

Improvement of patients reported outcomes and neurocognitive performances after Direct-Acting Antivirals: a longitudinal study

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ABSTRACT:

- **Background:** HCV chronic infection may affect Patient-Reported Outcomes (PROs) and HCV related neuroinflammation might correlate with neurocognitive performances (NCP) dysfunction.
- **Patients and methods:** A prospective observational study on HCV infected patients treated with direct-acting antivirals (DAA) was conducted at the University Department of Infectious and Tropical Diseases of Brescia, ASST Spedali Civili General Hospital (Italy) from October 2017 to June 2018. Data were collected at baseline (BL), end of treatment (EOT) and 12 weeks after EOT (FU12W). PROs were evaluated with Chronic Liver Disease Questionnaire (CLDQ), Fatigue Severity Scale (FSS), Visual Analogue Fatigue Scale (VAFS) and Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH). Montreal Cognitive Assessment (MoCA) test evaluated NCP. Exclusion criteria were: HIV infection with CD4+ nadir <200 cell/ μ L or encephalopathy, current alcohol or drug abuse and severe psychiatric disorders. Population features were analysed to identify factors related to PROs and NCP. Statistical significance was considered with p -value<0.05. .
- **Results:** 76 patients (60.5% males) were analysed: mean age was 60.7, 29 (38.1%) had advanced fibrosis, 6 (7.9%) were HIV/HCV co-infected, 18 (23.6%) took polytherapy (≥ 5 drugs), ribavirin (RBV) was added in 10 cases (13.1%). Improvements were registered in all questionnaires at FU12W, with significant changes in CLDQ, VAFS and MoCA. Quality of life (QoL) was lower in women and the elderly. RBV assumption temporarily affected QoL and fatigue. Female sex, age and polytherapy were related to worse NCP. HIV/HCV co-infection and fibrosis did not affect scores.
- **Conclusions:** DAA seem to be associated with improvement in PROs and NCP, regardless of fibrosis and HIV/HCV co-infection. These aspects must be considered in real settings, particularly in specific populations including women, the elderly or those assuming polytherapy.
- **Keywords:** HCV, Direct-Acting Antivirals (DAAs), Patients reported outcomes (PROs), Neurocognitive performances, HIV/HCV coinfection.



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INTRODUCTION

HCV chronic infection can lead to serious complications such as cirrhosis, hepatocarcinoma and liver failure, but it is also implicated in the onset of many relevant extra-hepatic manifestations. In particular 50% of HCV infected people complain of neurocognitive performance (NCP) alterations and neuropsychiatric disorders¹. Quality of life (QoL) is a multidimensional concept expressing the satisfaction for physical, mental, emotional and social wellness state. Several studies demonstrated that HCV infected patients reported a worsening in Health Related QoL (HRQoL), which is related to HCV clinical manifestations and to the concern due to the knowledge of infection and to stigma perception. HIV/HCV co-infection seems to be a detrimental factor. HRQoL is independent from disease severity, but sustained virological response (SVR) allows an improvement in life satisfaction. Factors related to this improvement are virus suppression and resolution of symptomatic and psychological legacy²⁻⁴. One third of patients with hepatitis C reported impairments in concentration, attention, memory, learning, executive functions and general psychomotor decline. The most frequent symptom is mental and physical fatigue referred by 53-80% of patients. These alterations are independent from hepatic fibrosis degree and there is evidence supporting that HCV can penetrate into Central Nervous System (CNS), causing local inflammatory response^{4,5} and giving a direct contribution to the development of cognitive and psychiatric disturbs. Patients with low cognitive reserve are more susceptible^{2,4,5,6}, neuropsychiatric disorders have been reported in up to 50% of chronic HCV infected patients. Both the central and peripheral nervous system may be involved with a wide variety of clinical manifestations. Main HCV-associated neurological conditions include cerebrovascular events, encephalopathy, myelitis, encephalomyelitis, and cognitive impairment, whereas "brain fog", depression, anxiety, and fatigue are at the top of the list of psychiatric disorders. Moreover, HCV infection is known to cause both motor and sensory peripheral neuropathy in the context of mixed cryoglobulinemia, and has also been recently recognized as an independent risk factor for stroke. These extrahepatic manifestations are independent of severity of the underlying chronic liver disease and hepatic encephalopathy. The brain is a suitable site for HCV replication, where the virus may directly exert neurotoxicity; other mechanisms proposed to explain the pathogenesis of neuropsychiatric disorders in chronic HCV infection include derangement of metabolic pathways of infected cells, alterations in neurotransmitter circuits, autoimmune disorders, and cerebral or systemic inflammation. A pathogenic role for HCV is also suggested by improvement of neurological and psychiatric symptoms in patients achieving a sustained virologic response following interferon treatment; however, further ad hoc trials are needed to fully assess the impact of HCV infection and specific antiviral treatments on associated neuropsychiatric disorders. Core tip: High prevalence of neuropsychiatric disorders has been reported in

