Characterizing HIV-1 Elite controllers within the Italian ICONA Cohort: implications for HIV functional cure

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BACKGROUND

A very small percentage of people with HIV-1, known as Elite Controllers (EC), can suppress viral replication without the need for antiretroviral therapy (ART). These individuals maintain undetectable viral loads, likely due to a combination of genetic factors and a strong immune response. How long can this status be maintained overtime remains to be fully studied. Studying Elite Controllers could offer key insights for developing treatments that mimic their natural viral control, potentially leading to long-term remission or a functional cure for HIV.

METHODOLOGY

EC-200 were defined as PWH with ≥3 consecutive HIV-RNA<200 copies/mL for ≥12 months without ART after enrolment in ICONA Foundation Study (baseline). We estimated cumulative probability of maintaining EC-200; **loss of EC-200** was defined as 2 consecutive HIV-RNA>200 copies/mL or initiation of ART with 1 HIV-RNA>200 copies/mL and/or with CD4⁺ cell count <500 cells/mmc. A competing risk survival analysis (Fine Gray, with competitive event defined as ART start with CD4>500 cells/mmc and/or HIV-RNA<200 copies/mL) was performed. The role of HIV-RNA <50 copies/mL (three consecutive values defined **EC-50**) for predicting maintenance of EC-200 was evaluated in PWH enrolled after 2003. Sensitivity survival analysis was done to evaluate the probability in maintaining EC-50 with a threshold of 50 copies/mL.

RESULTS

We identified in ICONA Database 123 **EC-200**, of whom 57 (46.3%) were EC-50 (Table 1). Median time from HIV diagnosis to enrolment was 2.0 (IQR:0.1-10.3) years, median CD4 count was 765 (IQR:578-965) cells/mmc, CD4/CD8 ratio 1.0 (IQR:0.7-1.5). Within this overall population, 40 (32.5%) PWH lost the EC status, according to the previously defined criteria.

Table 1. Sociodemographic and viro-immunological characteristics of the 123 Elite Controllers

	Overall EC$ (N=123)	Maintain EC Status (N=83)	Loss EC Status# (N=40)	P value
Total EC-200, N (%)	123 (100.0)	83 (67.5)	40 (32.5)	0.914
Presence of Competitive event*, N (%)	19 (15.5)	19 (22.9)	-	-
ART start, N (%)	49 (39.8)	19 (22.9)	30 (75.0)	**<0.001**
Age at enrollment, Median years (IQR)	37 (33-48)	38 (32-49)	36 (34-45)	0.914
Male, N (%)	77 (62.6)	51 (61.4)	26 (65.0)	0.703
Italian, N (%)	93 (75.6)	59 (71.1)	34 (85.0)	0.092
Year of HIV diagnosis, Median (IQR)	2002 (1990-2012)	2003 (1990-2013)	2001 (1988-2010)	0.230
Year of enrolment, Median (IQR)	2010 (2000-2014)	2011 (2000-2015)	2008 (1999-2012)	0.163
Years from diagnosis to enrolment, Median (IQR)	2 (0.1-10.3)	2.2 (0.2-9.3)	1.2 (0.1-11.7)	0.697
Year ART start, Median (IQR)	2016 (2015-2018)	2018 (2016-2019)	2016 (2006-2017)	**0.002**
Years from enrolment to ART, Median (IQR)	4.9 (2.8-7.1)	3.9 (1.5-6.7)	5.2 (3.5-8.1)	0.242
Mode of HIV transmission, N (%)				0.736
Hetero	45 (36.6)	30 (36.1)	15 (37.5)	1.000
IDU	48 (39.0)	33 (39.8)	15 (37.5)	0.846
MSM	20 (16.3)	12 (14.5)	8 (20.0)	0.444
Other/Unknown	10 (8.1)	8 (9.6)	2 (5.0)	0.497
Positive HCVAb, N (%)	51 (44.0)	35 (46.1)	16 (40.0)	0.532
Positive HBsAg, N (%)	7 (6.1)	4 (5.3)	3 (7.7)	0.619
CD4 cells/mmc at enrolment, Median (IQR)	765 (578-965)	830 (618-978)	664 (545-853)	**0.037**
CD8 cells/mmc at enrolment, Median (IQR)	742 (565-1,021)	722.5 (524-967)	850 (653-1,178)	**0.036**
Ratio CD4/CD8 at enrolment, Median (IQR)	1.0 (0.7-1.5)	1.2 (0.8-1.6)	0.7 (0.6-1.1)	**<0.001**
HIV-RNA copies/mL at enrolment, Median (IQR)	50 (27-114)	50 (25-106)	50 (36-143)	0.313
EC-50, with first 3 consecutive HIV-RNA<50 copies/mL, N (%)	57 (46.3)	48 (57.8)	9 (22.5)	<0.001
HIV-RNA always <50 copies/mL, N (%)	34 (27.6)	31 (37.3)	3 (7.5)	<0.001
HIV-RNA always <50 copies/mL, but start ART, N (%)	11 (32.3)	8 (25.8)	3 (100.0)	**0.028**

