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"CD4 exploders" and "CD4 peak achievers" under ART in a large Italian cohort of HIV-infected subjects

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Background

- The number of circulating CD4+ T lymphocytes in patients with human immunodeficiency virus is the most robust predictive factor for assessing HIV disease stage, predicting progression to clinical AIDS and AIDS-related death, determining antiretroviral treatment eligibility, and monitoring response to therapy.
- After a variable period of ART, the CD4+ T-cell count can reach a value that ensures protection against opportunistic infections – classically more than 200 × 10^6 cells/l. The kinetic and the magnitude of CD4+ T recovery is extremely variable among ART treated subjects.
- Two particular populations have been described:
  - The **'CD4-exploders' (CD4e),** defined as people gaining a large amount of cells under a defined time;
  - The **"CD4 peak achievers" (CD4a**), who reach a very high level of CD4+ T cells.
- The 'CD4-exploders' have been shown to display a high amount of virgin T cells and a reduced number of T cells with a phenotype typical of lymphocytes with an increased tendency to undergo cell activation/death (Mussini et al. 2000)
- The 'CD4-exploders' have been shown to have significantly higher plasma levels of IL-7, a cytokine with a crucial importance for the generation and survival of T cells. In some studies high amount of IL-7 has shown to be related to breast cancer, colon cancer, hematological malignancies, autoimmune diseases (such as multiple sclerosis, rheumatoid arthritis) (Kim et al., 2008).
- Moreover Bonnard described a cluster of patients HIV/HCV coinfected with high CD4 count with a faster fibrosis progression suggesting a potential detrimental role of large CD4 expansion.
- It is important to further characterize these populations and investigate whether such extreme CD4 recoveries might modify persons' risk of severe non-AIDS (sNAE) or death.

Aims of the study:

✓Incidence and clinical-demographic features of "CD4 exploder" (CD4e) and "CD4 peak achiever" (CD4pa) over suppressive cART in ICONA;
✓To evaluate the association between these conditions and the risk of serious non-AIDS events (sNAE)death.

Study population

Population- **5,795** Icona HIV+ patients who started cART from naïve and achieved/maintained VL<50cp/ml

- ✓**CD4 exploders (CD4e) =** gain/maintenance >600 cells/mm3 above pre-cART (n=306);
- ✓**CD4 peak achievers (CD4pa) =** achievement of absolute CD4>1000 followed by at least another consecutive >1000 value (n=249)

	N= 5795
Gender, n(%)	
Female	1431 (24.7%)
AIDS diagnosis, n(%)	
Yes	400 (6.9%)
Age, years	
Median (IQR)	37 (32, 43)
CD4 count, cells/mmc	
Median (IQR)	291 (162, 406)
CD8 count, cells/mmc	
Median (IQR)	863 (585, 1237)
Viral load**, log10 copies/mL	
Median (IQR)	4.73 (4.10, 5.23)

Methods

- ✓ **Endpoints: to be a CD4e; to be a CD4pa**
  Incidence by 3 years of suppressive cART; Kaplan-Meier curves/Cox regression model to identify factors independently associated;
- ✓ **Endpoint: sNAE (malignancies, CCVD, renal, liver, pneumonia, sepsis)/death**
  Survival analysis with T0 3 years from the date of VL suppression comparing the risk of sNAE/death based on the status of CD4e and CD4pa.

Results

Cumulative probability (Fig.1) and Factors independently associated of being an CD4 exploders (Table1)

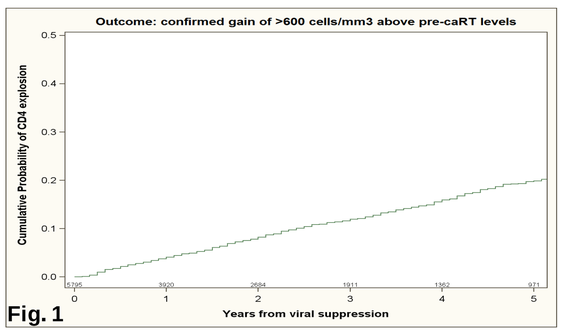

Fig. 1

Cumulative probability (Fig.2) and Factors independently associated of being an CD4 peak achievers (Table2)

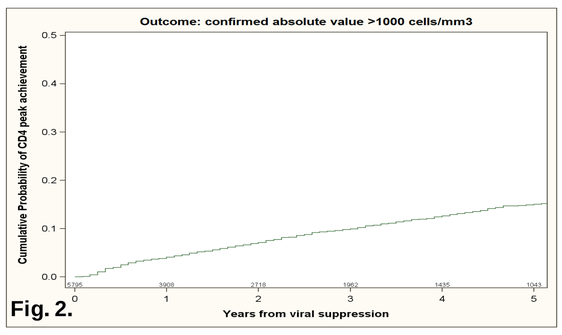

Fig. 2.

