Efficacia e tollerabilità dei DAA nei pazienti HIV/HCV coinfetti con disturbi psichiatrici.

Efficacy and tolerability of DAAs in HIV/HCV -coinfected patients with psychiatric disorders.

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Riassunto

L'avvento dei nuovi regimi senza interferone (antivirali diretti, direct-antiviral agents, DAAs) ha rivoluzionato il trattamento dell'epatite C cronica. Ad oggi pochi dati sono disponibili sul loro utilizzo nelle persone che vivono con hiv/AIDS (PLWHA) e hanno una comorbidità psichiatrica.

Con l'obiettivo di valutare la sicurezza e l'esito del trattamento con DAA nei pazienti coinfetti HIV/HCV con disordini psichiatrici, abbiamo condotto uno studio osservazionale monocentrico retrospettivo, in pazienti psichiatrici che hanno iniziato DAA tra il 2015 e il 2018.

I soggetti erano suddivisi in due gruppi: A (in trattamento con ansiolitici/antidepressivi) e B (in trattamento con antipsicotici. Sono state valutate la risposta a 24 settimane (sustained virological response (SVR-24) e la presenza di eventi avversi.

Sono stati inclusi 19 pazienti (A:9; B:10), per il 78.9% maschi, con età media 51 anni (deviazione standard 5.9); 31.6% erano cirrotici. Quattro pazienti (21%) hanno richiesto un cambio di terapia psichiatrica prima dell'inizio dei DAA. Nel complesso, SVR-24 è stata raggiunta nel 89.5% dei pazienti in un' analisi intention-to-treat. Tassi di SVR-24 inferiori erano osservati in coloro che cambiavano la terapia psichiatrica a confronto con quanti non la cambiavano (p=0.035). Nessuna differenza si osservava invece in funzione del cambiamento di terapia antiretrovirale prima del trattamento per HCV. Almeno un evento avverso da lieve a moderato si è verificato in 4 pazienti (21%); si sono verificati 3 eventi severi, due dei quali hanno condotto a interruzione del trattamento con DAA.

Questo studio conferma l'efficacia e la sicurezza del trattamento con DAA anche in qquesta popolazione speciale, nonostante sia necessario garantire un'attenta valutazione della storia del paziente e delle interazioni tra farmaci.

Abstract

The advent of new oral Interferon-free regimen (direct-antiviral agents, DAAs) has revolutionized the treatment of chronic hepatitis C. Nowadays few data are available regarding their use in people live with HIV/AIDS (PLWHA) with psychiatric comorbidity.

We aimed at assessing safety and outcome of DAAs in HIV/HCV-coinfected patients with psychiatric disorders in a real life setting.

This retrospective, observational, single-centre study enrolled patients treated with psychiatric drugs who initiated DAAs between 2015-2018. Patients were classified into two groups: A (on anxiolitycs/antidepressant) and B (on antipsychotics). Week-24 sustained virological response (SVR-24) and adverse events (AEs) were evaluated.

Nineteen patients were included (A:9; B:10). Patients were 78.9% males, mean age 51 years (Standard Deviation 5.9); 31.6% cirrhotic. Four patients (21%) required a change of psychiatric therapy before DAAs initiation. Overall, SVR-24 was achieved in 89.5% of subjects in Intention-To-Treat analysis. Lower SVR-24 rates were observed in those changing psychiatric drugs vs. others (p=0.035). No differences were observed according to antiretroviral treatment change before anti-HCV treatment. At least one mild-to-moderate AE occurred in 4 patients (21%). Three severe AEs occurred, leading to 2 DAA discontinuations.

The study confirms effectiveness and safety of DAA-based treatment also in this special population, even if a careful evaluation of patient history and drug-drug interactions is warranted.

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Introduction

Hepatitis C virus (HCV) and Human Immunodeficiency virus (HIV) share routes of transmission and therefore coinfection with both viruses is common. About 2.3 million people of the estimated 36.7 million living with HIV globally have serological evidence of past or present HCV infection (1); in Italy, about a quarter of people who live with HIV/AIDS (PLWHA) had a positive serology for HCV antibodies. Because of the longer life expectancy due to the efficacy of anti-retroviral therapy (ART), which transformed HIV infection into a lifelong condition (2,3), chronic hepatitis C has become a major cause of morbidity and mortality among PLWHA (4,5).

