Imperial College London

SPARTAC

Protective HLA Class I alleles are associated with reduced immune activation in Primary HIV infection

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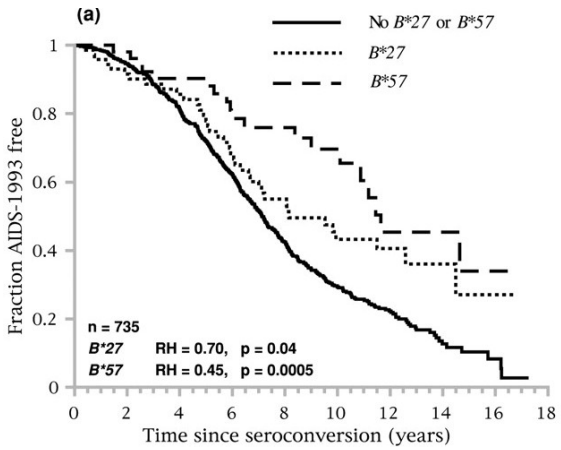
Background

- Immune activation is an independent predictor of HIV-1 disease progression[1]
- High CD38 expression on CD4 and CD8 cells associated with worse outcome
- Raised inflammatory and coagulation biomarkers IL-6 and D-dimer in chronic HIV infection predictive of adverse outcome[2]

[1]Hazenburg et al. AIDS. 2003 Sep 5;17(13):1881-8.

[2]Kuller et al PLoS Med. 2008 Oct 21;5(10):e203.

Carriers of class 1 alleles HLA-B*27 and B*57 have delayed HIV progression.



Carrington & O Brien. Annu. Rev. Med. 2003. 54:535–51

Hypothesis & Aims

- Hypothesis:

  Individuals with protective HLA types have low levels of immune activation and inflammatory biomarkers, contributing to reduced disease progression

- Aims:

  To examine the relationship between protective HLA types and markers of immune activation, inflammation and coagulation in individuals with Primary HIV infection

Methods

•Participants enrolled in the SPARTAC trial: a RCT of ART intervention versus no therapy in Primary HIV infection (PHI)

•Cross sectional analysis of UK participants at seroconversion (n=148)

•PBMCs analysed by flow cytometry for CD38 expression on CD8 and CD4 T-cells. IL-6 and D-dimer measured from stored plasma.

•HLA type determined by sequence specific PCR. Patients categorised as HLA B*57, HLA B*27, or other HLA type

•Relationship between HLA type, immune activation, plasma HIV-RNA, and other baseline factors examined using linear regression

Baseline Characteristics (n=148)

Baseline variable		Number or Median	(%) or [IQR]
Sex:	Male	142	(96)
	Female	6	(4)
Risk group:	MSM	138	(93)
	Heterosexual	9	(6)
	Other / unknown	1	(1)
Age (years)		34.5	[29,41]
Estimated time from infection (days)		73	[47,93]
Clade B		133	(90)
CD4 (cells/mm^3)		540	[405, 673]
HIV-RNA (copies/ml)		58835	[11827, 206822]

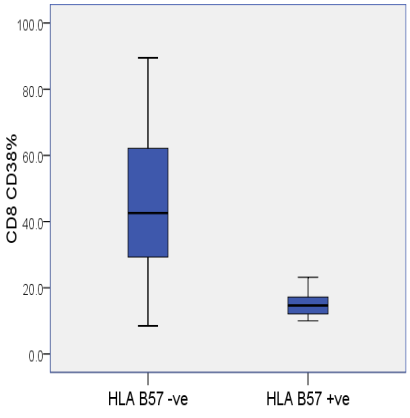
Results

Variable	Number or Median	(%) or [IQR]
HLA B*57 +ve	10/145	(7)
HLA B*27 +ve	14/145	(10)
CD8 CD38 expression (%)	40	[25.4, 60]
CD4 CD38 expression (%)	52	[38, 75]
IL-6 (pg/ml)	1.5	[0.9, 2.7]
D-dimer (μ g/ml)	0.38	[0.23, 0.6]

IL-6 and D-dimer correlated with each other (p=0.004) and CD8 CD38% expression (p=0.03 for IL-6, p=0.005 for d dimer).

