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Direct-acting antiviral treatment for chronic hepatitis C in people who use drugs in a real-world setting

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Abstract

Background Direct-acting antivirals (DAAs) offer high cure rates in people who inject drugs (PWID) with hepatitis C virus (HCV) infection. There are concerns regarding lower response rates among PWID in real life. We evaluated the outcome of DAA therapy in PWID in a real-world setting and the factors that affect it.

Methods We performed a retrospective analysis of 174 PWID with chronic hepatitis C who started DAAs in a Greek liver clinic in collaboration with an addiction program. Patients who did not return for reassessment were considered as lost to follow up (LTFU). A logistic regression model was used to assess factors associated with a sustained virological response 12 weeks after treatment completion (SVR12) and LTFU.

Results Patients' mean age was 48±9.2 years and 91/174 (52.3%) were attending opioid substitution treatment programs. Overall, 144/174 (82.8%) patients completed therapy and presented for SVR12 testing, 8/174 (4.6%) did not complete treatment and 22/174 (12.6%) were LTFU. Overall SVR12 was 79.9% (139/174). For those with an available SVR12 test the response rate reached 96.5% (139/144). Regression analysis did not indicate any significant association between patient characteristics and SVR12. Age <45 years and genotype 3 were independent predictors of LTFU. Parallel use was found to have a trend towards LTFU.

Conclusions HCV treatment by hepatologists and addiction specialists is feasible, effective and safe in a real-world setting. However, as 12% of patients appear to be LTFU, more emphasis should be placed on interventions guaranteeing follow up for SVR testing and general care.

Keywords Direct-acting antivirals, hepatitis C virus infection, people who inject drugs, sustained virological response, lost to follow up

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Introduction

Approximately 10% of people with chronic hepatitis C virus (HCV) infection globally are past or current illicit drug users [1]. Sharing needles and syringes among people who inject drugs (PWID) is the main route of HCV transmission in developed countries. HCV infection poses an important health issue among PWID, while in many countries the burden of liver disease due to chronic hepatitis C in this population is expected to increase over the next decade [1,2]. Therefore, there is a need to prioritize PWID for scaling up HCV testing and treatment.

The clear benefit of antiviral therapy after the introduction of direct-acting antivirals (DAAs) [3,4], along with the ambitious goal of the World Health Organization (WHO) for HCV elimination [5] and the recent clinical guidelines [6,7], could not allay the concerns regarding adherence, reinfection and overall outcome of anti-HCV treatment in PWID. Several reports from different countries have shown that

treatment uptake still remains low [8] and many clinicians are reluctant to treat active PWID [9], while in many parts of the United States of America active substance use remains an important barrier to treatment uptake [10]. On the other hand, PWID are facing many other barriers, particularly to accessing medical care, with the majority of these patients never having been examined by an expert hepatologist, while DAAs can be prescribed only by expert physicians in large liver centers.

However, there is a large body of evidence that DAA therapy in PWID offers sustained virological response rates 12 weeks after treatment completion (SVR12) similar to those in non-PWID populations [11-16]. A reasonable concern in a marginalized population is compliance with treatment; indeed, although the proportion of patients lost to follow up (LTFU) is small in randomized clinical trials [13,17], data from real-world settings are scanty and conflicting [12,18-21]. The rate of LTFU and the factors that may affect engagement with treatment and follow up will add crucial information to improve HCV service delivery and treatment.

Greece has expressed its willingness to contribute to the WHO strategy for HCV elimination, by scaling-up treatment for HCV infection in both the general population and the vulnerable population of PWID. The prevalence of HCV infection in Greece is estimated to be between 0.83% and 1.79% [22], while 20-40% of persons with chronic hepatitis C have a history of illicit drug injections [23-25]. In the present study, our primary objective was to evaluate the clinical outcome of HCV treatment with DAAs in a Greek cohort of PWID, as assessed by SVR12, and secondarily to define factors that may influence this outcome. This national-based approach aims to add extra knowledge to the international guidelines that encourage physicians to treat HCV-infected PWID.