Moreover, HCV infection should be considered a systemic disease because of the involvement of other organs and tissues concomitantly with liver disease. Among extrahepatic manifestations, neuropsychiatric disorders are frequent in HIV/HCV-coinfected patients and significantly influence the clinical presentation, care, and outcomes of coinfected persons (6). Psychiatric symptoms such as depression, fatigue, weakness, and anxiety have been reported with high frequency in patients with chronic HIV/HCV-coinfection, causing interference with patient's ability to perform daily activities, and impairment of quality of life (7). This evidence of neurocognitive impairment in patients with HIV/HCV-coinfection, is not fully attributable to liver dysfunction. Similarly to HIV (8), recent research has suggested that HCV may cross the blood brain barrier and may involve the Central Nervous System (CNS), leading to neuroinflammation and neurotrasmission changes (9). Moreover, the higher likelihood to acquire HCV and HIV infection can also be justified by the adoption of incorrect behaviors (10).

Patients with such comorbidity have often been excluded from treatment with Interferon (IFN)-based regimens because of the elevated risk of an exacerbation of psychiatric symptoms (11). In addition, studies indicated psychiatric comorbidity as a risk factor for non-adherence (12).

The recent introduction of IFN-free therapeutic regimens based on direct-acting antiviral agents (DAAs) has revolutionized HCV therapy (13). Viral cure, which is achieved in >95% across different patient populations (14) and is associated with improved quality of life, is now a reality. However, limited information is currently available regarding the use of DAAs in HCV-infected subjects with psychiatric comorbidity (15), while to our knowledge no studies were performed in the HIV/HCV-coinfected population. Moreover, the choice of the most correct therapeutic DAA regimen in these patients is complicated by drug-drug interactions (DDIs) with psychiatric drugs. Therefore, this study aimed at evaluating the efficacy and tolerability of DAAs-based antiviral therapy among HIV/HCV-coinfected patients with psychiatric comorbidity.

Materials and methods

All consecutive HIV/HCV-coinfected patients (≥18 years old) presenting a documented psychiatric comorbidity, who initiated an IFN-free, DAA-based regimen between February 2015 and June 2018 at the Clinic of Infectious Diseases, University of Bari, were included in this retrospective, observational study. Patients with a documented psychiatric comorbidity were defined as subjects who had received a previous diagnosis by a psychiatric specialist and for whom a psychiatric drug had been initiated. For purposes of analysis, patients were divided based on their psychiatric comorbidity into two groups: subjects experienced with anxiolytic and/or antidepressant (group A) and subjects on treatment with antipsychotic (group B), according to diagnostic criteria of DSM-V (16).

Demographic, clinical, biochemical and virological data were collected for all subjects. Data regarding the history of HIV infection, CDC classification, nadir CD4+ cell count, HIV viral load evaluated before the beginning of DAA-regimen and at SVR-12/SVR-24, and ART were also retrieved for all HIV/HCV-coinfected patients. Potential drug-drug interactions (DDIs) were evaluated before the administration of DAAs using the University of Liverpool web interaction-checker (available at www.hepdruginteractions.org) and changes in patients' comedications due to DDIs were also recorded. During treatment, all patients routinely underwent monthly monitoring, including clinical and laboratory assessment.

Efficacy assessment (primary endpoint: SVR-24) was based on an intention-to-treat (ITT) analysis, therefore all patients who received at least one dose of anti-HCV medication were included.

Safety profile of DAAs (secondary endpoint) was evaluated during each visit in all patients by a dedicated medical equipe, by means of focused questions regarding any signs and/or symptoms occurred during treatment; physicians recorded the number of adverse events (AEs) per person, as well as their type and grade of severity (Common Terminology Criteria for adverse events (CTCAE), 2017).

Statistical analysis

Descriptive statistics were calculated for demographic, clinical, and laboratory characteristics of cases. Mean and standard deviation (SD) were recorded for normally distributed variables, and the median and interquartile range (IQR) for non-normally distributed variables. The number and percentage were recorded for categorical variables. For purposes of analysis, patients were divided

according to their psychiatric comorbidity into two groups: subjects experienced with anxiolytic and/or antidepressant (group A) and subjects on treatment with antipsychotic (group B). Differences between groups were analyzed using the Fisher's exact test, t-test, or Mann–Whitney test, as appropriate. A p-value of <0.05 was considered to indicate significance.

Results

Clinical-demographical features of the study population

A total of 118 HIV/HCV-coinfected subjects initiated DAAs during the study period, and 19/118 (16.1% of the study population) presented psychiatric comorbidities and were included in the study. Nine patients (9/19, 47.4%) were on anxiolytic/antidepressant therapy (group A) and the remaining ten subjects (10/19, 52.6%) were treated with antipsychotic drugs (group B).

