


# Effect of Direct Antiviral Therapy Against HCV on CD4+ T Cell Count in Patients with HIV-HCV Coinfection

Biagio Pinchera , Emanuela Zappulo, Antonio Riccardo Buonomo, Maria Rosaria Cotugno, Giovanni Di Filippo, Francesco Borrelli, Simona Mercinelli, Riccardo Villari, Ivan Gentile

Department of Clinical Medicine and Surgery, Section of Infectious Diseases, University of Naples "Federico II", Naples, Italy

Correspondence: Biagio Pinchera, Email [biapin89@virgilio.it](mailto:biapin89@virgilio.it)

**Background:** HCV-related liver disease is an important cause of morbidity and mortality in patients with HIV infection. It is well known that the response rates to HCV therapy are similar between HCV-monoinfected patients and HIV-HCV coinfecting ones. The aim of this study was to evaluate the impact of HCV eradication on CD4 + T cell count in a population of HIV-HCV coinfecting patients.

**Materials and Methods:** We enrolled patients with HIV-HCV coinfection attending the Infectious Diseases Unit of the A.O.U. Federico II of Naples, from January 2016 to February 2019, treated with ART (AntiRetroviral Therapy) and DAAs (Direct Antiviral Agents). For each patient, we evaluated HIV and HCV viral load and CD4+ T cell count before starting therapy with DAAs, by SVR12 time and by SVR48 time. Fibrosis was evaluated by the mean of Fibroscan®.

**Results:** Fifty-two patients were enrolled, 40 males. Fibrosis score was F0-F3 in 15 patients and cirrhosis in the remaining 11 (all in Child-Pugh class A). All had been receiving ART, and all were treated with DAAs. Only patient who had not achieved HIV viral suppression for non-compliance also experienced a relapse of HCV infection after the end of DAAs. In all patients, we observed that the CD4+ T cell count at baseline did not show significant variations compared to SVR12 and SVR48 time. We also assessed CD4 count in relation to HIV categories and stage of liver disease, see Table 1. Also, based on the assessments of the subclasses considered, there were no significant changes in the CD4 + T cell count.

**Conclusion:** Our study shows that HCV viral eradication obtained with DAAs in patients with HIV-HCV coinfection is not associated with significant changes in the CD4 + T cell count, regardless of CDC category and stage of liver disease.

**Keywords:** HCV, HIV, fibrosis, cirrhosis, DAAs, CD4+ T cell, coinfection

## Introduction

About 2.3 million people worldwide are affected by HCV/HIV coinfection, and liver disease is the leading cause of death in coinfecting patients.<sup>1</sup> Co-infection constitutes a higher risk of morbidity and mortality than HCV monoinfection, in particular, it has been seen that in co-infected patients there is a more rapid progression and evolution towards fibrosis, with a higher risk of developing liver cirrhosis and hepatocarcinoma.<sup>2,3</sup>

The advent of DAAs has been a real revolution in the history of HCV infection.<sup>4,5</sup> While in the past there was a lower sustained virological response (SVR) among co-infected patients receiving Interferon therapy compared to monoinfected patients (18.4% –50% vs 36% –76%), current therapies with DAAs (Direct Acting Antivirals) in co-infected patients demonstrated sustained virological response (SVR) rates similar to those in patients with HCV infection alone, in particular, an SVR of 95–98% was observed among co-infected patients after treatment with DAAs, an SVR similar to 96–100% of monoinfected patients.<sup>6–8</sup>

Theoretically, since HCV has a tropism for the cells of the immune system, its elimination could lead to a functional recovery of the immune system itself. In this regard, few studies have evaluated the impact of HCV eradication with DAAs on CD4 T cell counts, in particular, J. Girón Ortega et al observed an improvement in CD4 T cell counts only in

co-infected patients without liver cirrhosis.<sup>9</sup> The study by Bono et al highlighted a decreased activation of  $\gamma\delta$  T- and B-cells as well as increases in the V $\delta$ 2/Th17 ratio and reduced  $\gamma$ -globulin concentrations in coinfecting patients treated with DAAs; these changes were associated with an improvement in liver function.<sup>10</sup> In another study conducted by the ICONA Foundation Cohort, it was observed that the eradication of HCV infection after treatment with DAAs showed no impact on CD4 T cell counts.<sup>11</sup>

The aim of this study was to evaluate the impact of HCV eradication on CD4 + T cell count in a population of HIV-HCV coinfecting patients.

