Research Article
Viral Hepatitis

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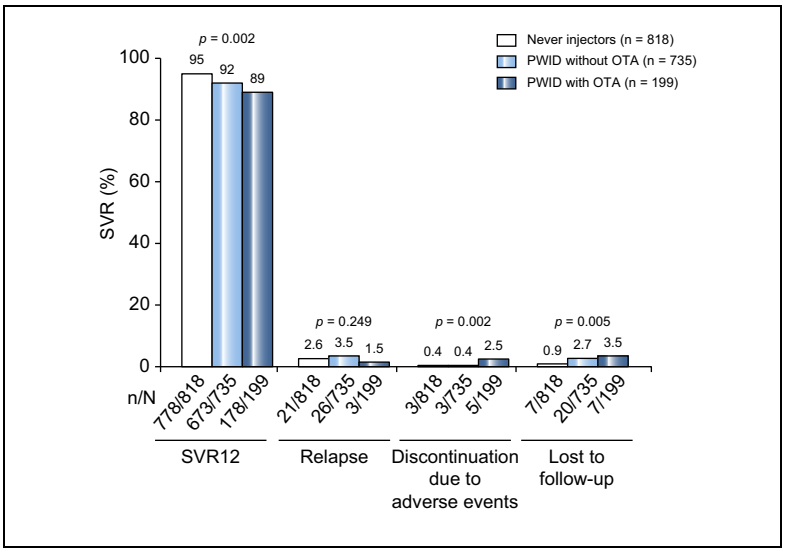
Response to direct-acting antiviral therapy among ongoing drug users and people receiving opioid substitution therapy

Graphical abstract



Highlights

- HCV-infected PWID achieve high SVR12 rates with IFN-free antiviral regimens in clinical practice.
- PWID have lower SVR12 rates than patients who never used drugs.
- Active drug use during antiviral treatment was an independent predictor of lower response, opioid agonist therapy was not.
- The main reasons for non-response among PWID are discontinuations due to adverse events and, particularly, drop-outs.

Authors

Juan Macías, Luis E. Morano, Francisco Téllez, ..., Antonio Rivero, Federico García, Juan A. Pineda

Correspondence

juan.macias.sanchez@gmail.com
(J. Macías)

Lay summary

Patients with hepatitis C virus infection who are on opioid agonist therapy can achieve high cure rates with current treatments. The use of illicit drugs during treatment can drive drop-outs and reduce cure rates. However, hepatitis C can be cured in most of those using drugs who complete treatment and follow-up.

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Response to direct-acting antiviral therapy among ongoing drug users and people receiving opioid substitution therapy

Juan Macías[1,*], Luis E. Morano[2], Francisco Téllez[3], Rafael Granados[4], Antonio Rivero-Juárez[5], Rosario Palacios[6], MªJosé Ríos[7], Dolores Merino[8], Montserrat Pérez-Pérez[9], Antonio Collado[10], Blanca Figueruela[11], Aitana Morano[2], Carolina Freyre-Carrillo[3], José M. Martín[12], Antonio Rivero[5], Federico García[13], Juan A. Pineda[1], for the HEPAVIR group from the Sociedad Andaluza de Enfermedades Infecciosas (SAEI) and the GEHEP group from the Sociedad Española de Enfermedades Infecciosas y Microbiología (SEIMC)

[1]*Infectious Diseases and Microbiology Unit, Hospital Universitario de Valme, Seville, Spain;* [2]*Infectious Diseases Unit, Hospital Universitario Alvaro Cunqueiro, Vigo, Spain;* [3]*Infectious Diseases and Microbiology Unit, Hospital Universitario de Puerto Real, School of Medicine, Cadiz University, Instituto de Investigación e Innovación en Ciencias Biomédicas de la Provincia de Cádiz (INiBICA), Cadiz, Spain;* [4]*Infectious Diseases Unit, Hospital Universitario de Gran Canaria Dr. Negrín, Gran Canaria, Spain;* [5]*Infectious Diseases Unit, Hospital Universitario Reina Sofía, Instituto Maimonides de Investigación Biomedica de Córdoba (IMIBIC), Cordoba University, Cordoba, Spain;* [6]*Infectious Diseases, Microbiology and Preventive Medicine Unit, Hospital Universitario Virgen de la Victoria, Malaga, Spain;* [7]*Infectious Diseases Unit, Hospital Universitario Virgen Macarena, Seville, Spain;* [8]*Infectious Diseases Unit, Hospital Universitario Juan Ramón Jiménez, Huelva, Spain;* [9]*Infectious Diseases and Microbiology Unit, Hospital de La Línea, Cadiz, Spain;* [10]*Infectious Diseases Unit, Hospital Torrecárdenas, Almeria, Spain;* [11]*Digestive Diseases Unit, Hospital Universitario de Valme, Seville, Spain;* [12]*Infectious Diseases Unit, Hospital Universitario de Gran Canaria Dr. Negrín, Gran Canaria, Spain;* [13]*Microbiology Service, Hospital Universitario San Cecilio, Granada, Spain*