The clinical characteristics of patients at baseline are summarized in **Table 1**.

Patients were 78.9% males with a mean age of 51 years (SD±5.9), and 31.6% of them were cirrhotic. The main route of transmission was intravenous drug use (73.7% overall); patients were more frequently infected with HCV genotype 1a (52.6%), without any statistically significant differences between the two groups.

All HIV/HCV-coinfected patients were aviremic at the time of DAAs initiation (HIV-RNA under the limit of detection of 25 cp/ml); the median CD4+ nadir reported was 85 cells/µl without any statistically significant differences between the two groups; seven patients (36.8% of the study population) presented a CDC stage C.

Most patients (78.9% of the study population) had at least one additional comorbidity (other than psychiatric): arterial hypertension was the most common reported comorbidity (26.3%), mainly diagnosed in patients belonging to group A (44.4% vs. 10%, p=0.14). Two patients had HBsAg positivity, both in the Group B.

Failure to a previous anti-HCV treatment was reported in 4 patients (21%), all patients in treatment with anxiolitycs and antidepressant (44.4% vs. 0%, p=0.032).

All patients had compensated liver disease according to the Child–Pugh classification. Group A subjects showed a higher FIB-4 score (2.40 vs. 1.67, p=0.041) and higher APRI score (2.21 vs. 0.46, p=0.027). No differences in liver stiffness and fibrosis stage distribution, MELD score, and HCV-RNA at baseline were observed between the two groups.

DAA regimens were chosen by treating clinicians based on clinical criteria and viral genotype. The most frequently prescribed DAA regimen was sofosbuvir + velpatasvir (52.5% overall), especially in subjects in treatment with antipsychotic (80% vs. 33%, p=0.023). In three patients ribavirin was also added.

In **Table 2** the characteristics of the psychiatric disorder are detailed for both groups. Only subjects belonging to group B were on substitution treatment with opioids (methadone) at the time of inclusion in the study (p= 0.473). No statistically significant differences between the two groups were found regarding the psychiatric illness duration and the referred alcohol consumption.

Change of psychiatric and antiretroviral treatment before DAAs initiation

Among the entire study population, a total of 4 patients (two in group A, 22.2% and two in group B, 20%) required a modification of psychiatric therapy based on DDIs and/or according to the psychiatrist's judgment before the beginning of the DAA regimen.

All patients were on ART at the initiation of DAA treatment and were aviremic. A total of 6/19 patients (31.6%) required a change of ART because of DDIs, of whom 4 patients from group A and two from group B (data not shown, p=0.349). Before the change of ART, 5/6 patients were in treatment with protease inhibitors (PIs): one with atazanavir unboosted, two with lopinavir/ritonavir, two with darunavir/ritonavir. Of the 6 patients who changed ART, only one returned to his previous ART regimen after the end of DAA treatment. No virological failure for HIV was observed up to 24 weeks after completion of DDAs; no viral blip was observed.

Outcome

Among the entire study population, 17/19 (89.5%) completed the prescribed DAA regimen accomplishing EOT, while two patients prematurely interrupted their therapy due to the occurrence of adverse events.

Overall, according to an ITT analysis, SVR-12 and SVR-24 were achieved in 17/19 subjects (89.5%)

