

# Impact of hepatitis C virus coinfection on T-cell dynamics in long-term HIV-suppressors under combined antiretroviral therapy

Olivia Zaegel-Faucher<sup>a</sup>, Sylvie Bregigeon<sup>a</sup>, Carla Eliana Cano<sup>a</sup>,  
Véronique Obry-Roguet<sup>a</sup>, Corinne Nicolino-Brunet<sup>b</sup>,  
Catherine Tamalet<sup>c,d</sup>, Françoise Dignat-George<sup>b</sup> and  
Isabelle Poizot-Martin<sup>a,e</sup>

**Objective:** The objective of this study is to evaluate the impact of hepatitis C virus (HCV) serostatus on the evolution of CD8<sup>+</sup> cells and CD4<sup>+</sup> : CD8<sup>+</sup> ratio in HIV-infected patients on combined antiretroviral therapy (cART) who achieve sustained undetectable viral load (HIV-pVL).

**Design and methods:** A longitudinal study performed in an outpatient HIV-unit following 1495 HIV-infected patients. Data of patients on cART achieving undetectable HIV-pVL for at least 3 years were collected retrospectively from our medical e-database NADIS from January 1997 to April 2005, a period defined in order to select patients who were naive of hepatitis treatment. T-cell counts were assessed every 6 months from HIV-suppression over the study period.

**Results:** Two hundred and twenty-six HIV mono-infected (group 1) and 130 HCV-coinfected patients (group 2; genotype prevalence: 42% HCV-G1, 26% HCV-G3, 11% HCV-G4 and 21% HCV-G2) fulfilled the selection criteria. cART regimens were comparable between the groups, as were CD4<sup>+</sup> and CD8<sup>+</sup> cell counts at the first undetectable HIV-pVL. After 3 years, both groups displayed similar CD4<sup>+</sup> cell reconstitution, although CD4<sup>+</sup> percentage was higher in group 1 (30.3 ± 1.1 vs. 27 ± 1.1%; *P* < 0.001). HIV suppression led to a significant drop of median CD8<sup>+</sup> cell counts in group 1 (*P* = 0.027), but not in group 2, which displayed higher CD8<sup>+</sup> cell counts all through the follow-up (mean diff. = 135.71 ± 26.89 cells/μl, *P* < 0.001). Moreover, the fraction of patients reaching CD4<sup>+</sup> : CD8<sup>+</sup> ratio ≥ 1 was lower in group 2 (14 vs. 27.7%; *P* < 0.05).

**Conclusion:** Despite sustained HIV suppression under cART, HCV coinfection was found to hamper CD8<sup>+</sup> downregulation. Further studies will determine the impact of treatment with direct-acting antiviral agents on the CD8<sup>+</sup> pool, and the advantage of systematic HCV-targeted therapy for HIV/HCV-coinfected patients.

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<sup>a</sup>Aix-Marseille University, APHM-Sainte Marguerite Hospital, Immunohematology Clinical Unit/HIV Clinical Center, <sup>b</sup>Aix-Marseille University, APHM-Conception Hospital, Service d'hématologie et de biologie vasculaire, <sup>c</sup>Aix-Marseille University, APHM-Timone Hospital, Fédération de Microbiologie Hospitalière, <sup>d</sup>URMITE CNRS-IRDUMR6236, and <sup>e</sup>Inserm U912 (SESSTIM), Marseille, France.

Correspondence to Isabelle Poizot-Martin, MD, Aix-Marseille University, APHM-Sainte-Marguerite Hospital, 13009 Marseille, France.

E-mail: isabelle.poizot@ap-hm.fr

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## Introduction

Most HIV1-infected patients initiating HAART (combined antiretroviral therapy, cART) experience an effective control of HIV replication in plasma associated with an increase of CD4<sup>+</sup> T-cell numbers [1]. However, many of them fail to restore CD4<sup>+</sup> T-cell counts above 500 cells/ $\mu$ l and/or a CD4<sup>+</sup> : CD8<sup>+</sup> ratio  $\geq$  1. This is partly due to persistent immune activation and inflammation, driven by residual HIV replication, microbial translocation and chronic viral infections [2] such as hepatitis C virus (HCV) infection, which concerns around 15–30% of HIV-infected patients in central Europe [3].

