

Supplementary Material

CD4 decline computation

To define the CD4 decline, we used the moving average (MA), i.e., the mean of CD4 counts at time t and the two consecutive counts:

Let us consider four consecutive CD4 counts: $\{CD4_1, CD4_2, CD4_3, CD4_4\}$. The two corresponding moving averages are computed as follows:

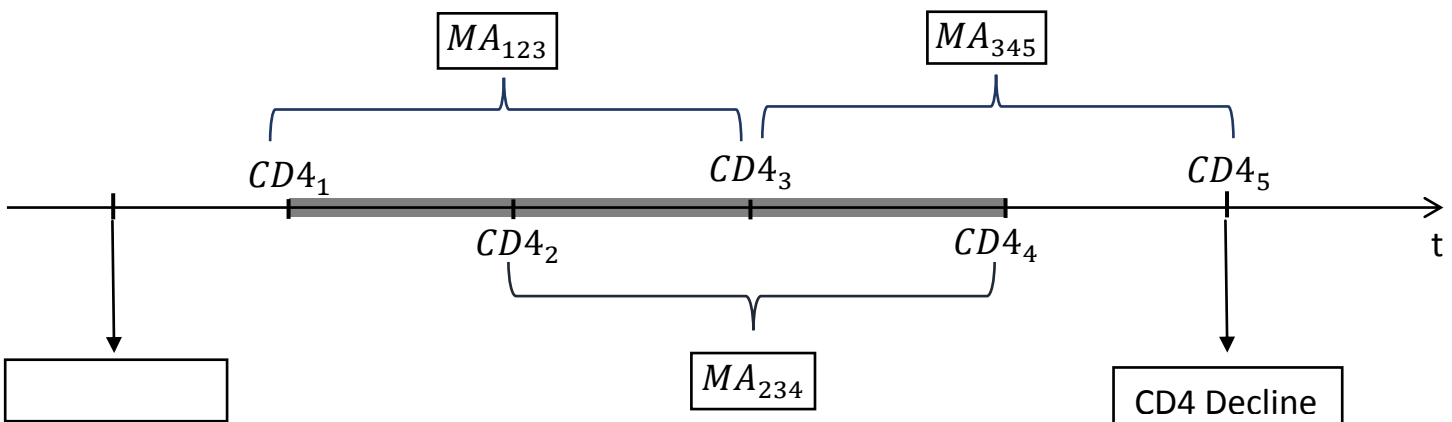
$$MA_{123} = \frac{CD4_1 + CD4_2 + CD4_3}{3} \text{ and } MA_{234} = \frac{CD4_2 + CD4_3 + CD4_4}{3}$$

The CD4 decline is defined according to the relative differences (RD) computed from the difference between two consecutive moving averages:

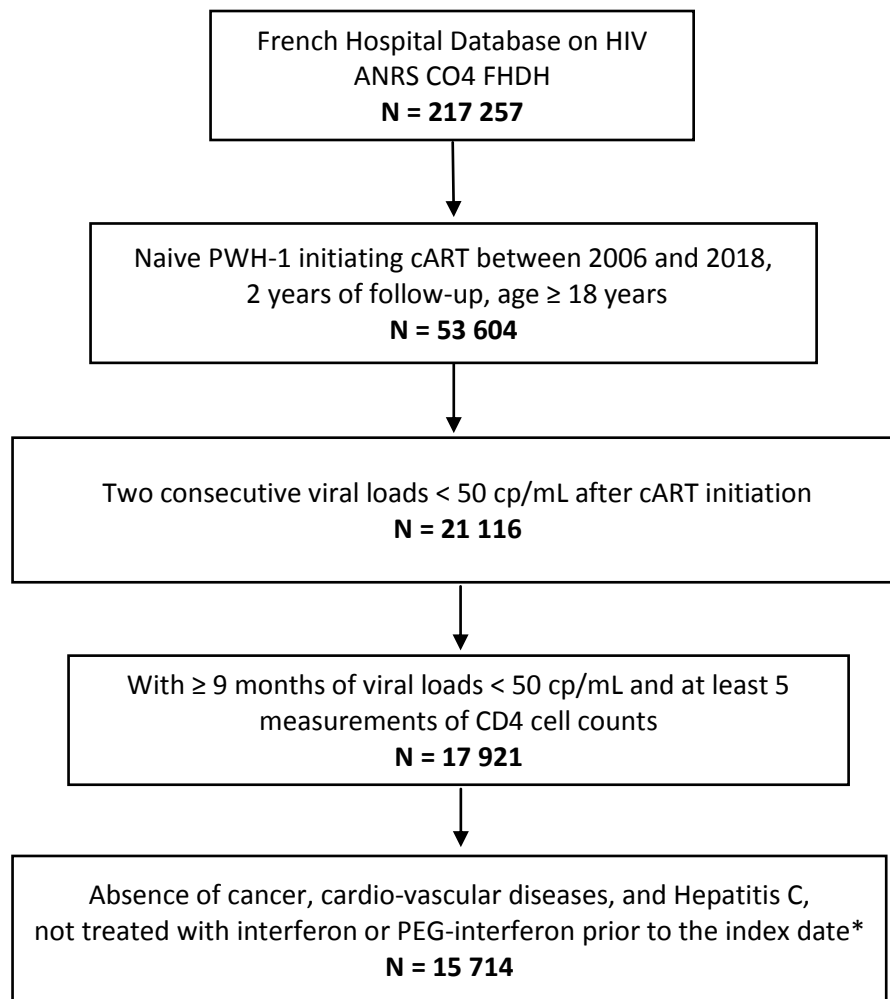
$$RD_1 = \frac{MA_{234} - MA_{123}}{MA_{123}},$$