	Patients (N=19)	Group A (N=9)	Group B (N=10)	p-value
Sex, males. *n* (%)	15 (78.9%)	7 (77.8%)	8 (80%)	1.000
Age, years, mean (SD)	51±5.9	51,1±3,9	51,2±7,4	0.594
Risk Factors *n* (%)				
IDU	14 (73.7%)	7 (77.8%)	7 (70%)	1.000
Heterosexual	3 (15.7%)	2 (22.2%)	1 (10%)	0.582
MSM	1 (5.3%)	0	1 (10%)	1.000
Unknown	1 (5.3%)	0	1 (10%)	1.000
Aviremic pts on ART, n (%)	19 (100%)	9 (100%)	10 (100%)	1.000
CD4+ nadir *(cells/µl)*, median (range)	85 (42-171)	98 (50-171)	83.5 (42-186.5)	0.902
CDC-C stage, *n* (%)	7 (36.8%)	4 (44.4%)	3 (30%)	0.649
HCV Genotypes *n* (%)				
1a	10 (52.6%)	5 (55.6%)	5 (50%)	1.000
1b	2 (10.5%)	1 (11.1%)	1 (10%)	1.000
2	1 (5.3%)	0	1 (10%)	1.000
3	3 (15.8%)	1 (11.1%)	2 (20%)	1.000
4	3 (15.8%)	2 (22.2%)	1 (10%)	0.582
Log 10 HCV-RNA, IU/mL, median (range)	6.23 (5.72-6.52)	6,24 (6.15-6.52)	6.21 (5.54-6.99)	0.513
Liver stiffness, Kpa, mean (SD)	13,7±14,9	17,1 ±20,4	10,7±7,1	0.623
Previous failure, *n* (%)	4 (21%)	4 (44.4%)	0	**0.032**
IFN-based tx	4	4	0	
DAAs-based tx	0	0	0	
Fibrosis stage, *n* (%)				
F0-F2	12 (63.2%)	5 (55.6%)	7 (70%)	0.649
F3	2(10.5%)	2 (22.2%)	0	0.210
F4	5(26.3%)	2 (22.2%)	3 (30%)	1.000
FIB-4 score median (range)	2.07 (1.41-3.92)	2.40 (1.64-4.47)	1.67 (1.29-2.51)	**0.041**
APRI score median (range)	1.10 (0.41-2.21)	2,21 (0.95-3.06)	0,46 (0.37-1.37)	**0.027**
MELD score median (range)	7 (6.5-8.0)	7 (8.0-9.5)	7 (6.0-7.5)	0.247
Child-Pugh class *n* (%)				
A	18 (94.7%)	9 (100%)	9 (90%)	1.000
B	1 (5.3%)	0	1 (10%)	1.000
Cirrhosis, *n* (%)	6 (31.6%)	2 (22.2%)	4 (40%)	0.628
Oesophageal-varices/portal hypertension,*n* (%)	2(10.5%)	1 (11.1%)	1 (10%)	1.000
Type of HCV therapy *n* (%)				
SOF + SMV	2 (10.5%)	1 (11.1%)	1 (10%)	1.000
SOF + LDV ± RBV	3 (15.8%)	2 (22.2%)	1 (10%)	0.528
SOF + DCV	1 (5.3%)	1 (11.1%)	0	0.473
OMB + PTV/r + DAS ± RBV	1 (5.3%)	1 (11.1%)	0	0.473
SOF + VEL	10 (52.5%)	2 (22.2%)	8 (80%)	**0.023**
GLE + PIB	1 (5.3%)	1 (11.1%)	0	0.473
GRZ + EBR ± RBV	1 (5.3%)	1 (11.1%)	0	0.473
Duration of therapy *n* (%)				
8w	0	0	0	
12w	15 (78.9%)	5 (55.6%)	10 (100%)	**0.032**
16w	1 (5.3%)	1 (11.1%)	0	0.473
24w	3 (15.8%)	3 (33.3%)	0	0.086
Addition of RBV *n* (%)	3 (15.7%)	2 (22.2%)	1 (10%)	0.582
ALT, UI/L, median (range)	67 (39-130)	129 (67-167)	51 (39-85.5)	0.072
Total bilirubin, mg/dL, median (range)	0.70 (0.42-1.09)	0.80 (0.49-1.09)	0.64 (0.42-1.1)	0.539
Serum creatinine, mg/dL, median (range)	0.79 (0.71-1.00)	0.73 (0.62-1.00)	0.79 (0.74-0.97)	0.412
Platelets (x10^9/L), median (range)	197(113-241)	157 (113-210)	213 (137-262)	0.327
Albumin, mg/dL, median (range)	4.0 (3.7-4.2)	3.9 (3.7-4.1)	4.0 (3.8-4.2)	0.592
Body mass index, median (range)	24.8 (20.7-27.5)	24.9 (20.7-27.7)	23.0 (20.5-26.5)	0.624
Pts with at least 1 other comorbidity, *n* (%)	15 (78.9%)	8 (88.8%)	7 (70%)	0.582
Hypertension, *n* (%)	5 (26.3%)	4 (44.4%)	1 (10%)	0.140
HBsAg positive, *n* (%)	2 (10.5%)	0	2 (20%)	0.473

Legend: IDU: injecting drug user, **MSM:** man who have sec with man; **ART:** antiretroviral therapy; **INF:** interferon; **DAA:** direct antiviral agent **SOF:** sofosbuvir; **RBV:** ribavirin; **SMV:** simeprevir; **LDV:** ledipasvir; **DCV:** daclatasvir; OMB: ombitasvir; **PTV/r:** paripatrevir/ritonavir; **DAS:** dasabuvir; **VEL:** velpatasvir; **GLE:** glecaprevir, **PIB:** pibrentasvir; **GRZ:** grazoprevir; **EBR:** elbasvir **ALT:** alanine aminotransferase.