Chronic HCV-infection is associated with CD8<sup>+</sup> T-cell dysfunction, ineffective viral control [4,5] and promotion of T-cell exhaustion and senescence [6]. Such abnormalities are enhanced during HIV infection. Therefore, HCV coinfection may interfere with immune restoration in HIV-infected patients achieving long-term HIV suppression.

This study aimed to determine the impact of HCV coinfection on longitudinal changes in CD4<sup>+</sup> and CD8<sup>+</sup> T-cell counts in HIV-infected patients under cART who achieved a sustained undetectable plasma HIV viral load (HIV-pVL) for at least 3 years. In order to focus on the actual effect of HCV infection on immune reconstitution, we analysed data collected from HIV/HCV-coinfecting patients who were naive of HCV-targeted treatment.

## Materials and methods

### Study design and procedures

This is a retrospective observational study conducted by the Clinical Research Department of the Immuno-Hematological clinical unit-Centre d'Information et Soins de l'Immunodéficience Humaine (CISIH) et des hépatites virales of the Sainte Marguerite – Marseille South Hospital. Data of patients under cART who achieved undetectable HIV-pVL for at least 3 years were collected from our electronic database, NADIS (Fedialis Medica, Marly le Roi, France) [7,8] from January 1997 to April 2005. This period was defined in order to select patients who were naive of interferon (IFN)-based hepatitis treatment. HCV coinfection was identified on the basis of HCV-positive serology. Splenectomized patients and patients who have received a course of IFN- $\alpha$  or IFN- $\beta$  prior to or during the study period were excluded. The characteristics of patients were described at the time of initiation of the long-term inhibitor antiretroviral treatment (LTIT) and at the first undetectable HIV-pVL (baseline). Dynamic of T-cell compartments (CD4<sup>+</sup> and CD8<sup>+</sup> T-cell counts and percentages) were assessed at baseline and every 6 months during the follow-up. Sex, age, duration of HIV follow-up, transmission risk

group, Centers for Disease Control and Prevention (CDC) stage, hepatitis B coinfection (positive hepatitis B surface antigen), duration of cART exposure and cART regimen [nucleoside reverse transcriptase inhibitor (NRTI)-based, nonnucleoside/NRTI (NNRTI)-based, protease inhibitor based] were analysed. For T-cell immunophenotyping, EDTA fresh whole blood (100  $\mu$ l) was incubated with combinations of fluorochrome-conjugated mAbs specific for CD3<sup>+</sup>, CD4<sup>+</sup> and CD8<sup>+</sup> (Beckman Coulter, Brea, California, USA) and the analysis was performed using an FC500 cytometer (Beckman Coulter). HCV-RNA was detected and/or quantified by real-time PCR assays using COBAS TaqMan-HCV (Roche Molecular Systems, Pleasanton, California, USA) assays [lower limits of detection (LLD) 15 IU/ml]. Plasma HIV-RNA was quantified by successive standardized assays including Roche Cobas HIV-1 monitor, Roche Cobas Ampliprep/Cobas Taqman HIV-1v.2 test and Abbott RealTime HIV-1 test with detection limits of 400, 200, 50 and 40 copies, according to the study period.

### Statistical analysis

All analyses used SPSS Advanced Statistics 20 (IBM Corp, Hong Kong). Univariate analyses of means and medians of independent samples were performed using Student's *t*-test and Pearson's chi-square tests, respectively, and paired samples were analysed using the Friedman test. Linear regression was performed for multivariate analyses.

### Ethics statement

All individuals provided written informed consent for the use of their medical records on NADIS. This electronic medical record was approved by the French Commission Nationale Informatique et Liberté (Registration number: 2001/762876/nadiscnil.doc). This study was carried out in compliance with the international guidelines for human research protection as per the Declaration of Helsinki and ICH-GCP.