Background & Aims: People who inject drugs (PWID) and are on opioid agonist therapy (OAT) might have lower adherence to direct-acting antivirals (DAAs) against hepatitis C virus (HCV) and, therefore, lower rates of sustained virologic response (SVR). Because of this, we compared the SVR rates to interferon-free DAA combinations in individuals receiving OAT and those not receiving OAT in a real-world setting.

Methods: The HEPAVIR-DAA cohort, recruiting HIV/HCV-coinfected patients (NCT02057003), and the GEHEP-MONO cohort (NCT02333292), including HCV-monoinfected individuals, are ongoing prospective multicenter cohorts of patients receiving DAAs in clinical practice. We compared SVR 12 weeks after treatment (SVR12) in non-drug users and PWID, including those receiving or not receiving OAT. Intention-to-treat and per protocol analyses were performed.

Results: Overall, 1,752 patients started interferon-free DAA treatment. By intention-to-treat analysis, 778 (95%, 95% CI 93%–96%) never injectors, 673 (92%, 95% CI 89%–93%) PWID not on OAT and 177 (89%, 95% CI 83%–92%) PWID on OAT achieved SVR12 ($p = 0.002$). SVR12 rates for ongoing drug users (with or without OAT) were 68 (79%) compared with 1,548 (95%) for non-drug users ($p < 0.001$). Among ongoing drug users, 15 (17%) were lost-to-follow-up, and 3 (3.5%) became reinfected. In the per protocol analysis, 97% never injectors, 95% PWID not on OAT and 95% PWID on OAT achieved SVR12 ($p = 0.246$). After adjustment, ongoing drug use was associated with SVR12 (intention-to-treat) and OAT use was not.

Conclusions: HCV-infected PWID achieve high SVR12 rates with DAAs whether they are on OAT or not, but their response rates are lower than those of patients who never used drugs. This is mainly attributable to more frequent loss to follow-up. Accounting for active drug use during DAA therapy nearly closed the gap in SVR rates between the study groups.

Lay summary: Patients with hepatitis C virus infection who are on opioid agonist therapy can achieve high cure rates with current treatments. The use of illicit drugs during treatment can drive drop-outs and reduce cure rates. However, hepatitis C can be cured in most of those using drugs who complete treatment and follow-up.

Clinical trial number: HEPAVIR-DAA cohort, NCT02057003; GEHEP-MONO cohort, NCT02333292.

Introduction

The epidemic of hepatitis C virus (HCV) infection has been driven in many countries by parenteral transmission through shared needles among people who inject drugs (PWID).[1,2] Some reports have found that many PWID have a high willingness to receive HCV treatment.[3,4] However, treatment uptake in the interferon era among PWID was very low, with about 1–2% of all HCV-infected PWID treated yearly.[5,6] Most probably, this low incorporation of PWID to HCV treatment was due to barriers at different levels, including the poor tolerability of interferon. Simple, highly effective and safer all-oral direct-acting antivirals (DAAs) should have increased the uptake of HCV

Keywords: HCV; People who injected drugs; Opioid agonist therapy; Direct-acting antiviral agents; Sustained virologic response.
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* Corresponding author. Address: Juan Macías. Infectious Diseases and Microbiology Unit, Hospital Universitario de Valme, Avda Bellavista s/n, 41014 Seville, Spain. Tel.: +34 955015736.
E-mail address: juan.macias.sanchez@gmail.com (J. Macías).

treatment among PWID. Indeed, current guidelines support the need to scale up treatment in PWID to effectively impact the HCV epidemic.[7,8] However, patients with ongoing drug use or on opioid agonist therapy (OAT) are ineligible in some settings[9] or might not be considered suitable to receive DAAs by some practitioners.[10] To further complicate the scenario, PWID with HCV infection have been underrepresented in most clinical trials with DAAs.[11–14] Indeed, only a few trials have specifically assessed treatment with all-oral DAA regimens in individuals on OAT.[15–18]