Table 1. Baseline features of study population.

	Patients (N=19)	Group A	Group B	p-value
Types of psychiatric illnesses, *n* (%)		9 (47.4%)	10 (52.6%)	
Anxiety disorders [a]		3		
Mood disorders [b]		*6*		
Psychotic disorder			10	
Duration psychiatric illness, years (range)	11 (6-16)	11 (7-14)	11.5 (3-20)	0.934
Suicide attempted, *n* (%)	3 (15.7%)	1 (11.1%)	2 (20%)	1.000
Psychiatric treatment modification before DAA tx, *n* (%)	4 (21%)	2 (22.2%)	2 (20%)	1.000
Opioid substitution treatment, *n* (%)	2 (10.5%)	0	2 (20%)	0.473
Methadone	2 (10.5%)	0	2 (20%)	0.473
Buprenorphine	0			
Referred alcohol consumption, *n* (%)	1 (5.2%)	1 (11.1%)	0	0.473

Legend: a-social phobia-posttraumatic stress disorder-panic disorder-generalized anxiety disorder; b-current major depressive episode-current manic episode-current hypomanic episode; **DAA:** direct antiviral agent

Table 2. Clinical characteristics concerning psychiatric disorders at baseline.

	Patients (N=19)	Group A (N=9)	Group B (N=10)	p-value
At least 1 adverse event, *n* (%)	4 (21.0%)	3 (33.3%)	1 (10%)	0.303
>2 adverse events, *n* (%)	3 (15.7%)	3 (33.3%)	0	0.086
Severe adverse events, *n* (%)	3 (15.7%)	2 (22.2%)	1 (10%)	0.582
Skin reactions [a], *n* (%)	1(5.2%)	1 (11.1%)	0	0.473
Gastrointestinal toxicity [b], *n* (%)	2 (10.5%)	1 (11.1%)	1 (10%)	1.000
Neurological symtomps, *n* (%)	2 (22.2%)	2 (22.2%)	0	0.210
Asthenia	1	1	0	
Headache	1	1	0	
Insomnia	1	1	0	
Amnesia	0	0	0	
Psychiatric symtomps, n (%)	2 (22.2%)	2 (22.2%)	0	0.210
Anxiety	0	0	0	
Mood disorders	2	2	0	

Legend: a-rash, pruritus, photosensitivity; b- diarrhea/constipation, dyspepsia, nausea.

Table 3. Safety profile of DAAs regimens.

of the study population, 8/9 (88.8%) in group A versus 9/10 (90%) in group B, respectively. None was lost to follow-up. Two patients who not achieved end of treatment (EOT) underwent a change of the psychiatric regimen before anti-HCV treatment (2/4 patients, 50%), compared to none of those who maintained their psychiatric therapy (p=0.035). No differences were observed according to ART change before anti-HCV treatment: no patient failed among those changing ART before baseline, while the two failures occurred among the remaining subjects.

Safety profile of DAAs

The safety profile was evaluated for the 19 enrolled subjects, and described in **Table 3**. Four patients (21%) experienced at least one mild-to-moderate adverse event (AEs) in course of DAAs, mostly in patients in treatment with anxiolytics and antidepressant (33.3% vs. 10%, p=0.303). The most common AEs were represented by neurological symptoms (10.5%) and gastrointestinal disorders (10.5%); although for three patients ribavirine was prescribed, none of them reported anemia during DAAs. No statistically significant differences in terms of occurrence of AEs were observed between the two groups. Psychiatric symptoms such as anxiety episodes and mood disorders were reported only among group A patients.

Severe AEs were ascertained in three patients (15.7%), leading to treatment discontinuation in two individuals (2/19, 10.5%) due to seizures occurence and severe headache. In addition, one hospitalization (not leading to treatment discontinuation) was reported due to hematemesis. No death was registered.

Discussion

The recent development of the new oral DAAs has revolutionized the treatment of chronic hepatitis C

virus infection, increasing the likelihood of cure (referred to as "sustained virological response") with a shorter duration of treatment and a better safety profile compared to previously used interferon-based regimens (17).