Table 1 CD4e	Hazard Ratio (95% CI) p-value			
	Unadjusted		Adjusted#	
Characteristics		p		p
CD4 count nadir (per 100 cells/mm3 higher)	1.00 (0.96, 1.04)	0.905	1.05 (1.00, 1.11)	0.063
Age per 10 years older	**0.79 (0.73, 0.87)**	**<.001**	**0.79 (0.71, 0.86)**	**<.001**
AIDS diagnosis				
No	1.00	0.194	1.00	0.103
Yes	1.18 (0.92, 1.52)		1.26 (0.95, 1.67)	
cART with PI				
No	1.00		1.00	
Yes	**1.57 (1.34, 1.85)**	**<.001**	**1.52 (1.28, 1.82)**	**<.001**
HCV co-infection				
No	1.00		1.00	
Yes	0.80 (0.62, 1.02)	0.076	**0.73 (0.54, 1.00)**	**0.050**
Not tested	1.17 (1.00, 1.38)	0.051	1.23 (0.81, 1.86)	0.326
#Adjusted for all factors shown in Table				

Table2 CD4pa	Hazard Ratio (95% CI) p-value			
	Unadjusted		Adjusted#	
Characteristics		p		p
CD4 count nadir per 100 cells/mm3 higher	**1.40 (1.37, 1.43)**	**<.001**	**1.53 (1.47, 1.59)**	**<.001**
Time since HIV diagnosis (per year longer)	**1.01 (0.99, 1.02)**	**0.409**	**1.03 (1.01, 1.06)**	**0.002**
Age (per 10 years older)	**0.77 (0.69, 0.84)**	**<.001**	**0.87 (0.79, 0.97)**	**0.011**
cART with PI				
No	1.00	0.049	1.00	**<.001**
Yes	1.19 (1.00, 1.41)		**1.39 (1.15, 1.68)**	
HCV co-infection				
No	1.00		1.00	
Yes	0.76 (0.58, 0.99)	0.040	**0.58 (0.41, 0.82)**	**0.002**
Not tested	0.83 (0.70, 0.99)	0.042	0.94 (0.63, 1.42)	0.782
#Adjusted for all factors shown in Table				

Survival analysis

CD4e and **CD4pa** have been used as covariates in a survival analysis with time zero 3 years after viral suppression and endpoint time to severe non-AIDS events in those who were still free from non-AIDS cancer at that point. Kaplan Maier curves of time to severe non-AIDS event/death for CD4e and CD4pa showed a decreased probability to reach the end point only for CD4e (fig. 3 and 4).

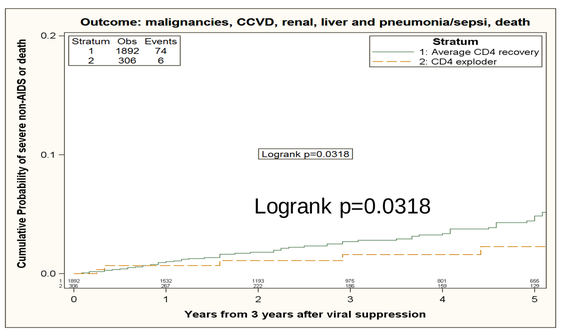

Fig. 4 Kaplan Maier curves of time to severe non-AIDS/death for ***CD4 exploders***

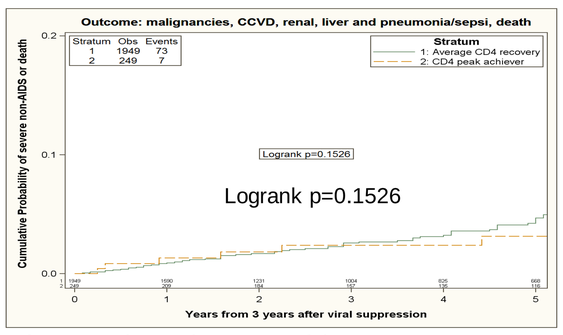

Fig. 3 Kaplan Maier curves of time to severe non-AIDS/death for ***CD4 peak achievers***

Cox regression model with sNAE/death as outcome revealed a decreased risk for patients CD4e

	Hazard Ratio (95% CI) p-value			
	Unadjusted		Adjusted#	
Characteristics		p		p
Mode of HIV transmission				
Heterosexual	1.00		1.00	
MSM	0.70 (0.37, 1.31)	0.264	0.73 (0.37, 1.44)	0.368
IVDU	1.54 (0.93, 2.54)	0.092	1.05 (0.47, 2.36)	0.907
Other/unknown	0.80 (0.28, 2.28)	0.680	0.82 (0.29, 2.33)	0.705
Time since HIV diagnosis				
per year longer	1.05 (1.01, 1.09)	0.008	1.04 (0.99, 1.08)	0.135
Age				
per 10 years older	1.41 (1.13, 1.75)	0.002	1.54 (1.20, 1.97)	<.001
AIDS diagnosis				
No	1.00		1.00	
Yes	1.01 (0.57, 1.77)	0.979	0.86 (0.46, 1.60)	0.631
cART with PI				
No	1.00		1.00	
Yes	1.29 (0.83, 2.01)	0.265	1.16 (0.73, 1.84)	0.519
HCV co-infection				
No	1.00		1.00	
Yes	1.78 (1.14, 2.78)	0.011	1.35 (0.68, 2.70)	0.392
CD4 exploder				
No	1.00		1.00	
Yes	0.41 (0.18, 0.95)	0.038	0.40 (0.14, 1.16)	0.093
CD4 peak achiever				
No	1.00		1.00	
Yes	1.38 (0.47, 4.04)	0.563	1.39 (0.46, 4.21)	0.565

#Adjusted for all factors shown in Table as well as gender, CD4 nadir, HBV, CMV coinfection and CD4/CD8 ratio

Conclusions

Approximately 10% of people have extreme CD4 count recovery by 3 years provided a VL≤50 copies/mL. CD4 count response is more likely in those of young age, without HCV infection and who started a PI based therapy. CD4e tended to have a lower risk of sNAE/death independently of CD4a, suggesting that a fast kinetic of immune recovery might be more important than the absolute number achieved.