In real-world conditions, the efficacy of DAAs may be lower, there may be more frequent severe adverse events, and there may be a higher rate of loss to follow-up and reinfection than in clinical trials. In a large study of people receiving stable OAT and DAA therapy, approximately two-thirds of PWID on stable OAT used illicit drugs before and during treatment with DAA combinations.[16,18] Due to concerns regarding the impact of ongoing drug use on adherence, response to therapy, and potential for reinfection, there are some clinicians who may not offer DAA therapy to people with ongoing drug use.[19] Moreover, the DAA efficacy reported in patients on OAT, based on trials with specific programs to supervise and enhance adherence, may not be generalizable to other people using drugs in the real-world setting.[15–17] Supervision of adherence within some clinical trials using electronic devices[17,18] or dedicated health care professionals to follow patients day by day[16,17] is ideal but not available nor reimbursed in most settings. Therefore, real-world studies assessing the efficacy of currently used HCV therapy in PWID on OAT are required. In the present study, we compared the rates of sustained virologic response (SVR) to interferon-free DAA combinations among individuals receiving or not receiving OAT in routine clinical practice.

Patients and methods

Design and patients

This was a prospective multicohort study of HCV-infected patients who started DAA combinations in 33 Infectious Diseases Units in Spain and who were recruited at the HEPAVIR-DAA cohort (NCT02057003) or at the GEHEP-MONO cohort (NCT02333292). The HEPAVIR-DAA cohort, which includes HIV/HCV-coinfected patients, and the GEHEP-MONO cohort, which recruits HCV-monoinfected individuals, are ongoing prospective multicenter cohorts of patients receiving DAA combinations prescribed in clinical practice. Patients included in both cohorts were managed within the same Infectious Diseases Units, regardless of HIV or drug use status. Patients were referred from primary care settings, including drug addiction clinics, to Infectious Diseases Units for HCV treatment. Patients were managed in a specialized setting that is separated from OAT programs.

All patients included in these cohorts who fulfilled the following criteria were included in the present analysis: i) Chronic HCV infection by any genotype; ii) Treatment with interferon-free DAA combination; iii) To have reached the scheduled date for SVR12 assessment.

Medications and follow-up

The first interferon-free DAA combinations were introduced in the cohorts in 2013. Since then, sofosbuvir (SOF) plus ribavirin (RBV), SOF plus daclastavir (DCV) with or without RBV, SOF plus simeprevir (SMV) with or without RBV, SOF/ledipasvir (LDV) with or without RBV, paritaprevir-ritonavir/ombitasvir plus dasabuvir (PrOD) with or without RBV, and paritaprevir-ritonavir/ombitasvir (PrO) with RBV and elbasvir/grazoprevir (EBR/GZR) have been prescribed in the Units participating in the cohorts. For the present analysis, patients treated with a SOF plus RBV regimen were excluded. The SOF plus RBV combination was excluded because it yields suboptimal responses, particularly in genotype 3 infections, which are more frequently found in PWIDs.

Patients were evaluated before starting therapy to assess whether they were candidates for treatment. A specific Plan for Tackling Hepatitis C in Spain, launched in 2015, stated that all patients with chronic hepatitis C must be considered candidates for antiviral treatment.[20] Some situations were considered as top-priority groups, among them those with a high risk of transmission, as recent or active drug users.

The DAA regimen was chosen based on the availability of DAAs, concomitant medications and comorbidities, and guidelines in force in Spain.[21] The caring physician took the final decision on individual DAA regimens. During treatment, patients were evaluated at baseline, the date of starting therapy, at week 4 and at the date of completing treatment. SVR was defined as plasma HCV RNA below the limit of detection 12 weeks after treatment completion. Afterwards, patients were evaluated at 24 weeks.

We considered as PWID all individuals with current or former injecting drug use. People with a history of injecting drug use (reported injecting drug use ever), people with recent drug use at the time of treatment commencement (in the previous 12 months), and people with ongoing drug use (reported injecting or non-injecting drug use during treatment) were identified by retrospective chart review of databases, clinical records and laboratory records. Ongoing drug use was determined by self-report at clinical visits or through positive urine drug testing. Individuals using cannabis alone were not classified as active drug users. OAT is managed by drug addiction facilities in Spain. Data on OAT use among patients included in the cohorts is prospectively recorded.

Laboratory determinations

Among patients with reemergence of HCV viremia after the completion of therapy, the NS5B polymerase, NS3 protease and/or NS5A protein were Sanger sequenced using assays developed *in house*[22] on samples both at failure and baseline time points, where available. To discriminate reinfection from relapse we used at least 2 regions from HCV genome, and if reinfection by a different genotype was observed next-generation sequencing of the NS5B PCR product was performed on both samples to rule out mixed infection. Reinfection was defined as a difference in HCV genotype or subtype, or as a significantly different clustering located in different clades in the phylogenetic tree; relapse was defined as significant clustering in the same clade using concatenated NS3-NS5A-NS5B, NS3-NS5A, NS3-NS5B or NS5A-NS5B sequences aligned by neighbor-joining and maximum-likelihood approaches.[23]

Statistical analysis

The primary outcome variable was SVR12 evaluated by intention-to-treat (ITT), considering all missing data at the date of SVR12 assessment as failures. Secondary sensitivity analyses were carried out following a per protocol (PP) approach. In the PP analysis, patients who voluntarily dropped-out or those with missing data were excluded.

