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RESEARCH LETTER

Sustained virological response after treatment with direct-acting antivirals can help immune reconstitution in HIV-HCV coinfected patients even in case of persistent HIV low-level viremia

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1 | INTRODUCTION

HCV infection promotes both a specific immune response against HCV and a nonspecific immune activation, which is more severe in HIV-positive subjects: serum biomarkers of inflammation, bacterial translocation, and endothelial disfunction are significantly higher in case of HIV-HCV coinfection with respect to HIV monoinfection and a significant decrease occurred in case of HCV clearance.[1,2] Once HCV is eradicated, the HIV involvement in the inflammatory process leading to liver fibrosis may disappear.[3] Low-level plasma HIV viremia is a parameter that can be related to immune activation[4-7]: the threshold value in copies/mL is object of great debate. Lesko et al[8] reported in a recently published work that common choices below which HIV viral load will be considered suppressed are 20, 50, 200, or 400 copies/mL and even higher plasma HIV-RNA levels were reported.[4,9] The clinical implications of low-level viremia are still not fully clear because of the differences in populations studied and in study designs but virological failure was associated to the detection of plasma HIV-RNA values between 201 and 500 copies/mL.[9-11] Now, direct-acting antiviral (DAA) therapy allows HCV eradication in over 95% of HIV-HCV coinfected subjects after a short treatment period. Hence, the treatment of HCV infection can be considered a simple clinical model of inflammatory status regression.[2]

The aim of this retrospective longitudinal study was to evaluate the influence of HCV-RNA clearance at SVR12 (persistently negative HCV-RNA at 12 weeks after completion of therapy) on CD4+ and CD8+ cell count and percentage and HIV virologic control.

2 | METHODS

The study population included HIV-1 infected adults with chronic HCV infection who were treated with DAA and achieved SVR12. Inclusion criteria were the availability of three plasma HIV-RNA determination by year at least in the 2 years before anti-HCV treatment started, a successful virologic control of HIV (defined as no plasma HIV-RNA value >200 copies/mL in the 2 years before anti-HCV treatment started), and plasma HIV viremia tested within a week from SVR 12. Patients who responded to the inclusion criteria were further classified as undetectable patients (Up) when plasma HIV-RNA was

TABLE 1 Main characteristics of the 104 HIV-HCV patients included in the study according to plasma HIV viremia control (Up: patients with undetectable plasma HIV viremia patients with plasma HIV-RNA undetectable in the 2 years before beginning the DAA treatment; LLVp: patients with low-level HIV viremia in the 2 years before beginning the DAA treatment

	Up (45 patients)	LLVp (59 patients)
Males, n (%)	32 (71.1)	44 (74.6)
Age[a] (years)[b]	53 (50-54)	53 (49-55)
CD4+ cell count at nadir (cells/mm^3) [b]	202 (86-296)	197 (86-306)
ART modified before anti-HCV therapy, n (%)	28 (62.2)	29 (49.2)
Pretreatment with HCV-RNA (IU/mL)[b]	1 320 000 (430775-3 372 446)	1 850 000 (402882-4 820 750)
Patients with F3-F4 fibrosis, n (%)	24 (53.3)	29 (49.2)
Patients treated with InSTI at HCV treatment start, n (%)	21 (46.7)	19 (32.2)
Patients treated with InSTI + PIs at HCV treatment start, n (%)	5 (11.1)	3 (5.1)
Patients treated with NNRTIs at HCV treatment start, n (%)	8 (17.8)	14 (23.7)
Patients treated with NRTIs at HCV treatment start, n (%)	0	1 (1.7)
Patients treated with PIs at HCV treatment start, n (%)	11 (24.4)	22 (37.3)

Abbreviations: ART, antiretroviral therapy; InSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.
[a]At HCV treatment start.
[b]Median and IQR range.

undetectable in the 2 years before the beginning of DAA treatment and as low-level viremia patients (LLVp) otherwise. A sub-analysis based on a lower viremia threshold (very low-level viremia, <40 copies/mL) was performed in LLVp. Study times: 24-month period before the start of anti-HCV treatment, including pre-DAA start (T0) and SVR12. The choice of ART and anti-HCV regimens was up to the discretion of the treating physician. CD4+ and CD8+ cell count and percentage were evaluated by flow-cytometry analysis; HIV-RNA and HCV-RNA viral loads were tested with a commercial quantitative PCR method. This study is a retrospective observational study and was approved by the local Ethic Committee: patients gave their informed consent and all data were anonymized prior to research use. Chi-squared test, Fisher's exact test, Mann-Whitney test, and Wilcoxon test were used as appropriate. Continuous variables were described as median and interquartile range (IQR) and categorical variables as absolute numbers and percentage. Statistical analysis was performed using MedCalc Statistical Software version 19.1 (MedCalc Software by Ostend, Belgium). A P value <.05 was considered statistically significant.

3 | RESULTS

Overall, 198 patients achieved SVR12, 104 patients complied with all the inclusion criteria, and 94 were excluded (Figure S1). All the patients were Caucasian and HBsAg negative. Overall, median CD4+ cell count was 621 cells/mm^3 (IQR 443-846 cells/mm^3) and median nadir value of 198 cells/mm^3 (IQR 87-301 cells/mm^3): 59 (56.7%) were LLVp and 45 were Up (43.3%).The main viroimmunological characteristics and prescribed ART were comparable in the two groups of patients (Table 1); DAA regimen is described in Table S1. The interval between the last plasma HIV-RNA testing and the start of anti-HCV therapy was 4 weeks (median value, IQR 2-5 weeks).

