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:

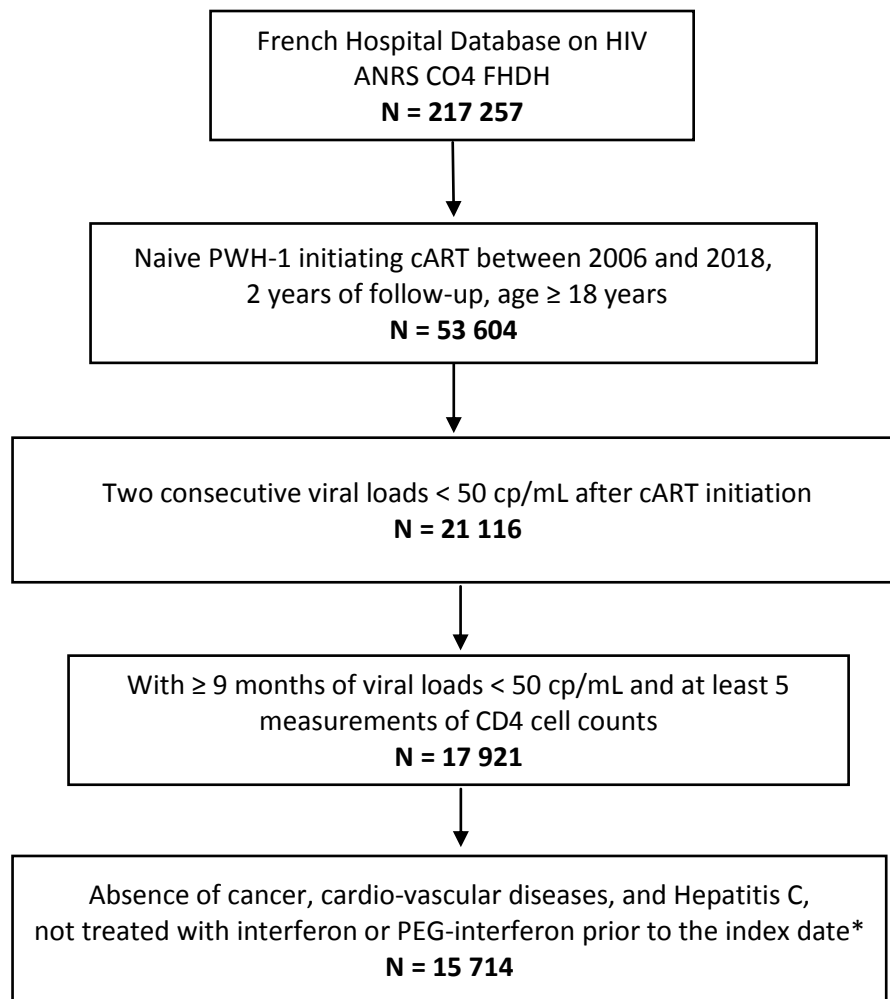$$RD_1 = \frac{\frac{MA_{234} - MA_{123}}{MA_{123}}}{t_{CD4_4} - t_{CD4_1}},$$

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 ≥ 15%. The date of CD4 decline is defined as the last CD4 count in the second consecutive moving average (See figure below).

1
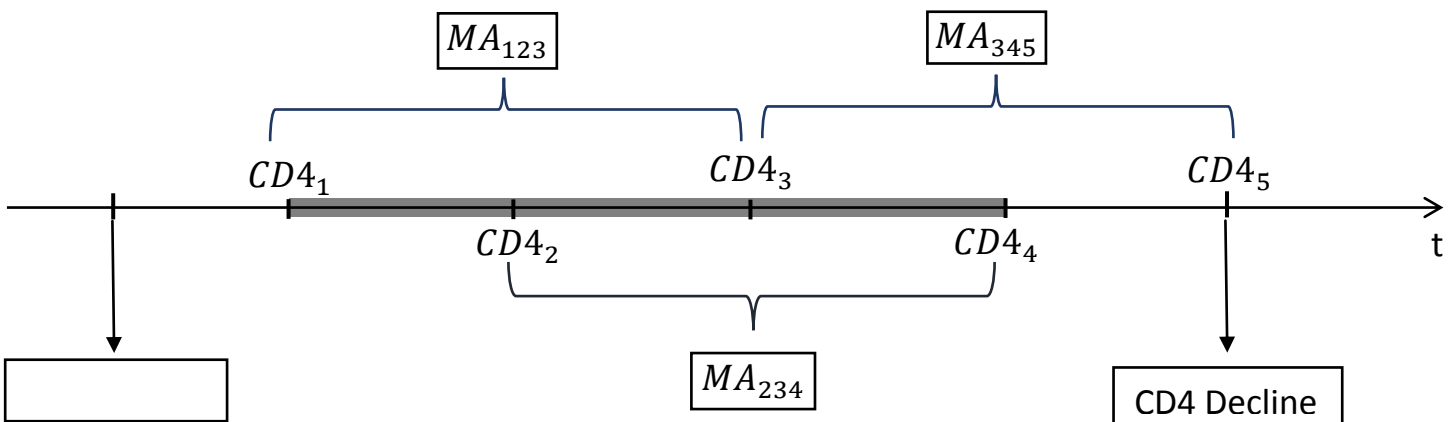
Supplementary Figure 1. Flowchart of the study population

