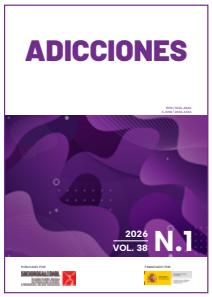
SOCIDROGALCOHOL
Sociedad Científica Española de Estudios sobre el Alcohol, el Alcoholismo y las otras Toxicomanías

ADICCIONES
2026 ■ VOL. 38 ■ N. 1 ■ PAGES 25–40
www.adicciones.es



ORIGINAL

Hepatitis C therapy with pangenotypic direct-acting antivirals: Drug-drug interactions in drug-using HCV patients and antipsychotic-treated HCV patients

Tratamiento de hepatitis C con antivirales pangenotípicos de acción directa: Interacciones farmacológicas en pacientes que consumen drogas y tratados con antipsicóticos

Juan Turnes*; Antonio García-Herola**; Marinela Méndez***; Cándido Hernández****; Alfonsina Trento*****; Ramón Morillo-Verdugo******; Francisco Pascual*******; Ignacio Hernandez*****.

* Department of Gastroenterology and Hepatology, CHU. Pontevedra, Spain.
** Digestive Diseases Section. Hospital Marina Baixa, Villajoyosa (Alicante), Spain.
*** Medical Affairs, Gilead Sciences S.L., Madrid, Spain.
**** Global Medical Affairs, Gilead Sciences Europe Ltd., United Kingdom.
***** Health Economics and Outcomes Research, Atrys Health, Barcelona, Spain.
****** Hospital Pharmacy, Hospital de Valme, AGS South of Seville, Spain.
******* Socidrogalcohol, Barcelona, Spain. [Advisor to CAARFE. Researcher, Prevengo Group UMH. Coordinator UCA-Alcoi. Ibero Ciência Group].

Abstract

People who use drugs (PWUD) are at high risk of hepatitis C virus (HCV) infection, and HCV patients often have psychiatric disorders requiring nervous system drugs, including antipsychotics. These medicines can interact with HCV treatment-related metabolic pathways producing DDIs (drug-drug interactions). This analysis focused on potential DDIs between direct-acting antivirals (DAAs) and concomitant medications used in PWUD/antipsychotics-treated HCV patients, alongside associated adverse events (AEs) and clinical interventions in Spain. Electronic medical records (BIG-PAC® database) were used to analyse adult HCV patients treated with glecaprevir/pibrentasvir (GLE/PIB) or sofosbuvir/velpatasvir (SOF/VEL) between 2017-2020. The study included 1,620 HCV patients, 985 identified as PWUD and 187 as antipsychotic users, 75% of whom were also PWUD. In the PWUD cohort, cardiovascular (CV) comorbidities were the most frequent; 22.7% patients were at risk of DDIs with CV, with the risk being higher in GLE/PIB-treated (36.8%) versus SOF/VEL (13.7%) (p<0.001). Cardiovascular AEs were more common in the GLE/PIB group. In the antipsychotic cohort, quetiapine was the most prescribed antipsychotic comedication (26.2%), followed by paliperidone (17.6%) and olanzapine (17.1%). Fifty-one per cent of those on GLE/PIB were at risk of DDIs versus 23% on SOF/VEL (p<0.001). Two AEs were reported in the GLE/PIB group (n=37): one patient on quetiapine at a dose <300mg/day experienced extrapyramidal symptoms, leading to DAA discontinuation, and another paliperidone-treated experienced sedation, necessitating a dose reduction. The findings highlight DDIs risks in HCV patients on antipsychotics or with substance addiction, particularly with GLE/PIB. Comprehensive clinical follow-up is essential to optimise treatment and improve patient safety.

Keywords: Hepatitis C virus, people who use drugs, drug-drug interactions, antipsychotic medication, direct-acting antivirals

Resumen

Los usuarios de drogas (UD) tienen un alto riesgo de infección por el virus de la hepatitis C (VHC), y muchos pacientes con VHC presentan trastornos psiquiátricos que requieren medicación del sistema nervioso, incluidos antipsicóticos. Estos medicamentos pueden interactuar con los antivirales de acción directa (AAD), produciendo interacciones farmacológicas (IF). En este estudio, nos centramos en las potenciales IF entre AAD y medicaciones concomitantes utilizadas en estos pacientes, así como en los eventos adversos (EA) asociados e intervenciones clínicas en España. El estudio, basado en registros electrónicos de BIG-PAC®, analizó a adultos tratados con glecaprevir/pibrentasvir (GLE/PIB) o sofosbuvir/velpatasvir (SOF/VEL) entre 2017 y 2020. Se incluyeron 1.620 pacientes con VHC, 985 UD y 187 usuarios de antipsicóticos, de los cuales el 75% también eran UD. En la cohorte UD, las comorbilidades cardiovasculares fueron más frecuentes; el 22,7% presentaba riesgo de IF con medicación cardiovascular, mayor con GLE/PIB que con SOF/VEL (36,8% vs.13,7%, p<0,001). Los EA cardiovasculares fueron más frecuentes en GLE/PIB. En la cohorte de antipsicóticos, quetiapina fue el más prescrito (26,2%), seguida de paliperidona (17,6%) y olanzapina (17,1%). El 51% de los tratados con GLE/PIB presentó riesgo de IF, frente al 23% con SOF/VEL (p<0,001). Se reportaron dos EA en GLE/PIB: un paciente con quetiapina (<300 mg/día) presentó síntomas extrapiramidales y otro con paliperidona sufrió sedación, que requirió suspensión o ajuste. Los resultados subrayan el riesgo de IF en estas cohortes, especialmente en pacientes con GLE/PIB, destacando la necesidad de un seguimiento clínico estrecho para optimizar la seguridad del tratamiento.