## Results

### Demographic and clinical characteristics of patients

Out of the 1495 HIV-infected patients registered in our database during the study period, 356 fulfilled the selection criteria, of whom 226 were HIV mono-infected (group 1) and 130 were HCV coinfecting (group 2). Patients' characteristics are reported in Table 1. Patients in the two groups were mostly men (66.8 and 76.2% for group 1 and 2, respectively) and differed in age (lower in group 1), HIV transmission risk group (mostly through intravenous drug use in group 2), CDC stage C (higher in group 1) and duration of HIV follow-up, which was longer in group 2 (10 [6–12] vs. 4 [1–8] years,  $P < 0.001$ ). Regardless of HCV status, most patients were receiving a triple combination of antiretroviral drugs

**Table 1. Demographical and clinical characteristics of HIV mono-infected and HIV/hepatitis C virus coinfecting cohorts.**

	HIV mono-infected cohort (group 1, n = 226)		HIV/HCV-coinfecting cohort (group 2, n = 130)		P
	N/median	%/IQR	N/median	%/IQR	
Female	75	33.2	31	23.8	0.71
Age	39	33–46	36	33–39	0.001
MSM	90	39.8	2	1.5	<0.001
Heterosexual	105	46.5	24	18.5	
Intravenous drug users	2	0.9	99	76.2	
Others	29	12.8	5	3.8	
CDC stage C	62	27.4	28	21.5	0.002
HBV sero-positive	16	7.5	9	7.2	1.000
HCV genotype					
G1			55	42.3	
G3	na	na	34	26.1	na
G4			14	10.8	
Unknown			27	20.8	
Duration of HIV follow-up (years)	4	1–8	10	6–12	<0.001
cART exposure at BL (months)	21.5	4–56	19	3–61	0.223
Lines of cART treatment at BL	2	1–4	2	1–4	0.627
Time to HIV suppression (months)	3	2–8	2	3–6	0.085
cART at baseline					
2 NRTIs and 1 PI	105	49.1	63	51.5	0.734
2 NRTIs and 1 NNRTI	29	13.6	14	11.5	0.615
3 NRTIs	33	15.4	17	13.9	0.752
CD4 <sup>+</sup> cell count at LTIT initiation	249	151–378	253	137–380	0.605
% CD4 <sup>+</sup> at LTIT initiation	17	12–24	17	9–24	0.466
CD8 <sup>+</sup> count at LTIT initiation	728	527–1088	828	482–1362	0.431
HIV load at LTIT initiation (log cp/ml)	4.4	3.6–5	4.5	3.6–5.2	0.451
BL-CD4 <sup>+</sup> cell count (per cells/μl)	342	231–495	341	191–471	0.299
BL-CD4 <sup>+</sup> %	21	15–30	21	14–27	0.3
BL-CD8 <sup>+</sup> cell count (per cells/μl)	750	537–1030	864	577–1170	0.076
BL-CD8 <sup>+</sup> %	50	39–57	52	43–59	0.052
BL-CD4 <sup>+</sup> : CD8 <sup>+</sup> ratio	0.413	0.27–0.71	0.383	0.21–0.55	0.739
CD4 <sup>+</sup> nadir (per cells/μl)	199	84–290	175	75–269	0.202

BL, baseline, first record of undetectable HIV-pVL; IQR, interquartile range; LTIT, long-term inhibitory antiretroviral treatment.

at baseline. LTIT regimens were comparable between groups, with the most frequent regimens being two NRTIs and one protease inhibitor (50%), three NRTIs (14.9%) and then two NRTIs and one NNRTI (12.8%).

Regarding HCV infection, 55 patients (42.3%) were HCV-genotype 1 coinfecting (G1), 34 (26.1%) with HCV-genotype 3 (G3), 14 (11.8%) with HCV-genotype 4 (G4), and genotype was not available for 27 (20.8%) patients. Qualitative HCV-RNA data were available for 88 patients (67.7%), of whom 76 were positive (86%), and only nine quantitative HCV-RNA assessments were available at baseline (median HCV viral load = 5.7 log UI/ml). Median CD8<sup>+</sup> T-cell counts were higher in group 2, although under significance threshold. Median CD4<sup>+</sup> : CD8<sup>+</sup> ratio at baseline was comparable between the groups; however, the proportion of patients with a CD4<sup>+</sup> : CD8<sup>+</sup> ratio at least 1 was significantly higher in group 1 (11.4 vs. 1.6% in group 1 and 2, respectively,  $P=0.001$ ).