chronic hepatitis C virus (HCV⁷ and predisposing factors are age, female sex and scarce social life^{6,7}. hepatitis C virus (HCV⁴. HCV infected patients have an increased risk of psychiatric disorders such as depression, anxiety, compulsive behaviour, insecurity, aggression, phobias and psychosis^{1,2}. Patients also refer sensation of brain fog, sexual dysfunction, emotional stress and insomnia³. Some patients showed an alteration in dopaminergic and cholinergic transmission, which can be related to psychiatric symptoms⁸. Finally HIV patients, particularly those co-infected with HCV worsened neurocognitive disorders⁹⁻¹¹. The introduction of Direct Acting Antivirals (DAA) led to an important innovation in hepatitis C treatment due to their efficacy and few side effects. In particular DAA have no impact on CNS while pegylated interferon (PegINF) may affect cerebral activity increasing the production of inflammatory cytokines (IL-6 and TNF- α) and influencing the release of neurotransmitters like serotonin and dopamine worsening cognitive abilities and, consequently, HRQoL^{12,13}. The resolution of systemic inflammatory state after SVR improves extra-hepatic complications¹⁴⁻¹⁶ and may allow resolution of neuropsychiatric and cognitive disorders with an improvement in HRQoL^{3,17}.neuropsychiatric disorders have been reported in up to 50% of chronic HCV infected patients. Both the central and peripheral nervous system may be involved with a wide variety of clinical manifestations. Main HCV-associated neurological conditions include cerebrovascular events, encephalopathy, myelitis, encephalomyelitis, and cognitive impairment, whereas "brain fog", depression, anxiety, and fatigue are at the top of the list of psychiatric disorders. Moreover, HCV infection is known to cause both motor and sensory peripheral neuropathy in the context of mixed cryoglobulinemia, and has also been recently recognized as an independent risk factor for stroke. These extrahepatic manifestations are independent of severity of the underlying chronic liver disease and hepatic encephalopathy. The brain is a suitable site for HCV replication, where the virus may directly exert neurotoxicity; other mechanisms proposed to explain the pathogenesis of neuropsychiatric disorders in chronic HCV infection include derangement of metabolic pathways of infected cells, alterations in neurotransmitter circuits, autoimmune disorders, and cerebral or systemic inflammation. A pathogenic role for HCV is also suggested by improvement of neurological and psychiatric symptoms in patients achieving a sustained virologic response following interferon treatment; however, further ad hoc trials are needed to fully assess the impact of HCV infection and specific antiviral treatments on associated neuropsychiatric disorders. Core tip: High prevalence of neuropsychiatric disorders has been reported in chronic hepatitis C virus (HCV¹⁸. In this study we aimed to evaluate impact of DAA on Patients Reported Outcomes (PROs), which include HRQoL, fatigue, daily activities and work performance, and on NCP in HCV mono-infected and HIV/HCV co-infected patients, in order to identify possible category risk patients.

PATIENTS AND METHODS

Setting and Patients

We evaluate a population of HCV infected people treated with DAAs at the University Department of Infectious and Tropical Diseases, University of Brescia and ASST Spedali Civili General Hospital of Brescia, Italy, from October 2017. Patients were followed for three months after the end of treatment; the global follow up ended in June 2018. We evaluated the impact of treatment on PROs and NCP. The evaluations were made at baseline (BL), end of treatment (EOT) and 12 weeks after the end of treatment (FU12W). Population features were analysed to identify potential outcome predictive factors. This study included HCV infected patients older than 18 years-old. Patients with HIV/HCV co-infection with nadir of CD4+ <200 cell/ μ L or HIV related encephalopathy, alcohol abuse (>1 litre/day), current drug abuse, severe psychiatric disorders (schizophrenia, bipolar disorder) were excluded.

Questionnaires

Four questionnaires were administered at BL, EOT and FU12W to every patient to evaluate PROs. Chronic Liver Disease Questionnaire (CLDQ) examined HRQoL with 28 questions, grouped in categories (abdominal symptoms, fatigue, systemic symptoms, activities, emotional function, worry). Higher scores were related to better HRQoL¹⁹. Fatigue Severity Scale (FSS) and Visual Analogue Fatigue Scale (VAFS) were used to evaluate fatigue in daily activities. In FSS questionnaire higher scores indicate higher fatigue, which is serious with values ≥ 4 ²⁰. VAFS is a visual numeric scale in which scores are reported in millimetres. Lower scores represent high levels of fatigue. Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) estimates the impact of the disease on daily and work activities²¹. Scores are expressed as percentage and increase in the score indicates worse results. Presenteeism is calculated on worked hours, where a greater number of hours mean a reduction in work efficiency. Montreal Cognitive Assessment test (MoCA) was used to establish patients' NCP. High scores indicate better levels of brain functions; normal score is ≥ 26 .