Palabras clave: virus de la Hepatitis C, usuarios de drogas, interacciones farmacológicas, antipsicóticos, antivirales de acción directa

■ *Received: February 2025; Accepted: January 2026.*

■ ISSN: 0214-4840 / E-ISSN: 2604-6334

■ **Corresponding author:**
Ignacio Hernández. Health Economics and Outcomes Research Department, Atrys Health. Calle Príncipe de Vergara, 132, planta 1.
Email: ihernandez@atryshealth.com

Chronic hepatitis C virus (HCV) infection affects an estimated 50 - 58 million individuals worldwide (POLARIS, 2024; World Health Organisation, 2023). The primary treatment for HCV are pangenotypic direct-acting antiviral agents (DAAs). Between 2014 and 2022, 13.2 million patients worldwide were treated for HCV using DAAs, 82% in sofosbuvir-based regimens (Voeller et al., 2023). DAAs are usually well tolerated; however, patients often present comorbidities that require concomitant medications, and these medications may cause potential drug-drug interactions (DDIs) that must be considered when choosing a DAA (European Association for the Study of the et al., 2020). These potential DDIs can either result in drug toxicity or reduced efficacy of either the DAA or the concomitant medications (Gao et al., 2021). Therefore, meticulous patient management is crucial for DAAs to achieve optimal treatment outcomes (Dick et al., 2016). Modern DAA based regimens, such as sofosbuvir/velpatasvir (SOF/VEL) and glecaprevir/pibrentasvir (GLE/PIB) present lower risk of DDIs than first-generation DAAs (Schulte et al., 2020). Despite this, around 40% of HCV patients present DDIs, commonly related to interactions of DAAs and the metabolic pathways involved in the patient's comedications (Moore et al., 2019; Schulte et al., 2020).

People who use drugs (PWUDs) have a higher risk of contracting HCV infection (Pineda et al., 2020). According to a recent systematic review, worldwide, more than 50% of PWUDs are positive for HCV antibodies (Degenhardt et al., 2017). Indeed, in England, PWUDs represent around 80% of all HCV infections, which reflects the disproportionate burden of disease in this group (Di Marco et al., 2022). Additionally, HCV infection is 3 to 20 times more common in patients with severe mental illness, who are often treated with nervous system drugs (Fiore et al., 2023). Historically, interferon-based HCV treatment caused neuropsychiatric side effects, which led to the exclusion of these patients from therapy and from clinical trials (Fiore et al., 2023; Rifai et al., 2010). Barriers such as poor adherence, limited healthcare access, stigma, and vulnerability further hindered treatment efficacy (Gutierrez-Rojas et al., 2023).

Despite these facts, few studies have comprehensively evaluated the use of comedication and the risk of DDIs in PWUDs with HCV who are treated with DAA (Hintz et al., 2021; Nava et al., 2023). None of these have studied adverse events (AEs) related to DDIs. These limited studies have also shown that the use of antipsychotics is frequent among PWUD, even among those who are not infected with HCV (Hintz et al., 2021; Nava et al., 2023; Rifai et al., 2010).

We recently assessed DDIs' clinical impact, including AEs and efficacy, in HCV patients treated with SOF/VEL and GLE/PIB, the two most widely used DAAs (Turnes et al., 2024). We found that 77.5% of HCV patients were on ≥2 comedications, with almost 10% at risk of multiple DDIs (≥2 DDIs). To shed some light on two of the most vulnerable groups of patients, we conducted a sub-analysis to assess the incidence and severity of DDIs in PWUDs and antipsychotic users treated with DAAs within a real-life cohort in Spain.

Methods

Study design and data collection

We conducted a sub-analysis of a database compiled for our recently published retrospective observational study on HCV patients treated with DAAs (Turnes et al., 2024). Briefly, anonymised patient electronic medical records (EMR) were obtained from the BIG-PAC® database (representative of the Spanish population), which compiles primary data from public primary care centres and hospitals across seven autonomous communities in Spain (Sicras-Mainar et al., 2019). EMR confidentiality (anonymous and dissociated) was respected according to the European General Data Protection Regulation (2016/679) and Organic Law (3/2018) on Data Protection and Guarantee of Digital Rights.

Study population

The study included HCV patients who initiated treatment with SOF/VEL or GLE/PIB between 2017 and 2020. The index date was the date of treatment initiation. Diagnosis of HCV and treatment selection were based on criteria and clinical judgment of attending physicians, reflecting routine clinical practice. A detailed explanation of inclusion/exclusion criteria and other aspects of the study can be found in Turnes et al. 2024.