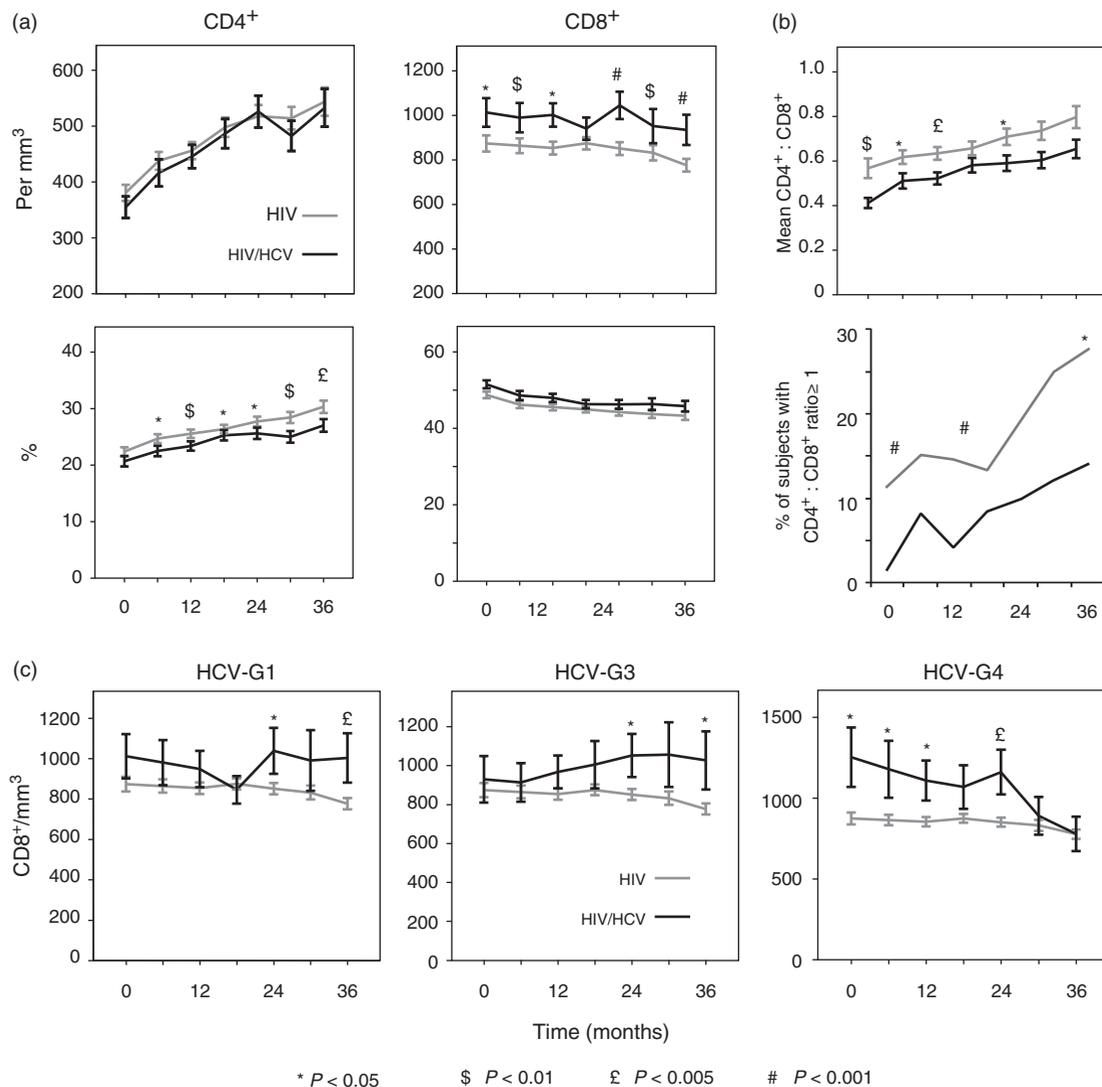
#### Evolution of CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells and the CD4<sup>+</sup> : CD8<sup>+</sup> ratio

During 3 years of follow-up starting from the first undetectable HIV-pVL, mean and median CD4<sup>+</sup> T-cell counts increased significantly regardless of HCV status