## Materials and Methods

We conducted an observational retrospective cohort study. We enrolled patients with HIV/HCV co-infection attending the Infectious Diseases Unit of the A.O.U. Federico II of Naples, from January 2016 to February 2019, treated with DAAs and antiretroviral therapy (ART). Diagnosis of HCV and HIV infection was based on the criteria established by the current International Guidelines.<sup>1,12</sup> Fibrosis was evaluated by the mean of Fibroscan<sup>®</sup>. The severity of liver disease was graduated according to the degree of liver fibrosis by Metavir stage or clinical signs. The Metavir score was estimated with a FibroScan<sup>®</sup> exam performed within 6 months before the beginning of the antiviral treatment. Moreover, clinical cirrhosis was identified according to the presence of clinical, biochemical and ultrasound signs including a blood platelet count lower than 100,000/mm<sup>3</sup>, hypertrophy of the caudate lobe, nodularity of the liver surfaces, altered straightness of hepatic veins, ascites, porto-systemic encephalopathy, esophageal varices and ultrasound evidence characterizing liver cirrhosis. Decompensated cirrhosis was defined as a cirrhosis in Child-Pugh stage of at least B7, while advanced liver fibrosis was defined as the presence of Metavir score  $\geq$ F4 or clinical cirrhosis.<sup>13</sup>

We evaluated for each patient the epidemiological characteristics, the laboratory data and the clinical characteristics. For each patient, we evaluated HIV and HCV viral load and CD4+ T cell count on the nadir, before starting therapy with DAAs, by SVR12 time and by SVR48 time.

Data were reported as median and interquartile range (IQR) given their non-parametric distribution. For comparisons between continuous variables, the U Mann–Whitney Test was performed. Co-variables significantly associated with death at the univariate analysis were also analyzed in a multivariate model. The p-value for statistical significance was set at  $<0.05$  for all the tests.

With respect to the ethical issues, the study was conducted in compliance with the Declaration of Helsinki and the principles of good clinical practice. For this study, informed consent was obtained from all subjects and/or their legal guardian(s). The study was approved by the “Federico II” Ethics Committee with the code number 242/19.

## Results

We enrolled 52 patients. The main demographics and clinical characteristics of the patients enrolled are shown in Table 1.

Of the 52 patients enrolled, 40 were male and 27 had HCV genotype 1 (22 subtype 1a), 3 HCV genotype 2, 17 HCV genotype 3, 5 HCV genotype 4). Fibrosis score was F0 in 6 patients, F1 in 13 patients, F2 in 7 patients, F3 in 15 patients and cirrhosis in the remaining 11 (all in Child-Pugh class A) (Table 1). All had been receiving ART, and all but one were virosuppressed (due to non-compliance). All were treated with DAAs (10 with Sofosbuvir-Ledipasvir, 2 with Sofosbuvir-Ribavirin, 13 with Sofosbuvir-Daclatasvir, 17 with Sofosbuvir-Velpatasvir, 9 with Glecaprevir/Pibrentasvir, 1 with Sofosbuvir-Simeprevir) and all but one achieved SVR12 and SVR48. The same patient who had not achieved HIV viral suppression for non-compliance also experimented a relapse of HCV infection after the end of DAAs.

Enrolled patients had a median with IQR of CD4 + nadir equal to 190 (16–670), while they had a CD4 + value before starting DAAs of 724 (203–1656). At the sustained virologic response (SVR12 and SVR 48) they had a CD4 + count, respectively, equal to 684 (201–1815) and 713 (117–1720) (OR for CD4+ count: 1.2, 95 CI (0.6–1.3) pre-treatment vs post-treatment at SVR12; p: 0.310 and OR for CD4+ count: 1.1, 95 CI (0.8–1.2) pre-treatment vs post-treatment at SVR48; p: 0.340) (Table 2). We evaluated the CD4 + count at the nadir, pre-DAA, at the SVR12 and at the SVR48, also in relation to the class to which the CDCs (Center for Diseases Control) belong (Table 2).

