



A low CD4 cell count after three years of active combination antiretroviral therapy is predictive of incomplete immune restoration at 7 years.

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Background: Despite a sustained full suppression of HIV replication under active combination antiretroviral therapy (cART), an incomplete immune recovery (<500 CD4 /mm3) is usually observed in about 16-30% of HIV-infected patients. Whether such a poor response could be predicted earlier remains unclear.

Methods: We conducted a retrospective study of all HIV-infected patients cared for in 2009 at the Hotel-Dieu hospital in Lyon, France, who achieved an effective cART (prolonged virological response with HIV viral load <400 copies/ml without any treatment interruption). Patients with cancer history, haematological disorders, chemotherapy or coinfection with hepatitis B or C were excluded. The last visit before prolonged undetectable HIV viral load was considered as baseline.

Results: 427 patients with at least 4 years of effective cART were analyzed. Median duration of effective cART was 6.6 years (range 4.1-13.2). At baseline, 341 patients (80%) had a CD4 cell count <500/mm3 (median age 49 years, 77% males, 25% CDC stage C, median CD4 cell count 278 and median HIV load 13364 copies/mL). At seven years, 58% of patients <200 CD4/mm3 at baseline remained under 500 CD4/mm3. This percentage decreased to 38% and 18% for those with a baseline CD4 cell count between 201-350 and 351-500, respectively. For patients with a baseline CD4 level <200, the risk for remaining below 500 at seven years was 6.4 fold higher than for those between 351-500 CD4 at baseline (p<0.001) and 2.23 higher than for patients between 201-350. All patients <200 CD4 and 84% of those between 201-350 at three years, did not reach the 500 threshold at seven years.

Conclusions: Patients under active and prolonged cART, which CD4 levels remain low at three years are doomed to failure in achieving full immune recovery at seven years. Adjuvant therapy to optimize their immunological response should be attempted.

INTRODUCTION

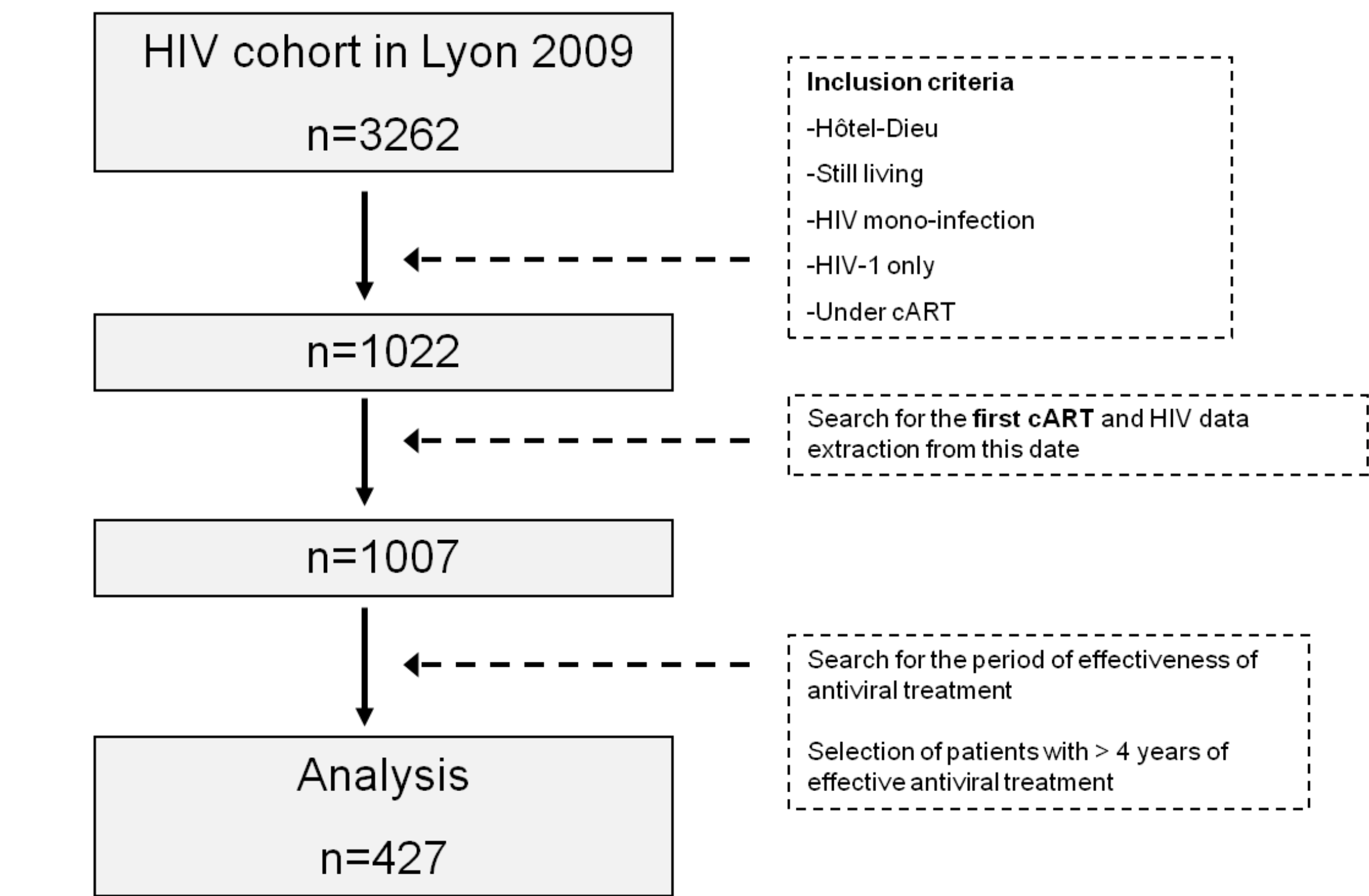
- Active combination antiretroviral therapy (cART) is associated with a decrease in plasma HIV viral load, and a rise in CD4 T cells in a process most often biphasic (Pakker et al., 1998)
- This allows most patients treated with effective cART to recover a normal immune status considered as a CD4 count> 500 cells/mm3 and to reach a rate of mortality comparable to the general HIV-negative population (Lewden et al., 2007)
- However, in a subpopulation of HIV patients, the suppression of viral replication following antiviral therapy is not accompanied by a sufficient increase of circulating CD4 T cells, even after several years of cART (Egger et al., 2002, Kelley et al., 2009). Some of these patients (16-30%) seem to reach a "plateau" of CD4 below the normal of 500 cells/mm3..