Continuous variables were expressed as median (Q1-Q3) and categorical variables as number (%). The Chi-square test or the Fisher's exact test, when appropriate, was used to compare proportions among treatment groups. The 1-way ANOVA test or the Kruskal-Wallis test, whenever necessary, was applied for comparisons of continuous variables among groups. A multivariate logistic regression was carried out to identify factors independently associated with SVR12. Variables associated with SVR12 with a univariate p value ≤0.2, age categorized by 50 years and gender were entered into the model. Data were analyzed using IBM SPSS 24.0 version (IBM Corporation, Somers, NY, USA) and STATA 9.0 (StataCorp LP, College Station, TX, USA).

Ethics

The study was designed and performed according to the Helsinki declaration and was approved by the local Ethics Committee. All patients gave their written informed consent before being included in the cohorts.

For further details regarding the materials used, please refer to the CTAT table.

Results

Baseline characteristics of the study population

Overall, 1,752 patients included in the cohorts started interferon-free DAA combinations between June 2013 and March 2017. Out of them, 818 (47%) participants reported no history of injecting drug use, 735 (42%) had a history of injecting drug use and were not receiving OAT and 199 (11%) had a history of injecting drug use and were receiving OAT (including methadone, n = 192; buprenorphine, n = 4; buprenorphine/naloxone, n = 3). Among PWID, 11% (103 of 934) reported recent drug use (47 of 199 in those receiving OAT) and 0.9% (8 of 934) reported recent injecting drug use (8 of 199 in those receiving OAT). The characteristics of the patients according to their history of injecting drug use and OAT at the date of starting DAA therapy are summarized in Table 1. There were significant differences among the groups in factors including the frequency of HIV coinfection, HCV genotype distribution, pretreatment with peg-interferon plus ribavirin or the proportion of individuals with cirrhosis. DAA combinations prescribed by group of patients are displayed in Table 2.

Response to treatment

In the ITT analysis, 93% (95% CI 91%–94%, n/N = 1,628/1,752) of patients achieved SVR12. The SVR12 rate was 95% (95% CI 93%–96%, n/N = 778/818) among people without a history of injecting drug use, 92% (95% CI 89%–93%, n = 673/735) among PWID not receiving OAT and 89% (95% CI 83%–92%, n = 177/199) among PWID receiving OAT (p = 0.002, Fig. 1). Both discontinuations of treatment due to adverse events and loss to follow-up were more frequent in the group of PWID receiving OAT (Fig. 1). Fifty-three patients had viral relapse after the end of treatment response, 20 (38%) of them could be evaluated by phylogenetic

Table 1. Baseline characteristics of the patients.

Characteristic	No history of injecting drugs (n = 818)	History of injecting drugs not receiving OAT (n = 735)	History of injecting drugs receiving OAT (n = 199)	p value
Male gender, n (%)	509 (62)	628 (85)	182 (92)	<0.001
Age[1], years	54 (49–63)	50 (47–54)	48 (45–51)	<0.001
HIV infection, n (%)	192 (24)	574 (78)	134 (67)	<0.001
HCV genotype[2], n (%)				<0.001
1a	252 (31)	313 (43)	89 (45)	
1b	369 (45)	127 (17)	35 (18)	
1 other	21 (2.6)	34 (4.6)	13 (6.5)	
3	54 (6.6)	91 (12)	22 (11)	
4	119 (15)	169 (23)	39 (20)	
HCV RNA[1], Log_{10} UI/ml	6.2 (5.8–6.6)	6.3 (5.8–6.7)	6.1 (5.5–6.5)	0.197
Previous treatment with PegIFN plus ribavirin, n (%)	408 (50)	370 (50)	59 (30)	<0.001
Liver stiffness[1,3], KPa	12.2 (8.3–21)	14.4 (9.5–27)	21.1 (10.4–34)	<0.001
Cirrhosis[4], n (%)	354 (44)	362 (50)	113 (57)	0.001
DAA combination, n (%)				<0.001
SOF plus DCV with/without RBV	74 (9)	133 (18)	30 (15)	
SOF plus SMV with/without RBV	111 (13)	137 (18)	24 (12)	
SOF/LDV with/without RBV	423 (51)	286 (38)	101 (51)	
PrOD with/without RBV	179 (22)	143 (19)	31 (16)	
PrO with RBV	31 (3.7)	36 (4.8)	9 (4.5)	
EBR/GZR	0	0	4 (2)	