Study Cohorts

Two cohorts were defined. The number of patients and study flow is shown in Figure 1:

i. Individuals with a history of drug use, including chronic alcoholism, prescribed opioids, sedatives/anxiolytics, cannabis, cocaine, or heroin (referred to as "PWUD cohort").
ii. Individuals using antipsychotic medication, considering both PWUD and those who do not (referred to as "Antipsychotic cohort")

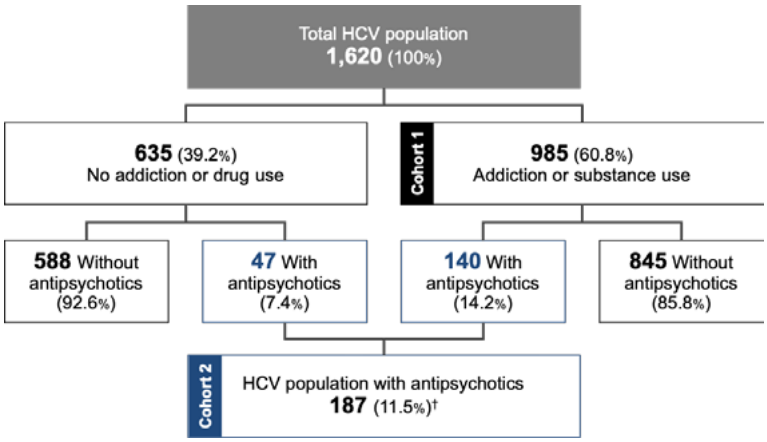
Objectives, Variables, and Assessments

Baseline demographic and clinical characteristics, concomitant medication, and potential DDIs associated with the most frequent comorbidity were described for both cohorts (PWUD cohort and antipsychotic cohort), whether as an adjunct to opioid substitution therapy (OST) or for the management of mental illness.

Patients receiving a protease inhibitor as DAA treatment (GLE/PIB) with those not (SOF/VEL) in terms of

Figure 1

Study diagram and patient populations stratified by addiction and use of antipsychotics



Note 1. † Percentage relative to the overall population. 75% (140/187) of patients with antipsychotics belonged to the population with addiction or substance use vs. 25% of the population without addictions or substance use (47/635), p<0.001.
Note 2. HCV = hepatitis C virus.

comorbidities, concomitant medications, and potential DDIs were compared. Additionally, AEs associated with these pharmacological interactions and the corresponding actions taken for their management were assessed.

Demographic variables, including age, sex, body mass index (BMI), comorbidities, and comedications of the study population, were collected at the entry to the study (index date). Patient comorbidities were recorded using the International Classification of Diseases, 9th edition, Clinical Modification (ICD-09-CM), and characterised by the Charlson comorbidity index (CCI) (Charlson et al., 1987). Comedications were categorised based on the Anatomical Classification (ATC) System, using data retrieved from prescription records in line with medical practice (World Health Organization, 2022). Comedications and possible DDIs were classified according to the strength of interaction and the predicted clinical outcome.

DDIs analysis

Potential DDIs between comedication taken by patients population (recorded in their medical record) and either SOF/VEL or GLE/PIB treatment were identified at the index date using the University of Liverpool's HEP Drug Interaction Checker (The University of Liverpool, 2024) (accessed November 2020 for PWUD cohort and May 2022 for antipsychotic cohort). The HEP Drug Interaction Checker, recommended by reputable medical associations including European Association for the Study of the Liver (EASL) (European Association for the Study of the et al., 2020), the American Association for the Study of Liver Diseases and the Infectious Disease Society of America (AASLD-IDSA) (AASLD, 2022; Bhattacharya et al., 2023) and the National Prisons Hepatitis Network (NPHN) (Winter et al., 2023), is an essential tool for evaluating potential DDIs before initiating new DAA therapy. It categorises interactions based on drug type, pharmacokinetic effects, and strength, aiding in identifying contraindications and significant interactions requiring monitoring or dosage adjustments. DDIs were classified as i) contraindications (drugs that should not be coadministered); ii) potential clinically significant interactions (requires additional monitoring, alteration of drug dosage, or timing of administration); iii) weak interactions (additional action is unlikely); or iv) no interaction expected. The effects of the DDIs were categorised as (i) an increase in plasma concentration of comedication, (ii) an increase in plasma concentration of DAAs, or (iii) a decrease in plasma concentration of DAAs. Multiple DDIs patients were those receiving ≥2 comedications with potential DDIs with the DAA. Those AEs that were probably connected to DDIs were described for the PWUD cohort and the antipsychotic cohort during the DAA treatment period. The comedications associated with AEs and their classification were recorded. We also analysed the actions taken by physicians during the DAA treatment regarding comedication with potential DDIs associated with AEs.

Statistical analysis

Data collected from the BIG-PAC® database were validated by Structured Query Language (SQL) commands and reviewed using an exploratory analysis to ensure quality and consistency (Sicras-Mainar et al., 2019). A descriptive univariate statistical analysis was performed, and absolute and relative frequencies were calculated for qualitative data. Quantitative data were expressed using means, standard deviations (SD), medians, and interquartile ranges (IQR). Bi-variant statistical analyses were carried out using the variance analysis (ANOVA) and Chi-squared tests for independent groups. The statistical software IBM/SPSS was used for analyses. Values of $p<0.05$ were considered statistically significant.

Results

Overall study population

In a previous study of 1,620 HCV patients treated with DAAs, 60.8% had a history of drug use (PWUD cohort), of whom 450 received SOF/VEL, and 535 received GLE/PIB (Turnes et al., 2024). Additionally, 11.5% were prescribed

antipsychotics (Antipsychotic cohort), the majority treated with SOF/VEL (80.2%). Among antipsychotic users, 75% also reported drug use, representing 14.2% of the PWUD cohort (Figure 1).

PWUD cohort

Baseline characteristics

Demographic and clinical characteristics of the PWUD cohort are summarised in Table 1. Substance use patterns varied across the cohort, with cannabis (44%), cocaine (26.2%), and chronic alcoholism (21.8%) being the most prevalent.

