PERSISTENT HIV CONTROLLERS ARE MORE PREDISPOSED TO SPONTANEOUSLY CLEAR HCV

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BACKGROUND

HIV-controllers have the ability to spontaneously maintain viremia at low or undetectable levels in absence of antiretroviral treatment. Furthermore, HIV controllers seem to have superior capacity to spontaneously clear hepatitis C virus (HCV) coinfection compared to non HIV-controllers. Some of these subjects eventually lose HIV-controller status ***(transient controllers)***, in contrast with HIV-controllers with persistent natural HIV control ***(persistent controllers)***. It is unknown whether persistent controllers have superior capacity to spontaneously clear HCV coinfection compared to transient controllers. **The aim of this study was to analyze whether persistent HIV-controllers had superior capacity to spontaneously clear HCV compared to transient HIV-controllers.**

METHODS

HIV-controllers with available data for antibodies to HCV (anti-HCV) were recruited from the HIV-controllers cohort of the AIDS Research Network (ECRIS) (n=744).

Factors associated with HIV spontaneous control were analyzed in ***persistent and transient HIV-controllers*** with anti-HCV positive (n=202 and n=138, respectively) in comparison with 1700 anti-HCV positive non HIV-controllers.

Factors related to the loss ***(persistent vs transient HIV-controllers)*** and time to lose HIV-controller status were explored (n=744).

Bivariate and multivariate analyses, following a logistic regression model, were applied for the analysis of factors associated with persistent and transient HIV spontaneous control and for the analysis of factors associated with loss of HIV-controller status. For the analysis of time to lose HIV-controller status, Log rank test and Kaplan-Meier curves were used. In this case the multivariate analysis consisted in a Cox regression model, using the enter procedure.

These models were adjusted by sex, age at HIV diagnosis, time of follow up, people who inject drugs as (PWID) as risk of HIV transmission, being elite, CD4+ T-cell nadir, HCV spontaneous clearance and HLA-B*57 typing, as potential confounders.

RESULTS

Table 1. Characteristics of persistent and transient HIV-controllers and non-controllers exposed to HCV

	Persistent HIV-controllers (n=202)	Transients HIV-controllers (n=138)	HIV non-controllers (n=1700)	Persistent HIV-controllers vs HIV non-controllers *p*; OR(CI95%)†	Transient HIV-controllers vs HIV non-controllers *p*; OR(CI95%)
Female sex (n.%)	66/202 (32.7)	49/138 (35.5)	235/1700 (13.8)	**<0.001; 3.025 (2.187-4.186)**	**<0.001; 3.432 (2.359-4.993)**
Age at HIV diagnosis	28 [24-33]	28 [23-33]	27 [23-33]	0.360; 1.008 (0.991-1.025)	0.667; 1.004 (0.984-1.025)
HIV transmission risk, PWID (n.%)	162/202 (80.2)	102/138 (73.9)	1379/1700 (83.6)	0.226; 0.796 (0.550-1.152)	**0.004; 0.557 (0.373-0.832)**
PWID, female (n.%)	47/66 (71.2)	32/49 (65.3)	161/235 (70.9)	0.964; 1.074 (0.554-1.857)	0.437; 0.772 (0.401-1.484)
CD4 nadir	520 [388-675]	285 [213-396]	111 [31-224]	**<0.001; 1.009 (1.008-1.010)**	**<0.001; 1.006 (1.005-1.007)**
Time of follow up (years)[&]	18.1 [11.7-23.7]	15.8 [8.0-21.0]	18.6 [11.8-24.9]	0.578; 0.995 (0.978-1.012)	**<0.001; 0.961 (0.942-0.981)**
Clinical stage C (n.%)*	7/107 (6.5)	10/121 (8.3)	275/1674 (16.4)	**0.009; 0.356 (0.164-0.775)**	**0.020; 0.458 (0.237-0.887)**
HCV PCR+ (n,%)**	99/123 (80.5)	113/130 (86.9)	1521/1694 (89.8)	**0.002; 0.469 (0.292-0.753)**	0.304; 0.756 (0.443-1.289)
HCV genotype detected (n.%)¶					
Genotype 1	28/132 (40.0)	37/84 (44.0)	616/1075 (57.3)	**0.005; 0.497 (0.303-0.813)**	**0.019; 0.587 (0.375-0.918)**
Genotype 2	2/132 (2.9)	3/84 (3.6)	9/1075 (0.8)	0.115; 3.484 (0.738-16.440)	**0.029; 4.387 (1.165-16.521)**
Genotype 3	23/132 (32.9)	31/84 (36.9)	237/1075 (22)	**0.038; 1.730 (1.030-2.908)**	**0.002; 2.068 (1.298-3.296)**
Genotype 4	17/132 (24.2)	13/84 (15.5)	213/1075 (19.8)	0.367; 1.298 (0.737-2.287)	0.335; 0.741 (0.403-1.364)
HCV spontaneous clearers (n.%)¤	24/94 (25.5)	17/117 (14.5)	173/1694 (10.2)	**<0.001; 3.014 (1.847-4.918)**	0.143; 1.495 (0.873-2.559)
HLA-B*57 (n.%) ±	25/79 (31.6)	12/56 (21.4)	41/818 (5)	**<0.001; 8.774 (4.968-15.45)**	**<0.001; 5.169 (2.538-10.53)**