Study cohort, n = 1,752.
DAA, direct-acting antiviral; DCV, daclastavir; EBR/GZR, elbasvir/grazoprevir; HCV, hepatitis C virus; LDV, ledipasvir; PegIFN, pegylated-interferon; PrO, paritaprevir-ritonavir/ombitasvir; PrOD, paritaprevir-ritonavir/ombitasvir plus dasabuvir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbubir.
[1] Median (Q1–Q3).
[2] Three patients were infected by genotype 5 in the group with no history of injecting drug use, 1 patient with a history of injecting drug use receiving OAT and 1 not receiving OAT carried mixed genotypes.
[3] Liver stiffness was available in 766 patients with no history of injecting drug use, 728 patients with history of injecting drug use not receiving OAT and 197 patients receiving OAT.
[4] Cirrhosis was diagnosed in patients with a liver biopsy showing fibrosis stage 4, or with liver stiffness ≥12.5 kPa, or with a previous decompensation of cirrhosis. The diagnosis of cirrhosis was available in 805 patients with no history of injecting drug use, 728 patients with history of injecting drug use not receiving OAT and 197 patients receiving OAT. p values refer to the Chi-square test or the Fisher's exact test, when appropriate, to compare proportions among treatment groups; and the 1-way ANOVA test or the Kruskal-Wallis test, whenever necessary, for comparisons of continuous variables among groups.

Table 2. Virologic and non-virologic outcomes.

Outcome	No history of injecting drugs (n = 818)	History of injecting drugs not receiving OAT (n = 735)	History of injecting drugs receiving OAT (n = 199)	*p* value
Discontinuation due to adverse events, n (%)	3 (0.4)	3 (0.4)	5 (2.5)	0.002
Lost-to-follow up during treatment[1], n (%)	7 (0.9)	20 (2.7)	7 (3.5)	0.005
Death, n (%)	3 (0.4)	7 (1)	4 (2)	0.054
Viral breakthrough, n (%)	1 (0.1)	1 (0.1)	2 (1)	0.051
Lost-to-follow up after the end of treatment, n (%)	0	1 (0.1)	0	0.500
SVR12, n (%)	778 (95)	673 (92)	178 (89)	0.002
Relapse, n (%)	21 (2.6)	26 (3.5)	3 (1.5)	0.249
Reinfections, n (%)	0	1 (0.1)	2 (1)	0.008

DAA, direct-acting antiviral; OAT, opioid agonist therapy; SVR, sustained virologic response; SVR12, SVR at 12 weeks; SVR24, SVR at 24 weeks.
[1] One patient with history of injecting drugs receiving OAT abandoned treatment and follow-up after 5 weeks, he was engaged to care 9 months after starting DAA and SVR24 was confirmed; he is now classified as having achieved SVR12. *p* values refer to the Chi-square test or the Fisher's exact test, when appropriate, to compare proportions among treatment groups.

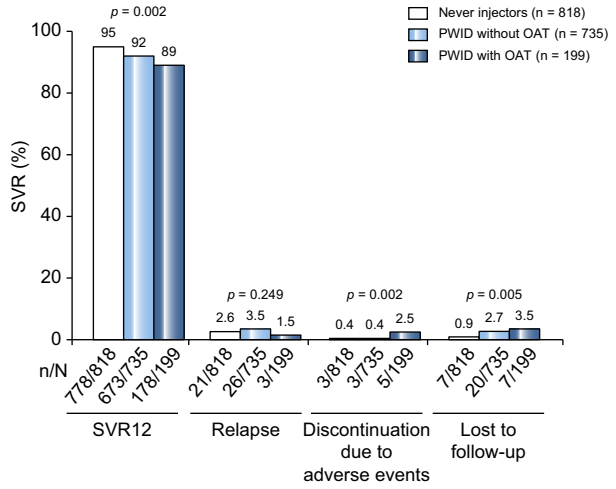

Fig. 1. Response to all-oral direct antiviral combinations among patients without history of injecting drugs, and PWID either receiving or not receiving OAT. *P* values refer to the Chi-squared test or, where appropriate, the Fisher's test. OAT, opioid agonist therapy; PWID, people who inject drugs; SVR, sustained virologic response; SVR12, SVR at 12 weeks.

analysis of samples at baseline and at the date of SVR12 evaluation. Out of 52 relapses with the same HCV genotype, 17 of them were confirmed as relapses by phylogenetic analysis. Three patients were classified as reinfections by phylogenetic analysis. They were active drug users, who achieved SVR 4 weeks after the end of therapy and became reinfected by the date of SVR12. One of them was reinfected by a different HCV genotype. Virologic and non-virologic outcomes by study group are summarized in Table 2 and Table S1. In the PP analysis, 97% (778 of 808) of patients that never injected drugs, 95% (673 of 708) of PWID not receiving OAT and 95% (178 of 188) of PWID receiving OAT achieved SVR12 ($p = 0.246$).