When comparing PWUD by group of treatment, individuals in the SOF/VEL group were significantly older, had higher comorbidity burden, and presented more advanced liver disease, including a greater prevalence of fibrosis stages F3 and cirrhosis (F4). Differences in substance use profiles were also observed, with higher rates of opioid and sedative–anxiolytic use in the SOF/VEL group.

Concomitant medication and DDI risk in the PWUD cohort

Concomitant medication use in the PWUD cohort is summarised in Table 2. A total of 2,888 active ingredients (AIs) were prescribed (mean 2.9 per patient), with SOF/VEL patients receiving nearly twice as many concomitant drugs as those on GLE/PIB. Cardiovascular (12%) and nervous system (40%) medications accounted for a substantial proportion of prescriptions. Hypertension was the most frequent comorbidity, renin-angiotensin inhibitors and diuretics were the main cardiovascular drugs (Figure 2), while psycholeptics and analgesics dominated nervous system prescriptions. Enalapril and quetiapine were the most common cardiovascular and antipsychotic agents, respectively.

Potential DDIs involving all prescribed AIs were more frequent in GLE/PIB than in SOF/VEL (15.2% vs 10.8%). The predicted severity of potential DDIs and associated clinical consequences are detailed in Table 3. Cardiovascular medications were particularly relevant in this regard: 22.7% were estimated to have DDIs in the overall population, with a higher proportion in GLE/PIB compared to SOF/VEL (13.7% vs 36.8%, $p<0.001$). Lipid-lowering agents and cardiac therapy medication had the highest potential interaction. Statins were a frequent source of clinically significant interactions in GLE/PIB, while interactions were less common in SOF/VEL. Renin-angiotensin inhibitors and eplerenone also showed clinically relevant risks in GLE/PIB.

AEs linked to comedications with potential DDIs by DAA

Adverse events (AEs) linked to potential DDIs in the PWUD cohort are detailed in Table 4. Five events were identified (two in SOF/VEL, three in GLE/PIB), most of which were associated with cardiovascular medications, particularly statins and renin–angiotensin system inhibitors. In the subgroup of renin–angiotensin system inhibitors, no AEs were reported with SOF/VEL, whereas GLE/PIB was associated with a respiratory adverse event requiring dose adjustment.

Lipid-lowering agents accounted for most of the remaining AEs. In patients treated with GLE/PIB, atorvastatin and simvastatin were associated with myalgia or myopathy, leading to discontinuation of either the statin or the antiviral. In the SOF/VEL group, statin-related AEs were less frequent and were managed with temporary cessation or clinical monitoring.

Antipsychotic cohort

Baseline characteristics

The antipsychotic cohort comprised HCV patients receiving antipsychotic medications, either as an adjunct to opioid substitution therapy or to manage mental illnesses. The median age was 53 years, although patients on GLE/PIB were slightly younger. Men represented 58.8% of the cohort, a lower proportion than in the PWUD cohort. Demographic and clinical characteristics are summarised in Table 5.

Metabolic comorbidities were common, including diabetes (20.9%), hypertension (19.8%), dyslipidaemia (19.3%), and obesity (17.1%). Depressive symptoms affected 13.4% of patients. Advanced fibrosis or cirrhosis was present in 44.4%. Drug use was also frequent (75%), predominantly cannabis (25.1%), sedatives–anxiolytics (21.4%), cocaine (14.4%), and alcohol (9.6%).

Concomitant medication and DDI risk

Concomitant medication pattern DDI risk of the PWUD cohort is shown in Table 6. A total of 963 AIs were prescribed (mean 5.1 per patient), with higher exposure in GLE/PIB compared to SOF/VEL (5.0 vs 5.9, $p<0.001$). Most patients (86.6%) received ≥2 AIs. Nervous system drugs accounted for 56.7% of prescriptions, with similar distribution across regimens (SOF/VEL: 58.4%; GLE/PIB: 50.7%). Psycholeptics, which include antipsychotics (quetiapine, paliperidone, olanzapine, aripiprazole, clotiapine, risperidone and clozapine), anxiolytics (diazepam, alprazolam and lorazepam) and sedative hypnotic agents (lormetazepam), were the most frequently prescribed (52.9%), followed by psychoanaleptics (15.4%), which include antidepressants and related agents (escitalopram and trazodone), analgesics (paracetamol, 14.7%) and antiepileptics (pregabalin, 11.7%). Analgesics were more common in GLE/PIB (19.1% vs 13.5%), while antiepileptics were more frequent in SOF/VEL (12.8% vs 7.3%). Quetiapine was the most commonly prescribed antipsychotic (Table 6).

Table 1

Demographic and clinical characteristics and concomitant medications of PWUD cohort