Patients with undetectable plasma HIV viremia at the anti-HCV treatment start and in the 2 years before (undetectable patients, Up) were 45 while patients who experienced plasma HIV viremia <200 copies/mL in the same study points were 59.

At SVR 12, 35 (77.8%) out of the 45 Up had undetectable plasma HIV viremia, 9 (20%) had detectable plasma HIV viremia <200 copies/mL, and 1 (2.2%) patient had plasma HIV viremia >200 copies/mL; 30 (50.8%) out of the 59 LLVp had undetectable plasma HIV viremia while 29 (49.2%) had detectable plasma HIV viremia <200 copies/mL.

Of the 59 LLVp, 39 (66.1%) had all plasma HIV-RNA values <40 copies/mL before anti-HCV treatment start: 23 (58.9%) of them had undetectable HIV viremia at SVR12, a frequency higher than that found in the 20 LLVp patients with at least one plasma HIV-RNA value >40 copies before anti-HCV treatment start (35%, seven patients). HCV clearance is not associated with any modification in median CD4 or CD8 absolute cell count and percentage at SVR12 in Up, while LLVp who had HIV-RNA undetectable at SVR12 showed a significant increase in median CD4+ cell count and percentage (658, IQR 398-829 CD4+ cell count/mm^3 vs 728, IQR 487-976 CD4+ cell

count/mm^3 and 33, IQR 28.5-39 CD4+ cell percentage vs 34, IQR 27.5-40.1 CD4+ cell percentage. Interestingly, LLVp with RV at SVR12 showed an increase in median CD4+ cell count/mm^3 (578, IQR 505-827 CD4+ cell count/mm^3 vs 659, IQR 498-951 CD4+ cell count/mm^3) and percentage, this last one significant (31, IQR 24.2-35.7 CD4+ cell percentage vs 32, IQR 24-38.5 CD4+ cell percentage, P = .01). The increase was significant for median CD4+ cell count and percentage when the analysis was made including only LLVp who had HIV-RNA <40 copies at SVR12 (588 CD4+ cells/mm^3, IQR 560-776 CD4+ cells/mm^3 vs 689 CD4+ cells/mm^3, IQR 548-980 CD4+ cells/mm^3, P = .02 and 31%, IQR 25-36% vs 31%, IQR 27-40%, P = .02). A complete description of CD4+ and CD8+ cell counts and percentages are reported in Table S2. The proportion of subjects who achieved HIV-RNA undetectability was comparable in those who modified ART and in those who did not both in Up (82.1% and 70.6%, respectively) and in LLVp (51.7% and 50%, respectively).

4 | DISCUSSION

The present study included two groups of HIV-HCV patients comparable for all the variables tested but with stable RV or stable HIV-RNA undetectability. We observed a favorable and fast effect of HCV-RNA clearance on the immunovirologic asset, and we supposed that the underlying mechanism in immunoactivation status decreases. The first main result observed was the increase of CD4+ cell count and percentage (significant for this parameter) in LLVs with detectable HIV viremia at SVR12. The difference was significant for both CD4+ number and percentage in the analysis restricted to patients with plasma HIV-RNA always <40 copies/mL. These results suggested that HCV clearance seemed to have a favorable impact on CD4 recovery regardless of the persistence of low-level HIV viremia and with more significant effects in case of lower HIV-RNA loads. Many markers of immune recovery were studied and not all of them were evaluated in clinical practice: absolute CD4 positive cell count is the parameter included in almost all published definitions of immunological responder and that is why we focused on it and on CD4+ cells percentage.[12] Our results are in accordance with those published by Doyle et al[13] on 23 patients, and with no data on CD4 cell count percentage; the reasons for these data may be the evidence that patients cured for HCV and with low-level HIV viremia (with the cut-off of 40 copies/mL and 50 copies/mL, respectively) had monocyte activation comparable to that of subjects with HIV monoinfection and normal ranges of pro-inflammatory and regulatory cytokines.[14,15]

The lower levels of T-cell activation described in patients with undetectable plasma HIV viremia with respect to those with detectable plasma HIV-RNA[16] could be the basis for the second main result of our study; about half the subjects with RV achieved HIV-RNA undetectability at SVR12. We could report these data because our study design distinguished patients with detectable plasma HIV viremia (even at low copy number) and those with a negative result, differently from previously published works, including HIV-HCV patients successfully treated with DAA, that define HIV suppression as having a plasma HIV-RNA lower than 50 copies/mL.[17,18] The percentage of subjects who achieved complete HIV viremia suppression was higher than that observed in a previous study including a lower number of patients.[19]The choice of SVR12 in the present study instead of a 24-week interval from anti-HCV treatment start may justify the different result and reinforce our hypothesis even though we cannot exclude that some patients could have a detectable but not quantifiable HIV-RNA if retested. However, a higher adherence to ART during DAA treatment should be taken into account as well.[20] We are aware that only slight differences in viroimmunological parameters were reported but, on the other hand, the patients included were immunocompetent and with an ongoing antiretroviral treatment, even if with a different level of virological suppression.

The current study has some limitations and strengths: the former are the retrospective study design and the numerosity of the four groups of patients, while the latter are the availability of plasma HIV-RNA data obtained in the 2 years before the start of the anti-HCV treatment to classify the HIV virologic control of the patients and the clinical practice approach.

In conclusion, we observed a positive influence of HCV cure in patients with low-level plasma HIV viremia before anti-HCV treatment start, possibly because of a reduction of immune activation: this is a preliminary study and these results should be confirmed after a longer follow-up.

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CONFLICT OF INTEREST

The authors declare no conflict of interest for this article.

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All Authors had read and approved the final version of the manuscript.

Saverio Giuseppe Parisi had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

Saverio Giuseppe Parisi confirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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