

Background

Helleberg et al. showed that a major decline in CD4 counts in persons living with HIV (PLHIV) with suppressed viral load under combined antiretroviral therapy (cART) was associated with an increased risk of severe morbidity (cardiovascular disease, cancer) and death

Objectives:

In PLHIV who initiated cART between 2006 and 2018:

- Assess the risk of a major CD4 decline
- Determine the associated factors
- Evaluate its association with the risk of severe morbidity

Patients

- Individuals from the ANRS CO4-FHDH, French Hospital Database on HIV
- PLHIV-1, initiating cART between 2006 and 2018, with 2 years of follow-up and age>18
- Individuals reaching virologic suppression, i.e. 2 consecutive VL<50 copies/mL
- Individuals remaining virologically suppressed at least 9 months, and without prior cancer or cardiovascular events



Methods

- To define a major CD4 decline, we computed consecutive relative differences from moving averages of 3 consecutive CD4 counts:

$$RD = \frac{MA_{234} - MA_{123}}{MA_{123}} \times 100$$

- CD4 decline occurs when 2 consecutive RD greater ≥ 15%

- Model CD4, CD8, and total lymphocyte counts before and after the beginning of the CD4 decline by using spline regression in participants with a major CD4 decline
- Estimate the incidence rate (IR) and incidence rate ratio (IRR) of a major CD4 decline, assess associated factors, and evaluate its association with the risk of severe morbidity (cardiovascular disease cancer) and death, during or after 6 months of the decline by using Poisson regression

- A major CD4 Decline is a rare event, related to global lymphopenia in PLHIV with a controlled viral load under cART
 - Older age is associated with the occurrence of a major CD4 decline
 - A major CD4 decline is associated with a higher risk of severe morbidity or death

Results

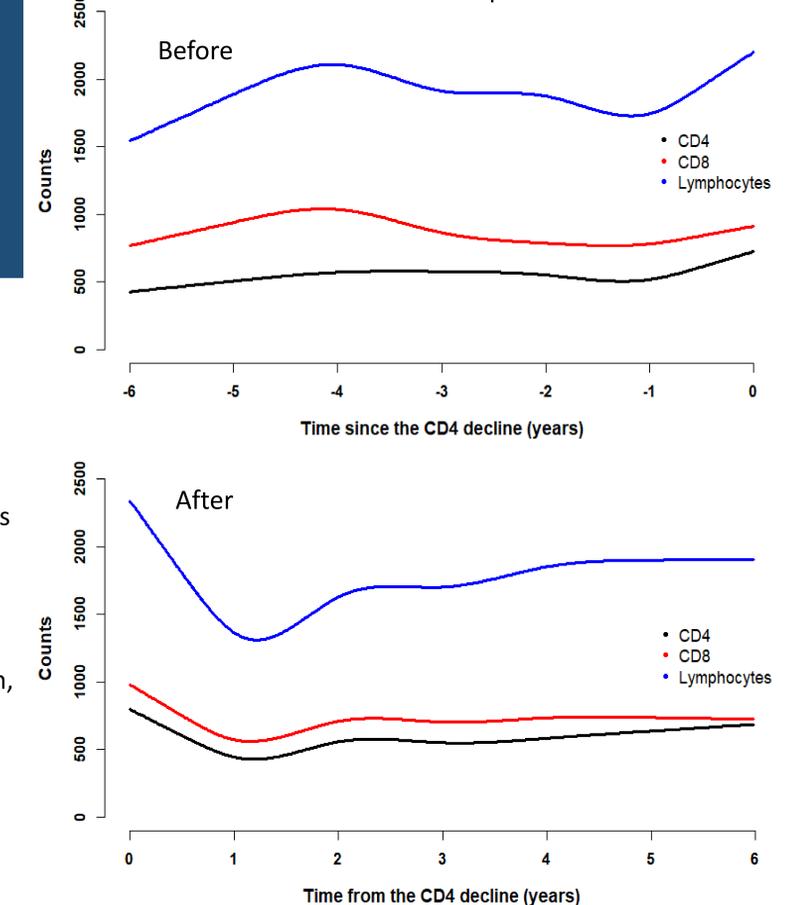
- 14 140 individuals were included in the study (50 372 person-years (PY))
- 122 individuals experienced a CD4 decline: IR = **2.4/1000 PY (CI 95%: 2.1-2.8)** with an average of follow-up time of 7.6 years
- Such a decline was also observed for the CD8 and total lymphocyte counts (Figure)
- The risk of a major CD4 decline was associated with increasing age: IR ratio, 5.0 [95% CI, 1.5-15.9] in those >50 years vs <30 years of age
- 1 participant experienced myocardial infarction after CD4 decline; 7 experienced cancer: 3 Hodgkin lymphoma, 1 bronchial or lung cancer, 1 prostate cancer, 1 cancer of the head of the pancreas, 1 bone and bone marrow cancer
- Results in multivariable analysis were adjusted for sex, origin, HIV transmission group, time to viral load suppression, CD4 cell count and age at cART initiation, and AIDS at index date
- The adjusted incidence rate of severe morbidity was 5.0 [95% CI, 4.0-6.2]/1000PY for persons with no decline, compared with 73.4 [95% CI, 32.1-168.6] during the first 6 months following the decline and 8.9 [95% CI, 3.3-24.1] after 6 months in persons with a decline