DAA group	**Total**	**SOF/VEL**	**GLE/PIB**	
N, %	**985 (100%)**	**450 (45.7%)**	**535 (54.3%)**	***p*-value†**
Demographic characteristics				
Age in years; mean (SD)	51.6 (10.3)	53.3 (10.6)	50.2 (9.8)	<0.001
Median (P25-P75)	52 (45 - 58)	53 (46 - 59)	51 (44 - 57)	
Age groups, n (%)				
18 - 44 years	239 (24.3%)	86 (19.1%)	153 (28.6%)	
45 - 64 years	674 (68.4%)	316 (70.2%)	358 (66.9%)	
≥ 65 years	72 (7.3%)	48 (10.7%)	24 (4.5%)	<0.001
Gender (male)	641 (65.1%)	292 (64.9%)	349 (65.2%)	
Associated comorbidities, n (%)				
Arterial hypertension	151 (15.3%)	76 (16.9%)	75 (14%)	
Dyslipidaemia	114 (11.6%)	52 (11.6%)	62 (11.6%)	
Depressive syndrome	112 (11.4%)	61 (13.6%)	51 (9.5%)	0.048
Diabetes	92 (9.3%)	49 (10.9%)	43 (8%)	
Obesity	70 (7.1%)	35 (7.8%)	35 (6.5%)	
COPD	66 (6.7%)	34 (7.6%)	32 (6%)	
Asthma	62 (6.3%)	25 (5.6%)	37 (6.9%)	
Malignant neoplasms	40 (4.1%)	16 (3.6%)	24 (4.5%)	
Others‡	116 (11.8%)	78 (17.3%)	38 (7.1%)	
General comorbidity				
CCI; mean (SD)	0.9 (1.6)	1.2 (1.9)	0.7 (1.3)	<0.001
Hepatic-specific comorbidities n (%)				
Cirrhosis	52 (5.3%)	37 (8.2%)	15 (2.8%)	<0.001
Fibrosis prediction. FIB-4 score				<0.001
Without fibrosis (F0 - F1), <1.45 points	436 (44.3%)	178 (39.6%)	258 (48.2%)	
Intermediate (F2), 1.45 - 3.25 points	202 (20.5%)	84 (18.7%)	118 (22.1%)	
Fibrosis (F3 - F4), >3.25 points	347 (35.2%)	188 (41.8%)	159 (29.7%)	
Addictions, n (%)				
Cannabis	433 (44%)	198 (44%)	235 (43.9%)	
Sedatives-anxiolytics	276 (28%)	140 (31.1%)	136 (25.4%)	0.048
Cocaine	258 (26.2%)	116 (25.8%)	142 (26.5%)	
Chronic alcoholism	215 (21.8%)	110 (24.4%)	105 (19.6%)	
Heroin	157 (15.9%)	80 (17.8%)	77 (14.4%)	
Opioids	107 (10.9%)	60 (13.3%)	47 (8.8%)	0.022
Duration of treatment with DAA, in weeks: n (%)				
8 weeks	501 (50.9%)	0 (0.0%)	501 (93.6%)	
12 weeks	468 (47.5%)	445 (98.9%)	23 (4.3%)	
16 weeks	16 (1.6%)	5 (1.1%)	11 (2.1%)	

Note 1. † Only p-values <0.05 are shown. ‡ Others (Total n): peripheral arterial disease (33); ischemic heart disease (26); brain disease (25); renal insufficiency (20); heart failure (12).
Note 2. BMI = body mass index; CCI = Charlson Comorbidity Index; DAA = direct-acting antivirals; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; GLE/PIB = glecaprevir/pibrentasvir; HIV = Human immunodeficiency virus; P25-P75 = 25th percentile - 75th percentile; PWUD = People who use drugs; SD = standard deviation; SOF/VEL = sofosbuvir/velpatasvir.

Across therapeutic classes, potential DDIs were frequent between DAAs and nervous system comedications (12.8%), particularly psycholeptics (18.3%), analgesics (16.2%), and antiepileptics (6.2%). The proportion of nervous system prescriptions with potential DDIs was more than twice as high in GLE/PIB compared to SOF/VEL (22.7% vs 10.3%, $p<0.001$).

For antipsychotics, GLE/PIB showed a markedly higher DDI risk (51% vs 23%, $p< 0.001$) compared to SOF/VEL (Table 7); with quetiapine prescribed to only 14.2% of GLE/PIB patients, while 85.7% for SOF/VEL. Notably, all patients on GLE/PIB with quetiapine required clinical intervention (Figure 3).

AEs linked to comedications with potential DDIs by DAA

The AEs linked to potential DDIs in the antipsychotic cohort are summarised in Table 8. Two AEs were identified, both in the GLE/PIB group ($p=0.038$). One patient receiving quetiapine at <300 mg/day and GLE/PIB developed extrapyramidal symptoms that led to DAA discontinuation. No AEs were reported with quetiapine at any dose in the SOF/VEL group.

Table 2

Concomitant medication and number of potential interactions (DDIs) by number of comedications and therapeutic groups/subgroups involved in PWUD cohort