Patients and methods

Study design and participants - data collection

We conducted a retrospective analysis of a cohort that included PWID with chronic HCV infection who had been treated with DAAs in our tertiary liver center in Athens. More specifically, we analyzed data from all PWID who had detectable serum HCV RNA for at least 6 months and had started antiviral treatment with DAAs between 1 September 2014 and 1 June 2018. Individuals were classified as PWID if they had a history of any illicit drug injection at any time. Those who reported a history of illicit drug injection during the last 12 months or had a positive urinalysis were classified as PWID with parallel drug use. A history of previous anti-HCV therapy, decompensated liver disease, liver transplantation, hepatitis B virus (HBV) or human immunodeficiency virus (HIV) coinfections, or parallel drug use were not considered exclusion criteria in our analysis. Opioid substitution treatment (OST) programs included substitution therapies with buprenorphine or methadone in a structured program under the supervision of a multidisciplinary health care team. Patients presented to our center either of their own volition or via collaboration with the practitioners at the addiction programs.

The decision for antiviral treatment initiation was made by an expert physician, and in case of patients attending OST programs by the interdisciplinary HCV group. We operate a specific outpatient clinic, once weekly, where PWID are examined by a group of addiction experts and hepatologists [26]. Apart from the stability of appointment attendance, mental or medical comorbidities and liver disease stages were also taken into consideration for treatment initiation. In Greece, reimbursement for DAAs was based on liver disease stages until September 2018, so until June 2017 only patients with fibrosis stage ≥F3 could receive DAA therapy. Between July 2017 and September 2018, public funding and DAA reimbursement was limited to patients with liver stiffness ≥F2, whereas patients with concomitant extrahepatic HCV manifestations and individuals with other comorbidities, such as hemoglobinopathies, end-stage renal disease, organ transplantation or HIV/HCV coinfection, were treated irrespectively of the liver stiffness score. The chosen elastography cutoff values for liver fibrosis stages were: stiffness <9 kPa, 9-12 kPa and >12kPa for no/mild/moderate fibrosis (Metavir Score F0-F1-F2), severe fibrosis (Metavir score F3), and cirrhosis (Metavir Score F4), respectively. The diagnosis of cirrhosis was based on the transient elastography score (>12 kPa), liver biopsy findings and clinical or imaging data.

We collected patients' baseline and demographic characteristics as part of standard clinical care. During the first visit, a complete blood count, liver function tests, HBV/HCV, HIV serology, quantitative serum HCV RNA levels and HCV genotyping were determined using standard commercial assays. We also recorded all treatment medications, HCV treatment plans, all visits to our center, treatment completion data and SVR12 testing results.

The specific DAA treatment was determined according to the physician's judgment, taking into account the HCV genotype, and the presence of cirrhosis and comorbidities. During the treatment period, all patients were assessed monthly in our department for treatment compliance, or earlier if possible adverse effects of therapy were present. SVR12 was defined as at least one polymerase chain reaction test with undetectable HCV RNA, 12 weeks after treatment completion. Individuals who did not complete the SVR12 testing within 24 weeks after treatment completion were considered as LTFU. Failure to respond to antiviral therapy was defined as detectable HCV RNA any time after treatment completion.

The study was approved by the Ethics committee of the Hippokration General Hospital of Athens and all the procedures followed were in accordance with the Helsinki Declaration.

Statistical analysis

Patient characteristics were compared using the Mann-Whitney test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Univariate and multivariable logistic regression analysis were applied for prediction of SVR12 or LTFU and 95% confidence intervals (95%CI) for the odds

ratios (OR) were calculated. Significant variables in the univariate analysis were included in the multivariate model. Statistical tests were performed using SPSS (version 25). A P-value <0.05 was considered statistically significant.