Statistical Analysis

Sample characteristics were summarised as absolute frequencies and percentages in case of categorical variables or with means and standard deviations if continuous variables. Questionnaires mean scores and relative 95% confidence intervals (95%CI) were estimated over time using Linear Mixed Models considering patient as *random effect* and time as the fixed effect of the model. Mean scores were also estimated using the same models also adjusting for sex, HIV-infection, fibrosis, use of ribavirin, polytherapy, age and transaminases (one model

for each covariate) as interaction with time. Since the WPAI:GH questionnaire produces factors expressed on percentage scale, the outcome was modelled through Generalized Linear Mixed Models using a Beta distribution with logit link function. All statistical analyses were performed assuming a level of significance of 5% and using the statistical software R (version 3.5.1).

Ethics

The Ethic Committee of ASST Spedali Civili General Hospital of Brescia approved this study. All patients included signed an informed consent.

RESULTS

The participation in the study was proposed to all patients who started DAA during the enrolment period: 76 patients were enrolled (Figure 1). The study population is described in Table 1. DAA regimens used were: Grazoprevir/Elbasvir (GRZ/EBR) in 21 patients (27.6%), Sofosbuvir/Velpatasvir (SOF/VEL) in 31 (40.8%), Ombitasvir/Paritaprevir/Ritonavir+Dasabuvir (OMB/PAR/RIT+DAS) in 22 (28.9%) and Ombitasvir/Paritaprevir/Ritonavir (OMB/PAR/RIT) in 2 (2.6%). RBV was added in 10/76 cases (13.1%) according to current recommendations²². In HIV/HCV population 3/6 patients were treated with SOF/VEL. GRZ/EBR, OMB/PAR/RIT+DAS, OMB/PAR/RIT were administered to one patient each. RBV was added in 3 cases. Nobody interrupted the treatment prematurely. One patient relapsed 17 weeks after EOT. At BL every patient completed all questionnaires.

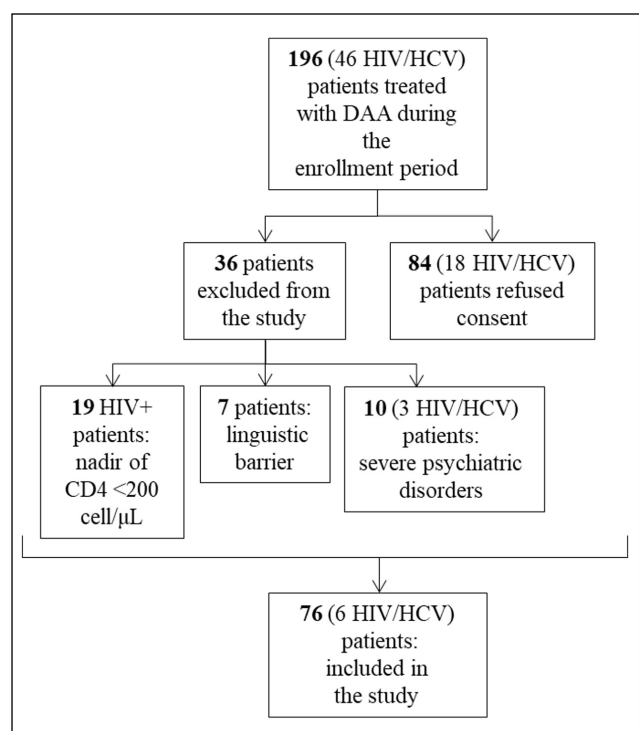


Figure 1. Flow chart of the patients included in the study.

Table 1. Study population.

Study Population	
Males	46 (61%)
Females	30 (39%)
Age (years)	60.7 [46.9-74.5]
HIV/HCV co-infection	6/76 (7.9%)
HCV Genotype	
1	50 (65.8%)
1a	10 (13.1%)
1b	39 (51.3%)
1a/1b	1 (0.1%)
2	11/76 (14.5%)
3	9/76 (11.8%)
4	6/76 (7.9%)
Drugs	
≥5/day (Polytherapy)	18/76 (23.7%)
<5/day	58/76 (76.3%)
Liver fibrosis	
F0-F2	47/76 (61.8%)
F3-F4	29/76 (38.1%)
HIV/HCV population	
Males	3 (50%)
Females	3 (50%)
Age	53.8 [49.5-58.1]
T-lymphocytes CD4+ (cell/μl)	814.8 [305.8-1323.8]
HIV RNA ≥50 cp/ml	0/6 (0%)
HCV Genotype	
1 (1a)	1/6 (17%)
2	0/6 (0%)
3	3/6 (50%)
4	2/6 (33%)
Polytherapy	1/6 (17%)
F0-F2	4 (67%)
F3-F4	2 (33%)

*Chi-square or Mann-Whitney U test as appropriate. MSM: man who have sex with man; PWID: people who inject drugs; IQR: interquartile range.

