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Factors enhancing treatment of HCV infected Italian people who use drugs: the CLEO-GRECAS experience

--Manuscript Draft--

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Full Title:	Factors enhancing treatment of HCV infected Italian people who use drugs: the CLEO-GRECAS experience
Article Type:	Article
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Abstract:	Objective We assessed the performance of direct-acting antivirals (DAAs) in hepatitis C virus (HCV)-infected people who use drugs (PWUD) in terms of sustained virological response (SVR) and adherence rates, in comparison to a location-matched cohort of non-PWUD HCV patients. Methods All consecutive HCV RNA-positive PWUDs were enrolled between 2015 and 2019. All subjects underwent DAA treatment according to international guidelines and then followed, at least, up to 12 weeks after the end of treatment (SVR12). The SVR and the adherence to treatment was compared to that of non-PWUD HCV patients observed at hepatological units of the CLEO platform. Intention-to-treat analysis was performed. Results 1786 PWUDs who were followed-up were available for assessment. The majority of PWUD (85.4%) were managed inside the specialized outpatient addiction clinics (SerDs). The overall SVR rate was 95.4%. The SerDs group achieved an SVR rate of 96.2% compared to 91.6% of the non-SerDs group ($p<0.001$). Comparison with non-SerDs group and the control HCV group showed a significant difference in the drop-out rate (0.6% in SerDs group versus 2.8% in non-SerDs group and 1.2% in control group; $p<0.001$). At multivariate analysis, factors independently associated with SVR were use of the most recent regimens (elbasvir/grazoprevir, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir; OR: 3.126; $p=0.000$) and belonging to the SerDs group (OR: 2.356; $p= 0.002$). Conclusions The performance of DAAs in PWUD is excellent, if two conditions are met: a) that the latest generation drugs are used and that the patients are managed within the SerDs.
Response to Reviewers:	Dear Editor, Below is the point-by-point letter generated by the comments of the Editorial Board and those of the reviewers. The work to which they have been subjected has been very useful for us and, certainly, the paper is improved. All the authors of the paper are grateful for your comments and suggestions. Editor/Editorial Board Comments: We read your submission with interest. Our board would like you to refrain from using the term "real world" in the title. We have deleted these two words from the title. In addition to the comments from the reviewers, we would like to have you include some more information about the qualifications of a Ser-D center. The SerD (Services for addiction) were established in Italy in 1990, with the task of taking care of patients with drug addiction disorders, alcohol and other forms of pathological addiction. The SerD take care of the treatment, both on the pharmacological and psychological side, with the overall management evaluating all

	the clinical aspects related to addiction. They also work on the side of primary and secondary prevention and social rehabilitation of a complex phenomenon with medical, neuropsychological as well as social and family consequences. The Italian legislation is at the forefront on the fight against addiction, not finding the same organization foreseen like the SerD in other Health Services, especially in the recognition of the specificity of the pathology that requires specialized multidisciplinary interventions. Part of this sentence was included in the paper. What would be required in a non-Italian environment to replicate the success of these centers? In general, in Europe, an approach based on general practitioners and on the possibility of withdrawing drugs directly in pharmacies prevails. A possible transition to SerD type centres would require a profound reform of national health systems with the establishment of Centres dedicated to this pathology in order to deal with the problem in a multidisciplinary way. We look forward to reviewing your revised manuscript. Reviewer #1: The manuscript is well written. The study design and methodology are fine. The statistical analyses are ok. Conducting multivariate adjustment for confounders is very important because it is well known that specially the genotype, the drug used and the stage of liver fibrosis have independent effects on the SVR12 rates. It would be much of value if authors elaborate more on these factors by doing sub analysis for SVR12 for each stage of liver fibrosis (F1 to 4) and for each drug combination in addition to the already done generation of DAAs. There was no difference between the stage of liver fibrosis and SVR both overall (p=0.8231) and each stage versus the other. Here you can see the results of this sub analysis, as you requested. We have not included this further analysis in the paper so as not to burden the reader with too much data. It would be beneficial to consider each drug regimen used separately including the treatment duration (for example 8 weeks on GP) As regards the single drugs used for HCV therapy, a further sub-analysis was made considering each therapeutic regimen and the sustained virological response. The analysis confirmed what has already been shown in the paper regarding the statistically significant association between third generation drugs (SOF/VEL or VOX, GLE/PIB, ELB/GRZ) compared to second generation antiviral drugs. The table shows the chi-square value for all drug classes and for each category with respect to each other. We also present a figure showing the SVR columns in each antiviral regimen category. Antiviral treatment (N.1801)SVR 1) SOF/VEL +/- R or VOX97.3% 2) GLE/PIB97.5% 3) ELB/GRZ +/- R96.3% 4) SOF/DCV +/- R95.7% 5) SOF/LDV +/- R90.7% 6) 2D or 3D or SOF/SIM +/- R79.1% Total95.4% $\chi 2 = 80.01$; $p < 0.001$

Comparison between drugs and SVR
Drugs
p*

1 vs 20.8455
1 vs 30.7152
1 vs 40.1787
1 vs 50.0080
1 vs 60.0001
2 vs 30.4666
2 vs 40.1273
2 vs 50.0053
2 vs 60.0001
3 vs 40.9999
3 vs 50.2109
3 vs 60.0005
4 vs 50.0614
4 vs 60.0001
5 vs 60.0306

*Fisher's exact test

Duration of treatment: at the time of the beginning of the study, international/national guidelines (EASL/AASLD/APASL/AISF) suggested a treatment duration for all DAA regimens of 12 weeks. The recommendation to also use an eight-week scheme for some drugs came after the end of enrollment in the study (June 2019)

Also the multivariate logistic regression adjusting for the type of drug abused (injection versus non injection); F stage and drug used rather than the generation will be more illuminating.The results of this regression model if included in tables with the squared F and slopes in addition to the ORs will be more illustrative.
In the multivariate logistic analysis, we included the F stage and the drug used, but it was not possible to separate those who had used only injected or non-injected drugs within the abused drug before the enrolment into the study. In fact, as is the case in general for this population of subjects, they alternatively use one or the other type of drug depending on both economic and local availability. The result of the multivariate logistic regression including the stages of fibrosis and the type of antiviral drug used has been included in the tables that has been added to the paper as table 6, which is reported below.

Table 4. Factors associated with sustained virologic response to DAA (#1709 patients)
Beta
coefficientpOdds Ratio (OR)95% Confidence intervals for OR
lowerUpper
Antiviral treatment
2D or 3D or SOF/SIM ±RBVreference category
GLE/PIB2.390<0.00110.915.1822.99
SOF/VEL or VOX ±RBV2.26<0.0019.614.5520.30
ELB/GRZ ±RBV1.830.0046.211.7821.73
SOF/DCV ±RBV1.77<0.0015.893.0811.26
SOF/LDV ±RBV1.120.0163.071.237.64
SerD
Noreference category
Yes0.700.0112.021.173.48
Constant0.760.0152.139
Multivariate logistic regression, backward stepwise (Likelihood Ratio) method. Dependent variable = SVR at week 12. Variables entered at step 1: age<50y vs >50y; gender; HCVRNA <6log vs ≥6log; GT 1a, 1b, 2, 3, 4 (reference category GT1a); fibrosis stage F1, F2, F3, F4 (reference category F1); Treatment DAA regimens: 1) 2D or 3D or SOF/SIM ±RBV, 2) GLE/PIB, 3) SOF/VEL or VOX ±RBV, 4) ELB/GRZ ±RBV,

5) SOF/DCV ±RBV, 6) SOF/LDV ±RBV (reference category #1); SerD category yes or no (reference category = no serD).
Omnibus test of model coefficients: $\chi 2 = 56.74$; $p < 0.001$; Hosmer and Lemeshow test: $p = 0.705$; Negelkerke R2 = 0.106

Reviewer #2: AJG-20-2536, review on DAA in PWUD

This is a large study in SVR on DAA in patient with history of drug use.

The paper states no difference in SVR between PWUD and controls, but there was a statistical difference but, I believe the authors meant to express, that the difference was not clinical meaningful. I would agree with that assessment, and the authors should not be "punished" by providing such a large data set. What may be a solution to this, if the authors, upfront provide a power calculation for a equivalence study or a non inferiority study.
Ok, that's true. We modified the phrase on page 4 line 18 "is comparable" in "although the difference is statistically significative this difference of 2.7% was not clinically meaningful. Moreover, as you suggest we made a power calculation for a non-inferiority study and we found that "if there is a true difference in favour of the control group of 2.7% (98.1% vs 95.4%), then 1013 patients in each group are required to be 90% sure that the upper limit of a one-sided 95% confidence interval will exclude a difference in favour of the control group of more than 5% .
Can the authors clarify, if there was indeed no patient declining enrolment, or is participation in documenting and analyzing patients' data part of being admitted to the SerD program.
None of the enrolled patients refused to carry out the therapy. Their adhesion was spontaneous and without any conditioning. This success is the result of the presence in the Center, alongside infectious disease and hepatologists, of psychologists particularly experienced in the treatment of this type of patient.

If analysis would be limited to cirrhotic patient, would there still be similar results between controls and PWUDs?
Yes, the results do not change by extrapolating the cirrhosis, as can be seen from the table showing the result and statistical significance. As written above, this difference of 2.8% is not clinically meaningful.