DAA group	**Total**	**SOF/VEL**	**GLE/PIB**	
N (%)	**985 (100%)**	**450 (45.7%)**	**535 (54.3%)**	***p*-value†**
Concomitant medication				
Total number of prescribed medications (AI)	2.888	1.734	1.154	
Number of AI	625	337	288	
AI prescribed per patient, mean (SD)	2.9 (1.1)	3.9 (1.1)	2.1 (1.1)	<0.001
Patients with ≥ 2 AI, n (%)	749 (76%)	373 (82.9%)	376 (70.3%)	<0.001
According to % of total prescriptions and per group				
C - Cardiovascular system‡	348 (12.0%)	212 (12.2%)	136 (11.8%)	<0.001
C09 Renin-angiotensin agents	118 (33.9%)	64 (30.2%)	54 (39.7%)	
C03 Diuretics	66 (19.0%)	53 (25.0%)	13 (9.6%)	
C10 Lipid-lowering agents	55 (15.8%)	37 (17.5%)	18 (13.2%)	
C07 Beta blockers	55 (15.8%)	33 (15.6%)	22 (16.2%)	
C08 Calcium channel blockers	31 (8.9%)	18 (8.5%)	13 (9.6%)	
C01 Cardiac therapy	12 (3.4%)	4 (1.9%)	8 (5.9%)	
C02 Antihypertensives	11 (3.2%)	3 (1.4%)	8 (5.9%)	
N - Nervous system‡	1.152 (39.9%)	718 (41.4%)	434 (37.6%)	0.04
N05 Psycholeptics	500 (43.4%)	326 (45.4%)	174 (40.1%)	
N02 Analgesics	237 (20.6%)	143 (19.9%)	94 (21.7%)	
N06 Psychoanaleptics	203 (17.6%)	119 (16.6%)	84 (19.4%)	
N03 Antiepileptics	146 (12.7%)	96 (13.4%)	50 (11.5%)	
N07 Other nervous system drugs	66 (5.7%)	34 (4.7%)	32 (7.4%)	
According to main therapeutic group, (%)&				
C - Cardiovascular drugs				
Enalapril	43 (12.4%)	26 (12.3%)	17 (12.5%)	
Furosemide	28 (8.0%)	22 (10.4%)	6 (4.4%)	
Spironolactone	21 (6.0%)	20 (9.4%)	1 (0.7%)	
Bisoprolol	20 (5.7%)	11 (5.2%)	9 (6.6%)	
Propranolol	18 (5.2%)	15 (7.1%)	3 (2.2%)	
Amlodipine	18 (5.2%)	12 (5.7%)	6 (4.4%)	
N - Nervous system drugs				
Antipsychotics				
Quetiapine	39 (3.4%)	33 (4.6%)	6 (1.4%)	
Paliperidone	26 (2.3%)	22 (3.1%)	4 (0.9%)	
Others				
Alprazolam	118 (10.2%)	74 (10.3%)	44 (10.1%)	
Paracetamol	83 (7.2%)	52 (7.2%)	31 (7.1%)	
Diazepam	81 (7.0%)	47 (6.5%)	34 (7.8%)	
Potential drug-drug interactions, n (%)				
Patients with potential DDI	264 (26.8%)	149 (33.1%)	115 (21.5%)	<0.001
Total of active ingredients prescribed with potential DDI	363 (12.6%)	188 (10.8%)	175 (15.2%)	
Number of AI with potential DDI	68 (10.9%)	28 (8.3%)	40 (13.9%)	0.025
Patients with ≥ 2 comedications with potential DDI	68 (6.9%)	30 (6.7%)	38 (7.1%)	
DDIs by therapeutic groups (% relative to prescriptions per group and sub-group) &				
C - Cardiovascular comedication	79 (22.7%)	29 (13.7%)	50 (36.8%)	0.001
C10 Lipid-lowering agents	38 (69.1%)	23 (62.2%)	15 (83.3%)	
C01 Cardiac therapy	7 (58.3%)	2 (50.0%)	5 (62.5%)	
C09 Renin-angiotensin agents	23 (19.5%)	0	23 (42.6%)	
C02 Antihypertensives	2 (18.2%)	1 (33.3%)	1 (12.5%)	
C07 Beta blockers	7 (12.7%)	2 (6.1%)	5 (22.7%)	
C08 Calcium channel blockers	2 (6.5%)	1 (5.6%)	1 (7.7%)	
C03 Diuretics	2 (3.0%)	0	1 (7.7%)	

Note 1. † Only p-values <0.05 are shown. ‡ATC therapeutic group and sub-group (% of total prescriptions). & Percentage relative to the number of the therapeutic group.
Note 2. AI = active ingredient; DDI = drug-drug interactions; GLE/PIB = glecaprevir/pibrentasvir; PWUD = People who use drugs; SD = standard deviation; SOF/VEL = sofosbuvir/velpatasvir.

Table 3

Strength of potential DDIs and predicted clinical outcomes of patients in PWUD cohort

PWUD cohort: patients addicted to substances (cardiovascular comedication)		
Therapeutic Group / **DAA**	**SOF/VEL**	**GLE/PIB**
Patients with CV medication, *n*	**212**	**136**
Patients with CV DDIs, *n* (%)	**29 (13,7%)**	**50 (36,8%)***
Renin-angiotensin agents (n/N [%])	Enalapril (26/64 [40.6%])	↑ Enalapril (17/54 [31.5%])
	Irbesartan (0/64 [0%])	↑ Irbesartan (2/54 [3.7%])
	Olmesartan (2/64 [3.1%])	↑ Olmesartan (3/54 [5.6%])
	Telmisartan (2/64 [3.1%])	↑ Telmisartan (1/54 [1.9%])
Diuretics (n/N [%])	Eplerenone (1/53 [1.9%])	↑ Eplerenone (1/13 [7.7%])
Beta Blockers (n/N [%])	↑ Carvedilol (2/33 [6.1%])	↑↑ Carvedilol (5/22 [22.7%])
Lipid Lowering Agents (n/N [%])	↑ Atorvastatin (12/37 [32.4%])	↑ Atorvastatin (5/18 [27.8%])
	↑ Simvastatin (7/37 [18.9%])	↑ Simvastatin (4/18 [22.2%])
	Ezetimibe (2/37 [5.4%])	↑ Ezetimibe (1/18 [5.6%])
	Gemfibrozil (0/37 [0%])	↑↑ Gemfibrozil (1/18 [5.6%])
	Pitavastatin (0/37 [0%])	↑ Pitavastatin (2/18 [11.1%])
	Pravastatin (1/37 [2.7%])	↑ Pravastatin (1/18 [5.6%])
	↑ Rosuvastatin (3/37 [8.1%])	↑ Rosuvastatin (1/18 [5.6%])
	↓ Colestyramine (1/37 [2.7%])	Colestyramine (0/18 [0%])
Calcium Channel Blockers (n/N [%])	↑↑ Diltiazem (n=1/18 [5.6%])	↑ Diltiazem (1/13 [7.7%])
Cardiac therapy (n/N [%])	Amiodarone (0/4 [0%])	↑ Amiodarone (4/8 [50.0%])
	↑ Digoxin (2/4 [50.0%])	↑ Digoxin (1/8 [12.5%])
Antihypertensives (n/N [%])	↑ Prazosin (1/3 [33.3%])	↑ Prazosin (0/8 [0%])