(Fig. 1a and Supplementary Table 1, <http://links.lww.com/QAD/A676>, respectively), although mean CD4<sup>+</sup> cell percentage increased significantly in group 1 only (Fig. 1a). In contrast, median CD8<sup>+</sup> counts decreased significantly only in group 1 (Supplementary Table 1, <http://links.lww.com/QAD/A676>). More strikingly, patients from group 2 displayed higher mean CD8<sup>+</sup> counts than group 1 at all times but 18 months (Fig. 1a; mean diff. =  $135.71 \pm 26.89$  cells/μl,  $P < 0.001$ ). A higher mean CD8<sup>+</sup> cell percentage under significance threshold was also observed in group 2 than group 1 (mean diff. =  $2.427 \pm 0.572\%$ ,  $P = 0.12$ ). A similar pattern of CD8<sup>+</sup> evolution was observed when focusing on patients with detectable HCV-RNA (Supplementary Fig. 1, <http://links.lww.com/QAD/A676>). Mean CD4<sup>+</sup> : CD8<sup>+</sup> ratio as well as the proportion of patients with CD4<sup>+</sup> : CD8<sup>+</sup> ratio  $\geq 1$  remained significantly higher in HIV mono-infected patients all through the follow-up (Fig. 1b).

#### Impact of hepatitis C virus genotype on CD8<sup>+</sup> T-cell dynamics

Analysis of the evolution of CD4<sup>+</sup> and CD8<sup>+</sup> T-cell counts according to HCV genotype showed that HCV-G1 coinfecting patients displayed higher CD8<sup>+</sup> counts at all times but 18 months, without significant



**Fig. 1. Longitudinal evolution of T-cell subsets in HIV mono-infected and HIV/hepatitis C virus coinfected HIV suppressors on combination antiretroviral therapy.** (a) Graphs show mean counts and percentages of CD4<sup>+</sup> and CD8<sup>+</sup> cells in HIV mono-infected (gray) and HIV/HCV-coinfected (black) patients on cART at the time of their first undetectable HIV-pVL(t<sub>0</sub>), and every 6 months thereafter during a 3 years long follow-up. (b) Graphs show the mean CD4<sup>+</sup> : CD8<sup>+</sup> ratio ± SEM (top) and percentage of patients presenting a CD4<sup>+</sup> : CD8<sup>+</sup> ratio ≥ 1 (bottom). (c) Graphs show kinetics of CD8<sup>+</sup> counts of HIV suppressors that are either HIV mono-infected (gray) or coinfected (black) with HCV genotype G1, G3 or G4, as indicated. Data are mean ± SEM. Error bars illustrate SEM. \**P* < 0.05, \*\**P* < 0.01, \*\*\**P* < 0.005, †*P* < 0.001.

variation throughout the study period (Fig. 1c). No significant differences were observed between HCV-G1 subtype 1a (*n* = 44) and 1b (*n* = 11) (data not shown). HCV-G3 coinfected patients presented mean CD8<sup>+</sup> values comparable to group 1 at baseline, which became higher than group 1 after 24 months. In contrast, for HCV-G4 coinfected patients, mean CD8<sup>+</sup> counts steadily dropped from baseline and became comparable to the group 1 after 3 years.

#### Factors associated with CD8<sup>+</sup> T-cell rates and hepatitis C virus infection

We performed bivariate Pearson's analysis in order to identify variables among the clinical/demographic

characteristics of our cohort that were correlated to CD8<sup>+</sup> counts at baseline, to CD8<sup>+</sup> counts after 3 years of HIV suppression on cART or to HCV-positive serology. The results of this analysis are summarized in the Supplementary Table 2, <http://links.lww.com/QAD/A676>. On this basis, we identified baseline CD4<sup>+</sup> : CD8<sup>+</sup> ratio, CD4<sup>+</sup> and CD8<sup>+</sup> cell counts at baseline, sex, age and the duration of HIV follow-up as potential confounding factors. Therefore, we performed multivariate linear regression analysis adjusting by these variables, which corroborated the correlation between HCV-positive serology and CD8<sup>+</sup> cell counts after 3 years of HIV suppression (coeff. = 0.167, *P* < 0.05). A stronger correlation was observed when the analysis was restricted

to HIV/HCV-coinfected patients with a positive HCV-PCR record (HCV coinfection<sub>3 yrs</sub>: coeff=0.212,  $P=0.006$ ; Supplementary Figure 1, <http://links.lww.com/QAD/A676>).