The evaluation of the CD4 + count at the nadir, before the start of therapy with DAAs, at the SVR12 and at the SVR48 was also performed by distinguishing the stage of chronic liver disease, in particular, distinguishing the co-

**Table 1** Anagraphic Clinical Features of Enrolled Patients

<b>Age (Median, IQR)</b>	59.2 (27–64)
<b>Gender</b>	
M	40 (77%)
F	12 (23%)
<b>HCV-RNA (IU/mL; median, IQR)</b>	720.000 (21.000–1.670.000)
<b>Genotype</b>	
1a	22 (42.3%)
1b	5 (9.6%)
2	3 (5.8%)
3	17 (32.7%)
4	5 (9.6%)
<b>Staging (Metavir score)</b>	
F0	6 (11.5%)
F1	13 (25%)
F2	7 (13.5%)
F3	15 (28.8%)
F4	11 (21.2%)
<b>Clinical cirrhosis (n, %)</b>	11 (21.2%)
<b>Child Pugh stage (n, %) (among clinical cirrhosis)</b>	
A	11 (100%)
<b>MELD (among clinical cirrhosis) (median, IQR)</b>	9 (6–13)
<b>Antiviral therapy</b>	
Sofosbuvir-Ledipasvir	10 (19.2%)
Sofosbuvir-Ribavirin	2 (3.8%)
Sofosbuvir-Daclatasvir	13 (25%)
Sofosbuvir-Velpatasvir	17 (32.7%)
Glecaprevir-Pibrentasvir	9 (17.3%)
Sofosbuvir-Simperevir	1 (2%)
<b>CDC Classification System for HIV Infection</b>	A: 15 (28.9%) B: 21 (40.4%) C: 16 (30.7%)
<b>HIV-RNA (copies/mL, median, IQR)</b>	532.380 (65.180–1.370.000)
<b>Lymphocytes (cell/<math>\mu</math>L, median, IQR)</b>	1190 (160–1980)
<b>CD4+ pre-DAA (cell/<math>\mu</math>L, median, IQR)</b>	724 (203–1656)
<b>Albumin (g/dl; median, IQR)</b>	3.5 (2.4–4.1)
<b>Platelets (elements/<math>\mu</math>L; median, IQR)</b>	157.000 (73.000–342.000)
<b>INR (median, IQR)</b>	1.1 (0.7–1.5)
<b>ALT (IU/l, median, IQR)</b>	69 (26–153)
<b>AST (IU/l, median, IQR)</b>	62 (23–132)
<b>Tot. Bil. (mg/dl; median, IQR)</b>	1.1 (0.7–1.7)

**Abbreviations:** INR, International Normalized Ratio; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

**Table 2** CD4+ T Cell Count in Patients with HIV-HCV Coinfection by Pre-DAA, by SVR12 and by SVR48

Total HIV/HCV co- Infected (52)	Nadir CD4*	CD4 pre-DAA*	CD4 SVR12*	CD4 SVR48*
A1 (0)				
A2 (6)	363 (307–460)	774 (355–1656)	800 (558–1815)	780 (542–1720)
A3 (9)	126 (93–157)	426 (203–1027)	438 (201–721)	421 (117–725)
B1 (2)	544 (418–670)	1011 (971–1051)	1018 (951–1085)	1039.5 (989–1090)
B2 (7)	254 (201–300)	1139 (663–1397)	1123 (695–1729)	1008 (681–1120)
B3 (12)	110,5 (16–195)	620 (346–962)	626.5 (355–1103)	646.5 (402–925)
C1 (0)				
C2 (1)	311	854	742	845
C3 (15)	106 (8–190)	475 (332–790)	468 (220–853)	504 (246–853)
	190 (16–670)	724 (203–1656)	684 (201–1815)	713 (117–1720)
<b>HIV/HCV co-infected without cirrhosis (39)</b>				
A1 (0)				
A2 (4)	363 (307–460)	896 (774–1656)	880 (800–1815)	901 (780–1720)
A3 (6)	194 (93–157)	675 (319–1027)	698 (387–622)	
B1 (2)	544 (418–670)	1011 (971–1051)	1018 (951–1085)	1039.5 (989–1090)
B2 (6)	255,5 (191–300)	999,5 (663–1397)	980 (695–1729)	1012 (681–1120)
B3 (11)	101 (16–195)	688 (346–962)	679 (355–1103)	724 (402–925)
C1 (0)				
C2 (1)	311	854	742	845
C3 (10)	62,5 (8–190)	506 (332–790)	480.5 (220–846)	497.5 (273–853)
	225 (8–670)	771 (319–1656)	720 (220–1815)	783 (273–1720)
<b>HIV/HCV co-infected with Cirrhosis (12)</b>				
A1 (0)				
A2 (2)	559 (355–408)	566 (355–422)	574 (558–590)	571.5 (542–601)
A3 (3)	125 (117–155)	390 (203–524)	438 (201–721)	421 (117–725)
B1 (0)				
B2 (1)	254	1139	1148	848
B3 (1)	187	483	601	569
C1 (0)				
C2 (0)				
C3 (5)	140 (88–159)	436 (351–696)	353 (310–853)	504 (246–715)
	220 (88–408)	554.5 (203–696)	587.5 (201–853)	570.5 (117–725)