$t_{CD4_4} - t_{CD4_1}$

where, t_{CD4_1} is the date of the first measurement of CD4, and t_{CD4_4} the fourth one. A CD4 decline occurs when two consecutive RDs are $\geq 15\%$. The date of CD4 decline is defined as the last CD4 count in the second consecutive moving average (See figure below).



Supplementary Figure 1. Flowchart of the study population



*Index date: Date of 5th CD4 measurement after two consecutive viral loads < 50 cp/mL

Supplementary Table 1. Sensitivity analysis of the risk of severe morbidity and death comparing the results for a relative difference (RD) $\geq 15\%$ or a RD $\geq 10\%$

CD4 Decline	RD $\geq 15\%$: N = 181		RD $\geq 10\%$: N = 673	
	No. events	Adjusted IRR	No. events	Adjusted IRR
Cardiovascular event				
No decline	173	1	168	1
< 6 months after decline	1	4.1 (0.6-29.2)	1	1.3 (0.2-9.6)
≥ 6 months after decline	1	0.6 (0.1-4.1)	6	0.9 (0.4-2.1)
Cancer				
No decline	291	1	284	1
< 6 months after decline	5	15.3 (6.3-36.9)	7	6.7 (3.1-14.1)
≥ 6 months after decline	5	2.1 (0.9-5.1)	11	1.1 (0.6-2.1)
Death				
No decline	92	1	85	1
< 6 months after decline	2	19.2 (4.7-78.6)	3	9.2 (2.9-29.0)
≥ 6 months after decline	1	1.2 (0.2-9.0)	7	2.4 (1.1-5.2)
Cardiovascular or cancer or death				
No decline	541	1	522	1
< 6 months after decline	7	10.8 (5.1-22.8)	10	4.9 (2.6-9.1)
≥ 6 months after decline	7	1.6 (0.8-3.4)	24	1.3 (0.9-2.0)

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; RD, relative difference

Supplementary Table 2: Comparison of the associations between CD4 decline and risk of a severe morbidity obtained for the ANRS CO4 FHDH (**in bold**) and Danish Cohort (Helleberg et al. 2013)

CD4 Decline	No. events	IR/1000 PY (95%CI)		
		Non-adjusted	IRR (95%CI) Non-adjusted Adjusted	
Cardiovascular event				
No decline	173 112	2.2 (1.9-2.6) 8.9 (7.4-10.7)	1	1
< 6 months after decline	1 3	12.1 (1.7-85.9) 132.3 (42.7-410.3)	5.5 (0.8-39.2) 14.8 (4.7-46.7)	4.1 (0.6-29.2) 11.7 (3.6-37.4)
≥ 6 months after decline	1 4	1.7 (0.2-11.8) 26.5 (10.0-70.7)	0.8 (0.1-5.4) 3.0 (1.1-8.1)	0.6 (0.1-4.1) 2.7 (1.0-7.5)
Cancer				
No decline	291 87	3.7 (3.3-4.4) 6.6 (5.4-8.2)	1	1
< 6 months after decline	5 3	70.4 (29.3-169.1) 115.8 (37.4-359.1)	19.0 (7.8-45.9) 17.5 (5.5-55.4)	15.3 (6.3-36.9) 13.7 (4.3-43.6)
≥ 6 months after decline	5 3	9.0 (3.7-21.5) 17.0 (5.5-52.7)	2.4 (1.0-5.8) 2.6 (0.8-8.1)	2.1 (0.9-5.1) 2.2 (0.7-7.2)
Death				
No decline	92 138	1.2 (1.0-1.5) 10.5 (8.9-12.4)	1	1
< 6 months after decline	2 2	28.5 (7.1-114.1) 77.2 (19.3-309)	24.1 (5.9-98.0) 7.4 (1.8-29.7)	19.2 (4.7-78.6) 4.3 (1.1-17.6)
≥ 6 months after decline	1 7	1.8 (0.3-13.0) 39.6 (18.9-83.1)	1.5 (0.2-11.1) 3.8 (1.8-8.1)	1.2 (0.2-9.0) 1.8 (0.8-4.1)

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval

The study of the Danish cohort included 2,584 participants between 1995-2010, with 56 participants having a CD4 decline, resulting in an IR of 4.2/1000 PY (95%CI: 3.2-5.4).

The study of the ANRS CO4 FHDH cohort included 15,714 participants between 2006-2020, with 181 participants having a CD4 decline, resulting in an IR of 2.4/1000 PY (95%CI: 2.1-2.8).