Among 934 PWID evaluated in the study, we were able to gather information on drug use status during DAA treatment in 915 (96%) of them. Eighty-six (9%) PWID used drugs during treatment, namely 42 (5.8%) PWID not receiving OAT and 44 (23%) PWID receiving OAT. Baseline characteristics of patients with ongoing drug use are summarized in Table S2. The rates of SVR12 for ongoing drug users were 79% (68 of 86) compared with 95% (1,548 of 1,632) for individuals without ongoing drug use during treatment ($p < 0.001$). Among the 86 ongoing drug users during treatment, 15 (17%) were lost-to-follow-up, there were no discontinuations due to adverse effects nor viral breakthrough. The remaining 71 individuals reached end of treatment response and SVR4. Afterwards, 3 (3.5%) of them were reinfected by the date of SVR12. In the PP analysis, the proportion with SVR12 among people with ongoing drug use during treatment was 96% (68 of 71) compared with 96% (1,548 of 1,616) in individuals without ongoing drug use ($p = 0.994$). Among individuals who reported recent drug use before starting DAAs, 80% (82 of 103) reached SVR12. Fifteen (15%) were lost to follow-up, 3 (2.9%) relapsed and 3 (2.9%) were reinfected.

Factors associated with response to treatment

In the univariate analysis, ongoing drug use during treatment, HIV coinfection, HCV genotype 3 and cirrhosis were also associated with lower rates of SVR12 (Table 3). In the multivariate analysis, adjusted for age and gender, ongoing drug use during treatment, HCV genotype 3, cirrhosis, and HIV coinfection were independent predictors of response (Table 3). After controlling for other variables, PWID did not have a lower likelihood of SVR12, whether or not they received OAT (Table 3).

Discussion

HCV-infected PWID, particularly active drug users, have a lower SVR12 rate to DAA combinations in clinical practice. This fact is mainly attributable to higher rates of discontinuations due to adverse events and, especially, loss to follow-up, and not to virologic failure. A number of key factors related with a lower likelihood of SVR are more frequently observed in PWIDs, but accounting for ongoing drug use during DAA therapy nearly closed the gap in SVR rates between the study groups.

One of the barriers to DAA access is physicians, who are often reticent to prescribe DAAs to individuals with potentially ongoing drug use.[10,19] In the EDGE CO-STAR trial, adherence to EBR/GRZ was similar to that in other interferon-free DAA trials in the general HCV population, which excluded patients with active drug use.[16] However, the intensive adherence monitoring in the EDGE CO-STAR is hard to transfer to clinical practice in a real-world setting. In the present study, PWID with and without OAT, who were outside a specific adherence program, achieved high SVR rates. The frequency of loss to follow-up was small for

Table 3. Factors associated with sustained virologic response (ITT) to direct-acting antiviral combinations.

Variable	n	SVR12[1] n (%)	Univariate *p* value	Adjusted odds ratio (95% CI)	Multivariate *p* value
Age			0.431		0.112
>50 years	780	729 (94)		0.7 (0.46–1.09)	
≤50 years	972	899 (93)			
Gender			0.099		0.644
Male	1,319	1,218 (92)		0.88 (0.52–1.51)	
Female	433	410 (95)			
History of injecting drugs			0.002		0.409
No	818	778 (95)		Reference category	
Yes not receiving OAT	735	673 (92)		1.46 (0.84–2.56)	
Yes receiving OAT	199	177 (89)		1.34 (0.64–2.83)	
Active drug use during treatment			<0.001		<0.001
Yes	86	68 (79)		0.22 (0.11–0.42)	
No	1,632	1,548 (95)			
HIV infection			0.008		0.036
Yes	900	822 (91)		0.57 (0.34–0.96)	
No	852	806 (95)			
HCV genotype[2]			0.012		0.115
1a	722	668 (93)		Reference category	
1b	531	506 (95)		1.20 (0.67–2.14)	0.542
3	167	147 (88)		0.53 (0.28–1.01)	0.050
4	327	302 (92)		0.76 (0.44–1.30)	0.317
Baseline HCV RNA			0.335		–
<6 MIU/ml	1,490	1,381 (93)			
≥6 MIU/ml	262	247 (94)			
Cirrhosis[3]			<0.001		<0.001
Yes	829	750 (91)		0.46 (0.30–0.71)	
No	901	858 (95)			
Previous treatment			0.322		–
No	913	843 (92)			
Yes	837	783 (94)			
DAA combination			0.445		–
SOF + DCV ± RBV	237	215 (91)			
SOF + SMV ± RBV	272	248 (91)			
SOF/LDV ± RBV	810	757 (94)			
PrOD ± RBV	353	333 (94)			
PrO + RBV	76	71 (93)			
EBR/GZR	4	4 (100)			

