Better CD4/CD8 restoration during first-line ART in CMV-seronegative HIV+ patients.

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Background

- Most HIV1-infected patients initiating highly active antiretroviral therapy (cART) experience an effective and prolonged control of HIV replication in plasma associated with increased CD4 T cell-counts[1].
- However, many of them fail to restore CD4 cell counts above 500/mm3 and/or a CD4:CD8 ratio ≥1. This is partly due to persistent immune activation and inflammation, driven by residual HIV replication, microbial translocation and chronic viral infections[2].
- CMV-infection is highly prevalent among HIV-infected patient and its role as a risk factor for severe non–aids-defining events/non-AIDS related death was recently highlighted[3].
- The purpose of this study was to investigate the impact of CMV-infection on immune reconstitution in HIV-infected patients receiving their first cART line.

Methods

- ***A retrospective longitudinal study*** from "The multicenter Dat'AIDS Cohort", following in 2014, 26,959 HIV infected patients in 15 major French HIV centers using NADIS® (*Fedialis Medica, Marly le Roi, France*), an electronic medical record for HIV-, HBV- or HCV-infected adults (4). All patients signed informed consent before registering in the database.

- ***Data were selected if patients :***

1. Initiated a first cART line between 2002 and 2009 and
2. Maintained a sustained undetectable HIV plasma viral load (pVL) for ≥12 months with the same cART regimen and
3. Have a documented CMV serostatus (CMV IgG+ or IgG-).

- T-cell immuno-phenotyping (CD4, CD8 T cell counts and CD4:CD8 ratio) were collected prior to cART initiation (Pre-cART), at the first undetectable pVL (D0), and every 6 months during 3 years.
- T cell dynamics according to CMV serostatus were analyzed.

- Analyses of independent samples were performed using Student t-test and multivariate analysis was performed by a linear regression model using SPSS Advanced Statistics 20(IBM Corp).

References

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Results

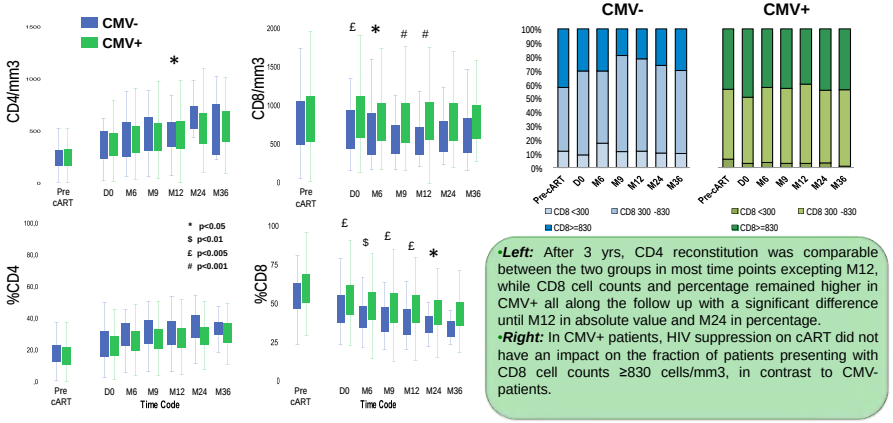
1. Patients characteristics

- Among the 5,688 patients that initiated their first cART line during the study period, 503 fulfilled the selection criteria and 88% had CMV- IgG positive with a median time of follow up of 32 [23.7;42.6] months.
- Selected patients had similar clinical characteristics regardless of CMV status, excepted for median duration of HIV infection, shorter in CMV+ patients and HIV transmission risk group, which had a higher proportion of MSM among CMV+ patients.