Results

Baseline characteristics

We enrolled 174 patients who started therapy with DAAs between 1 September 2014 and 1 June 2018 and were due for SVR12 testing by 31st December 2018. The baseline characteristics of our cohort are shown in Table 1. The patients had a mean age of 48±9.2 years and most were male (83.9%). Of the 174 PWID, 91 (52.3%) were attending OST programs during the DAA treatment period and 68 (39.1%) revealed parallel active drug use. Four patients (2.3%) had HBsAg detectable and were receiving tenofovir fumarate 245 mg daily, while 8 (4.6%) patients with HIV/HCV coinfection were under highly active antiretroviral therapy. Previous HCV treatment experience was reported by 44 of the 174 (25.3%) patients and 72 patients (41.4%) had evidence of cirrhosis. The most prevalent genotype was genotype 3 (61.5%), with genotype 1 following at a rate of 23%. There were no patients infected with genotype 5 or 6. Two patients had decompensated liver disease at baseline with Child-Pugh-Turcotte scores C and B, and model for end-stage liver disease scores 18 and 10, respectively. The DAA regimens and the number of patients per regimen are shown in Table 2.

Table 1 Baseline characteristics of PWID who initiated treatment with DAAs

Characteristics	Value
Mean age±SD years	48±9.2
Male sex, n (%)	146 (83.9%)
Addiction treatment program, n (%)	
Methadone	64 (36.8%)
Buprenorphine	27 (15.5%)
Dry program	14 (8%)
Parallel drug use, n (%)	68 (39.1%)
Comorbidities, n (%)	49 (28.2%)
HCV genotype, n (%)	
1a	34 (19.5%)
1b	6 (3.5%)
2	5 (2.9%)
3	107 (61.5%)
4	22 (12.6%)
Treatment-experienced, n (%)	44 (25.3%)
HCV/HBV coinfection	4 (2.3%)
HCV/HIV coinfection	8 (4.6%)
Stiffness±SD kPa	13.9±8.9
Stage of fibrosis, n (%)	
F0-F2 (none/mild/moderate fibrosis)	70 (40.2%)
F3 (severe fibrosis)	32 (18.4%)
F4 (cirrhosis)	72 (41.4%)
• Decompensated cirrhosis	2 (1.1%)

PWID, people who inject drugs; DAAs, direct-acting antivirals; HBV, hepatitis B virus; HIV, human immunodeficiency virus; SD, standard deviation; HCV, hepatitis C virus

Table 2 Antiviral treatment options for the 174 PWID who initiated DAAs, n (%)

Treatment	No. of patients
SOF+RBV	4 (2.3)
SOF+DCV	2 (1.1)
SOF+DCV+RBV	24 (13.8)
SOF/LDV	7 (4.0)
SOF/LDV+RBV	4 (2.3)
3D	3 (1.7)
3D+RBV	24 (13.8)
2D+RBV	10 (5.7)
SOF/VEL	50 (28.7)
SOF/VEL+RBV	35 (20.1)
EBR/GZR	11 (6.3)

PWID, people who inject drugs; DAAs, direct-acting antivirals; SOF, sofosbuvir; RBV, ribavirin; DCV, daclatasvir; LDV, ledipasvir; 2D, paritaprevir/ritonavir-ombitasvir; 3D, paritaprevir/ritonavir-ombitasvirdasabuvir; VEL, velpatasvir; EBR, elbasvir; GZR, grazoprevir

Treatment outcomes

The vast majority of the patients (166/174, 95.4%) completed treatment. Eight of the 174 patients (4.6%) did not complete therapy: poor compliance was the main reason for early cessation (4/8 patients); one patient died early after treatment initiation; one patient discontinued treatment because of pregnancy; and 2 patients were diagnosed with malignancies (acute leukemia and rectal cancer) and discontinued DAA treatment on their own decision. Two of them, who had HCV testing approximately 1 year after treatment discontinuation, showed a sustained virological response.

