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Detection of Non-R5 HIV by Ultrasensitive Genotypic Testing Is Associated with CD4+ Count Decreases Also After the Initiation of ART

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Background

The prognostic value of HIV-1 tropism to predict CD4 and clinical outcomes in HIV-1-infected subjects receiving ART is unclear.

Methods

We conducted a nested case-control study within the EuroSIDA cohort, where people with an AIDS diagnosis or who died for any causes for whom there was a stored plasma sample available in the time window of 3 to 12 months prior to the event were identified. Two controls were selected for each case matched for age (+/- 5 years), viral load (+/- 0.5 log) and HCV status at the time of sampling. Controls were still event-free after a matched duration of time from the date of sampling.

HIV tropism was estimated using 454 sequencing of the V3-loop (non-R5 HIV defined as ≥2% of sequences with a Geno2Pheno FPR≤3.75%). In this analysis we compared the CD4 slope in people with R5 and non-R5 HIV over the 12 months following the date of sampling.

A linear mixed model with random intercept and slope was used to estimate the difference in the two groups by fitting an interaction term. Analyses were controlled for gender, age, race, HCV co-infection, current viral load, use of ART and calendar year of sample, and were performed using all CD4 values, as well as after restricting to those determined while subjects were ART naïve, or to those obtained following ART initiation.

Results (I)

Tropism estimates were available for 113 patients (39 cases and 74 controls) tested on a sample stored on average in 2004 (IQR:2002-2008). 20% of subjects had non-R5 HIV. At the time of sampling 50% were ART-treated, 39% were ART-naïve and remained untreated and 11% were ART-naïve and started ART within the year. Baseline characteristics were well balanced by tropism (Table1)

Table1

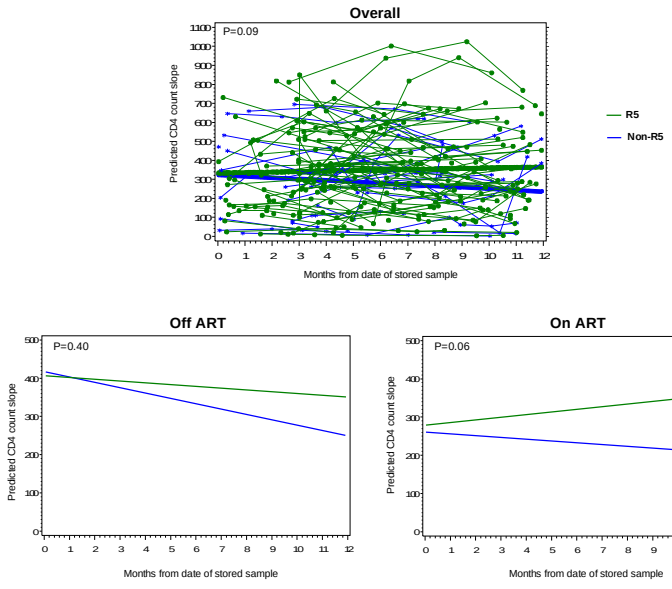
Characteristics	Non-R5	R5	Total	*p-value*
	N= 23	N= 90	N= 113	
Age, years				0.257
Median (IQR)	37 (33, 41)	34 (31, 43)	35 (31, 42)	
Viral load, log10 copies/mL				0.604
Median (IQR)	4.85 (4.54, 5.13)	4.81 (4.40, 5.20)	4.82 (4.41, 5.19)	
Gender, n(%)				0.462
Female	4 (17.4%)	22 (24.4%)	26 (23.0%)	
Ethnicity, n(%)				0.650
White	21 (91%)	84 (93%)	105 (93%)	
Asian	0 (0%)	1 (1%)	1 (1%)	
Black	1 (4%)	0 (0%)	1 (1%)	
Other/unknown	1 (4%)	5 (6%)	6 (5%)	
Mode of HIV transmission, n(%)				0.893
Homosexual contacts	9 (39%)	42 (47%)	51 (45%)	
Heterosexual contacts	4 (17%)	25 (28%)	29 (26%)	
IDU	8 (35%)	15 (17%)	23 (20%)	
Other/unknown	2 (9%)	8 (9%)	10 (9%)	
Geographical region, n(%)				0.181
Argentina	0 (0%)	0 (0%)	0 (0%)	
Belgium	2 (9%)	5 (6%)	7 (6%)	
Central East Europe	4 (17%)	24 (27%)	28 (25%)	
South East Europe	1 (4%)	11 (12%)	12 (11%)	
France	1 (4%)	9 (10%)	10 (9%)	
Germany	5 (22%)	12 (13%)	17 (15%)	
Greece	0 (0%)	1 (1%)	1 (1%)	
Spain	0 (0%)	0 (0%)	0 (0%)	
Italy	1 (4%)	1 (1%)	2 (2%)	
Scandinavia	3 (13%)	21 (23%)	24 (21%)	
Switzerland	1 (4%)	3 (3%)	4 (4%)	
United Kingdom	5 (22%)	3 (3%)	8 (7%)	
CD4 count, cells/mm³				0.929
Median (IQR)	365 (187, 538)	351 (172, 548)	352 (182, 548)	
Hepatitis co-infection, n(%)				0.955
No	17 (74%)	66 (73%)	83 (73%)	
Yes	5 (22%)	19 (21%)	24 (21%)	
Unknown	1 (4%)	5 (6%)	6 (5%)	
Calendar year of test				0.222
Median (IQR)	2003 (2001, 2008)	2005 (2002, 2008)	2004 (2002, 2008)	
Clinical outcome, n(%)				0.604
Case	9 (39%)	30 (33%)	39 (35%)	
ART-naive, n(%)				0.779
Yes	12 (52%)	44 (49%)	56 (50%)	