Study Group SVR, N./Total (%)
Difference between the proportion and 95% CI
PWUD Cirrhosis741/781 (94.9)2.8% (0.88% - 4.77%)
Control Group Cirrhosis714/731 (97.7)
P = 0.0044

For patients on OST, were they or what percentage was on direct observed therapy (DOT), and was DAA also DOT?
Patients on OST in the SerD group were all on DOT. A small percentage of the non-SerD group took OST, as noted in the paper and below.

Did the time since starting in SerD in relation to start of DAA mattered?
Patients referred to SerD and who needed therapy were immediately treated as soon as all preparatory examinations were completed. There was no delay between enrollment in the SerD and initiation of therapy.

Was compliance measured?
Compliance was measured by checking adherence to scheduled visits. Furthermore,

	the definitive analysis was made on the number of drop out. This difference was statistically significant between SerDs and non-SerDs group (0.5% vs 0.8%, p<0.001) as shown in fig.1 Page 9 21.2% alcohol users: Is that abusers or users? This percentage concerns a relatively small group of patients who used alcohol sporadically, with a total consumption below the threshold to qualify them as abusers (30 grs/daily for male and 20 for female) The non-SerD group did not received OST, right? No. As written in the text, 85.4% of PWUDs were taking OST, with the description of the medications taken. 14.6% of the patients followed in the non-SerD group took OST, predominantly methadone. What is the definition of NR? NR (Non-response to DAA treatment) can be defined by detectable serum HCV RNA during DAA treatment or at the end of DAA treatment. Time to HCV RNA negatively during treatment would be interesting to see. Was time to negative different between SerD and nonSerD. If so, it could support the idea of better upfront education on the importance of compliance once negativity is achieved, as sometimes patients stop therapy once they learn HCV is undetectable, not understanding the importance on consolidation therapy. In the two groups, none discontinued therapy after the first HCV RNA negativization, except three (one in the SerD Group and two in the non-SerD). Furthermore, it must also be said that we do not have all the necessary data for regulatory reasons. In fact, for economic reasons, the regional rules that previously required a control of HCV RNA at time 0, at week 2, 4, 12 and 24, with the advent of third generation drugs, only required testing at time zero and at w12 and 24 to evaluate the SVR. Of the patients for whom we had continuous monitoring of HCV RNA, only very few, as mentioned above, gave up on continuing by not showing up at the pre-established checks. How were the 15 lost to follow-up counted, as relapse or NR? The 15 patients lost to follow-up were counted as NR.
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Naples, 29th July 2020

TO THE EDITOR OF "AMERICAN JOURNAL OF GASTROENTEROLOGY"

Dear Editors,

Please find the enclosed manuscript entitled: " **Factors enhancing treatment of HCV infected Italian people who use drugs: the CLEO-GRECAS real-world experience"**

which we would like to be considered for publication as original article in American Journal of Gastroenterology.
The strength of this contribution is that it enrolled the largest number of patients included in a real-life study published in Europe, dealing with a group of patients who use drugs. Data were collected from all Italian territory.
The excellent results clearly indicate that this therapy can be administered to this type of patient, a population that has always been considered "difficult-to-treat". We believe that this result is mainly due to the Italian Centre for drug Addict (SerDs) system. We propose the Italian model based on the SerDs as the best model to treat this population and the way to improve the health and the social reintegration of this population.

I declare that:

1. The manuscript has not been published previously, and is not under consideration (in whole or in part) for publication elsewhere.
2. All Authors have significantly contributed to the work
3. The manuscript has been approved by all Authors.
4. The CLEO (Club Epatologi Ospedalieri) Group provided a grant for the study to the principal investigator.
5. In case of acceptance of the manuscript, the copyright is transferred to the Journal.

Thank you very much indeed for the attention.

Kindest regards,

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Factors enhancing treatment of HCV infected Italian people who use drugs: the CLEO-GRECAS experience

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Conflict of interest

The authors have no affiliations with or involvement in any organization or entity, with any financial interest or non- financial interest in the subject matter or materials discussed in this manuscript.

Guarantor of the article: Luca Rinaldi accept full responsibility for the conduct of the study and have

access to the data and have control of the decision to publish

Authors' contributions

Luca Rinaldi: study design, data collection, data analysis, data interpretation, writing and reviewing the paper. Vincenzo Messina, Vito Di Marco: data collection, data analysis, data interpretation and reviewing the paper. Vincenzo Iovinella, Ernesto Claar, Giuseppe Cariti, Rodolfo Sacco: data collection and reviewing the paper. Massimo de Luca: statistical analysis. Gaetano Scifo, Pietro Gatti, Giorgio Barbarini, Valeria Pace Palitti, Mariano Quartini, Paolo Tundo, Gianpiero D'Offizi, Giustino Parruti, Maria Antonietta di Rosolini, Giovanni Garrucciu, Lucio Cosco, Francesco Benanti, Giancarlo Gimignani, Umberto Vespasiani Gentilucci, Francesco Di Lorenzo, Maria D'Antò, Riccardo Nevola, Tommaso Lupia, Valerio Rosato, Valeria Morbiducci, Ilaria Luzzitelli, Federica Sozio, Marco Di Stefano, Emanuela Ciraci, Fabio Bulla, Riccardo Guarisco, Cecilia Cangiano, Michele Imparato, Paolo Maggi: data collection and reviewing the paper. Antonio Ascione, Antonio Craxì, Antonio Izzi: Study design, data interpretation, writing and reviewing the final version of the paper. All the authors approved the final version of the paper.

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Study highlights:

What is known

The lack of experience in the clinic real life of people who use drugs (PWUD) could be a bias in the evaluation of effectiveness of antiviral treatment by direct acting antivirals (DAAs).

What is new here:

The results showed the pivotal role of the close cooperation between the Centres for drug addicts (SerDs) and the territorial hepatologists Centres in the high SVR achievement.

PWUDs followed up at a SerD improves adherence to therapy, reduces dropouts and re-infections regardless of the degree of liver disease.

The Italian model has been successfully applied to a large national cohort and allowed comparable results to non-drugs users.

Abstract

Objective We assessed the performance of direct-acting antivirals (DAAs) in hepatitis C virus (HCV)-infected people who use drugs (PWUD) in terms of sustained virological response (SVR) and adherence rates, in comparison to a location-matched cohort of non-PWUD HCV patients.

Methods All consecutive HCV RNA-positive PWUDs were enrolled between 2015 and 2019. All subjects underwent DAA treatment according to international guidelines and then followed, at least, up to 12 weeks after the end of treatment (SVR12). The SVR and the adherence to treatment was compared to that of non-PWUD HCV patients observed at hepatological units of the CLEO platform. Intention-to-treat analysis was performed.

Results 1786 PWUDs who were followed-up were available for assessment. The majority of PWUD (85.4%) were managed inside the specialized outpatient addiction clinics (SerDs). The overall SVR rate was 95.4%. The SerDs group achieved an SVR rate of 96.2% compared to 91.6% of the non-SerDs group ($p<0.001$). Comparison with non-SerDs group and the control HCV group showed a significant difference in the drop-out rate (0.6% in SerDs group versus 2.8% in non-SerDs group and 1.2% in control group; $p<0.001$). At multivariate analysis, factors independently associated with SVR were use of the most recent regimens (elbasvir/grazoprevir, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir; OR: 3.126; $p=0.000$) and belonging to the SerDs group (OR: 2.356; $p= 0.002$).

Conclusions The performance of DAAs in PWUD is excellent, if two conditions are met: a) that the latest generation drugs are used and that the patients are managed within the SerDs.

Keywords: Chronic hepatitis C, direct-acting antivirals, PWUD, centre for drug addict, adherence to treatment

INTRODUCTION

People who use drugs (PWUD) represent a large population worldwide and are a relevant contributor to HCV transmission. Overall, HCV infection among PWUD is estimated at around 50% [1]. In 2016, WHO faced the challenge to achieve the elimination of HCV infection and its spread by 2030 [2]. In this perspective, the European Association for the Study of Liver (EASL) and International Liver Foundation indicated HCV "micro-elimination" in certain selected populations in the path to reach global HCV elimination, starting from people most affected by the HCV infection, such as socially marginalized subjects or PWUD [3].

Globally, HCV treatment from direct-acting antivirals (DAAs) allowed a very high rate (>95%) of sustained virological response (SVR); since 2015, more than 2 million HCV- positive patients have undergone DAA treatment [4-6].

So far, the prevailing reluctance in the prescription of DAAs in the setting of PWUD could be explained by the barriers, which include the poor adherence, reduced tolerability and the risk of HCV reinfection. Moreover, some papers reported a very low compliance to treatment among PWUD in the interferon era, with approximately 1–2% of all HCV-infected patients treated yearly [7,8]. Conversely, two recent trials, showed an improvement in the DAA era, with a high SVR rate and adherence either in the PWUD setting or in patients treated with opioid substitution therapy (OST) [9,10]. These promising results obtained in the specific trials program could also apply to the large-scale real-world practice where the expected achievements could be less satisfactory. In Italy, DAA therapy has been prescribed for almost 205,000 patients at present, with a success rate of about 98% [11]. An estimated prevalence of HCV infection in Italian PWUD is about 50% with a 23% of new infections due to drug injection [12]; the management of PWUD is mainly performed in specialized outpatient centres for drug addicts (SerDs) [13]. The SerDs were established in Italy in 1990, with the task of taking care of patients with drug addiction disorders, alcohol and other forms of pathological addiction. The SerDs take care of the treatment, both on the pharmacological and psychological side, with the overall management

evaluating all the clinical aspects related to addiction. They also work on the side of primary and secondary prevention and social rehabilitation of a complex phenomenon with medical, neuropsychological as well as social and family consequences. In 2012, 543 drug addicts were evaluated in 25 Italian SerDs; the results of this study showed an HCV-Ab prevalence of 63.9%; however, only 19.3% of them received antiviral treatment [14].