Despite these overwhelming advances, challenges remain in eliminating HCV in some patient subgroups, such as subjects with decompensated cirrhosis, severe kidney disease, and in the elderly (18). In addition, among these vulnerable populations, also patients who have psychiatric disorders should be taken into account; in these patients, in fact, IFN-treatment was eluded in previous years or discontinued for serious long-term and incapacitating neuropsychiatric side effects (15,19). The coexistence of HCV and HIV infection with cognitive disorders is well known, based on studies demonstrating the entrance of both viruses in CNS as well as the higher exposure to HIV/HCV-coinfection in patients with psychiatric comorbidities, due to more frequent risk behaviors compared to the general population (20). However, if depression and/or anxiety have been reported in a third of HIV/HCV-coinfected patients according to different studies (21,22), on the contrary the prevalence of psychotic disorders (such as schizophrenia, delirious disorder) among these subjects is not well established, but is estimated about 2% in a previous study (22).

It should be taken into account that patients who had a treatment discontinuation with previous IFN-based regimen due to side effects, nowadays are eligible to receive the DAA-based regimen. This contest could explain the inclusion of a remarkable proportion of subjects in last years. In our study, the proportion of HIV/HCV-coinfected patients with psychiatric comorbidity who underwent antiviral therapy was about 16% of the entire study population. To date, little is known concerning viral eradication and adherence during DAAs-based regimens in patients with psychiatric disorders. Our study demonstrates, in real life conditions, that HCV patients with psychiatric comorbidity can be treated with DAAs with high efficacy. The high rate of SVR-24 obtained in our study (89.5% in ITT analysis) was consistent with the recent study conducted by Sundberg et al. on a limited HCV-monoinfected population of 17 patients with severe psychiatric morbidity, which successfully completed DAA treatment with a comparable SVR (88%) (23). These SVR rates appear only slightly lower compared to those currently reported (>90%) in the general HIV/HCV-coinfected population, also in our real life experience (24).

Moreover, one of our main concerns before starting DAAs and during the course of treatment was the need of an adjustment or modification of the baseline psychiatric comedication, which was prescribed in 21% of our patients, in agreement with psychiatrists; psychiatric drugs modifications were adopted with the same frequency among patients in both groups. In fact, in our study a half of patients who underwent a change of psychiatric comedications before DAA initiation interrupted anti-HCV treatment (2/4), whereas in those who maintained their psychiatric therapy none discontinued DAAs. Therefore, a psychiatric stabilization of the patient prior to initiating HCV treatment is critical to successful treatment, in terms of reducing adverse neuropsychiatric events and early treatment discontinuation (25) . Fortunately, the wide availability of new DAA regimens has nowadays reduced the need of mandatory therapeutic changes. Our study suggests that in these cases caution is warranted, considering the risk of altering a previous stable mental condition, and a long period of patient monitoring before starting DAAs is desirable. On the contrary, changes should be avoided if not strictly required. No differences were observed according to ART change before anti HCV treatment.

Overall, DAA-based treatment was safe. Almost a quarter of patients (21%) experienced at least one mild-to-moderate adverse event. In general, no significant difference was observed in the occurrence and number of AEs between the two groups. Severe AEs occurred in only 3 patients. However, SAEs were less frequent than expected, probably due to the fact that the vast majority of patients had a compensated liver disease. Two individuals did not achieve EOT and reported a treatment discontinuation due to SAEs including seizure and intense headache. Nevertheless, the few patients who experienced psychiatric symptoms, such as depressive disorder and/or isolated generalized anxiety episode during DAA treatment, were exclusively among subjects in treatment with anxiolytics/antidepressants, whereas none of the patients receiving antipsychotics showed the same disorders. Probably, this interesting evidence might be explained by an aptitude of these patients to perceive the ini-

tiation of a new treatment as a stressing factor (26). Usually, these symptoms were reported within the first month of treatment. Further studies are needed to establish if HCV eradication could be associated with an improvement of psychiatric symptoms.

In conclusion, our study points out the complexity of the management of HCV treatment with DAAs among HIV/HCV-coinfected patients with psychiatric comorbidity, and suggests that similar SVR rates can be expected in anxious/depressive and psychotic patients. The study underlines as a careful evaluation of the clinical history and of all possible drug-drug interactions before starting therapy can have a remarkable impact on the patient outcome, which was overall successful and safe in our experience, thus encouraging a widespread use of DAAs also in such a "special population". ■

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