N (%)/ Median [IQR]	CMV seropositive n= 444	CMV seronegative n= 59	p
Age, years	43 [36;51]	45 [40;49]	-
Males	326 (73.4)	45(76.3)	-
MSM	189 **(42.6)**	15 **(25.4)**	
Heterosexual	202 (45.5)	33 (55.9)	
IV Drug users	15 (3.4)	3 (5.1)	**0.03**
Others	10 (2.2)	4 (6.8)	
Unknown	28 (6.3)	4 (6.8)	
Follow-up of HIV infection(y)	**1 [0.2;3.4]**	**3.4 [0.3;8.4]**	**0.011**
CDC stage C	65 (14.7)	13(22)	-
HCV- RNA+	23 (5.2)	3(5.2)	-
Time to HIV suppression (m)	3.05 [1.9;5.2]	3.4 [1.9;5.1]	-
Duration of 1rst cART line (months)	32 [23.7;42.5]	32.6 [23;43]	-
Long Term Inhibitor ART			
2NRTI + 1PI	223 (52.2)	24 (44.4)	
2NRTI + 1 NNRTI	150 (35.1)	23 (42.6)	
3NRTI	54 (12.1)	7 (13)	
Others	17 (3.8)	5 (8.4)	
CD4 Nadir (/mm³)	222 [136;281]	221 [157;282]	-
CD4 cells* (/mm³)	250 [160;319]	261 [165;321]	-
CD4 (%) (n=420/ 57 patients)	16.7 [11.1;22]	17.2 [11.9 ;23.7]	-
CD4<200mm³	152 (34.2)	19 (32.2)	-
CD8 cells** (/mm³)	777 [537;1132]	755 [491;1082]	-
CD8(%) (n=412/57 patients)	59.7 [51;69]	57.2 [47;63.8]	-
CD8 >830/mm³	223 (50.2)	27 (45.8)	-
CD4:CD8 ratio	0.3 [0.2 ;0.4]	0.3 [0.2;0.4]	-
CD4:CD8 ratio ≥1	6 (1.4)	2 (3.4)	-
HIV-RNA Log/mL	4.75 [4.27;5.26]	4.67 [4.26;5.05]	-

* Normal range: 500 to 1200/mm3 **Normal range: 300 to 830/mm3.

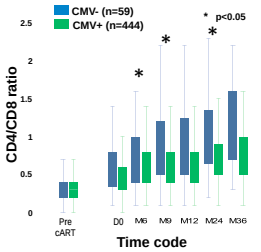
2. Dynamics of T-CD4 and T-CD8 over 3 years



- ***Left:*** After 3 yrs, CD4 reconstitution was comparable between the two groups in most time points excepting M12, while CD8 cell counts and percentage remained higher in CMV+ all along the follow up with a significant difference until M12 in absolute value and M24 in percentage.
- ***Right:*** In CMV+ patients, HIV suppression on cART did not have an impact on the fraction of patients presenting with CD8 cell counts ≥830 cells/mm3, in contrast to CMV- patients.

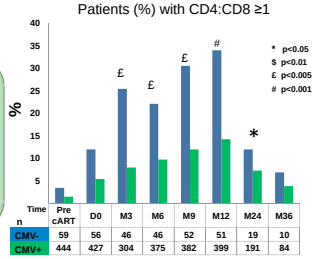
3. Dynamics of CD4:CD8 ratio over 3 years

- Bivariate analysis revealed a negative correlation between CMV+ status and CD4:CD8 ratio from D0 of HIV suppression (r= -0.18; p=0.02).



Linear regression analyses using CD8 or CD4:CD8 ratio as dependent variables, and CMV serology, duration of HIV exposure, CD4 nadir and cART regimen as independent variables, confirmed a **negative correlation between CMV+ status and CD4:CD8 ratio after 1, 2 and 3 yrs of cART initiation (p<0.05, <0.001 and <0.001, respectively).**

Patients (%) with CD4:CD8 ≥1



n	Pre cART	D0	M3	M6	M9	M12	M24	M36
CMV-	59	56	46	46	52	51	19	10
CMV+	444	427	304	375	382	399	191	84

Discussion

- Reversed CD4:CD8 ratio and positive CMV serology, combined with an increase of senescent CD8+CD28- cells and poor T-cell proliferative responses, defined the immune risk phenotype (IRP) that has been described in the elderly. IRP was associated with an increased risk of morbidities and mortality in this population (5).
- Previous studies reported a premature immunosenescence in naïve HIV-infected patients without normalization under cART (6,7) and an association between chronic CMV infection, immunosenescence and immunoactivation (8). The senescent T CD8 lymphocytes are characterized by apoptose resistance, leading to an accumulation of memory T cells pool and overproduction of pro-inflammatory mediators such as TNFα, IL1β and IL6, increasing the risk of co-morbidities.
- The design of this study did not allow us to measure the proportion of CD8+CD28- or the telomere lengths, but 35.8% of CMV+ and 18.6% of CMV- (p=0.005) kept CD8 ≥830 cells/mm3 which could be explained by a premature immunosenescence in CMV+ patients.

Conclusion

A CMV+ serostatus is associated with poorer immunological restoration after cART initiation despite an effective control of HIV replication, with a high proportion of patient maintaining a high rate of CD8 T cell count and a reversed CD4:CD8 ratio. These characteristics might be due to a premature immunosenescence in CMV+ patients. Up to now, immunosenescence is considered as non reversible in general population and data are scarce for HIV-infected patients (7). Therefore, our results question the need of a specific monitoring and/or therapeutic approach for CMV+ HIV infected patients. Furthermore, this study highlights that CMV serological status should be taken into account when measuring the effectiveness of antiretroviral therapy on immune restoration and for designing "cure" interventions in the future.