To date, the exact proportion of HCV PWUD treated and the effectiveness of DAAs among PWUD in Italy is unknown.

In this perspective, the Italian CLEO-GRECAS group conducted a multicentre prospective study, to evaluate the effectiveness and the adherence of DAA therapy in PWUD, most of them strictly followed within a continuous interdisciplinary collaborative programme between SerDs and territorial centres for liver diseases.

PATIENTS AND METHODS

Study design and patient population

This is an observational, retrospective/prospective, multicentre, study conducted by an Italian group of Hospital and Academic hepatologists (Club Epatologi Ospedalieri [CLEO] – Gruppo Epatologico Clinico Associativo Siciliano [GRECAS]).

From 1 July 2015 to 1 June 2019, all consecutive HCV RNA serum-positive PWUD were recruited inside SerDs, which are distributed all over Italy or by dedicated liver centres. All stages of fibrosis, HCV genotype and co-infection with HBV or HIV were included in the study. Treatment-experienced to previous interferon PWUD were also enrolled.

Cirrhosis patients with decompensated liver disease or diagnosis of hepatocellular carcinoma (HCC), heart, kidney and pulmonary failure, pregnant women and people <18 years old were excluded.

All patients enrolled were submitted to clinical evaluation, standard biochemistry, ultrasound (US) and transient elastography by Fibroscan following the standard criteria to evaluate the diagnosis and staging of liver disease. The diagnosis of cirrhosis was also based on a compatible clinical picture and

laboratory parameters (platelet <90000 mm^3, albumin <2.5 g/dl), ultrasound parameters (coarse pattern, irregular liver surface, evidence of portal hypertension, such as splenomegaly) and/or liver stiffness >13.5 kPa. US was carried out at the baseline to exclude the presence of HCC [15].

Liver biopsy was not performed because it was judged unethical in this specific context.

PWUD were defined as people who have taken injection or non-injection drugs (i.e. by inhalator route) in the last 6 months, including receiving OST (information reported by SerDs or by dedicated hepatological centres at enrolment, determined by clinical visits or through positive urine/serum drug testing). People who use cannabis alone have not been classified as active addicts and were not included in the study. Each centre recorded the data directly on a specially prepared database.

PWUD were followed up for at least 12 weeks after the end of treatment. HCV relapse drop out during the treatment and the follow-up were recorded.

The management of the PWUD during all time of the study, including data report, was carried out through the interdisciplinary cooperation between hepatologists inside the SerDs and the reference territorial specialist centres.

A control group of HCV patients that underwent DAAs and never drugs users were taken from the CLEO platform.

The CLEO platform is an Italian multicentre cohort of clinical and academic hepatologists collecting data from several Liver Units of Italian Hospitals aimed at the optimization of care and research for patients with liver diseases.

Antiviral therapy

Patients underwent DAA therapy, following international guidelines [16,17]. Eligibility for DAA treatment was assessed by the priority criteria established first, in February 2015, by the Italian Medicines Agency Committee (AIFA) and then updated on March 2017 [11]. The DAA regimen and the treatment duration was chosen based on the availability of drugs, severity of liver disease and comorbidities, according to the Italian ministerial guidelines for DAA treatment and its update [18].

Patients enrolled were treated with either sofosbuvir + daclatasvir (SOF/DCV) ± ribavirin, ledipasvir

+ sofosbuvir (SOF/LED) ± ribavirin or ombitasvir/paritaprevir/ritonavir (2D) ± dasabuvir (3D) ± ribavirin. Since May 2017, patients were treated only with third generation DAAs: elbasvir/grazoprevir (GRZ/EBR), glecaprevir/pibrentasvir (GLE/PIB) or sofosbuvir/velpatasvir (SOF/VEL).

Serum HCV RNA was assessed by real-time PCR (COBAS® TaqMan, AmpliPrep, Roche), with a lower detection limit of 15 IU/mL. Serum HCV RNA was first detected at baseline and then at the end of treatment (EOT). Lack of detectable serum HCV RNA at 12 weeks after EOT was defined as SVR12. Detection of serum HCV RNA after EOT and within the following 12 weeks was defined as relapse.

Demographic characteristics and clinical parameters at baseline, HIV or HBV co-infection, chronic alcohol intake (>30 g/daily for more than 5 years, 20 g/daily for women), substance abuse and the OST were recorded.

Endpoints of the study

The primary endpoint was to assess the safety and effectiveness of DAA therapy in the setting of PWUD by detection of SVR12 and adherence to therapy.

Additional endpoints were a comparison between the results obtained by SerD and non-SerD patients, and a sub-analysis comparing the cohort of PWUD and a control group of HCV patients who never used drugs (CLEO platform), in order to evaluate the effectiveness and the adherence to DAA therapy.

Statistical analysis

Continuous variables were reported as the mean with standard deviation or the median with interquartile range (IQR), and categorical variables were reported as number and percentages with 95% confidence interval (CI). Comparison between categorical variables were performed using chi-square or Fisher's exact test when appropriate. For all statistical comparisons, a two-tailed significance level of 0.05 was used. Multivariate analysis was performed using logistic regression to evaluate independent factors associated with SVR12 to DAAs. Moreover, a stratification analysis for type of DAA was also performed to better assess the association between SerDs group and SVR in each DAA group. For all statistical comparisons, a two-tailed significance level of 0.05 was used. Analysis was performed using statistical software package IBM SPSS Statistics for Windows, Version 25.0 (SPSS

Inc. Chicago, IL, USA). Intention-to-treat analysis was performed.

Ethics

The study was performed according to the 1976 Declaration of Helsinki and its later amendments and approved by our Internal Review Board. All patients gave their informed consent to the study.

RESULTS

Baseline characteristics of study population

A total of 1801 PWUD were enrolled, out of which 1786 completed the follow-up according to the study design. The study population was distributed as follows in the different Italian regions: 14.1% from northern Italy, 29.7% from central Italy, 36.4% from southern Italy and 19.8% from the islands. The baseline demographic and clinical features of the patients are shown in Table 1. In particular, we observed a strong prevalence of the male sex (83.1%) with a mean±SD age of 50.2±10.2 years. A total of 40.2% were cirrhotic patients. The most frequent HCV genotypes were genotype 3 (45%) and genotype 1a (27.3%). Two genotype 7s were also found. HCV RNA >6 Log IU/mL was found in 983 (54.6%) patients. HBV co-infection was 2.6%, while HIV co-infection was 3.8%; alcohol users were 21.2%.

The majority of PWUD (85.4%) were routinely followed within the SerDs (SerDs group) and were undergoing contemporary treatment with OST: methadone 59.6%, buprenorphine 8.8%, naloxone plus buprenorphine 6.5% and naltrexone 20%. The remaining 14.6%, reported a current drug use and was followed by liver centres (non-SerDs group). The SerDs group showed a prevalence of male (84.8%); age of 49±9.8 years; HCV genotype 3 (50.6%) in comparison with the non-SerDs group in which prevalence of male gender (75.5%), older age (53±11.3 years) and HCV genotype 1a (35.7%) were found ($p<0.001$) (Table 2).

Overall, the substances used were heroin 35.2%, cocaine 10.3% and opiates 8.6%; 44.8% were contemporary cocaine and heroin users.

Response to antiviral treatment

In total, 75.1% of patients were treatment-naïve; only 0.4% of patients were previously treated with DAAs. Moreover, 35.6% of the population were treated with first- and second-generation DAAs between 2015 and 2017. In this period, the main DAA regimen used was SOF/DCV (29.6%). The third generation DAA regimens (2017–2019) were: SOF/VEL 31.3%, GLE/PIB 28.7%, GZR/EBR 4.4%.

The overall PWUD SVR rate was 95.4%. SerDs group achieved an SVR rate of 96.2% compared with 91.6% in the non-SerDs group ($p<0.001$) (Table 2). Non-responder and relapse rates were 0.6% and 2.4% in SerDs group in comparison with 1.2% and 3.6% in non-SerDs group, respectively. Globally, only 0.7% stopped the antiviral therapy for side effects. The drop-out rate in SerDs and non-SerDs group was 0.5% and 2.8%, respectively ($p<0.001$) (Figure 1). No serious adverse events occurred during the treatment. One patient died of non-liver-related and non-therapy-related reasons. One patient underwent orthotopic liver transplantation. We compared the SVR rates of second-generation DAAs (prescribed in 2015–2017) with third generation DAAs (2017–2019): SVR rate was 92.6% and 97.3%, respectively ($p<0.0001$). The relapse rate was 5.0% and 1.0%, respectively ($p<0.001$) **(**Figure 2**)**.

A sub-analysis on HIV/HCV co-infected PWUD was also conducted: prevalence of male sex (76.8%) and genotype 3 (62.3%) was found. Most of them (84.1%) were followed in the SerDs and the prevalent DAA regimen was based on DCV (69.6%). The SVR rate was 95.7% with a drop-out rate of 1.4% (Table 3). A sub-analysis on HBV/HCV co-infected PWUD was not performed because the number was very small.