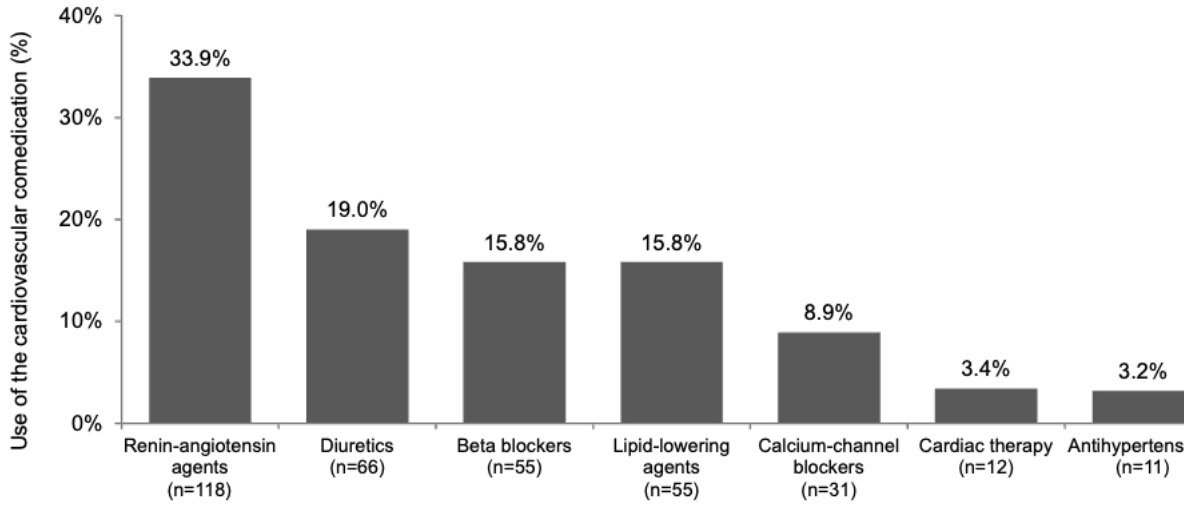
Strength of interaction

Contraindicated	**Significant interaction**	**Weak interaction**	**No interaction**

Note 1. *p <0.001.
Note 2. (↑) = increase in comedication. (↑↑) = increase in comedication + increase in DAA. (↓) = decrease in DAA. n = number of patients on treatment with the corresponding comedication within a therapeutic group (TG). (N) = total number of patients by TG. Percentages were estimated by dividing n (drug prescribed with DDI)/N (total prescribed DDI per subgroup).
Note 3. AP = antipsychotic; CV = cardiovascular; DAA = direct-acting antivirals; DDI = drug-drug interactions; GLE/PIB = glecaprevir/pibrentasvir; PWUD = People who use drugs; SOF/VEL = sofosbuvir/velpatasvir.

Figure 2

Cardiovascular comedications prescribed to the PWUD cohort



Note 1. PWUD = People who use drugs.

Table 4

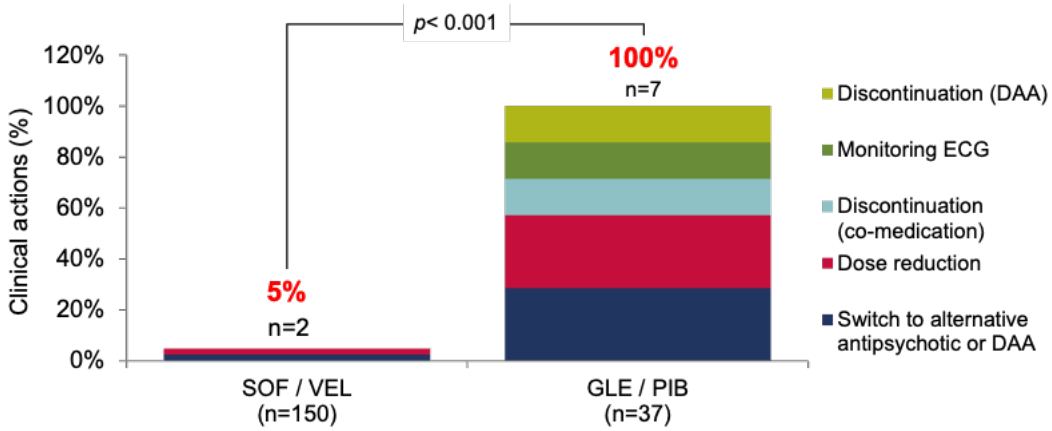
Adverse events (AE) linked to comedications with potential DDIs by DAA in PWUD cohort