## Discussion

This study demonstrates that in spite of long-term sustained undetectable HIV-pVL and concomitant CD4<sup>+</sup> reconstitution on cART, HCV coinfection supports an expansion of the CD8<sup>+</sup> T-cell compartment, which results in a poorer restoration of the CD4<sup>+</sup> : CD8<sup>+</sup> ratio than HIV mono-infected patients.

An expansion of CD8<sup>+</sup> T cells was previously reported in studies involving smaller cohorts of HIV/HCV-coinfected patients [9–11]. However, the number/heterogeneity of the individuals regarding HIV status and/or previous hepatitis treatment in these studies did not allow drawing conclusions about this immune condition. Our selection of HIV/HCV seropositive patients among HIV suppressors on cART followed between 1997 and 2005 provides a homogeneous cohort of naive HIV/HCV-infected patients for which an eventual contribution of HIV on CD8<sup>+</sup> amplification can be ruled out. Although only a small number of these patients had a documented HCV-RNA status, results from HCV-RNA positive patients were consistent with those from the whole HCV sero-positive cohort. Hence, our results allow clear conclusions to be made regarding the enhanced expansion of the CD8<sup>+</sup> compartment related to HCV coinfection.

cART-induced HIV suppression is expected to trigger immune restoration. However, we observed that untreated HCV coinfection was paralleled by a lower CD4<sup>+</sup> : CD8<sup>+</sup> ratio and a smaller proportion of coinfecting patients achieving CD4<sup>+</sup> : CD8<sup>+</sup> ratio  $\geq 1$  after 3 years of HIV suppression on cART. This is of clinical relevance, as recent studies demonstrated that the failure to normalize CD4<sup>+</sup> : CD8<sup>+</sup> ratio under cART increases the risk of incidence of non-AIDS related events, even when CD4<sup>+</sup> cell counts are restored ( $>500$  cells/ $\mu$ l) [12,13].

HCV-specific CD8<sup>+</sup> T cells from HIV-infected patients were shown to be less efficient at clearing infection than their HIV-free counterparts [14]. This paradox of expansion and dysfunction of CD8<sup>+</sup> T cells may be explained by the fact that chronic HCV infection may favour the continual expansion of short-lived cells, while dampening the regeneration of ready-to-kill long-lived ones. This situation was reported in naive HIV-infected patients, for whom persistent HIV replication was associated with accelerated CD8<sup>+</sup> T-cell turnover [15], which normalized on cART [16].

An impaired CD4<sup>+</sup> recovery was previously reported in HIV/HCV-G3 coinfecting patients after a year of HIV suppression [17]. In our study, we found a greater expansion of the CD8<sup>+</sup> compartment in HIV/HCV-G1 and HCV-G3 coinfecting patients, with no significant impact on CD4<sup>+</sup> restoration. To our knowledge, this is the first report of such an impact of HCV genotype on CD8<sup>+</sup> T-cell compartment regulation.

HCV mono-infected patients are known to harbour a high level of exhausted HCV-specific CD8<sup>+</sup> T cells [6], which also seems to be higher in HIV/HCV-coinfected patients as recently reported [5]. The retrospective design of our study did not allow performing further immunophenotyping analysis to document the nature (activated, memory, exhausted) of CD8<sup>+</sup> T cells amplified during HCV coinfection. Unfortunately, quantitative data on HCV-RNA were available for only a few patients, which made it impossible to estimate the impact of HCV viral load on CD8<sup>+</sup> T-cell regulation.

As inflammation fosters the most severe comorbidities of HIV, our results are supportive of initiating HCV treatment in HIV/HCV-coinfected patients regardless of fibrosis score. Preliminary data supporting this viewpoint were provided recently in a study of eight acute HCV-infected patients receiving PEG-IFN/RBV displaying a reduction in CD8<sup>+</sup> responses [18].

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## Conflicts of interest

The authors declare no potential conflicts of interest.

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