Between treatment initiation and the end of treatment (EoT), 4 (2.3%) of the 174 patients were LTFU, while 18 (10.3%) patients were LTFU after treatment completion; therefore, overall 22/174 (12.6%) patients were LTFU with no SVR12 test available.

Serum HCV RNA testing 12 weeks after the EoT was performed in 144/174 (82.8%) patients. Finally, 139 patients achieved SVR12. The SVR12 rate in an intention-to-treat analysis (ITT) was 79.9% (139/174), while for those with an SVR12 test available the response rate reached 96.5% (139/144) (Fig. 1).

Univariate and multivariate analyses were performed to identify factors (age, sex, OST, cirrhosis, history of previous anti-HCV therapy, genotype, parallel drug use, comorbidity and HIV coinfection) that might be associated with SVR rate or LTFU. Univariate logistic regression analysis demonstrated that age <45 years (OR 3.269, 95%CI 1.289-8.289; P=0.013), parallel drug use (OR 2.547, 95%CI 1.023-6.342; P=0.044) and genotype 3 (OR 4.659, 95%CI 1.322-16.420; P=0.017)

were significantly associated with LTFU. Multivariate analysis showed that age <45 years (OR 3.600, 95%CI 1.361-9.521; P=0.010) and genotype 3 (OR 5.443, 95%CI 1.492-19.861; P=0.010) were significantly associated with LTFU (Table 3). A significant trend towards LTFU was also observed for patients with parallel use (P=0.085).

In addition, univariate logistic regression analysis did not indicate a significant association between any of the baseline factors and the achievement of SVR12 in the ITT population (Table 4). Indicatively, SVR12 rates were similar between OST and non-OST groups (79.1% and 80.7%, respectively, P>0.05) as well as between cirrhotic and non-cirrhotic subgroups (80.6% and 79.4%, respectively, P>0.05).

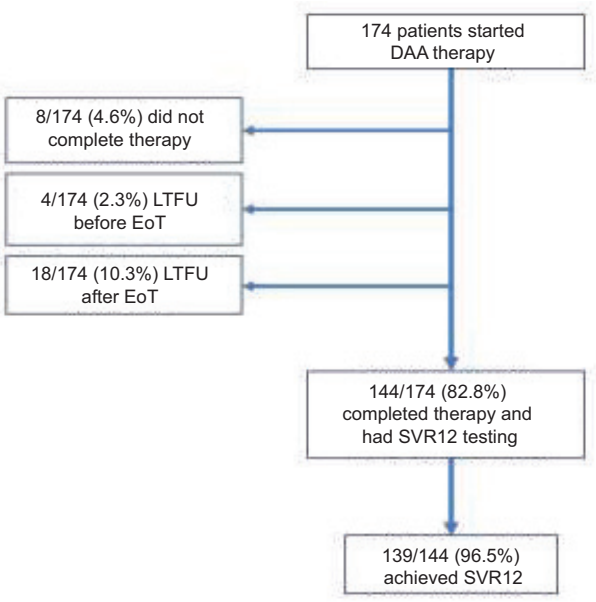

Figure 1 Patients' flowchart
DAA, direct-acting antiviral; LTFU, lost to follow up; EoT, end of treatment; SVR12, sustained virological response 12 weeks after treatment completion

Safety and tolerability

No serious adverse event was reported during the treatment period and no patient stopped therapy because of adverse events. Anemia (hemoglobin <10 g/dL) was reported in 2 patients receiving ribavirin and resolved after dose reduction in both cases. One patient died from progressive liver disease during the first month of treatment. No deaths or hospital admissions due to opioid overdose or other drug-related problems were reported.

Discussion

In this study we reported real-world experience of more than 3 and a half years from a cohort of PWID with chronic HCV infection treated with DAAs. Our results clearly showed that DAAs are very effective and well tolerated in this population, achieving an SVR in 96.5% of the patients who had an HCV RNA test available by the 12th week post therapy. However, in the ITT analysis a drop in SVR12 rate (79.9%) was recorded. This was attributed mainly to the LTFU patients, highlighting that guaranteeing the follow up and SVR12 visit represents a challenging goal.