The comparison between PWUD and the control HCV group showed an SVR of 98.1% in the control group versus 95.4% in the overall PWUD population ($p<0.0001$). This difference of 2.7%, although is statistically significative, was not clinically meaningful. Furthermore, by calculating a power of 90% non-inferiority of the PWUD group compared to the control group greater than 5%, the difference obtained by 2.7% in the control group is not statistically significant. Moreover, the relapse rate was 0.2 in control group versus 2.4% and 3.6% in SerDs group and non-SerDs group, respectively ($p<0.001$).

Drop-out rate was lower in the SerDs group (0.6%) with respect to the non-SerDs group (2.8%) and control group (1.2%) ($p<0.0001$) (Figure 1).

Factors associated with response to treatment

Table 4 shows the results of multivariate logistic regression analysis adjusting for age, gender, baseline HCVRNA, genotypes, fibrosis stage, DAA used and SerD category. Only DAA regimen used and SerD category were the independent variables statistically associated with SVR.

A further stratification in order to evaluate SVR in the SerDs and non-SerDs groups with respect the new and old DAA regimens was also performed. The SerDs group achieved a statistically significant higher SVR rate compared to the non-SerDs group for both DAA regimens (97.9% vs 94.5%, p=0.01; 93.6% vs 87.5%, p=0.02, respectively) (Table 5).

DISCUSSION

The purpose of this research was to evaluate the safety and effectiveness of DAAs in a population of PWUDs in the real world. It is known that this patient population has always been listed as difficult-to-treat due to poor compliance. The results obtained were excellent with a global SVR of 95.4%, while the group of the co-infected patients with HIV obtained a similar result (95.7%); the control group obtained a statistically better result (98.1%, p<0.00001). The patients reported in this study have somewhat similar characteristics to the patients reported in the other studies in terms of genotypes, but, with regards to the number of co-infected, both HIV and HBV, the number is lower [1,9,10,19]. One of the relevant characteristics of this study, compared to the others, is the presence of a large number of patients suffering from compensated cirrhosis [20]. These data are in agreement with other studies conducted in Italy on patients who, in general, had a long history of drug abuse and a widespread contemporary use of heroin and cocaine [21-23]. Furthermore, this type of multiple abuse could also explain the excess mortality in patients co-infected with HCV, before the advent of the drugs we have today [24]. However, we believe that if this study has obtained excellent results also in a view of HCC prevention [25,26], both for the high percentage of SVR and for the high adherence to treatment, was because of the operating model adopted in our country.

To our knowledge, Italy is the only nation where PWUD are cared and managed in the SerDs, which

are specialized centres exclusively for PWUD, created about 40 years ago, in the holistic vision to protect their health for a lifetime, within rehabilitation programs performed by a multidisciplinary team. SerDs are disseminated homogeneously throughout Italy, accounting for 568 centres, and are present in all 20 Italian regions [12]. In this context, PWUD are not only regularly monitored for the OST, but also undergo periodic blood, physical and psychological examinations in the aim of a social recovery. Based on these considerations, we divided the study population into the two groups as described above. Our results showed a significantly higher SVR rate and treatment adherence among PWUD followed in the SerDs group.

Moreover, the drop-out rate among PWUD in SerDs group was significantly lower than the HCV control group. These data are mainly due to the success of this organizational system; in fact, the "non-SerDs" PWUD showed a significant lower adherence and SVR rate. Furthermore, the non-SerDs PWUD are predominantly current drugs users and this aspect represents a clear caveat about an unfavourable treatment adherence. In many clinical studies, Authors have mainly divided the population into OST and non-OST PWUD with quite different results, often due to the use of different recruiting methods [9,19,27].

Recently, an interesting study (Project ITTREAT), aimed to facilitate the access to HCV care in alcohol and drug abusers, by mitigating previous negative hospital-based experiences, has been published. The results indicated the positive impact of an integrated and personalized community-based service delivered by a dedicated hepatitis nurse similar to the Italian SerDs system [28]. At the multivariate analysis, the only factors independently associated with SVR were to be followed at SerDs and have been treated with third generation DAA regimens.

This study has some limitations. First, it is a real-life, not controlled study and the data collection was carried out by each participating centre; for this reason, there were some missing data that have partially limited the sub-analysis. Second, the non-drug-using control group was retrospectively evaluated by the platforms involved in management of HCV patients. The clinic and demographic characteristics were similar, but we did not perform a real case–control study. Nevertheless, the platform recruited HCV patients from the same geographical area, providing a suitable comparison group and reducing bias as

much as possible.

Finally, we assumed all recurrences of HCV as relapse rather than possible early re-infections; the distinction between the two conditions would have required the molecular sequence of the two genomes, hardly feasible in a real-practice study. In addition, the follow-up after the end of treatment limited to 12 weeks, could only guarantee an adequate information in term of relapse, but cannot estimate the long-term outcome. However, we believed that reinfection could mainly concern the non-SerDs group for the lack of control of the subjects and for the involvement in risky behaviours, such as further drug use [29]. Moreover, the non-SerDs group is only a small part of the population enrolled in this study. Our hypothesis is supported by data showing that, in patients who obtained SVR after DAAs therapy, reinfection is generally early post-treatment and associated with continuation or recent use of injection drugs during follow-up [30,31].

This real-life study, which has collected data from Italian SerDs is, to our knowledge, one of the largest European studies that prospectively evaluated a PWUD population and the impact of HCV treatment with DAAs. Despite the possible risk to treat this population, the SVR was higher than reported by any other experience with PWUD with a very low adverse events and improvement of depression and quality of life, ensured by an optimal therapeutic appropriateness [19-20,32,33].

In conclusion, the Italian SerD-based model is the pillar to optimize the effectiveness of the new-generation DAAs on PWUD, enhancing the path of the "micro-elimination" among them, towards global HCV elimination. Therefore, we would like to propose the Italian SerDs system, as the best model to treat this population, which has always been considered difficult-to-treat and therefore often marginalized. This is the only way to improve the health status of these particular patients and promote their social reintegration.

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Table 1. Baseline characteristics of patients (n=1801)	
Characteristics	**n (%)**[†]
Males	1496 (83.1)
Age (years), mean (SD)	50.2 (10.2)
Age ≤50 years	883 (49.0)
Caucasian	1759 (97.7)
Cirrhosis (Fibroscan or clinical diagnosis)	724 (40.2%)
HCV genotype:	
• 1a	491 (27.3)
• 1b	234 (13.0)
• 2	113 (6.3)
• 3	810 (45.0)
• 4	148 (8.2)
• Other*	5 (0.3)
Baseline HCV RNA $>10^6$ IU/mL	983 (54.6)
ALT (IU/L), median (IQR)	72 (75)
HBV coinfection**:	
• Negative	889 (53.8)
• HBsAg positive	43 (2.6)
• HBcAb positive	721 (43.6)
HIV coinfection	69 (3.8)
DAA treatment:	
• SOF/VEL or LDV ± RBV or VOX	563 (31.3)
• SOF/DCV ± RBV	533 (29.6)
• GLE/PIB	516 (28.7)

• GRZ/ELB	80 (4.4)
• Other	109 (6.1)
SERD[#]:	
• Yes	1460 (85.4)
• No	249 (14.6)
Previous treatments[##]:	
• Naïve	1274 (75.1)
• Peg-IFN/IFN with/without ribavirin	380 (22.4)
• First-generation PI	35 (2.1)
• DAA	7 (0.4)

[†]Unless otherwise specified.

*Genotype 7 (2 patients) and genotype mixed (3 patients); **Data available on 1653 patients (91.8%).

 Data on 1709 patients (94.9%); ##Data available on 1696 patients (94.2%).

DAA direct acting antivirals; SOF sofosbuvir; VEL velpatasvir; LDV ledipasvir; RBV ribavirin; VOX voxilaprevir; DCV daclatasvir; GLE glecaprevir; PBV pibrentasvir; GRZ grazoprevir; ELB elbasvir; SERD centres for drug addicts; IFN interferon

Table 2. Comparison between SerD and non-SerD (n=1709)

	SerD (n=1460), n (%)	**Non-SerD (n=249), n (%)**	**p-value**
Male, n (%)	1238 (84.8)	188 (75.5)	<0.001
Age (years), mean (SD)	49.4 (9.8)	53.0 (11.3)	<0.001
Genotype:			
• 1a	369 (25.3)	89 (35.7)	
• 1b	154 (10.5)	53 (21.3)	
• 2	65 (4.5)	28 (11.2)	<0.001
• 3	739 (50.6)	61 (24.5)	
• 4	129 (8.8)	17 (6.8)	
• Other*	4 (0.3)	1 (0.4)	
HCV RNA IU/mL × 10^6, mean (SD)	2.80 (6.01)	3.07 (8.54)	0.544
Clinical cirrhosis	299 (20.5)	53 (21.3)	0.771
Cirrhosis (Fibroscan)	304 (20.8)	41 (16.5)	0.250
Third generation DAA	884 (60.5)	145 (58.2)	0.490
SVR12 weeks	1404 (96.2)	228 (91.6)	<0.001
Drop out	9 (0.62)	8 (3.21)	<0.001