$Elite Controllers (ECs) were defined as PWH with at least 3 consecutive HIV-RNA <200 copies/ml for at least 12 months without ART; #Loss EC Status defined as 2 consecutive HIV-RNA >200 copies/ml or initiation of antiretroviral therapy with one HIV-RNA >200 copies/ml and/or with CD4+ cell count <500 cells/mmc; *Competitive event defined as ART start with CD4+>500 cells/mmc and/or HIV-RNA <200 copies/ml

The probability of maintaining the EC-200 status was 70.9% (95%CI:61.7-79.5%) by 5 years, 54.5% (95%CI: 43.6-66.2%) by 10 years (40 events by end of follow-up: 28 with 2 HIV-RNA>200 copies/mL, 8 start ART with CD4<500 cells/mmc and 4 with 1 HIV-RNA>200 copies/mL; Figure 1A). This probability was higher in EC-50: by 5 years maintenance of EC-200 87.8% (95%CI:74.0-96.3%, p=0.017; Figure1B). Among EC-50, the 5 years probability of maintaining EC-50 was 83.6% (95%CI:70.9-92.9%; Figure 1C).

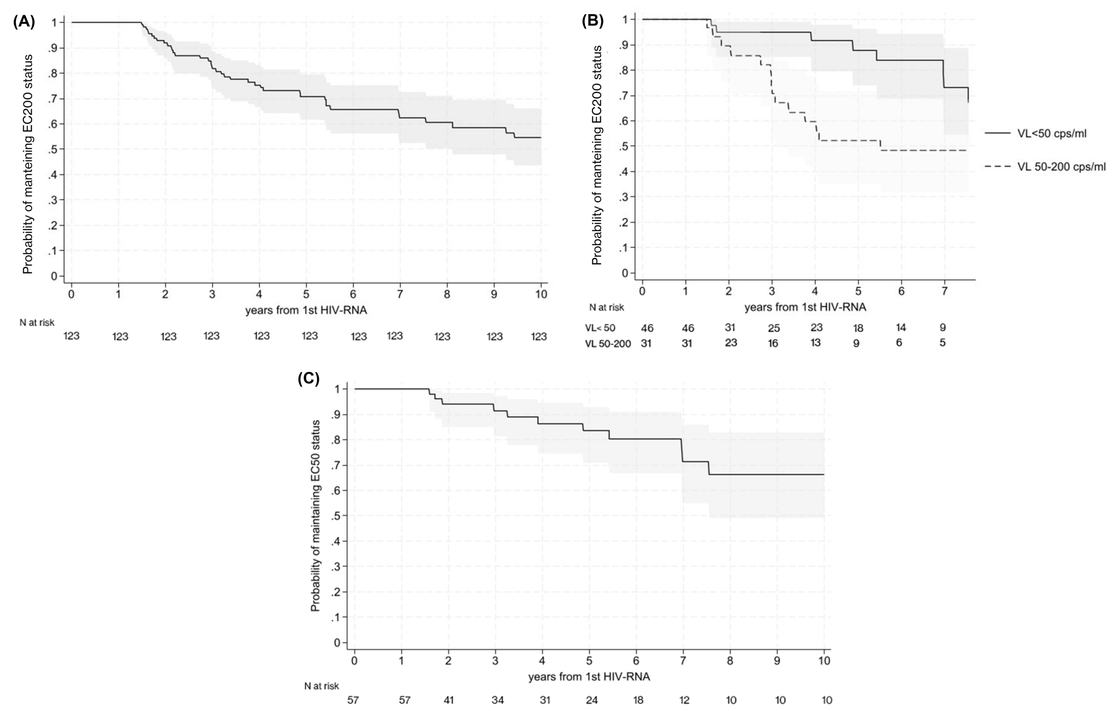

Figure 1. Competing-risk curves estimating the probability of maintaining the EC-200 status overall (A) and stratified by baseline HIV-RNA (B); and maintaining the EC-50 status in the EC-50 group (C)

After controlling for confounding factors (age, sex, year of enrolment, years from diagnosis to enrollment) EC-50, higher CD4 and CD4/CD8 were associated with longer maintenance of EC-200 status (Table 2).

Table 2. Fine Gray regression models estimating the sub-hazard ratio (SHR) of losing the EC-200 status

	SHR	95%CI	p value	aSHR*	95%CI	p value
EC-50						
No	1			1		
Yes	0.33	0.14-0.75	0.008	0.29	0.11-0.76	0.012
Baseline CD4, per 100 cells/mmc higher	0.85	0.77-0.99	0.035	0.85	0.73-0.99	0.038
Baseline CD4/CD8 ratio, per 0.1 higher	0.87	0.80-0.94	0.001	0.87	0.80-0.94	0.001

*Adjusted for age, sex, calendar year of enrolment, years from HIV diagnosis to enrolment

CONCLUSIONS

Approximately 50% of our population lost their EC-200 status within 10 years from enrolment. Baseline HIV-RNA, CD4, and CD8 values are crucial for controlling viral replication without treatment. Thanks to samples availability in the ICONA-biological-bank, ongoing deeper viro-immunological characterization may offer more insights into this rare-group of individuals and could serve as models for a functional HIV cure.

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