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Plasma HIV-1 tropism and risk of short-term clinical progression to AIDS or death

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BACKGROUND

It is uncertain if plasma HIV-1 tropism is able to predict short term risk of clinical progression/death, independently of current CD4 count and HIV RNA level. We conducted a nested case-control study within EuroSIDA to assess this question amongst people with current HIV RNA level >1000 cps/mL, including both people on ART and those ART naive.

METHODS

People with an AIDS diagnosis or who died from any causes for whom there was a stored plasma sample with HIV-1 RNA (VL)≥1000 copies/mL available in the time window of 3 to 12 months prior to the event were identified. At least 1 control was selected for each case matched for age, VL and HCV status at the time of sampling. Controls were event-free after a matched duration of time from the date of sampling. Plasma HIV tropism was estimated using 454 and population sequencing (PS). Non-R5 HIV was defined as: (a) ≥2% of sequences with a Geno2Pheno (G2P) FPR≤3.75% by 454, and (b) a G2P FPR≤10% by PS. We also compared CD4 slopes over the 12 months following the date of sampling using a linear mixed model with random intercept and slope according to HIV tropism and ART status.

RESULTS

The study included 266 subjects, 100 cases and 166 controls, with sample taken on average in 2006; 23% and 24% had non-R5 HIV by 454 and PS respectively. There were 19% women, 25% MSM, 92% Caucasians, 22% HCV+. At the time of sampling, 26% were ART-naïve, 25% had previously started but were off ART and 49% were receiving ART. The median age, CD4 and viral load was 41 years, 350 cells/mm^3 and 4.81 log c/mL, respectively. Baseline characteristics were well balanced in the groups stratified by tropism (**Table 1**).

Factors independently associated with clinical progression or death, adjusted for matching factors, CD4+ counts and calendar year of sample were female gender (OR=2.12 vs. male; 95%CI= 1.04, 4.36; p=0.038), CD4+ count (OR=0.90 per 100 cells/mm^3 higher; 95%CI: 0.80, 1.00; p=0.058), being on ART (OR=2.72 vs. ART-naive; 95%CI: 1.15, 6.41; p=0.022) and calendar year of sample (OR=0.84 per more recent year; 95%CI=0.77, 0.91; p<0.001). Baseline plasma tropism was not an independent risk factor for clinical progression or death by either 454 or PS (**Table 2**). In the analysis adjusted for matching factors only the OR for X4 vs. R5 was 0.90 (p=0.737); this estimate changed to OR=0.84 (p=0.582) after further adjusting for CD4 count. This was expected as CD4 count was lower in persons with X4 vs. R5 (**Table 1)**, and a low CD4 count is associated with higher risk of AIDS/death. No significant interaction was observed between tropism and ART status, suggesting that the lack of association was consistent regardless of ART use (**Figure 1**). Conclusions were unchanged when we restricted to AIDS and HIV-mortality as definition of case (not shown). Consistently, there were no significant differences in the CD4+ slope within or between tropism groups (**Figure 1**).

CONCLUSIONS

Plasma HIV-1 tropism does not appear to predict the short term risk of the composite outcome of AIDS or death, after controlling for co-infection with HCV, age and current viral load, even though 454 sequencing was used.