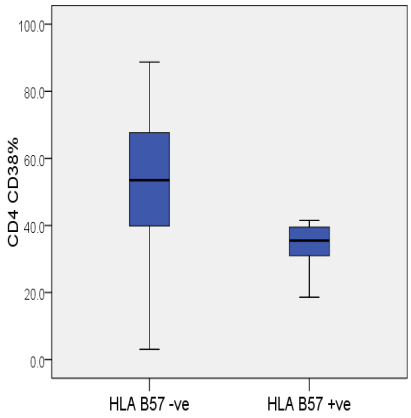
CD4 CD38 expression correlated with CD8 CD38 expression (p<0.0001)

CD8 activation and HLA B*57



•Mean activation 46% vs. 15% p<0.0001
•Relative difference of 31%

CD4 activation and HLA B*57



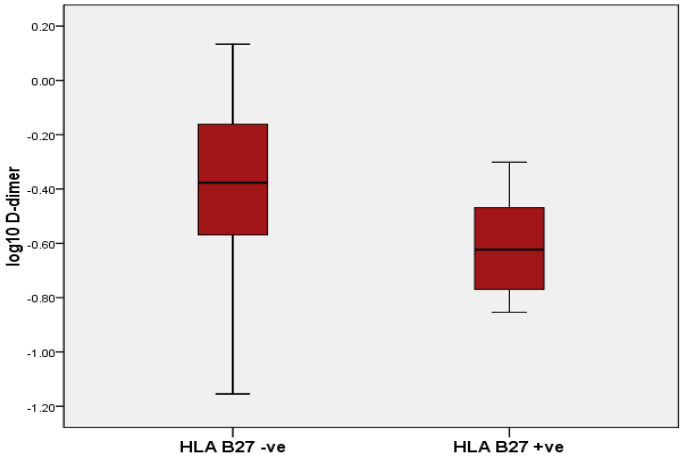
•Mean activation 53% vs. 36% p=0.005
Relative difference of 17%

Factors associated with immune activation in Primary HIV infection

	Parameter	Univariate p-value	Univariate 95% CI	Multivariate* p-value	Multivariate* 95% CI
CD8 CD38 %	Age (+10 years)	0.8	-3, 4.7		
	CD4 (+100 cells)	**0.01**	-4.3, -0.5		
	HIV-RNA (+1og)	**<0.0001**	6.7, 14	**<0.0001**	4.6, 12
	HLA B*57	**<0.0001**	-43, -18	**<0.0001**	-34.8, -10
	HLA B*27	0.2	-24, 5.2		
	BMI (+1 kg/m^2)	0.4	-2, 0.6		
	BP >140/90	0.5	-23, 11		
CD4 CD38 %	Age (+10 years)	0.07	-0.6, 0.03	**0.01**	-0.8, -0.12
	CD4(+100 cells)	**0.01**	-3.4, -0.4	0.07	-3.1, 0. 1
	HIV-RNA (+1og)	0.4	-2, 4.7		
	HLA B*57	**0.005**	-28, -5	**0.02**	-26, -2
	HLA B*27	0.9	-12, 12		
	BMI (+1 kg/m^2)	0.4	-1.3, 0.5		
	BP > 140/90	0.06	-0.3, 28	**0.01**	5.4, 33

* variable carried through to multivariate analysis if p<0.1 in univariate model

D dimer and HLA B*27 status



- Geometric mean D-dimer 0.40 vs.0.24 μg/ml p=0.003
- Relative difference of 40% (95% CI 15%, 58%).

Factors associated with D dimer in Primary HIV infection

	Parameter	Univariate		Multivariate	
		p-value	95% CI	p-value	95% CI
D dimer	Age (+10 years)	**0.001**	0.03, 0.13	**0.005**	0.02, 0.1
	CD4 (+100 cells)	0.1	-0.04, 0.004		
	HIV-RNA (+1log)	**<0.0001**	0.08, 0.2	**<0.0001**	0.05, 0.1
	HLA B*57	0.4	-0.3, 0.1		
	HLA B*27	**0.003**	-0.4, -0.07	**0.016**	-0.3,-0.03
	BMI (+1 kg/m^2)	0.6	-0.01, 0.02		
	BP>140/90	0.3	-0.3, 0.1		

Discussion

- Protective HLA types associated with lower immune activation and fibrinolysis
- This effect is independent of plasma HIV-RNA.
- T cell activation also associated with increased viral load, age and hypertension
- Future analysis to develop algorithm for predicting disease progression at time of Primary HIV diagnosis

Conclusion

- HLA B*57 positive individuals had lower levels of both CD8 and CD4 immune activation in Primary HIV Infection.
- HLA B*27 positive individuals had lower D-dimer levels
- HLA associated limitation of immune activation and/or fibrinolysis may additively contribute towards delayed HIV progression in individuals with protective HLA types.

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