SERD centres for drug addicts; DAA direct acting antivirals; SVR sustained virological response

Table 3. Sub analysis of PWUD coinfected with HIV (n=69)

	N.	%
Age >50 years	43	62.3
Male	53	76.8
HCV RNA >6 MIU/mL	43	62.3
Genotype:		
• 1a	11	15.9
• 1b	7	10.1
• 2	3	4.3
• 3	43	62.3
• 4	5	7.2
Treatment:		
• SOF/VEL or LDV ± RBV or VOX	6	8.7
• GLE/PIB	13	18.8
• SOF/DCV ± RBV	48	69.6
• Other	2	2.9
SERD	58	84.1
SVR	66	95.7
Drop out	1	1.4

SOF sofosbuvir; VEL velpatasvir; LDV ledipasvir; RBV ribavirin; VOX voxilaprevir; GLE glecaprevir; PBV pibrentasvir; DCV daclatasvir; SERD centres for drug addicts; SVR sustained virological response

Table 4. Factors associated with sustained virologic response to DAA (#1709 patients)

	Beta coefficient	p	Odds Ratio (OR)	95% Confidence intervals for OR	
				lower	Upper
Antiviral treatment					
2D or 3D or SOF/SIM ±RBV			reference category		
GLE/PIB	2.390	<0.001	10.91	5.18	22.99
SOF/VEL or VOX ±RBV	2.26	<0.001	9.61	4.55	20.30
ELB/GRZ ±RBV	1.83	0.004	6.21	1.78	21.73
SOF/DCV ±RBV	1.77	<0.001	5.89	3.08	11.26
SOF/LDV ±RBV	1.12	0.016	3.07	1.23	7.64
SerD					
No			reference category		
Yes	0.70	0.011	2.02	1.17	3.48
Constant	0.76	0.015	2.139		

Multivariate logistic regression, backward stepwise (Likelihood Ratio) method. Dependent variable = SVR at week 12. Variables entered at step 1: age<50y vs >50y; gender; HCVRNA <6log vs ≥6log; GT 1a, 1b, 2, 3, 4 (reference category GT1a); fibrosis stage F1, F2, F3, F4 (reference category F1); Treatment DAA regimens: 1) 2D or 3D or SOF/SIM ±RBV, 2) GLE/PIB, 3) SOF/VEL or VOX ±RBV, 4) ELB/GRZ ±RBV, 5) SOF/DCV ±RBV, 6) SOF/LDV ±RBV (reference category #1); SerD category yes or no (reference category = no serD). Omnibus test of model coefficients: $\chi^2 = 56.74$; p <0.001; Hosmer and Lemeshow test: p 0.705; Negelkerke $R^2 = 0.106$

DAA direct acting antivirals; SOF sofosbuvir; SIM simepprevir; RBV ribavirin; GLE glecaprevir; PBV pibrentasvir; VEL velpatasvir; VOX voxilaprevir; GRZ grazoprevir; ELB elbasvir; DCV daclatasvir; LDV ledipasvir; SERD centres for drug addicts

Table 5. SVR in SerD and non-SerD group stratified for DAA regimen

	SVR, n (%)		**p-value**
	SerD ***(n=1460)***	***Non-SerD*** ***(n=249)***	
Third generation DAA (n=1029)	865/884 (97.9)	137/145 (94.5)	0.019
Second-generation DAA (n=576)	539/576 (93.6)	91/104 (87.5)	0.029
Total (n=1709)	1404/1460 (96.2)	228/249 (91.6)	<0.001

SVR sustained virological response; SERD centres for drug addicts

Figure legends:

Figure 1. Response to treatment in PWUD and control group

Figure 2. SVR rate of the old and new DAA regimen

Factors enhancing treatment of HCV infected Italian people who use drugs: the CLEO-GRECAS ~~real-world~~ experience

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Conflict of interest

The authors have no affiliations with or involvement in any organization or entity, with any financial interest or non- financial interest in the subject matter or materials discussed in this manuscript.

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Authors' contributions

Luca Rinaldi: study design, data collection, data analysis, data interpretation, writing and reviewing the paper. Vincenzo Messina, Vito Di Marco: data collection, data analysis, data interpretation and reviewing the paper. Vincenzo Iovinella, Ernesto Claar, Giuseppe Cariti, Rodolfo Sacco: data collection and reviewing the paper. Massimo de Luca: statistical analysis. Gaetano Scifo, Pietro Gatti, Giorgio Barbarini, Valeria Pace Palitti, Mariano Quartini, Paolo Tundo, Gianpiero D'Offizi, Giustino Parruti, Maria Antonietta di Rosolini, Giovanni Garrucciu, Lucio Cosco, Francesco Benanti, Giancarlo Gimignani, Umberto Vespasiani Gentilucci, Francesco Di Lorenzo, Maria D'Antò, Riccardo Nevola, Tommaso Lupia, Valerio Rosato, Valeria Morbiducci, Ilaria Luzzitelli, Federica Sozio, Marco Di Stefano, Emanuela Ciraci, Fabio Bulla, Riccardo Guarisco, Cecilia Cangiano, Michele Imparato, Paolo Maggi: data collection and reviewing the paper. Antonio Ascione, Antonio Craxì, Antonio Izzi: Study design, data interpretation, writing and reviewing the final version of the paper. All the authors approved the final version of the paper.

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Study highlights:

What is known

The lack of experience in the clinic real life of people who use drugs (PWUD) could be a bias in the evaluation of effectiveness of antiviral treatment by direct acting antivirals (DAAs).

What is new here:

The results showed the pivotal role of the close cooperation between the Centres for drug addicts (SerDs) and the territorial hepatologists Centres in the high SVR achievement.

PWUDs followed up at a SerD improves adherence to therapy, reduces dropouts and re-infections regardless of the degree of liver disease.

The Italian model has been successfully applied to a large national cohort and allowed comparable

results to non-drugs users.

Abstract

Objective We assessed the performance of direct-acting antivirals (DAAs) in hepatitis C virus (HCV)-infected people who use drugs (PWUD) in terms of sustained virological response (SVR) and adherence rates, in comparison to a location-matched cohort of non-PWUD HCV patients.

Methods All consecutive HCV RNA-positive PWUDs were enrolled between 2015 and 2019. All subjects underwent DAA treatment according to international guidelines and then followed, at least, up to 12 weeks after the end of treatment (SVR12). The SVR and the adherence to treatment was compared to that of non-PWUD HCV patients observed at hepatological units of the CLEO platform. Intention-to-treat analysis was performed.

Results 1786 PWUDs who were followed-up were available for assessment. The majority of PWUD (85.4%) were managed inside the specialized outpatient addiction clinics (SerDs). The overall SVR rate was 95.4%. The SerDs group achieved an SVR rate of 96.2% compared to 91.6% of the non-SerDs group ($p<0.001$). Comparison with non-SerDs group and the control HCV group showed a significant difference in the drop-out rate (0.6% in SerDs group versus 2.8% in non-SerDs group and 1.2% in control group; $p<0.001$). At multivariate analysis, factors independently associated with SVR were use of the most recent regimens (elbasvir/grazoprevir, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir; OR: 3.126; $p=0.000$) and belonging to the SerDs group (OR: 2.356; $p= 0.002$).

Conclusions The performance of DAAs is excellent ~~is comparable to that obtained in the normal population~~, if two conditions are met: a) that the latest generation drugs are used and that the patients are managed within the SerDs.

Keywords: Chronic hepatitis C, direct-acting antivirals, PWUD, centre for drug addict, adherence to treatment

INTRODUCTION

People who use drugs (PWUD) represent a large population worldwide and are a relevant contributor to HCV transmission. Overall, HCV infection among PWUD is estimated at around 50% [1]. In 2016, WHO faced the challenge to achieve the elimination of HCV infection and its spread by 2030 [2]. In this perspective, the European Association for the Study of Liver (EASL) and International Liver Foundation indicated HCV "micro-elimination" in certain selected populations in the path to reach global HCV elimination, starting from people most affected by the HCV infection, such as socially marginalized subjects or PWUD [3].

Globally, HCV treatment from direct-acting antivirals (DAAs) allowed a very high rate (>95%) of sustained virological response (SVR); since 2015, more than 2 million HCV- positive patients have undergone DAA treatment [4-6].

So far, the prevailing reluctance in the prescription of DAAs in the setting of PWUD could be explained by the barriers, which include the poor adherence, reduced tolerability and the risk of HCV reinfection. Moreover, some papers reported a very low compliance to treatment among PWUD in the interferon era, with approximately 1–2% of all HCV-infected patients treated yearly [7,8]. Conversely, two recent trials, showed an improvement in the DAA era, with a high SVR rate and adherence either in the PWUD setting or in patients treated with opioid substitution therapy (OST) [9,10]. These promising results obtained in the specific trials program could also apply to the large-scale real-world practice where the expected achievements could be less satisfactory. In Italy, DAA therapy has been prescribed for almost 205,000 patients at present, with a success rate of about 98% [11]. An estimated prevalence of HCV infection in Italian PWUD is about 50% with a 23% of new infections due to drug injection [12]; the management of PWUD is mainly performed in specialized outpatient centres for drug addicts (SerDs) [13]. The SerDs were established in Italy in 1990, with the task of taking care of patients with drug addiction disorders, alcohol and other forms of pathological addiction. The SerDs take care of the treatment, both on the pharmacological and psychological side, with the overall management

evaluating all the clinical aspects related to addiction. They also work on the side of primary and secondary prevention and social rehabilitation of a complex phenomenon with medical, neuropsychological as well as social and family consequences. In 2012, 543 drug addicts were evaluated in 25 Italian SerDs; the results of this study showed an HCV-Ab prevalence of 63.9%; however, only 19.3% of them received antiviral treatment [14].