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Table 1

Subjects' characteristics, stratified by tropism determination

Characteristics	X4	R5	Total	p-value
	N= 61	N= 205	N= 266	
Age, years				0.301
Median (IQR)	42 (37, 47)	41 (35, 49)	41 (36, 49)	
Viral load, log10 copies/mL				0.764
Median (IQR)	4.85 (4.45, 5.29)	4.81 (4.47, 5.38)	4.81 (4.46, 5.36)	
Gender, n(%)				0.135
Female	8 (13.1%)	44 (21.5%)	52 (19.5%)	
Ethnicity, n(%)				0.235
White	54 (89%)	190 (93%)	244 (92%)	
Asian	0 (0%)	2 (1%)	2 (1%)	
Black	1 (2%)	2 (1%)	3 (1%)	
Other/unknown	6 (10%)	11 (5%)	17 (6%)	
Mode of HIV transmission, n(%)				0.587
Homosexual contacts	9 (15%)	57 (28%)	66 (25%)	
Heterosexual contacts	6 (10%)	16 (8%)	22 (8%)	
IDU	18 (30%)	36 (18%)	54 (20%)	
Other/unknown	9 (15%)	57 (28%)	66 (25%)	
Geographical region, n(%)				0.396
Argentina	0 (0%)	4 (2%)	4 (2%)	
Belgium	2 (3%)	8 (4%)	10 (4%)	
Central East Europe	16 (26%)	53 (26%)	69 (26%)	
South East Europe	2 (3%)	17 (8%)	19 (7%)	
France	6 (10%)	20 (10%)	26 (10%)	
Germany	13 (21%)	26 (13%)	39 (15%)	
Greece	0 (0%)	1 (0%)	1 (0%)	
Spain	0 (0%)	0 (0%)	0 (0%)	
Italy	1 (2%)	3 (1%)	4 (2%)	
Scandinavia	10 (16%)	46 (22%)	56 (21%)	
Switzerland	2 (3%)	5 (2%)	7 (3%)	
United Kingdom	9 (15%)	16 (8%)	25 (9%)	
CD4 count, cells/mm^3				0.348
Median (IQR)	279 (150, 471)	351 (150, 530)	350 (150, 490)	
HCV co-infection, n(%)				0.116
No	52 (85%)	156 (76%)	208 (78%)	
Yes	9 (15%)	49 (24%)	58 (22%)	
Calendar year of test				0.680
Median (IQR)	2006 (2001, 2009)	2006 (2003, 2008)	2006 (2003, 2009)	
Clinical outcome, n(%)				0.559
Case	21 (34%)	79 (39%)	100 (38%)	
ART-naive, n(%)				0.736
Yes	20 (33%)	49 (24%)	69 (26%)	

Table 2

Factors association with risk of AIDS or death, adjusted for: 1) matching factors (age, VL and HCV co-infection); 2) matching factors and CD4$^+$T-cell counts; 3) matching factors, CD4$^+$T-cell counts and calendar year of sample

	Association with risk of AIDS/death from fitting a conditional logistic regression								
	Event	Event free	Adjustment(1)		Adjustment(2)		Adjustment(3)		
Factor	N= 100	N= 166	OR[1] (95% CI)	P-value	OR[1] (95% CI)	P-value	OR[1] (95% CI)	P-value	
Tropism (454 estimate[***]), n(%)									
R5	79 (79.0%)	126 (75.9%)	1.00		1.00		1.00		
X4	21 (21.0%)	40 (24.1%)	0.90 (0.49, 1.66)	0.737	0.84 (0.45, 1.57)	0.582	0.66 (0.33, 1.33)	0.245	
Gender, n(%)									
Male	75 (75.0%)	139 (83.7%)	1.00		1.00		1.00		
Female	25 (25.0%)	27 (16.3%)	1.86 (1.00, 3.49)	0.051	1.63 (0.85, 3.14)	0.140	2.13 (1.04, 4.36)	0.038	
Age[*], years									
Median (IQR)[**]	40 (35, 48)	42 (36, 50)							
Viral load, log10 copies/mL									
Median (IQR)[**]	2.50 (2.30, 2.64)	2.59 (2.42, 2.76)							
CD4 count [***], cells/mm3									
Median (IQR)	285 (132, 417)	357 (201, 548)	0.87 (0.78, 0.96)	0.009			0.90 (0.80, 1.00)	0.058	
ART use, n(%)									
Not started	20 (20.0%)	49 (29.5%)	1.00		1.00		1.00		
Started, currently on ART	31 (31.0%)	35 (21.1%)	2.52 (1.18, 5.40)	0.017	2.39 (1.09, 5.21)	0.029	2.72 (1.15, 6.41)	0.022	
Started, currently off ART	49 (49.0%)	82 (49.4%)	1.46 (0.75, 2.83)	0.264	1.06 (0.52, 2.16)	0.878	1.42 (0.65, 3.09)	0.381	
Co-infection with HCV[**], n(%)									
No	77 (77.0%)	131 (78.9%)							
Yes	23 (23.0%)	35 (21.1%)							
Mode of HIV transmission, n(%)									
Homosexual contacts	27 (27.0%)	39 (23.5%)	1.00		1.00		1.00		
IVDU	21 (21.0%)	33 (19.9%)	1.55 (0.70, 3.45)	0.281	1.43 (0.62, 3.29)	0.401	1.16 (0.47, 2.90)	0.745	
Heterosexual contacts	10 (10.0%)	12 (7.2%)	1.74 (0.68, 4.43)	0.246	1.57 (0.61, 4.01)	0.350	0.91 (0.32, 2.58)	0.859	
Other/unknown	27 (27.0%)	39 (23.5%)	1.51 (0.77, 2.95)	0.225	1.26 (0.63, 2.54)	0.513	1.84 (0.86, 3.97)	0.117	
CD4 count nadir, n(%)									
Median (IQR)	174 (58, 289)	202 (55, 360)	0.87 (0.75, 1.01)	0.074	1.03 (0.83, 1.29)	0.774	1.06 (0.84, 1.34)	0.642	
Calendar year of sample[***]									
Median (IQR)	2004 (2002, 2006)	2007 (2004, 2010)	0.82 (0.76, 0.90)	<.001	0.84 (0.77, 0.91)	<.001	0.84 (0.77, 0.91)	<.001	
Ethnicity, n(%)									
White	90 (90.0%)	154 (92.8%)	1.00		1.00		1.00		
Non white	10 (10.0%)	12 (7.2%)	1.31 (0.54, 3.17)	0.544	1.38 (0.56, 3.43)	0.488	1.02 (0.35, 2.92)	0.976	
Drug resistance, n(%)									
None	65 (65.0%)	131 (78.9%)	1.00		1.00		1.00		
≥1 class	35 (35.0%)	35 (21.1%)	1.95 (1.03, 3.71)	0.040	1.60 (0.82, 3.13)	0.170	1.31 (0.63, 2.73)	0.476	