At EOT, 2 patients did not complete MoCA. At FU12W, 19 patients dropped out the study and one patient did not complete MoCA. Aggregate results are shown in Table 2.

CLDQ Result

There was a significant gain (*p*-value 0.0001) in CLDQ total score from BL to EOT and from BL to FU12W (Table 2). Every item increased but fatigue, systemic symptoms, worry and emotional function reported a statistically significant increase. Systemic symptoms worry and fatigue scores statistically increased over time while emotional function reached a statistically significant increase at FU12W. RBV use negatively affected CLDQ only at EOT, but not at FU12W. Scores in women were statistically lower than males, but they had the same time trend, and for this reason, interaction was not statistically significant. No differences were found due to polytherapy but assumption of ≥5 medication was linked to lower values and to a less significant increase in scores. Age had no impact on the total score (Table 3).

FSS Results

Total score decreased over time, without statistical significance (Tables 1-4).

VAFS Results

Total score statistically increased both at EOT and at FU12W (*p*<0.0001) (Table 2). None of the considered variables significantly affected the score at each time considered (Table 5). RBV caused a decrease in the score at EOT, but not at FU12W. Polytherapy correlated with lower scores.

WPAI:GH Results

Workers were 26/76 (34.2%) at BL, 28/76 (36.8%) at EOT and 17/57 at FU12W (29.8%). No statistically significant differences were found (Table 2) and no analysis adjustment was performed due to the large number of missing data. However, it is important to highlight that absenteeism, presenteeism and work activity worsened at the EOT, but improved at FU12W. The impact of the disease on daily activities decreased progressively.

MoCA Results

At BL 68.4% (52/76) of patients had a score ≤25. Patients with a score lower than normality decreased at EOT (58.6%-42/74) and at FU12W, reaching 48.2% (27/56). Score of global study population remained constant between BL and EOT, while at FU12W it showed a significant increase (*p* = 0.0009). Women had statistically lower scores than men. Patients taking <5 drugs had better performances than those who received polytherapy. Older age was related to a decrease in the score (*p* = 0.0002) (Table 6).

DISCUSSION

The present study showed that effective treatment with DAA is associated with improvement in PROs and NCP, regardless of fibrosis degree and HIV/HCV co-infection. PROs are indicators of direct patient experience of HCV chronic infection and its treatment. Given the evidence about the invasion and the effect of HCV on CNS^{4,23}, this study also examined NCP. In the present study, there was an improvement in all questionnaires at FU12W compared to BL. HRQoL assessed with CLDQ questionnaire improved significantly: the increase was already evident at EOT and was accentuated at FU12W (both *p* <0.0001)^{15,24}. These results could also be obtained with pegIFN-based therapies^{12,17,25}, but, if pegIFN caused a reduction in PROs especially during the first 12-24 weeks of therapy, regimens including DAA and RBV/pegIFN-free may result in improvement in outcome very early during treatment²⁶⁻²⁹. The worry is the item that re-

Table 2. Averages (CI 95%) of the scores at BL, EOT and FU12W with difference in the averages of the scores at EOT and FU12W, compared to BL and relative *p*-values.

TEST	BL	EOT	FU12W	MeanΔ BL-EOT	MeanΔ BL-FU12W	<i>p</i> -value EOT vs BL	<i>p</i> -value FU12W vs BL
CLDQ-Abdominal symptoms	5.7 [5.4;6]	6 [5.7;6.2]	5.9 [5.6;6.2]	+0.3	+0.2	0.073	0.15
CLDQ-Fatigue	4.7 [4.4;5]	5.1 [4.8;5.4]	5.4 [5.1;5.7]	+0.4	+0.7	0.004	<0.0001
CLDQ-Systemic symptoms	5.2 [5;5.5]	5.6 [5.4;5.9]	5.6 [5.3;5.9]	+0.4	+0.4	0.0004	0.003
CLDQ-Activity	5.7 [5.5;6]	6 [5.8;6.3]	5.8 [5.6;6.1]	+0.3	+0.1	0.020	0.52
CLDQ-Emotional function	5.3 [5;5.5]	5.5 [5.2;5.7]	5.7 [5.4;5.9]	+0.2	+0.4	0.13	0.002
CLDQ-Worries	5.4 [5.2;5.6]	6.1 [5.9;6.4]	6.1 [5.8;6.4]	+0.7	+0.7	<0.0001	<0.0001
Total Score CLDQ	5.3 [5.1;5.5]	5.7 [5.5;5.9]	5.8 [5.5;6]	+0.4	+0.5	<0.0001	<0.0001
FSS	3.8 [3.4;4.2]	3.6 [3.2;4]	3.6 [3.1;4]	-0.2	-0.2	0.34	0.27
VAFS	57.6 [52.5;62.7]	66.8 [61.8;71.9]	71.7 [66;77.3]	+9.2	+14.1	<0.0001	<0.0001
WPAI:GH-Absenteeism	9.6% [5.5;16.2]	11.5% [5.4;23.1]	9.3% [4.0;20.3]	+1.9%	-0.3%	0.50	0.93
WPAI:GH-Presenteeism	18.8% [11.3;26.9]	19.6% [9.7;35.5]	16.2% [7.3;32.1]	+0.8%	-2.6%	0.71	0.76
WPAI:GH-Work productivity reduction	19.7% [13.3;28.2]	23.7% [12.9;39.5]	17.9% [8.7;33.5]	+4.0%	-1.8%	0.44	0.74
WPAI:GH-Daily activity reduction	21.6% [6.9;33.5]	19.9% [9.9;36.1]	17.6% [6.9;38.0]	-1.7%	-4.0%	0.74	0.52
MoCA	23.9 [23;24.7]	24.3 [23.5;25.2]	25.1 [24.2;26]	+0.4	+1.2	0.17	0.0009