To date, the exact proportion of HCV PWUD treated and the effectiveness of DAAs among PWUD in Italy is unknown.

In this perspective, the Italian CLEO-GRECAS group conducted a multicentre prospective real-world study, to evaluate the effectiveness and the adherence of DAA therapy in PWUD, most of them strictly followed within a continuous interdisciplinary collaborative programme between SerDs and territorial centres for liver diseases.

PATIENTS AND METHODS

Study design and patient population

This is an observational, retrospective/prospective, multicentre, real-world study conducted by an Italian group of Hospital and Academic hepatologists (Club Epatologi Ospedalieri [CLEO] – Gruppo Epatologico Clinico Associativo Siciliano [GRECAS]).

From 1 July 2015 to 1 June 2019, all consecutive HCV RNA serum-positive PWUD were recruited inside SerDs, which are distributed all over Italy or by dedicated liver centres. All stages of fibrosis and HCV genotype and co-infection with HBV or HIV were included in the study. Treatment-experienced to previous interferon PWUD were also enrolled.

Cirrhosis patients with decompensated liver disease or diagnosis of hepatocellular carcinoma (HCC), heart, kidney and pulmonary failure, pregnant women and people <18 years old were excluded.

All patients enrolled were submitted to clinical evaluation, standard biochemistry, ultrasound (US) and transient elastography by FibroScan following the standard criteria to evaluate the diagnosis and staging of liver disease. The diagnosis of cirrhosis was based on a compatible clinical picture and

laboratory parameters (platelet <90000 mm^3, albumin <2.5 g/dl), ultrasound parameters (coarse pattern, irregular liver surface, evidence of portal hypertension, such as splenomegaly) and/or liver stiffness >13.5 kPa. US was carried out at the baseline to exclude the presence of HCC [15].

Liver biopsy was not performed because it was judged unethical in this specific context.

PWUD were defined as people who have taken injection or non-injection drugs (i.e. by inhalator route) in the last 6 months, including receiving OST (information reported by SerDs or by dedicated hepatological centres at enrolment, determined by clinical visits or through positive urine/serum drug testing). People who use cannabis alone have not been classified as active addicts and were not included in the study. Each centre recorded the data directly on a specially prepared database.

PWUD were followed up for at least 12 weeks after the end of treatment. HCV relapse drop out during the treatment and the follow-up were recorded.

The management of the PWUD during all time of the study, including data report, was carried out through the interdisciplinary cooperation between hepatologists inside the SerDs and the reference territorial specialist centres.

A control group of HCV patients that underwent DAAs and never drugs users were taken from the CLEO platform.

The CLEO platform is an Italian multicentre cohort of clinical and academic hepatologists collecting data from several Liver Units of Italian Hospitals aimed at the optimization of care and research for patients with liver diseases.

Antiviral therapy

Patients underwent DAA therapy, following international guidelines [16,17]. Eligibility for DAA treatment was assessed by the priority criteria established first, in February 2015, by the Italian Medicines Agency Committee (AIFA) and then updated on March 2017 [11]. The DAA regimen and the treatment duration was chosen based on the availability of drugs, severity of liver disease and comorbidities, according to the Italian ministerial guidelines for DAA treatment and its update [18].

Patients enrolled were treated with either sofosbuvir + daclatasvir (SOF/DCV) ± ribavirin, ledipasvir

+ sofosbuvir (SOF/LED) ± ribavirin or ombitasvir/paritaprevir/ritonavir (2D) ± dasabuvir (3D) ± ribavirin. Since May 2017, patients were treated only with third-generation DAAs: elbasvir/grazoprevir (GRZ/EBR), glecaprevir/pibrentasvir (GLE/PIB) or sofosbuvir/velpatasvir (SOF/VEL).

Serum HCV RNA was assessed by real-time PCR (COBAS® TaqMan, AmpliPrep, Roche), with a lower detection limit of 15 IU/mL. Serum HCV RNA was first detected at baseline and then at the end of treatment (EOT). Lack of detectable serum HCV RNA at 12 weeks after EOT was defined as SVR12. Detection of serum HCV RNA after EOT and within the following 12 weeks was defined as relapse.

Demographic characteristics and clinical parameters at baseline, HIV or HBV co-infection, chronic alcohol intake (>30 g/daily for more than 5 years, 20 g/daily for women), substance abuse and the OST were recorded.

Endpoints of the study

The primary endpoint was to assess the safety and effectiveness of DAA therapy in the setting of PWUD by detection of SVR12 and adherence to therapy.

Additional endpoints were a comparison between the results obtained by SerD and non-SerD patients, and a sub-analysis comparing the cohort of PWUD and a control group of HCV patients who never used drugs (CLEO platform), in order to evaluate the effectiveness and the adherence to DAA therapy.

Statistical analysis

Continuous variables were reported as the mean with standard deviation or the median with interquartile range (IQR), and categorical variables were reported as number and percentages with 95% confidence interval (CI). Comparison between categorical variables were performed using chi-square or Fisher's exact test when appropriate. For all statistical comparisons, a two-tailed significance level of 0.05 was used. Multivariate analysis was performed using logistic regression to evaluate independent factors associated with SVR12 to DAAs. Moreover, a stratification analysis for type of DAA was also performed to better assess the association between SerDs group and SVR in each DAA group. For all statistical comparisons, a two-tailed significance level of 0.05 was used. Analysis was performed using statistical software package IBM SPSS Statistics for Windows, Version 25.0 (SPSS

Inc. Chicago, IL, USA). Intention-to-treat analysis was performed.

Ethics

The study was performed according to the 1976 Declaration of Helsinki and its later amendments and approved by our Internal Review Board. All patients gave their informed consent to the study.

RESULTS

Baseline characteristics of study population

A total of 1801 PWUD were enrolled, out of which 1786 completed the follow-up according to the study design. The study population was distributed as follows in the different Italian regions: 14.1% from northern Italy, 29.7% from central Italy, 36.4% from southern Italy and 19.8% from the islands. The baseline demographic and clinical features of the patients are shown in Table 1. In particular, we observed a strong prevalence of the male sex (83.1%) with a mean±SD age of 50.2±10.2 years. A total of 40.2% were cirrhotic patients. The most frequent HCV genotypes were genotype 3 (45%) and genotype 1a (27.3%). Two genotype 7s were also found. HCV RNA >6 Log IU/mL was found in 983 (54.6%) patients. HBV co-infection was 2.6%, while HIV co-infection was 3.8%; alcohol users were 21.2%.

The majority of PWUD (85.4%) were routinely followed within the SerDs (SerDs group) and were undergoing contemporary treatment with OST: methadone 59.6%, buprenorphine 8.8%, naloxone plus buprenorphine 6.5% and naltrexone 20%. The remaining 14.6%, reported a current drug use and was followed by liver centres (non-SerDs group). The SerDs group showed a prevalence of male (84.8%); age of 49±9.8 years; HCV genotype 3 (50.6%) in comparison with the non-SerDs group in which prevalence of male gender (75.5%), older age (53±11.3 years) and HCV genotype 1a (35.7%) were found ($p<0.001$) (Table 2).

Overall, the substances used were heroin 35.2%, cocaine 10.3% and opiates 8.6%; 44.8% were contemporary cocaine and heroin users.

Response to antiviral treatment

In total, 75.1% of patients were treatment-naïve; only 0.4% of patients were previously treated with DAAs. Moreover, 35.6% of the population were treated with first- and second-generation DAAs between 2015 and 2017. In this period, the main DAA regimen used was SOF/DCV (29.6%). The third-generation DAA regimens (2017–2019) were: SOF/VEL 31.3%, GLE/PIB 28.7%, GZR/EBR 4.4%.

The overall PWUD SVR rate was 95.4%. SerDs group achieved an SVR rate of 96.2% compared with 91.6% in the non-SerDs group ($p<0.001$) (Table 2). Non-responder and relapse rates were 0.6% and 2.4% in SerDs group in comparison with 1.2% and 3.6% in non-SerDs group, respectively. Globally, only 0.7% stopped the antiviral therapy for side effects. The drop-out rate in SerDs and non-SerDs group was 0.5% and 2.8%, respectively ($p<0.001$) (Figure 1). No serious adverse events occurred during the treatment. One patient died of non-liver-related and non-therapy-related reasons. One patient underwent orthotopic liver transplantation. We compared the SVR rates of second-generation DAAs (prescribed in 2015–2017) with third-generation DAAs (2017–2019): SVR rate was 92.6% and 97.3%, respectively ($p<0.0001$). The relapse rate was 5.0% and 1.0%, respectively ($p<0.001$) (Figure 2).

A sub-analysis on HIV/HCV co-infected PWUD was also conducted: prevalence of male sex (76.8%) and genotype 3 (62.3%) was found. Most of them (84.1%) were followed in the SerDs and the prevalent DAA regimen was based on DCV (69.6%). The SVR rate was 95.7% with a drop-out rate of 1.4% (Table 3). A sub-analysis on HBV/HCV co-infected PWUD was not performed because the number was very small.