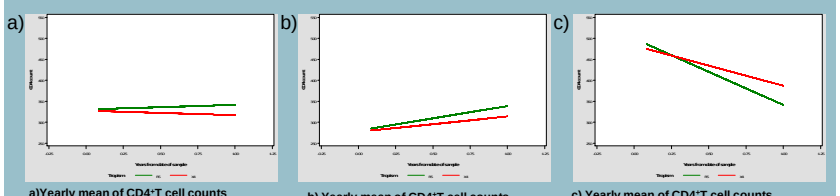
[*]OR per 10 years older
[**]OR per 100 cells/mm3 higher
[***] OR per more recent year
[**]Matching factor
[***]Declared X4 if ≥2% of minority population when using a 3.75% FPR

Figure 1

Investigation of *Interaction between effects of tropism and ART status on CD4 slope*. No significant interaction was found between tropism and ART status

Period	Tropism[&]					
	X4		R5		Difference X4 vs. R5	
All periods	Mean CD4 count change[*] (95% CI)	p-value	Mean CD4 count change[*] (95% CI)	p-value	Mean CD4 count change[*] (95% CI)	p-value
	-10 (-104, 83)	0.830	11 (-46, 69)	0.701	-21 (-120, 77)	0.670
Periods before starting ART	Mean CD4 count change[*] (95% CI)	p-value	Mean CD4 count change[*] (95% CI)	p-value	Mean CD4 count change[*] (95% CI)	p-value
	-96 (-325, 133)	0.414	-158 (-283, -34)	0.014	63 (-198, 323)	0.638
Periods after starting ART	Mean CD4 count change[*] (95% CI)	p-value	Mean CD4 count change[*] (95% CI)	p-value	Mean CD4 count change[*] (95% CI)	p-value
	36 (-62, 134)	0.468	59 (-2, 119)	0.057	-23 (-125, 80)	0.666

&Declared X4 if >=2% of minority population when using a 3.75% FPR
*per year



a)Yearly mean of CD4$^+$T cell counts changes from fitting a mixed linear model from all periods.

b) Yearly mean of CD4$^+$T cell counts changes from fitting a mixed linear model before treatment was started.

c) Yearly mean of CD4$^+$T cell counts changes from fitting a mixed linear model after treatment initiation.

No significant differences in CD4$^+$ T-cell slope were observed within or between tropism groups.

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