corded a particularly significant increase in our study. Along with other studies^{30,31} our results demonstrated how influential is the awareness of having a chronic disease and, consequently, its treatment on a person's well-being. Moreover, during treatment and even more with SVR, fatigue tended to decrease in CLDQ. FSS and VAFS, which analyse this symptom specifically, confirmed this result. Fatigue was the most frequent side effect of pegINF-regimens; DAA did not present this side effect and caused an early improvement in fatigue. Our results are consistent with other studies^{18,32}. Another PRO that is normally considered is work productivity³³. Work productivity is strongly influenced by presentism³⁴ because the increase in work hours must be interpreted as deterioration in work performances. Compared to HCV-negative workers, among HCV-positive subjects absenteeism is higher, productivity decreases significantly and the overall costs (direct and indirect) due to HCV infection are greater³⁵⁻³⁷. Evaluating the trend over time, we noticed a slight worsening in presentism, absenteeism and work productivity at EOT. In the literature, similar results were found with pegIFN and RBV therapies, due to their side effects, but not with DAA^{28,38}. In our opinion, the worsening reported at EOT is really due to RBV, in fact the items tended to improve on FU12W, when the side effects of RBV were

resolved, as seen in other studies^{26,27,39}. Performances in daily activities reported a gradual improvement at EOT and at FU12W. Finally, we analysed NCP variation with MoCA. In previous studies controversial results on NCP were reported due to the use of pegINF, but most studies reported worsening of neurocognitive faculties during treatment^{13,40-45} with subsequent improvement after SVR^{46,47}. Although other evidence is still scarce⁴⁸, in our analysis, it was found that DAA therapy, due to the absence of side effects on CNS, and the SVR, had a positive effect on brain functions.

Many patient-related factors could influence the scores. Female sex was a pejorative factor for HRQoL and cognitive faculties, but did not seem to influence the score trend over time. Female sex had already been related to a worse HRQoL in numerous other studies, regardless of therapeutic regimen used^{27,49-52}. In our study MoCA results were also influenced by sex. The women recruited in the study had a higher average age than men and, considering that NCP tend to worsen with increasing age, it is likely that the greatest cognitive impairment reported by women may depend on this factor. Unfortunately, no multivariate analysis was performed to verify this hypothesis. In addition, 80% of women (24/30) but only 72% of men (33/46) have studied for ≤ 12 years: this difference

Table 3. Average (CI 95%) of the overall score of CLDQ questionnaire for the variables considered at BL, EOT and FU12W.