Results (II)

Subjects contributed 347 CD4 measurements (70 X4 and 277 R5) over the year after the genotypic test (5% over 3 months; 11% over 3-6 months; 20% over 6-9 months, and 64% over 9-12 months). In the multivariable analysis controlled for gender, age, race, HCV co-infection, current viral load, calendar year of sample and use of ART (the latter only in the model including all counts), the mean (95% CI) non-R5 - R5 difference in CD4 count change/year was (p-value for interaction): -122 (-252,0) (P=0.05); -115 (-374,+144) (P=0.37), and -164 (-296,-32) (P=0.02), in the overall analysis (n=347 counts), after restricting to CD4+ counts obtained while subjects were ART naïve (n=117 counts), and after restricting to CD4+ counts obtained after ART initiation (n=230 counts), respectively.

HIV Tropism*	Mean (95% CI) CD4 count decrease/year	
	Univariable	Multivariable**
	Overall (n=347 counts)	
R5	+32 (-29;+93)	-25 (-87;+37)
Non-R5	-87 (-210; +37)	-146 (-266; -26)
Difference Non-R5 - R5	-119 (-256; +18)	-122 (-252; 0)
p-value for interaction	P=0.09	P=0.05
	Restricting to CD4+ counts obtained while subjects were ART naïve (n=117 counts)	
R5	-56 (-175; +63)	-68 (-183;+48)
Non-R5	-169 (-413; +75)	-183 (-411; +47)
Difference Non-R5 - R5	-113 (-387; +161)	-115 (-374;+144)
p-value for interaction	P=0.40	P=0.37
	Restricting to CD4+ counts obtained after ART initiation (n=230 counts)	
R5	+86 (+17; +154)	+20 (-46; +86)
Non-R5	-56 (-189; +77)	-144 (-269; +20)
Difference Non-R5 - R5	-141 (-290; +6)	-164 (-296; -32)
p-value for interaction	P=0.06	P=0.02

**454 estimate, non-R5 HIV defined as ≥2% of virus populations with FPR ≤ 3.75%*
***Controlled for gender, age, race, HCV co-infection, current viral load, use of ART (model including all counts only) and calendar month of sample.*



Conclusions

Non-R5 HIV estimated using 454 sequencing was associated with steeper CD4 count decreases also after ART initiation, which suggests a higher risk of clinical complications for subjects with non-R5 HIV even in time periods following the initiation of treatment. Ongoing analyses will verify if this observation may result in a different risk of progression to AIDS or death.

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