PURPOSE

- Early identification of an incomplete immune restoration in HIV patients under antiretroviral therapy

METHODS

- Rétrospective study among HIV+ patients regularly followed at the Hotel-Dieu in Lyon in 2009.
- Selection of patients with undetectable HIV viral load (<400 copies without interruption of treatment) for at least 4 years. The date of inclusion was defined by the last visit before obtaining an undetectable HIV viral load.
- Excluding patients with an history of hematological or solid tumors , or Hepatitis B or C coinfections.



- Classification of patients into immunological responders (IR) or immunological non responders (INR) according to changes in their CD4 cell count during follow-up:
 - From inclusion (baseline) to 7 years of follow-up:
 - IR : <350 CD4 at baseline and >500 at 7 years (n=63)
 - INR : <350 CD4 at baseline and <500 at 7 years (n=53)
 - Between 3 to 7 years of follow-up.
 - IR : <500 CD4 at 3 years and >500 at 7 years (n=40)
 - INR : <500 CD4 at 3 years and <500 at 7 years (n=55)

RESULTS

- Characteristics of the 427 patients are presented in Table 1.
- During a median follow-up of 6,7 years (4-13,2) of active cART, the annual average of immunological and virological analysis (CD4 and HIV viral load) was 3,9/patient.

Table 1 : Characteristics of the 427 patients

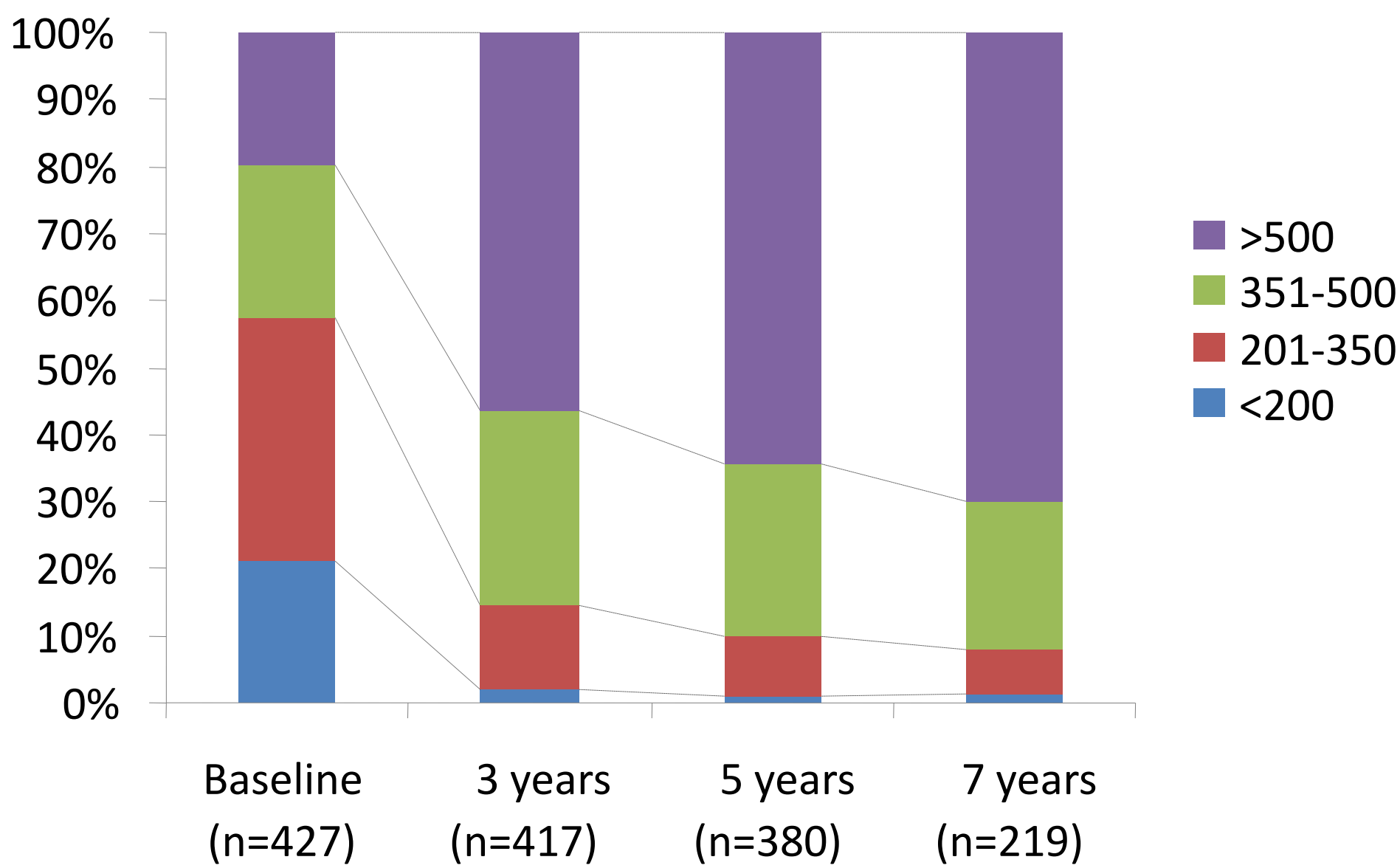
		n	%
Sex	male	331	77,5
	Female	96	22,5
Age	Median (min - max)	40,6 (12,2 –78,6)	