CLDQ	BL	EOT	FU12W	<i>p</i> -value EOT*variable	<i>p</i> -value FU12W*variable
Sex					
<i>Females</i>	5.1 [4.7;5.4]	5.5 [5.2;5.8]	5.5 [5.1;5.8]	0.66	0.82
<i>Males</i>	5.5 [5.2;5.7]	5.8 [5.6;6.1]	5.9 [5.7;6.2]		
<i>p</i> -value M vs F	0.034	0.085	0.029		
<i>p</i> -value vs T0	–	0.004	0.010		
HIV status					
<i>Negative</i>	5.3 [5.1;5.5]	5.7 [5.5;5.9]	5.7 [5.5;6]	0.78	0.62
<i>Positive</i>	5.7 [5;6.4]	5.9 [5.2;6.7]	5.9 [5.1;6.7]		
<i>p</i> -value HIV+ vs HIV-	0.33	0.50	0.68		
<i>p</i> -value vs T0	–	<0.0001	<0.0001		
Fibrosis					
<i>F0-F2</i>	5.3 [5;5.5]	5.7 [5.4;5.9]	5.8 [5.5;6]	0.80	0.50
<i>F3-F4</i>	5.4 [5.1;5.7]	5.7 [5.4;6.1]	5.7 [5.4;6.1]		
<i>p</i> -value F0-2 vs F3-4	0.55	0.71	0.94		
<i>p</i> -value vs T0	–	0.001	0.0002		
RBV					
<i>No</i>	5.3 [5;5.5]	5.7 [5.5;6]	5.7 [5.5;5.9]	0.003	0.77
<i>Yes</i>	5.7 [5.2;6.2]	5.4 [4.9;6]	6.1 [5.4;6.7]		
<i>p</i> -value No vs Yes	0.28	0.11	0.96		
<i>p</i> -value vs T0	–	<0.0001	<0.0001		
Polytherapy					
<i>No</i>	5.4 [5.1;5.6]	5.7 [5.5;6]	5.9 [5.6;6.1]	0.81	0.37
<i>Yes</i>	5.2 [4.7;5.7]	5.6 [5.1;6.1]	5.5 [5;6]		
<i>p</i> -value NO vs Yes	0.42	0.56	0.11		
<i>p</i> -value vs T0	–	0.0006	<0.0001		
AST					
Mean value: 31.73	5.3 [5.1;5.5]	5.5 [5.2;5.8]	5.6 [5.2;6.1]	0.22	0.56
<i>p</i> -value vs T0	–	0.015	0.071		
ALT					
Mean value: 43.96	5.3 [5.1;5.5]	5.6 [5.4;5.9]	5.9 [5.5;6.4]	0.61	0.45
<i>p</i> -value vs T0	–	0.020	0.35		

could have partly influenced the results. As discussed before, PROs were also significantly influenced by the use of RBV. RBV has often been described as an independent risk factor for a lower HRQoL¹², but some studies^{26,28,29} have shown that the impairment of PROs determined by RBV is lower than that caused by interferon. In case of treatment with DAA, some studies^{27,52} reported a decrease in some PROs at the EOT, but only in patients who had

taken RBV. This is also confirmed in our study, with a rapidly reversible effect of RBV on HRQoL, fatigue and work productivity. People who took polytherapy reported significantly lower results to the MoCA. It is well known that some commonly used drugs such as antihistamines and antidepressants are able to cause anticholinergic effects. This may result in secondary alterations including impairment of memory, attention and psychomotor speed

Table 4. Average (CI 95%) of the overall score related to the FSS questionnaire for the variables considered at BL, EOT and FU12W.

FSS	BL	EOT	FU12W	<i>p</i> -value EOT*variable	<i>p</i> -value FU12W*variable
Sex					
<i>Females</i>	3.7 [3.1;4.4]	3.8 [3.2;4.5]	3.7 [3;4.4]		
<i>Males</i>	3.9 [3.4;4.4]	3.5 [3.0;4.0]	3.5 [2.9;4]	0.24	0.37
<i>p</i> -value M vs F	0.67	0.38	0.55		
<i>p</i> -value vs T0	–	0.75	0.99		
HIV status					
<i>Negative</i>	3.8 [3.4;4.3]	3.7 [3.3;4.1]	3.5 [3.1;4.0]	0.51	0.33
<i>Positive</i>	3.7 [2.4;5.1]	3.0 [1.7;4.4]	4.3 [2.7;5.9]		
<i>p</i> -value HIV+ vs HIV-	0.86	0.38	0.37		
<i>p</i> -value vs T0	–	0.47	0.19		
Fibrosis					
<i>F0-F2</i>	3.9 [3.4;4.4]	3.7 [3.3;4.2]	3.6 [3.1;4.2]	0.78	0.98
<i>F3-F4</i>	3.7 [3.1;4.4]	3.4 [2.8;4.1]	3.4 [2.7;4.2]		
<i>p</i> -value F0-2 vs F3-4	0.64	0.44	0.66		
<i>p</i> -value vs T0	–	0.56	0.38		
RBV					
<i>No</i>	3.9 [3.5;4.3]	3.7 [3.3;4.1]	3.6 [3.1;4]	0.90	0.40
<i>Yes</i>	3.3 [2.2;4.4]	3.0 [1.9;4.1]	3.6 [2.2;5]		
<i>p</i> -value No vs Yes	0.28	0.11	0.96		
<i>p</i> -value vs T0	–	0.40	0.18		
Polytherapy					
<i>No</i>	3.8 [3.4;4.3]	3.6 [3.2;4.1]	3.6 [3.0;4.1]	0.98	0.94
<i>Yes</i>	3.9 [3.1;4.7]	3.7 [2.9;4.5]	3.6 [2.8;4.4]		
<i>p</i> -value NO vs Yes	0.86	0.84	0.93		
<i>p</i> -value vs T0	–	0.40	0.36		
AST					
Mean value: 31.94	3.7 [3.2;4.1]	3.3 [2.7;3.9]	2.9 [1.9;3.9]	0.12	0.049
<i>p</i> -value vs T0	–	0.19	0.061		
ALT					
Mean value: 44.56	3.7 [3.2;4.1]	3.5 [3.0;4.1]	3.0 [2.0;4.0]	0.46	0.12
<i>p</i> -value vs T0	–	0.19	0.061		

