Factors associated with incomplete immunologic recovery in HIV-infected patients with clinical and virologic success after 10 years of antiretroviral therapy: a prospective cohort study

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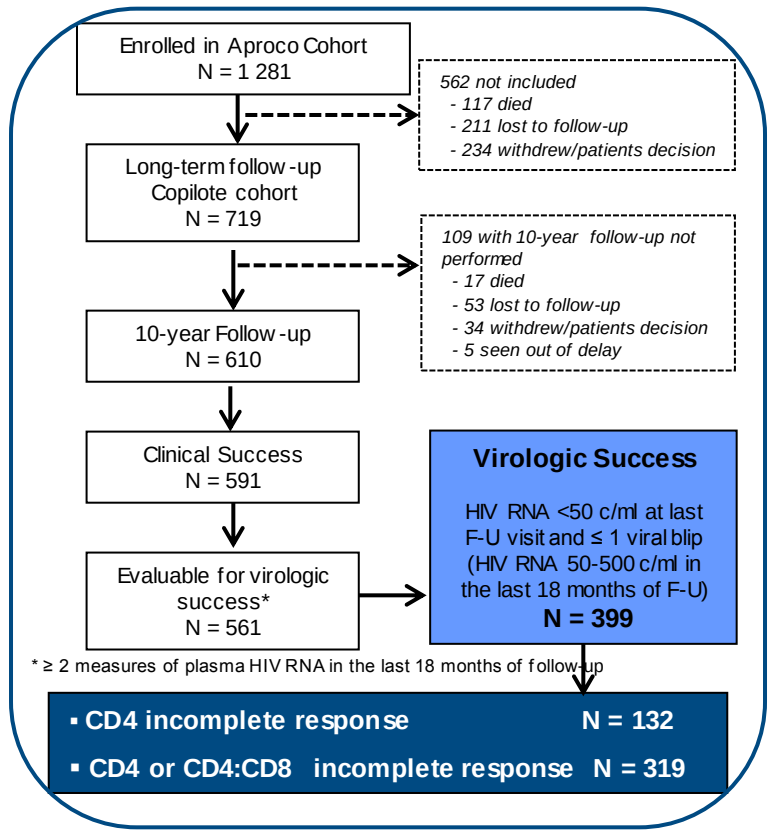
BACKGROUND

HIV-1 infected patients with virologic suppression and absence of recent clinical events after 10 years of antiretroviral therapy (cART) might have incomplete immune recovery. Besides immuno-virologic characteristics, assessment of factors related to treatment history are scarce.

METHODS

Prospective APROCO-COPILOTE cohort of patients started on protease inhibitor (PI)-containing regimen in 1997-1999. Evaluation of patients with 10 year follow-up and clinico-virological success.
Outcome variables were CD4 incomplete response (CD4 cell counts ≤ 500/ µl) and CD4 & CD4:CD8 ratio incomplete response (CD4 cell counts ≤ 500/ µl or CD4:CD8 ratio ≤ 1). Impact of cART history on the immunologic response measured at 10 years was assessed by multivariate logistic regression models.
Treatment regimens were defined as different types of treatment among : cART 2 NRTI + 1 PI(±r), cART with 2 NRTI + 1 NNRTI, cART with NRTI + PI(±r) + NNRTI, mono or dual therapy, other combinations, treatment interruption.
Treatment sequences were defined as the different lines of therapy (each treatment change = a new line)

Flow-Chart



RESULTS

Table 1 : Baseline characteristics of patients with virologic success

	N=399	
Age, years, median (IQR)	39	(33 - 45)
Male, n (%)	321	(81)
Transmission group, n (%)		
- Homosexual/bisexual	169	(42)
- Toxicomania	46	(12)
- Heterosexual or other	184	(46)
CDC stage C, n (%)	97	(24)
Antiretroviral-naïve, n (%)	197	(49)
CD4 cell counts/µl, median (IQR)	254	(111 - 398)
CD4 ≤ 200/µl, n (%)	157	(39)
CD4 > 500/µl, n (%)	51	(13)
HIV RNA $\log_{10}$ c/ml, median (IQR)	4.6	(3.7 - 5.2)
PI initially prescribed, n (%)		
Saquinavir	44	(11)
Ritonavir	77	(19)
Indinavir	178	(45)
Nelfinavir	126	(32)
Combination of PI	34	(9)

Table 2 : Final multivariate logistic regression model of factors associated with incomplete CD4 response (CD4 ≤ 500/µl) or incomplete immunologic response (CD4 ≤ 500/µl or CD4:CD8 ratio ≤ 1) after 10 years of follow-up

Factor	OR [95% CI]	p
Incomplete CD4 response (CD4 ≤500/µl)		
Age at M0 (≥ vs < 40 years)	2.55 [1.57-4.12]	< 0.001
CD4 cell counts at M4 (≤ 500 vs > 500/µl)	2.79 [1.21-6.42]	0.016
CD4 cell counts at M12 (≤ 500 vs > 500/µl)	3.56 [1.81-6.99]	< 0.001
Total duration of ART interruption (≥ 3 months vs < 3 months)	2.32 [1.17-4.58]	0.016
Incomplete immunologic response (CD4 ≤500/µl or CD4:CD8 ratio ≤1)		
CD4:CD8 ratio at M8 (≤ 0.8 vs > 0.8)	6.14 [2.21-17.1]	< 0.001
CD4:CD8 ratio at M12 (≤ 0.8 vs > 0.8)	5.53 [2.18-14.0]	< 0.001
Total duration of ART interruption (≥ 3 months vs < 3 months)	4.44 [1.41-13.9]	0.011
Number of treatment regimens (≥ 3 vs < 3)	2.97 [1.31-6.75]	0.009
Number of treatment sequences (Ref = 0-4)		0.015
4-6	0.33 [0.14-0.75]	0.008
6-9	0.58 [0.19-1.77]	0.34
≥ 10	0.19 [0.06-0.62]	0.006

DISCUSSION

Among the 610 patients (median follow-up on ART: 120 months), 399 had no clinical progression and sustained virologic suppression during the last year. Baseline characteristics (median) : age 39 years, CD4 254/µl, HIV-1 RNA 4.6 $\log_{10}$ c/mL, similar to the total cohort patients.
In this population having started ART with first generation PI, long-term immunologic recovery was rarely complete after 10 years of antiretroviral therapy despite clinical and virological success : 33% had incomplete CD4 response and 80% had incomplete CD4 & CD4:CD8 response.
Failure to achieve long-term immunologic response was not associated with baseline immunological parameters but with immunologic response during the first year of treatment. Less frequent number of treatment regimens and shorter duration of treatment interruptions were also associated with failure. Of note, the positive impact of higher number of treatment sequences on complete immunologic recovery might be a proxy of more frequent antiretroviral therapy optimisation in these patients.

CONCLUSION

This study confirms the deleterious effect of treatment interruption on long term immunologic recovery on cART. It also points out the predictivity of early (1 year) CD4 and CD4:CD8 response on long-term (10 years) recovery. The beneficial effect of multiple ARV sequences needs further analyses

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