The efficacy of DAA therapy in PWID with HCV infection has been examined in 2 large prospective studies, in a number of *post hoc* analyses and in several real world studies [11-13,16,17,19,20,27-29]. In the prospective cohorts, ITT SVR12 rates were 94% and 92%, with 3% of the patients being LTFU [13,17]. The well-organized prospective selection of the patients, in combination with the meticulous follow-up methodology, might be the explanation for the high adherence and SVR12 rates. The 96.5% SVR12 rate in our patients who had an HCV RNA test 12 weeks post treatment is comparable with the results of these prospective studies, demonstrating that DAAs can offer high SVR rates in PWID, similar to those reported in the general population. However, one might argue that the practices and methodology of prospective clinical trials cannot be reproduced in the real world, particularly in PWID

Table 3 Logistic regression analysis for predictors of LTFU (ITT population)

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Age <45 years	3.269 (1.289-8.289)	0.013	3.600 (1.361-9.521)	0.010
Male sex	0.485 (0.107-2.02)	0.348		
Genotype 3	4.659 (1.322-16.420)	0.017	5.443 (1.492-19.861)	0.010
Cirrhosis	0.489 (0.181-1.317)	0.157		
OST	1.109 (0.452-2.721)	0.821		
Parallel drug use	2.547 (1.023-6.342)	0.044	2.316 (0.889-6.030)	0.085
Comorbidities	0.951 (0.349-2.590)	0.921		
HIV	2.433 (0.459-12.889)	0.296		
Past treatment	0.852 (0.295-2.463)	0.768		

LTFU, lost to follow up; OST, opioid substitution treatment; ITT, intention-to-treat; HIV, human immunodeficiency virus; RBV, ribavirin; OR, odds ratio; CI, confidence interval

Table 4 Logistic regression analysis for predictors of SVR12 (ITT population)

Variable	Univariate analysis	
	OR (95%CI)	P-value
Age <45 years	1.225 (0.359-4.183)	0.746
Male sex	2.632 (0.327-21.179)	0.363
Genotype 3	1.658 (0.529-5.193)	0.386
Cirrhosis	0.448 (0.139-1.438)	0.177
OST	0.921 (0.295-2.880)	0.888
Parallel drug use	0.319 (0.099-1.030)	0.056
Comorbidities	0.423 (0.134-1.341)	0.144
HIV	0.448 (0.048-4.151)	0.479
Past treatment	0.757 (0.219-2.613)	0.660

SVR12, Sustained virological response 12 weeks after the end of treatment; OST, opioid substitution treatment; ITT, intention-to-treat; HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval

groups. In the ITT analysis we clearly observed lower SVR12 rates: 79.9% of our population achieved SVR12, with the absence of HCV RNA testing after treatment completion being the main reason for the lower SVR12. Our data are in accordance with other real-world studies that reported SVR12 rates ranging between 80-87% [19,20,27]. Furthermore, the percentage of 10.3% LTFU after treatment completion was similar to that in several real-world studies [12,19,27], although others [18,20,21] reported significantly lower LTFU rates (0.6-2%). The different LTFU rates across the studies might be related to the context of treatment delivery and follow up (i.e., frequency of study visits, engagement in active follow up by study personnel, patient-friendly schedule of appointments), the special characteristics of the PWID treated and the definition of LTFU in the real-world setting. In our cohort we observed that 55 patients underwent SVR12 lab testing after the 12th post-therapy week, while the mean time to SVR12 was 19 weeks after treatment completion; therefore, an extended follow up in the PWID population might be a reasonable option for SVR12 assessment.