of work⁵³⁻⁵⁵. In conclusion, the lower scores at the MoCa reported by patients taking polytherapy could be traced back to the anticholinergic load attributable to the drugs received. Unfortunately, in our study the anticholinergic load of the drugs taken by the patients could not be calculated. We also analysed the presence of HIV/HCV co-infection, due to the fact that co-infection is related to an accelerated progression of liver disease, clinical events

and a higher mortality⁵⁶. HIV/HCV co-infection did not influence significantly any score in our study. As seen in other studies, HRQoL increased over time and did not report substantial differences between mono-infects and co-infects^{29,32,57}. Cognitive functions, fatigue and mental health also improved at SVR in HIV/HCV co-infects⁴⁷. We found a superiority of the BL scores in HIV-positive patients, although without statistical significance, which

Table 5. Average (CI 95%) of the overall score related to the VAFS questionnaire for the variables considered at BL, EOT and FU12W.

VAFS	BL	EOT	FU12W	<i>p</i> -value EOT*variable	<i>p</i> -value FU12W*variable
Sex					
<i>Females</i>	56.4 [48.4;64.5]	61.4 [53.3;69.5]	72.8 [63.9;81.7]	0.24	0.37
<i>Males</i>	58.4 [51.8;64.9]	70.4 [63.9;76.9]	70.9 [63.6;78.2]		
<i>p</i> -value M vs F	0.72	0.089	0.75		
<i>p</i> -value vs T0	–	0.26	0.0009		
HIV status					
<i>Negative</i>	57.8 [52.5;63.2]	67 [61.7;72.3]	71.2 [65.3;77.1]	0.91	0.42
<i>Positive</i>	55 [36.8;73.2]	65.3 [47.2;83.5]	78.1 [56.8;99.4]		
<i>p</i> -value HIV+ vs HIV-	0.77	0.86	0.54		
<i>p</i> -value vs T0	–	0.002	<0.0001		
Fibrosis					
<i>F0-F2</i>	57.5 [50.9;64]	65 [58.5;71.5]	72.3 [65.3;79.3]	0.43	0.70
<i>F3-F4</i>	57.8 [49.6;66.1]	69.9 [61.6;78.1]	70.2 [60.4;79.9]		
<i>p</i> -value F0-2 vs F3-4	0.94	0.36	0.73		
<i>p</i> -value vs T0	–	0.037	0.0002		
RBV					
<i>No</i>	57 [51.5;62.4]	68.1 [62.6;73.5]	72.4 [66.4;78.4]	0.087	0.25
<i>Yes</i>	61.7 [47.7;75.7]	58.7 [44.7;72.7]	66.1 [48.9;83.2]		
<i>p</i> -value No vs Yes	0.53	0.22	0.49		
<i>p</i> -value vs T0	–	0.0003	<0.0001		
Polytherapy					
<i>No</i>	60 [54.2;65.7]	67.9 [62.2;73.7]	72.6 [65.9;79.2]	0.39	0.36
<i>Yes</i>	49.6 [39;60.2]	63.3 [52.9;73.7]	68.7 [57.8;79.6]		
<i>p</i> -value NO vs Yes	0.092	0.44	0.55		
<i>p</i> -value vs T0	–	0.014	0.0006		
AST					
Mean value: 31.94	58.1 [52.4;63.9]	64.6 [56.5;72.7]	65.3 [52.6;78]	0.59	0.28
<i>p</i> -value vs T0	–	0.11	0.021		
ALT					
Mean value: 44.56	58.3 [52.5;64]	66.1 [58.7;73.5]	72.7 [59.2;86.2]	0.95	0.84
<i>p</i> -value vs T0	–	0.13	0.160		

is not consistent with other studies. HIV infection is usually considered a detrimental factor in PROs^{29,57} and is a recognised risk factor for neurocognitive disturbances even in patients under effective antiretroviral therapy⁵⁸. It should be noted that the number of HIV/HCV patients recruited in our study was only 6. The achievement of superior results could be explained by the fact that those patients started from a better health condition because they

were younger. From the neurocognitive point of view, HIV/HCV co-infected patients have been shown to have worse performance than HIV-mono-infects^{10,43,47}. Therefore, HCV seemed to have the main impact, since the co-existence of HIV did not influence the scores trend and, following the eradication of HCV, there is an improvement in the parameters similar to the mono-infects. The degree of fibrosis is another factor that did not have an

Table 6. Average (CI 95%) of the global score at the MoCA for the variables considered at BL, EOT and FU12W.