*Clinical stage C data from 107 persistent HIV-controllers, 121 transient HIV-controllers and 1674 non-controllers; ** HCV PCR+ was considered before HCV treatment onset in those who were treated.; & Time period between HIV diagnosis and loss of HIV-controller status or last monitored visit point; ¶HCV genotype detected from 132 persistent HIV-controllers, 84 transient HIV-controllers and 1075 non-controllers; ¤For HCV spontaneous clearance calculation we only considered patients with available data of anti-HCV, HCV PCR and HCV treatment. 94 persistent HIV-controllers, 117 transient HIV-controllers and 1694 non-controllers accomplished all data. ±HLA-B*57 data from 79 persistent HIV-controllers, 56 transient HIV-controllers and 818 non-controllers †*p* values <0.05 are shown in bold. OR: Odd Ratio, CI: Confidence interval.

Table 2. Factors associated with persistent and transient HIV spontaneous control

Variables	Persistent HIV-control	Transient HIV-control
	Adjusted *p*; OR(IC95%)†	Adjusted *p*; OR(IC95%)
HCV spontaneous clearance	**0.002; 2.573 (1.428-4.633)**	0.119; 1.589 (0.888-2.845)
Female sex	**0.006; 2.176 (1.250-3.790)**	**<0.001; 2.854 (1.823-4.467)**
CD4 nadir	**<0.001; 1.009 (1.008-1.010)**	**<0.001; 1.006 (1.005-1.007)**
Time of follow up	N.A.	**0.002; 0.961 (0.938-0.985)**
HIV transmission risk, PWID	N.A.	0.530; 0.855 (0.523-1.396)

†*p* values <0.05 are shown in bold. OR: Odd Ratio, CI: Confidence interval. N.A.: Not applicable.

Table 3. HIV-controllers stratified according to the loss of HIV control status

	Persistent controllers (411)	Transient controllers (n=333)	*p*; OR(IC95%)
Female sex (n.%)	114/417 (27.7)	111/333 (33.3)	**0.099; 1.303 (0.952-1.783)**
Age at HIV diagnosis	29 [24-35]	30 [25-36]	0.334; 1.008 (0.992-1.024)
Calendar year of HIV diagnosis			
1980-1989	91/411 (22.1)	52/332 (15.7)	**0.027; 0.653 (0.448-0.952)**
1990-1999	99/411 (24.1)	94/332 (28.3)	0.192; 1.245 (0.896-1.729)
2000-2009	157/411 (38.2)	174/332 (52.4)	**<0.001; 1.782 (1.329-2.389)**
2010-2015	64/411 (15.6)	12/332 (3.6)	**<0.001; 0.203 (0.108-0.384)**
Time of follow up (years)[&]	9.4 [4.1-19.1]	5.7 [3.0-14.7]	**<0.001; 0.960 (0.942-0.977)**
HIV transmission risk, PWID (n.%)	167/411 (40.6)	106/333 (31.8)	**0.013; 0.682 (0.504-0.924)**
CD4 T-cell nadir	550 [419-710]	327 [253-443]	**<0.001; 0.994 (0.993-0.995)**
Clinical stage C (n.%)*	7/296 (2.4)	12/305 (3.9)	0.277; 1.691 (0.656-4.356)
Elite (n.%)	207/411 (50.4)	66/333 (19.8)	**<0.001; 0.244 (0.175-0.339)**
Anti-HCV+ (n, %)	202/411 (49.1)	138/333 (41.4)	**0.036; 0.732 (0.547-0.980)**
HCV PCR+ (n,%)**	99/332 (29.8)	113/325 (34.8)	0.175; 1.254 (0.904-1.741)
Log_{10} HCV VL (IU/mL)#	5.85 [5.40-6.40]	6.07 [5.41-6.60]	0.289; 1.166 [0.878-1.550]
HCV genotype detected (n.%)¶			
Genotype 1	28/70 (40)	37/84 (44)	0.613; 1.181 (0.620-2.248)
Genotype 2	2/70 (2.9)	3/84 (3.6)	0.804; 1.259 (0.204-7.756)
Genotype 3	23/70 (32.9)	31/84 (36.9)	0.600; 1.195 (0.613-2.329)
Genotype 4	17/70 (24.3)	13/84 (15.5)	0.172; 0.571 (0.255-1.277)
HCV clearance (n%)¤	24/94 (25.5)	17/117 (14.5)	**0.047; 0.496 (0.248-0.991)**
HLA-B*57 (n.%)±	31/105 (29.5)	15/96 (15.6)	**0.021; 0.442 (0.221-0.883)**

