2.058, 0.202)	0.106
Years HIV infection	Per year longer			0.611
CD4+ nadir	Per 100-cells/µL higher		-0.257 (-0.462, -0.052)	0.015
Zenith HIV-RNA	Per log_{10}copies/mL higher		0.134 (-0.181, 0.449)	0.400
*HLA-B*27 rs4349859*	GG	1.217 (0.312, 2.122)	-0.778 (-1.556, -0.0003)	0.049
	non-GG	1.995 (1.423, 2.567)	Ref	-
CCR5Δ32	HT	1.246 (0.317, 2.130)	-0.720 (-1.495, 0.054)	0.068
	WT	1.966 (1.364, 2.567)	Ref	-
IL28B rs12979860				0.683
	CC	1.633 (0.944, 2.322)	0.191 (-0.446, 0.827)	0.553
	CT	1.743 (1.022, 2.464)	0.300 (-0.381, 0.982)	0.384
	TT	1.442 (0.629, 2.256)	Ref	-
CD4+ cell count	Per 100-cells/µL higher		0.149 (-0.0005,0.298)	0.051

After adjusting for patients' group, age, gender, years of infection, nadir CD4+, zenith HIV-RNA, CD4+ cell count, CCR5Δ32, IL28B rs12979860 genotypes and rs4349859, lower HIV-DNA levels were associated with a higher nadir CD4+ (p=.015), rs4349859 GG genotype (p=.049); a marginal association was also observed for CCR5 heterozygous genotype (Table 2). No significant association was found between HIV-DNA values and HLA -DRB1*13:03 rs424232.

CONCLUSIONS

Significative differences among groups in regard to undetectable HIV-DNA levels were found in pts with rs4349859 AG genotype; lower values of HIV-DNA were found to be associated with the presence of HLA-B*27 rs4349859 GG genotype and with a higher nadir of CD4+ lymphocytes.

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Contact Information: **arianna.gabrieli@asst-fbf-sacco.it**