MoCA	BL	EOT	FU12W	<i>p</i> -value EOT*variable	<i>p</i> -value FU12W*variable
Sex					
<i>Females</i>	22.7 [21.5;23.9]	22.4 [21.2;23.7]	23.1 [21.7;24.4]		
<i>Males</i>	24.7 [23.6;25.7]	25.5 [24.5;26.6]	26.3 [25.3;27.4]	0.061	0.062
<i>p</i> -value M vs F	0.018	0.0002	0.0003		
<i>p</i> -value vs T0	–	0.55	0.49		
HIV status					
<i>Negative</i>	23.7 [22.9;24.6]	24.2 [23.3;25.1]	25 [24.1;25.9]		
<i>Positive</i>	25.5 [22.5;28.5]	25.9 [22.8;29]	25.2 [21.7;28.7]	0.99	0.31
<i>p</i> -value HIV+ vs HIV-	0.26	0.28	0.91		
<i>p</i> -value vs T0	–	0.19	0.0006		
Fibrosis					
<i>F0-F2</i>	24.1 [50.9;64]	24.6 [58.5;71.5]	24.9 [65.3;79.3]		
<i>F3-F4</i>	23.5 [22.2;24.9]	23.8 [22.4;25.2]	25.4 [23.9;26.9]	0.69	0.14
<i>p</i> -value F0-2 vs F3-4	0.50	0.34	0.61		
<i>p</i> -value vs T0	–	0.18	0.057		
RBV					
<i>No</i>	23.7 [5;5.5]	24.1 [5.5;6]	24.8 [5.5;5.9]		
<i>Yes</i>	24.8 [22.5;27.1]	25.7 [23.4;28]	27.1 [24.5;29.7]	0.55	0.25
<i>p</i> -value No vs Yes	0.40	0.20	0.094		
<i>p</i> -value vs T0	–	0.29	0.005		
Polytherapy					
<i>No</i>	24.3 [23.4;25.2]	25.2 [24.2;26.1]	25.8 [24.8;26.8]		
<i>Yes</i>	22.5 [20.9;24.1]	21.5 [19.9;23.2]	22.8 [21.1;24.5]	0.013	0.11
<i>p</i> -value NO vs Yes	0.058	0.0002	0.003		
<i>p</i> -value vs T0	–	0.016	0.0002		
AST					
Mean value: 32.28	23.7 [22.8;24.6]	24.5 [23.4;25.7]	26.1 [24.4;27.7]	0.63	0.15
<i>p</i> -value vs T0	–	0.75	0.850		
ALT					
Mean value: 45.0	23.6 [22.7;24.5]	24.9 [23.8;25.9]	26.5 [24.8;28.1]	0.15	0.068
<i>p</i> -value vs T0	–	0.89	0.98		

impact on PROs. In fact, in both groups of patients (F0-F2 vs. F3-F4) there was an improvement in the scores of all the tests and there were no significant differences between them and over time^{31,48,57}. Cirrhosis was also related to a worse HRQoL at baseline⁵⁰, but it is now well established that even patients presenting cirrhosis tolerate DAA very well, have good response rates and reported an improvement in PROs comparable to non-cirrhotic ones^{17,48,57,59}.

The main limitations of the study were the reduced sample and the number of lost to follow up. Another factor that may have influenced our data was the fact that patients were aware of their virological response and of the fact that the therapeutic path was continuing in a positive way. We did not study the effect of some biochemical markers such as lipid profile that can be altered in HIV-infected patients to compare these markers to cognitive profile⁶⁰.

Only one patient has experienced a relapse and, considering the limited influence it may have had on the total patients, we have decided not to eliminate him from the analysis. A study that reported an improvement in PROs at FU12W in patients treated with DAA hypothesized that these initial results could be influenced by a state of “euphoria” following the effectiveness of the therapy. By extending the FU to 24 weeks, it has been confirmed that the improvement of PROs is sustained over time and, indeed, is increasingly accentuated²⁸.

CONCLUSIONS

This study confirmed that DAA are effective in the improvement of PROs and NCP, due to the low frequency of side effects and to the high rate of HCV infection eradication, fundamental element for obtaining these results. The improvements were sustained over time and were not influenced by fibrosis grade. Although RBV is less used in clinical practice, in our study we demonstrated that its use is associated with a worse HRQoL and greater grade of asthenia. Albeit these effects are rapidly reversible, it is important for physicians to evaluate appropriately when to use RBV in clinical practice. Finally, this study emphasizes the importance of considering PROs as an integral part of HCV infection treatment. Greater attention must be paid to certain categories of patients, especially women, older patients, and those who take polytherapy.

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The authors declare that they have no conflict of interests.

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