Table: Risk of severe morbidity and death before and after CD4 Decline

(Yes <6 months: in the first 6 months after the decline; Yes ≥ 6 months: after the first 6 months after the decline)

RD> 15%	CD4 Decline	Nb events	PY	IR/1000 PY (CI 95 %)		IRR/1000 PY (CI 95 %)
				Non-adjusted	Adjusted	Adjusted
Cardio	No	105	53680	2.0 (1.6-2.4)	1.2 (0.8-1.8)	
	Yes < 6 months	1	55	18.3 (2.6-129.8)	8.2 (1.1-60.7)	6.8 (0.95-49.1)
	Yes ≥ 6 months	0	335			
Cancer	No	208	53562	3.9 (3.4-4.4)	2.2 (1.6-2.95)	
	Yes < 6 months	4	47	84.3 (31.6-224.6)	39.05 (14.0-108.9)	17.95 (6.6-48.5)
	Yes ≥ 6 months	3	310	9.7 (3.1-30.0)	5.2 (1.6-16.8)	2.4 (0.8-7.6)
Death	No	63	53268	1.2 (0.9-1.5)	1.0 (0.6-1.6)	
	Yes < 6 months	2	47	42.5 (10.6-170.1)	27.9 (6.5-120.3)	27.9 (6.75-115.6)
	Yes ≥ 6 months	1	307	3.3 (0.5-23.1)	2.2 (0.3-16.3)	2.2 (0.29-16.0)

Figure: CD4, CD8, Lymphocytes counts before and after CD4 decline modelled with cubic splines



Conclusions

In virally suppressed PLHIV living in France between 2006 and 2018 :

- ✓CD4 decline is a rare event
- ✓CD4 decline is associated with age and related to global lymphopenia

Compared to PLHIV who do not exhibit a drop, PLHIV who had a drop in CD4 counts :

- ✓Increased risk of a severe morbidity after CD4 decline, especially in the 6 months after the decline:
- 15-fold significantly higher risk of severe morbidity or death (IR ratio, 14.7[95% CI, 6.6-33.1])

Limits:

- ❖Small number of cardiovascular events (n=1) and deaths (n=3)

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Reference

Helleberg M, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Obel N, et al. CD4 decline is associated with increased risk of cardiovascular disease, cancer, and death in virally suppressed patients with HIV. Clin Infect Dis. 2013 Jul;57(2):314-21