The comparison between PWUD and the control HCV group showed an SVR of 98.1% in the control group versus 95.4% in the overall PWUD population ($p<0.0001$). This difference of 2.7%, although is statistically significative, was not clinically meaningful. Furthermore, by calculating a power of 90% non-inferiority of the PWUD group compared to the control group greater than 5%, the difference obtained by 2.7% in the control group is not statistical significant. Moreover, the relapse rate was 0.2 in control group versus 2.4% and 3.6% in SerDs group and non-SerDs group, respectively ($p<0.001$).

Drop-out rate was lower in the SerDs group (0.6%) with respect to the non-SerDs group (2.8%) and

control group (1.2%) (p<0.0001) (Figure 1).

Factors associated with response to treatment

Table 4 shows the results of multivariate logistic regression analysis adjusting for age, gender, baseline HCVRNA, genotypes, fibrosis stage, DAA used and SerD category. Only DAA regimen used and SerD category were the independent variables statistically associated with SVR.

~~In the univariate analysis, the SerDs group and third-generation DAAs were associated with a better SVR rate. At multivariate analysis (data corrected for age, gender, baseline HCV RNA, cirrhosis, old vs new DAA regimen, SerDs vs non-SerDs group), third-generation DAA regimen (odds ratio [OR]: 3.126; p=0.000) and the SerDs group (OR: 2.356; p=0.002) were independently associated with SVR (Table 4).~~

A further stratification in order to evaluate SVR in the SerDs and non-SerDs groups with respect the new and old DAA regimens was also performed. The SerDs group achieved a statistically significant higher SVR rate compared to the non-SerDs group for both DAA regimens (97.9% vs 94.5%, p=0.01; 93.6% vs 87.5%, p=0.02, respectively) (Table 5).

DISCUSSION

The purpose of this research was to evaluate the safety and effectiveness of DAAs in a population of PWUDs in the real world. It is known that this patient population has always been listed as difficult-to-treat due to poor compliance. The results obtained were excellent with a global SVR of 95.4%, while the group of the co-infected patients with HIV obtained a similar result (95.7%); the control group obtained a statistically better result (98.1%, p<0.00001). The patients reported in this study have somewhat similar characteristics to the patients reported in the other studies in terms of genotypes, but, with regards to the number of co-infected, both HIV and HBV, the number is lower [1,9,10,19]. One of the relevant characteristics of this study, compared to the others, is the presence of a large number of patients suffering from compensated cirrhosis [20]. These data are in agreement with other studies conducted in Italy on patients who, in general, had a long history of drug abuse and a widespread

contemporary use of heroin and cocaine [21-23]. Furthermore, this type of multiple abuse could also explain the excess mortality in patients co-infected with HCV, before the advent of the drugs we have today [24]. However, we believe that if this study has obtained excellent results also in a view of HCC prevention [25,26], both for the high percentage of SVR and for the high adherence to treatment, was because of the operating model adopted in our country.

To our knowledge, Italy is the only nation where PWUD are cared and managed in the SerDs, which are specialized centres exclusively for PWUD, created about 40 years ago, in the holistic vision to protect their health for a lifetime, within rehabilitation programs performed by a multidisciplinary team. SerDs are disseminated homogeneously throughout Italy, accounting for 568 centres, and are present in all 20 Italian regions [12]. In this context, PWUD are not only regularly monitored for the OST, but also undergo periodic blood, physical and psychological examinations in the aim of a social recovery. Based on these considerations, we divided the study population into the two groups as described above. Our results showed a significantly higher SVR rate and treatment adherence among PWUD followed in the SerDs group.

Moreover, the drop-out rate among PWUD in SerDs group was significantly lower than the HCV control group. These data are mainly due to the success of this organizational system; in fact, the "non-SerDs" PWUD showed a significant lower adherence and SVR rate. Furthermore, the non-SerDs PWUD are predominantly current drugs users and this aspect represents a clear caveat about an unfavourable treatment adherence. In many clinical studies, Authors have mainly divided the population into OST and non-OST PWUD with quite different results, often due to the use of different recruiting methods [9,19,27].

Recently, an interesting study (Project ITTREAT), aimed to facilitate the access to HCV care in alcohol and drug abusers, by mitigating previous negative hospital-based experiences, has been published. The results indicated the positive impact of an integrated and personalized community-based service delivered by a dedicated hepatitis nurse similar to the Italian SerDs system [28]. At the multivariate analysis, the only factors independently associated with SVR were to be followed at SerDs and have been treated with third-generation DAA regimens.

This study has some limitations. First, it is a real-life, not controlled study and the data collection was carried out by each participating centre; for this reason, there were some missing data that have partially limited the sub-analysis. Second, the non-drug-using control group was retrospectively evaluated by the platforms involved in management of HCV patients. The clinic and demographic characteristics were similar, but we did not perform a real case–control study. Nevertheless, the platform recruited HCV patients from the same geographical area, providing a suitable comparison group and reducing bias as much as possible.

Finally, we assumed all recurrences of HCV as relapse rather than possible early re-infections; the distinction between the two conditions would have required the molecular sequence of the two genomes, hardly feasible in a real-practice study. In addition, the follow-up after the end of treatment limited to 12 weeks, could only guarantee an adequate information in term of relapse, but cannot estimate the long-term outcome. However, we believed that reinfection could mainly concern the non-SerDs group for the lack of control of the subjects and for the involvement in risky behaviours, such as further drug use [29]. Moreover, the non-SerDs group is only a small part of the population enrolled in this study. Our hypothesis is supported by data showing that, in patients who obtained SVR after DAAs therapy, reinfection is generally early post-treatment and associated with continuation or recent use of injection drugs during follow-up [30,31].

This real-life study, which has collected data from Italian SerDs is, to our knowledge, one of the largest European studies that prospectively evaluated a PWUD population and the impact of HCV treatment with DAAs. Despite the possible risk to treat this population, the SVR was higher than reported by any other experience with PWUD with a very low adverse effects and improvement of depression and quality of life, ensured by an optimal therapeutic appropriateness [19-20,32,33].

In conclusion, the Italian SerD-based model is the pillar to optimize the effectiveness of the new-generation DAAs on PWUD, enhancing the path of the "micro-elimination" among them, towards global HCV elimination. Therefore, we would like to propose the Italian SerDs system, as the best model to treat this population, which has always been considered difficult-to-treat and therefore often marginalized. This is the only way to improve the health status of these particular patients and promote

their social reintegration.

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Table 1. Baseline characteristics of patients (n=1801)	
Characteristics	**n (%)**[†]
Males	1496 (83.1)
Age (years), mean (SD)	50.2 (10.2)
Age ≤50 years	883 (49.0)
Caucasian	1759 (97.7)
Cirrhosis (FibroScan or clinical diagnosis)	724 (40.2%)
HCV genotype:	
• 1a	491 (27.3)
• 1b	234 (13.0)
• 2	113 (6.3)
• 3	810 (45.0)
• 4	148 (8.2)
• Other*	5 (0.3)
Baseline HCV RNA >10^6 IU/mL	983 (54.6)
ALT (IU/L), median (IQR)	72 (75)
HBV coinfection**:	
• Negative	889 (53.8)
• HBsAg positive	43 (2.6)
• HBcAb positive	721 (43.6)
HIV coinfection	69 (3.8)
DAA treatment:	
• SOF/VEL or LDV ± RBV or VOX	563 (31.3)
• SOF/DCV ± RBV	533 (29.6)
• GLE/PIB	516 (28.7)

• GRZ/ELB	80 (4.4)
• Other	109 (6.1)
SERD[#]:	
• Yes	1460 (85.4)
• No	249 (14.6)
Previous treatments[##]:	
• Naïve	1274 (75.1)
• Peg-IFN/IFN with/without ribavirin	380 (22.4)
• First-generation PI	35 (2.1)
• DAA	7 (0.4)

[†]Unless otherwise specified.

*Genotype 7 (2 patients) and genotype mixed (3 patients); **Data available on 1653 patients (91.8%).

Data on 1709 patients (94.9%); ##Data available on 1696 patients (94.2%).