*Clinical stage C data from 296 persistent controllers, and 305 transient controllers; **HCV PCR data available for 332 persistent controllers and 325 transient controllers. HCV PCR+ was considered before HCV treatment onset in those who were treated; &Time period between HIV diagnosis and loss of HIV-controller status or last monitored visit point; #HCV VL data from 96 persistent controllers and 101 transient controllers; ¶HCV genotype detected in 70 persistent controllers, and 84 transient controllers; ¤For HCV spontaneous clearance calculation we only considered patients with anti-HCV+ and available data of HCV PCR and HCV treatment. HCV spontaneous clearance was calculated in 94 persistent controllers and 117 transient controllers; ±HLA-B*57 data from 105 persistent controllers, and 96 transient controllers.

Table 4. Factors associated with loss of HIV-controller status

	Adjusted *p*; OR(IC95%)
Female sex	0.373; 1.382 (0.679-2.815)
Time of follow up	0.328; 0.978 (0.936-1.022)
HIV transmission risk, PWID	0.149;1.767 (0.816-3.827)
CD4 T-cell nadir	**<0.001; 0.995 (0.993-0.997)**
Elite	**<0.001; 0.136 (0.068-0.274)**
HCV spontaneous clearance	**0.027; 0.377 (0.159-0.893)**

†*p* values <0.05 are shown in bold. OR: Odd Ratio, CI: Confidence interval.

Figure 1. Kaplan–Meier curves for time to loose HIV-controller status.

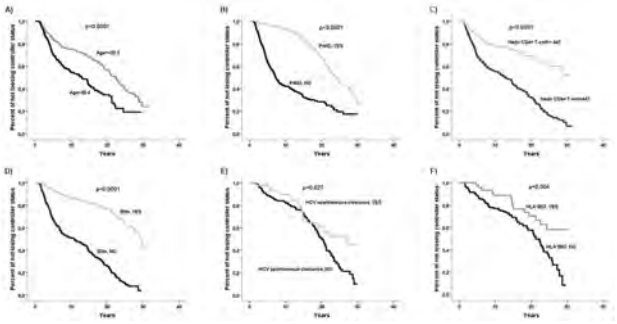


Table 5. Factors associated with the time to lose HIV-controller status

	Univariate, *p*; OR(IC95%)	Adjusted, *p*; OR(IC95%)
Female sex (n.%)	0.831; 1.025 (0.816-1.288)	
Age at HIV diagnosis >29.4 years*	**<0.001; 1.929 (1.541-2.416)**	**<0.001; 2.301 (1.545-3.427)**
HIV transmission risk, PWID (n.%)	**<0.001; 0.262 (0.206-0.334)**	**0.016; 0.587 (0.380-0.906)**
CD4 T-cell nadir >447 cells/mm^3**	**<0.001; 0.337 (0.262-0.432)**	**0.003; 0.478 (0.296-0.772)**
Elite (n.%)	**<0.001; 0.199 (0.151-0.263)**	**<0.001; 0.264 (0.172-0.406)**
HCV spontaneous clearance (n%)	**0.029; 0.562 (0.335-0.943)**	**0.010; 0.503 (0.297-0.850)**
HLA-B*57 (n.%)	**0.004; 0.446 (0.256-0.779)**	

CONCLUSIONS

This study shows an association between spontaneous persistent HIV-control and HCV spontaneous clearance. Our results support common mechanisms involved in spontaneous persistent HIV control and HCV clearance. These results suggest persistent but not transient HIV-controllers as a good model of functional HIV cure.