DAA, direct-acting antiviral; DCV, daclastavir; EBR/GZR, elbasvir/grazoprevir; HCV, hepatitis C virus; ITT, intention-to-treat; LDV, ledipasvir; OAT, opioid agonist therapy; PrO, paritaprevir-ritonavir/ombitasvir; PrOD, paritaprevir-ritonavir/ombitasvir plus dasabuvir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.
[1] SVR12: Sustained virologic response 12 weeks after the scheduled end of treatment.
[2] Genotype 1a includes for this analysis genotype 1a plus mixed subtypes of genotype 1 and other non-1b subtypes.
[3] Available in 1,730 patients. Univariate *p* values refer to the Chi-square test. Multivariate *p* values correspond to multivariate logistic regression analysis.

PWID, but higher than for patients who never injected drugs. Moreover, early discontinuations and loss to follow-up in PWIDs had an impact on the overall response in the present study. In the present study, the response results among PWIDs on OAT are mostly in agreement with other real-world studies. Among people receiving OAT treated with DAA combinations in clinical practice, SVR was 84%–100%.[17] In a recent analysis of the German Hepatitis C registry, the ITT SVR rate was lower among people receiving OAT than those not receiving OAT, namely 85% *vs.* 91%.[24] This lower response was mainly driven by a higher frequency of loss to follow-up in those receiving OAT. Thus, as in the herein reported study, the PP analysis yielded similar SVR rates for those with and without OAT.[24] Among PWID, with and without recent drug use, real-world studies of DAA therapy have demonstrated SVR rates of 80%–96%, which are in agreement with our results. Again, the majority of non-response occurred as a result of loss to follow-up. Therefore, the present study and previous study results suggest that practical strategies to enhance treatment retention among PWIDs are needed, given that some approaches followed in clinical trials are difficult to implement in daily practice. The potential strategies include: providing OAT and DAA therapy at the same institutions, which has demonstrated better results in the German Hepatitis C registry;[24] peer support or patient navigators,[25] which are alternatives if OAT and DAA treatment cannot be provided at the same location; cash incentives, which may improve linkage to care and treatment outcomes.[26]

Active drug use during treatment was frequently observed in the study cohorts. One-fourth of PWID on OAT and 6% of PWID not on OAT reported being active drug users. In a trial in patients on OAT, more than 50% of the participants had positive results in urinary drug screening.[16] The proportion of patients on OAT identified as active drug users in the present study is lower than that found in the EDGE CO-STAR trial. This finding is likely due to an underestimation of active drug use in our study. In spite of this, an analysis that did not include patients with drug use during therapy, identified by review of archived records, increased the SVR rates of PWID groups. In fact, similar SVR rates were found among patients who never injected drugs and PWID, receiving or not receiving OAT, in analyses that did not include individuals with current drug use. Additionally, PWID status was not associated with lower SVR likelihood after adjustment for drug use during treatment with DAAs in the multivariate analysis. As a consequence, interventions to

improve adherence to DAAs in PWID at risk of drug use recurrence are needed in real-world settings.

We found that some expected baseline factors, such as cirrhosis and HCV genotype 3, were associated with SVR. In addition, we found that HIV coinfection was related to lower SVR rates. We have reported this association before[27] and a lower rate of SVR has been found in patients with lower CD4 cell count.[28] Herein, we confirm our previous results in a larger study, after considering the use of drugs and inclusion in OAT programs. Some experts, based on the results of DAA trials, have considered that HIV/HCV-coinfected patients should not be regarded as a "special population" or a "difficult to cure" group.[29] However, DAA trial results may have limited generalizability, since the majority of HIV/HCV-coinfected individuals in real-world cohorts were not eligible to participate.[11,30] Other authors have not found a negative effect of HIV coinfection on the response to DAAs in observational studies.[28,31] However, as stated above, worse SVR rates among those with lower CD4 cell counts have recently been reported.[32] Finally, treatment of acute HCV infection in HIV seropositive patients with short duration regimens, that are efficacious in HIV seronegative individuals, yields suboptimal SVR rates.[33,34] Therefore, DAA treatment in HIV/HCV-coinfected patients should be managed conservatively, offering them DAA regimens with high proven efficacy in HIV/HCV coinfection.