DAA direct acting antivirals; SOF sofosbuvir; VEL velpatasvir; LDV ledipasvir; RBV ribavirin; VOX voxilaprevir; DCV daclatasvir; GLE glecaprevir; PBV pibrentasvir; GRZ grazoprevir; ELB elbasvir; SERD centres for drug addicts; IFN interferon

Table 2. Comparison between SerD and non-SerD (n=1709)

	SerD (n=1460), n (%)	Non-SerD (n=249), n (%)	p-value
Male, n (%)	1238 (84.8)	188 (75.5)	<0.001
Age (years), mean (SD)	49.4 (9.8)	53.0 (11.3)	<0.001
Genotype:			
• 1a	369 (25.3)	89 (35.7)	
• 1b	154 (10.5)	53 (21.3)	
• 2	65 (4.5)	28 (11.2)	<0.001
• 3	739 (50.6)	61 (24.5)	
• 4	129 (8.8)	17 (6.8)	
• Other*	4 (0.3)	1 (0.4)	
HCV RNA IU/mL × 10^6, mean (SD)	2.80 (6.01)	3.07 (8.54)	0.544
Clinical cirrhosis	299 (20.5)	53 (21.3)	0.771
Cirrhosis (FibroScan)	304 (20.8)	41 (16.5)	0.250
Third-generation DAA	884 (60.5)	145 (58.2)	0.490
SVR12 weeks	1404 (96.2)	228 (91.6)	<0.001
Drop out	9 (0.62)	8 (3.21)	<0.001

SERD centres for drug addicts; DAA direct acting antivirals; SVR sustained virological response

Table 3. Subanalysis of PWUD coinfected with HIV (n=69)

	N.	%
Age >50 years	43	62.3
Male	53	76.8
HCV RNA >6 MIU/mL	43	62.3
Genotype:		
• 1a	11	15.9
• 1b	7	10.1
• 2	3	4.3
• 3	43	62.3
• 4	5	7.2
Treatment:		
• SOF/VEL or LDV ± RBV or VOX	6	8.7
• GLE/PIB	13	18.8
• SOF/DCV ± RBV	48	69.6
• Other	2	2.9
SERD	58	84.1
SVR	66	95.7
Drop out	1	1.4

SOF sofosbuvir; VEL velpatasvir; LDV ledipasvir; RBV ribavirin; VOX voxilaprevir; GLE glecaprevir; PBV pibrentasvir; DCV daclatasvir; SERD centres for drug addicts; SVR sustained virological response

Table 4. Factors associated with sustained virologic response to DAA (n=1801)				
Variables	SVR (n=1718)	Univariate p-value	Adjusted OR (95% CI)	Multivariate p-value
Age:				
≤50 years	840 (95.1)	0.604	0.65 (0.398 - 1.54)	0.08
>50 years	878 (95.6)			
Gender:				
Male	1426 (95.3)	0.752	0.638 (0.319 - 1.274)	0.202
Female	292 (95.7)			
SerD*:				
Yes (1460)	1404 (96.2)	0.001	2.356 (1.371 - 4.046)	0.002
No (249)	228 (91.6)			
HCV genotype:				
1a	469 (95.5)		1.306 (0.646 - 2.643)	0.458
1b	225 (96.2)	0.493	2.329 (0.875 - 6.196)	0.09
3	775 (95.7)		1.439 (0.750 - 2.763)	0.274

Other	249 (93.6)		ref.	ref.
Baseline HCV RNA:	785 (96.0)			
<6 MIU/mL		0.289	0.768 (0.475 - 1.242)	0.282
≥6 MIU/mL	333 (94.8)			
DAA therapy:				
Third generation	1045 (97.3)	0.0001	3.126 (1.899 - 5.145)	<0.001
Second generation	673 (92.6)			

*Analysis based on 1709 patients

Table 4. Factors associated with sustained virologic response to DAA (#1709 patients)

	Beta coefficient	p	Odds Ratio (OR)	95% Confidence intervals for OR	
				lower	Upper
Antiviral treatment					
2D or 3D or SOF/SIM ±RBV			reference category		
GLE/PIB	2.390	<0.001	10.91	5.18	22.99
SOF/VEL or VOX ±RBV	2.26	<0.001	9.61	4.55	20.30
ELB/GRZ ±RBV	1.83	0.004	6.21	1.78	21.73
SOF/DCV ±RBV	1.77	<0.001	5.89	3.08	11.26
SOF/LDV ±RBV	1.12	0.016	3.07	1.23	7.64
SerD					
No			reference category		
Yes	0.70	0.011	2.02	1.17	3.48
Constant	0.76	0.015	2.139		

Multivariate logistic regression, backward stepwise (Likelihood Ratio) method. Dependent variable = SVR at week 12. Variables entered at step 1: age<50y vs >50y; gender; HCVRNA <6log vs ≥6log; GT 1a, 1b, 2, 3, 4 (reference category GT1a); fibrosis stage F1, F2, F3, F4 (reference category F1); Treatment DAA regimens: 1) 2D or 3D or SOF/SIM ±RBV, 2) GLE/PIB, 3) SOF/VEL or VOX ±RBV, 4) ELB/GRZ ±RBV, 5) SOF/DCV ±RBV, 6) SOF/LDV ±RBV (reference category #1); SerD category yes or no (reference category = no serD). Omnibus test of model coefficients: $\chi^2 = 56.74$; p <0.001; Hosmer and Lemeshow test: p 0.705; Negelkerke $R^2 = 0.106$

DAA direct acting antivirals; SOF sofosbuvir; SIM simepprevir; RBV ribavirin; GLE glecaprevir; PBV pibrentasvir; VEL velpatasvir; VOX voxilaprevir; GRZ grazoprevir; ELB elbasvir; DCV daclatasvir; LDV ledipasvir; SERD centres for drug addicts

Table 5. SVR in SerD and non-SerD group stratified for DAA regimen

	SVR, n (%)		**p-value**
	SerD ***(n=1460)***	***Non-SerD*** ***(n=249)***	
Third-generation DAA (n=1029)	865/884 (97.9)	137/145 (94.5)	0.019
Second-generation DAA (n=576)	539/576 (93.6)	91/104 (87.5)	0.029
Total (n=1709)	1404/1460 (96.2)	228/249 (91.6)	<0.001

SVR sustained virological response; SERD centres for drug addicts

Figure legends:

Figure 1. Response to treatment in PWUD and control group

Figure 2. SVR rate of the old and new DAA regimen

Figure 1

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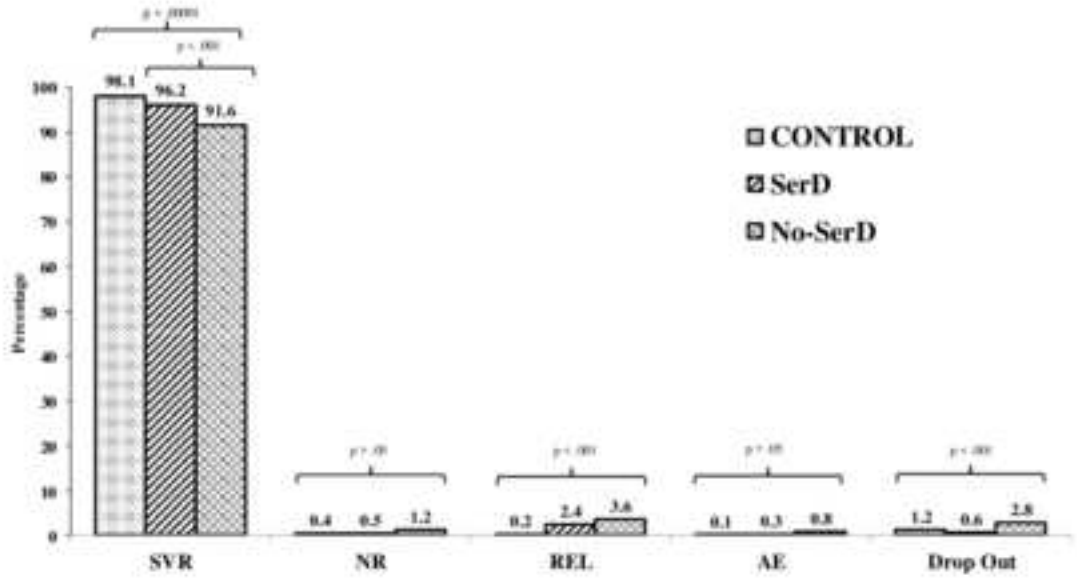

Figure 1

Figure 2

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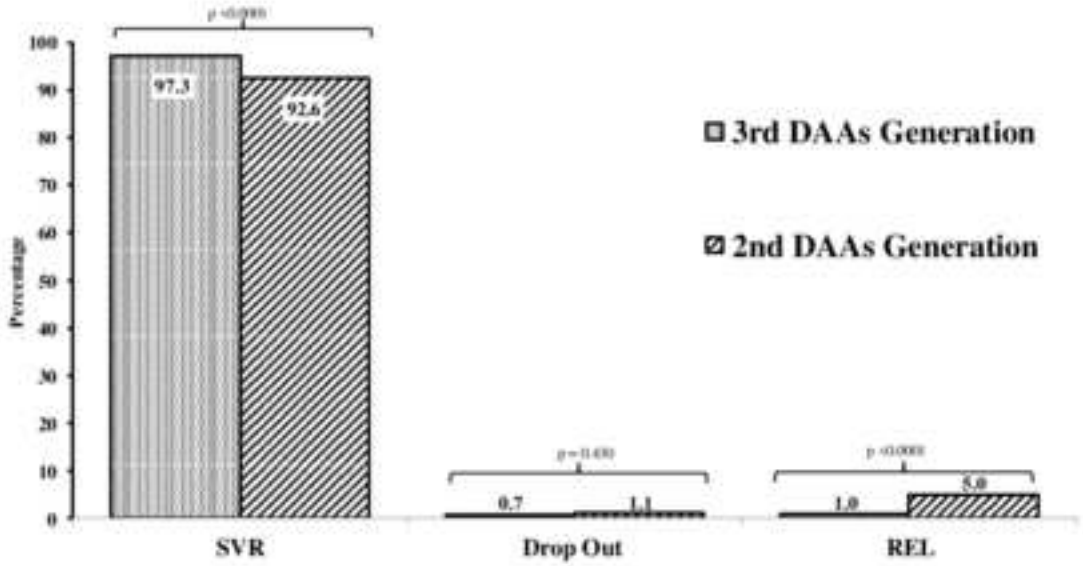

Figure 2