Serum HCV RNA testing 12 weeks after treatment completion and long-term follow up is of major clinical importance. It may be argued, however, that in the era of HCV elimination, post-therapy testing and care may not be the priority; however, a lack of SVR documentation, reinfection rate assessment after therapy and surveillance for the early diagnosis of hepatocellular carcinoma are important clinical issues from an individual point of view [30]. Identifying factors that can predict lower adherence during treatment or loss during the follow-up period might be helpful in reducing LTFU rates. Our analysis showed that PWID who were <45 years old and those infected with genotype 3 were at higher risk for LTFU. The higher risk behavior in the younger population and the rather earlier stages of HCV disease may explain the association between age and LTFU rates. This finding was also reported in a recent review that included 1909 PWID [31]. In contrast, the association between genotype 3 and LTFU is difficult to explain. It is known that HCV is transmitted through injecting networks, which have significant differences in epidemiological and disease-related characteristics. Our analysis is not sufficient to confirm or rule out the likelihood that genotype 3 predominates in networks composed of individuals with a chaotic lifestyle and a higher probability of failure to comply with treatment and follow-up schedules [32].

Interestingly, in the multivariate regression model we observed a significant tendency towards LTFU in those PWID with parallel active drug use at the time of DAA therapy. The results are in accordance with our previous analysis regarding treatment uptake: a proportion of PWID with HCV infection did not start treatment, despite the availability DAA, and the probability of treatment initiation was negatively associated with ongoing benzodiazepine use [33]. Therefore, further investigation in order to explore the associations between type of use, mental comorbidities and LTFU will reveal the importance of our finding.

Treatment adherence-enhancing strategies, including special nurses engaged in hepatitis C treatment in the hospital settings, could be a promising approach to deal with the problem of LTFU in this marginalized population. However, the implementation of such an approach is problematic, as it is associated with a cost increase that is not feasible for the majority of countries; our data are therefore of clinical importance, because intensifying support and follow-up visits only for those PWID who are at higher risk of being lost could reduce the LTFU rates.

Overall, DAA therapy was well-tolerated and safe; 3 patients discontinued treatment for non-liver-related reasons and 1 with decompensated disease at baseline died from liver failure. In addition, the most common adverse event was anemia, which was observed in 2 cirrhotic patients receiving ribavirin. Neither of these patients needed to discontinue treatment and their anemia improved with ribavirin dose reduction. In addition, none of the treated PWID developed hepatocellular carcinoma between treatment initiation and SVR12 testing.

Our study had several limitations, mostly related with the design. It was a single-center retrospective analysis and therefore the results should not be generalized without caution. Incomplete or missing data, entry errors and differences between active or former drug users are possible in a study with such a design. However, despite the above limitations our data points were complete (>95%) as regards the vast majority of the parameters analyzed. Furthermore, we included patients who represented all subgroups of PWID in real-world settings who had completed at least a 12-week follow-up period after treatment. Patients with parallel drug use and HBV or HIV coinfections, reflecting those with more hazardous behaviors, were not excluded from our analysis, giving our results extra validity.

In conclusion, our results confirm the excellent efficacy of DAAs in PWID with HCV infection; therefore, PWID should no longer face barriers to HCV treatment access. However, in a real-world setting 1 of 10 PWID is LTFU after DAA therapy completion. As a lack of follow up in this vulnerable population could have unfavorable consequences, we need more real-world data in order to develop strategies to reduce LTFU, improve care and testing and get closer to HCV elimination.

Summary Box

What is already known:

- Direct acting-antivirals (DAAs) are highly effective for the treatment of hepatitis C virus (HCV) infection
- Compared to the general population, DAAs have shown similar efficacy in clinical trials in people who inject drugs (PWID) and have HCV infection
- There has been evidence for lower response rates for PWID in a real-life setting
- Adherence to DAA therapy and loss to follow up (LTFU) during treatment are major concerns regarding antiviral treatment in the PWID population

What the new findings are:

- Our real-world data confirm the high rates of sustained virological response (SVR) following DAA therapy in PWID
- Approximately 1 of 10 PWID was LTFU during or after treatment completion, with no SVR test available
- LTFU seems to be related with younger age and genotype 3
- Parallel drug use was associated with a trend towards LTFU

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