**Notes:** \*Quantitative data are expressed as median and IQR in brackets. SVR12 weeks and SVR48 weeks.

infected patients from those without cirrhosis and those with liver cirrhosis. In particular, co-infected patients without liver cirrhosis had pre-DAA CD4 + counts equal to 771 (319–1656), while at SVR12 and SVR48 CD4 + counts, respectively, equal to 720 (220–1815) and 783 (273–1720) (OR for CD4+ count in patients without cirrhosis: 1.1, 95 CI (0.7–1.4) pre-treatment vs post-treatment at SVR12; p: 0.420 and OR for CD4+ count: 1.2, 95 CI (0.9–1.3) pre-treatment vs post-treatment at SVR48; p: 0.470) (Table 2). Instead, co-infected patients with liver cirrhosis had pre-DAA CD4 + counts equal to 554.5 (203–696), while at SVR12 and SVR48 CD4 + counts, respectively, equal to 587.5 (201–853) and 570.5 (117–725) (OR for CD4+ count in patients with cirrhosis: 1.2, 95 CI (0.8–1.3) pre-treatment vs post-treatment at SVR12; p: 0.360 and OR for CD4+ count: 1.1, 95 CI (0.7–1.4) pre-treatment vs post-treatment at SVR48; p: 0.380) (Table 2).

## Discussion

Our clinical experience confirmed the prevalence of genotype 1 among the enrolled patients, but at the same time the high prevalence of genotype 3 among co-infected patients was highlighted, probably due to the risk factors of this category of patients, in particular, intravenous drug abuse. Indeed, it is known in the literature that genotype 3 is often associated with patients with a history of intravenous drug abuse.<sup>14–17</sup>

From our data, it emerged that most of the patients with HIV/HCV co-infection had an advanced stage of liver disease, in particular, 50% of the enrolled patients had an advanced stage of liver disease (15 with F3 and 11 with liver cirrhosis).

In all patients, we observed that the CD4+ T cell count at baseline did not show significant variations compared to SVR12 and SVR48 time figures (724 vs 684, vs 713, respectively; see Table 2). We also assessed CD4 count in relation to HIV categories and stage of liver disease, see Table 2. Also, based on the assessments of the subclasses considered, there were no significant changes in the CD4 + T cell count. These data agreed with the study conducted by ICONA Foundation Studio, in which it was highlighted that the eradication of HCV infection after treatment with DAAs showed no impact on CD4 T cell counts.<sup>11</sup> Also, in evaluating the impact of the eradication of HCV infection on the CD4 + count, distinguishing the co-infected patients without liver cirrhosis from those with no change in the CD4 + count was evident. These data contrasted with what was observed by Girón Ortega et al that observed an improvement in CD4 T cell counts only in co-infected patients without liver cirrhosis.<sup>9</sup>

Moreover, our study has some important limitations, in particular, the small sample size and the limited observation in time. In light of what has been reported, we believe that it is essential to deepen this topic with further studies that involve a larger sample and that consider an observation longer in time.

## Conclusions

Our study shows that viral eradication obtained with DAAs in patients with HIV-HCV coinfection is not associated with significant changes in the CD4 + T cell count, regardless of CDC category and stage of liver disease. Further studies with larger sample size are necessary to confirm these data.

## Disclosure

The authors report no conflicts of interest in this work.

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