	> 50 years	104	24,4
Route of infection	Heterosexual	193	45,2
	Homosexual	166	38,9
	Other	68	15,9
CDC stage	Stage C (AIDS)	92	21,5
Duration of active cART (years)	Median (min - max)	6,7 (4,0 –13,2)	
	< 500	341	79,9
HIV viral load (copies/mL)	Median (min - max)	9692 (20 –1304800)	
	2NRTI + 1 NNRTI	167	44,2
	2NRTI + 1 bPI	120	31,7
	3NRTI	30	7,9
	1NRTI + 1NNRTI + 1bPI	11	2,9
	2NRTI + 1PI	11	2,9
Nadir of CD4 (/mm³)	Median (min - max)	195 (1 –789)	
	Other	39	10,3
Duration of HIV infection (years)	Median (min - max)	4,4 (0 –20,7)	
	Naïve patients	221	51,8

* NRTI =nucleosides, NNRTI=non nucleosides,, bPI = boosted protease inhibitor, PI=Protease inhibitor .

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Figure 1 : Changes in CD4 count during follow-up (% patients in each category)



- After 7 years of active cART, among 219 patients followed, 69.9% (n = 153) exceeded the threshold of 500 CD4, 22.4% (n = 49) are between 350 and 500 and 7.8% are below 350 (Figure 1).
- Table 2 shows CD4 value at 7 years depending on the level of immune restoration obtained at 3 years of cART : 86.5% (32/37) of patients with a CD4 count <350 at 3 years do not reach the threshold of 500 CD4 at 7 years. In contrast, for patients with CD4 counts> 350 at 3 years, 60.3% (35/58) exceed 500 CD4 at the end of follow-up.
- Thus, the risk of an incomplete immune restoration at 7 years (CD4 <500) was 4.7 times higher in patients remaining <350 at 3 years of cART effective.