This study may have some limitations. First, illicit drug use during DAA was retrospectively assessed. Thus, an underestimation of drug use during treatment is likely. Most probably, we classified as ongoing drug users those with a more disruptive behavior, with more frequent and problematic drug use. Importantly, these people with more problematic drug use may be more likely to skip appointments and abandon follow-up. Second, there were large differences in strong predictors of SVR among patients who never injected drugs and PWIDs. These differences could explain the lower rates of SVR among PWIDs. However, we found that SVR rates were similar among groups in PP analyses, which means that differences in response were mainly because of DAA discontinuations due to adverse effects and loss to follow-up. In addition, an analysis restricted to patients without active drug use during treatment gave similar results. Third, reinfections were not systematically evaluated in patients with relapse and reinfections should have been regarded as treatment successes. Because of this, reinfections might have gone unnoticed in the study population. This might have underestimated the SVR rate, particularly among patients with ongoing drug use. However, the period of observation after the end of treatment was limited to 12 weeks and most patients were not engaged in ongoing risk behaviors, we assume that most recurrences must have been true relapses, rather than reinfections. In addition, as stated above, lower rates of SVR among patients on OAT were due to a higher rate of discontinuations, rather than to relapses. Fourth, the PWID without OAT group comprised both abstinent drug users and ongoing drug users not engaged in OAT programs. The latter are a set of patients that could be harder to treat, and that might lower SVR results in the PWID without OAT group. However, ongoing drug users represented a small proportion of PWID without OAT. This study reports real-world results of interferon-free DAA efficacy in cohorts that included a large group of PWID, either receiving or not receiving OAT. Our results lend support to the efficacy of all-oral DAA combinations for PWIDs on OAT found in clinical trials[15,16] and generalize those results to a broader population managed with different DAA combinations, which is a strength of our study.

In conclusion, HCV cure rates with interferon-free DAA combinations are high among PWID, either receiving or not receiving OAT. However, the overall efficacy of DAAs in active drug users is lower, mainly because of loss to follow-up. Thus, strategies targeting drug users to reduce their risk of abandoning follow-up are needed.

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Conflict of interest

JM has been an investigator in clinical trials supported by Bristol-Myers Squibb, Gilead and Merck Sharp & Dome. He has received lectures fees from Gilead, Bristol-Myers Squibb, and Merck Sharp & Dome, and consulting fees from Bristol-Myers-Squibb, Gilead, and Merck Sharp & Dome. JAP reports having received consulting fees from Bristol-Myers Squibb, Abbvie, Gilead, Merck Sharp & Dome, and Janssen Cilag. He has received research support from Bristol-Myers Squibb, Abbvie and Gilead and has received lecture fees from Abbvie, Bristol-Myers Squibb, Janssen Cilag, and Gilead. DM has received lectures fees from Abbvie, Gilead, ViiV Healthcare, Janssen Cilag, and Merck Sharp & Dome, and consulting fees from Janssen Cilag. The remaining authors report no conflict of interest.

Authors' contributions

Juan Macías: Study design, data collection, data analysis, data interpretation, writing and reviewing the paper. Luis E. Morano: Data collection, data analysis, data interpretation, reviewing the paper. Francisco Téllez: Data collection, data analysis, data interpretation, reviewing the paper. Rafael Granados: Data collection, data analysis, data interpretation, reviewing the paper. Antonio Rivero-Juárez: Data collection, data analysis, data interpretation, reviewing the paper. Rosario Palacios: Data collection, data analysis, data interpretation, reviewing the paper. Mª José Ríos: Data collection, data analysis, data interpretation, reviewing the paper. Dolores Merino: Data collection, data analysis, data interpretation, reviewing the paper. Montserrat Pérez-Pérez: Data collection, data analysis, data interpretation, reviewing the paper. Antonio Collado: Data collection, data analysis, data interpretation, reviewing the paper. Blanca Figueruela: Data collection, data analysis, data interpretation, reviewing the paper. Aitana Morano: Data collection, data

analysis, data interpretation, reviewing the paper. Carolina Freyre-Carrillo: Data collection, data analysis, data interpretation, reviewing the paper. José M. Martin: Data collection, data analysis, data interpretation, reviewing the paper. Antonio Rivero: Data collection, data analysis, data interpretation, reviewing the paper. Federico García: Phylogenetic analysis, data interpretation, writing and reviewing the paper. Juan A. Pineda: Study design, data collection, data analysis, data interpretation, writing and reviewing the paper.

Supplementary data

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