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┌─────────────────────────────────────┐
│     French Hospital Database on HIV   │
│           ANRS CO4 FHDH               │
│           N = 217 257                 │
└─────────────────────────────────────┘
                   │
                   ▼
┌─────────────────────────────────────┐
│ Naive PWH-1 initiating cART between   │
│ 2006 and 2018,                        │
│ 2 years of follow-up, age ≥ 18 years  │
│           N = 53 604                  │
└─────────────────────────────────────┘
                   │
                   ▼
┌───────────────────────────────────────────────┐
│ Two consecutive viral loads < 50 cp/mL after   │
│ cART initiation                                 │
│               N = 21 116                        │
└───────────────────────────────────────────────┘
                   │
                   ▼
┌───────────────────────────────────────────────┐
│ With ≥ 9 months of viral loads < 50 cp/mL and  │
│ at least 5 measurements of CD4 cell counts      │
│               N = 17 921                        │
└───────────────────────────────────────────────┘
                   │
                   ▼
┌───────────────────────────────────────────────────┐
│ Absence of cancer, cardio-vascular diseases, and   │
│ Hepatitis C, not treated with interferon or        │
│ PEG-interferon prior to the index date*            │
│               N = 15 714                           │
└───────────────────────────────────────────────────┘
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*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) ≥ 15% or a RD ≥ 10%

CD4 Decline	RD ≥ 15%: N = 181		RD ≥ 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)	IRR (95%CI)	
		Non-adjusted	**Non-adjusted**	**Adjusted**
Cardiovascular event				
No decline	**173**	**2.2 (1.9-2.6)**	1	1
	112	8.9 (7.4-10.7)		
< 6 months after decline	**1**	**12.1 (1.7-85.9)**	**5.5 (0.8-39.2)**	**4.1 (0.6-29.2)**
	3	132.3 (42.7-410.3)	14.8 (4.7-46.7)	11.7 (3.6-37.4)
≥ 6 months after decline	**1**	**1.7 (0.2-11.8)**	**0.8 (0.1-5.4)**	**0.6 (0.1-4.1)**
	4	26.5 (10.0-70.7)	3.0 (1.1-8.1)	2.7 (1.0-7.5)
Cancer				
No decline	**291**	**3.7 (3.3-4.4)**	1	1
	87	6.6 (5.4-8.2)		
< 6 months after decline	**5**	**70.4 (29.3-169.1)**	**19.0 (7.8-45.9)**	**15.3 (6.3-36.9)**
	3	115.8 (37.4-359.1)	17.5 (5.5-55.4)	13.7 (4.3-43.6)
≥ 6 months after decline	**5**	**9.0 (3.7-21.5)**	**2.4 (1.0-5.8)**	**2.1 (0.9-5.1)**
	3	17.0 (5.5-52.7)	2.6 (0.8-8.1)	2.2 (0.7-7.2)
Death				
No decline	**92**	**1.2 (1.0-1.5)**	1	1
	138	10.5 (8.9-12.4)		
< 6 months after decline	**2**	**28.5 (7.1-114.1)**	**24.1 (5.9-98.0)**	**19.2 (4.7-78.6)**
	2	77.2 (19.3-309)	7.4 (1.8-29.7)	4.3 (1.1-17.6)
≥ 6 months after decline	**1**	**1.8 (0.3-13.0)**	**1.5 (0.2-11.1)**	**1.2 (0.2-9.0)**
	7	39.6 (18.9-83.1)	3.8 (1.8-8.1)	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).