Table 2 : CD4 count obtained at 7 years depending on the value at 3 years of active cART (number of patients and % : n = 212)

CD4 at 3 years	CD4 at 7 years				Total
	<200	201-350	351-500	>500	
	2 (40)	3 (60)	0 (0,0)	0 (0,0)	5
	0 (0,0)	9 (28,1)	18 (56,3)	5 (15,6)	32
	0 (0,0)	1 (1,7)	22 (37,9)	35 (60,3)	58
	0 (0,0)	0 (0,0)	9 (7,7)	108 (92,3)	117

- At baseline, CDC stage C (OR = 0.44, 95% CI 0.20 to 0.97), nadir of CD4 >200 (OR = 2.47, 95% CI 1.05 to 5.83) and naive status (OR = 3.62, 95% CI 1.56 to 8.46) were significantly associated with a complete immune restoration (Figure 2a).
- Depending on CD4 value obtained at 3 years, only naive status (OR = 3.86, 95% CI 1.51 to 9.85) is associated with a complete immune response at 7 years (Figure 2b)

Figure 2a : Association between a complete immune response (CD4> 500 to 7 years) and baseline characteristics

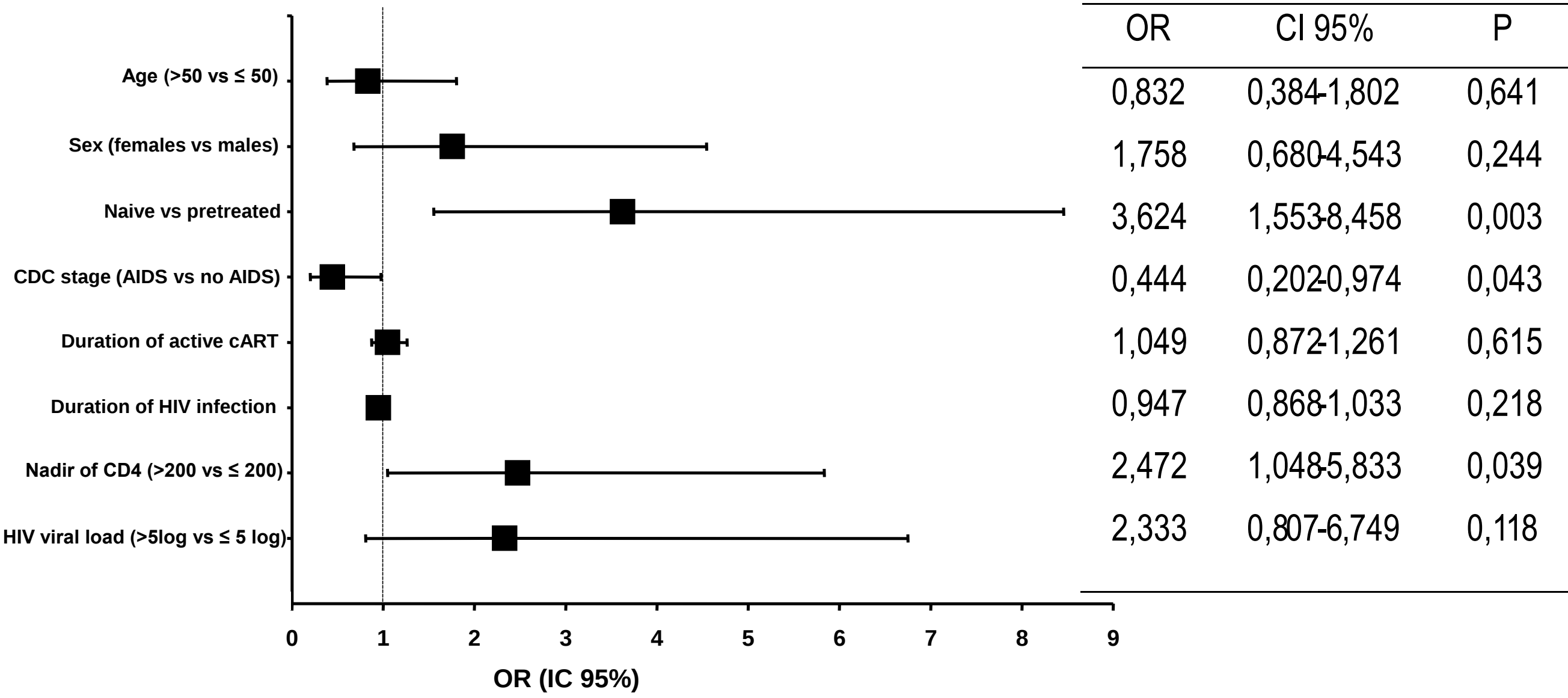
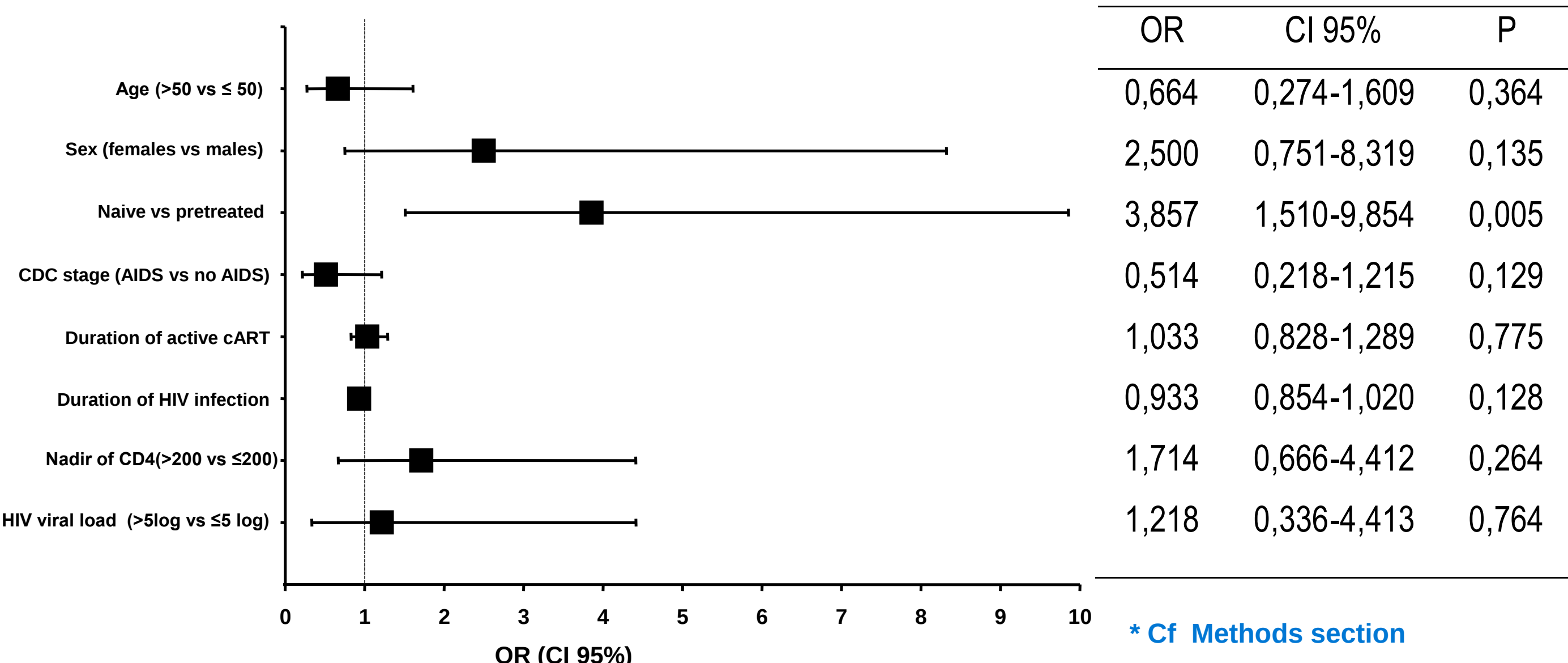


Figure 2b : Association between a complete immune response at 7 years depending on the CD4 value obtained at 3 years (IR vs. INR *)



Conclusion

- A value of CD4 <350 at 3 years of active cART seems to be a factor of incomplete immune restoration thereafter (4.7 times the risk of INR at 7 years).
- This risk appears significantly higher (OR = 3.86) in pretreated patients compared to ART-naïve, irrespective of advanced age (> 50 years), low CD4 nadir (<200), factors usually associated with an incomplete immune restoration (Gazzola et al, 2009).
- For INR patients , adjuvant strategies to improve their immune recovery should be developed.

References

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