AEs linked to cardiovascular medication with potential DDIs by DAA in PWUD cohort (*n*=985)		
DAA	SOF / VEL	GLE / PIB
Number of patients with CV medication, n	212	136
Number of patients with CV DDIs, n (%)	29 (13.7%)	50 (36.8%)*
Adverse Events reported, AE n (%)	2 (0.9%)	3 (2.2%)
Renin-angiotensin agents associated with AE		
Enalapril†	0% AE (0 AE/ 26), [Sin AA] *(No Action)*	5,9% (1 AE / 17), [Respiratory] *(Dose Reduction)*
Lipid Lowering agents		
Atorvastatin†	8.3% AE (1 AE/ 12), [Myalgia/myopathy] *(Statin discontinued)*	20% (1 AE/ 5),), [Myalgia/myopathy] *(DAA discontinued)‡*
Simvastatin†	14.3% (1 AE/ 7), [Myalgia/myopathy] *(Clinical monitoring)**	25% (1 AE/ 4),), [myalgia/myopathy] *(Statin discontinued)‡*

Note 1. * $p < 0.001$.
Note 2. † Results expressed as %AE (#AE/ patients), [AE description], (action required due to AE). ‡ New treatment with DAA was required within 6 months after the end of treatment with SOF/VEL or GLE/PIB, which was considered an indirect indicator of lack of efficacy of the DAA regimen.
Note 3. The colours green or orange represent the strength of interaction. % = The percentage of adverse events associated with medication was calculated by dividing the number of patients with AE between the total patients treated with the corresponding medication by DAA group.
Note 4. AE = adverse events; AP = antipsychotic; CV = cardiovascular; DAA = direct-acting antivirals; DDI = drug-drug interactions GLE/PIB = glecaprevir/pibrentasvir; n = number; PWUD = People who use drugs; SOF/VEL = sofosbuvir/velpatasvir.

Figure 3

Clinical actions reported in patients of the antipsychotic cohort prescribed quetiapine



DAA	SOF/VEL	GLE/PIB	*p*-value
Total patients taking quetiapine, N (%)	42 (100%)	7 (100%)	
Total clinical actions in patients taking quetiapine, N (%)	2 (4.8%)	7 (100%)	<0.001
<300 mg quetiapine	0	5 (71.4%)	
>300 mg quetiapine	2 (100%)	2 (28.6%)	

Note 1. DAA = direct-acting antivirals DDI = direct-drug interaction; ECG = electrocardiogram; GLE/PIB = glecaprevir/pibrentasvir; SOF/VEL = sofosbuvir/velpatasvir.

Table 5

Demographic and clinical characteristics and concomitant medication in the antipsychotic cohort

DAA group	**Total**	**SOF/VEL**	**GLE/PIB**	
N, %	**187 (100%)**	**150 (80.2%)**	**37 (19.8%)**	***p*-value[†]**
Demographic characteristics				
Age in years; mean (SD)	52 (10.8)	52.5 (9.4)	50.1 (15.3)	
Median (P25-P75)	53 (46 - 57)	53 (46 - 56)	48 (36 - 61)	
Age groups, n (%)				
18 - 44 years	44 (23.5%)	28 (18.7)	16 (43.2%)	
45 - 64 years	125 (66.8%)	110 (73.3)	15 (40.5%)	
≥ 65 years	18 (9.6%)	12 (8.0%)	6 (16.2%)	0.001
Gender (male)	110 (58.8%)	88 (58.7%)	22 (59.5%)	
Associated comorbidities (Top 6), n (%)				
Diabetes	39 (20.9%)	31 (20.7%)	8 (21.6%)	
Arterial hypertension	37 (19.8%)	30 (20%)	7 (18.9%)	
Dyslipidaemia	36 (19.3%)	29 (19.3%)	7 (18.9%)	
Obesity	32 (17.1%)	26 (17.3%)	6 (16.2%)	
Depressive syndrome	25 (13.4%)	20 (13.3%)	5 (13.5%)	
COPD	18 (9.6%)	15 (10.0%)	3 (8.1%)	
Others [‡]				
CCI, mean (SD)	1.0 (1.0)	1.0 (1.1)	0.9 (0.9)	
Specific comorbidities, n (%)				
Cirrhosis	10 (5.3%)	8 (5.3%)	2 (5.4%)	
Fibrosis prediction. FIB-4 score				
Without fibrosis (F0 - F1), <1.45 points	64 (34.2%)	49 (32.7%)	15 (40.5%)	
Intermediate (F2), 1.45 - 3.25 points	40 (21.4%)	35 (23.3%)	5 (13.5%)	
Fibrosis (F3 - F4), >3.25 points	83 (44.4%)	66 (44.0%)	17 (45.9%)	
Addictions				
Chronic alcoholism	18 (9.6%)	14 (9.3%)	4 (10.8%)	
Opioids	13 (7.0%)	10 (6.7%)	3 (8.1%)	
Sedatives-anxiolytics	40 (21.4%)	32 (21.3%)	8 (21.6%)	
Cannabis	47 (25.1%)	38 (25.3%)	9 (24.3%)	
Cocaine	27 (14.4%)	22 (14.7%)	5 (13.5%)	
Heroin	15 (8.0%)	12 (8.0%)	3 (8.1%)	
Duration of treatment with DAA, in weeks: n (%)				
8 weeks	30 (16.0%)	0 (0.0%)	30 (81.1%)	
12 weeks	155 (82.9%)	149 (99.3%)	6 (16.2%)	
16 weeks	2 (1.14%)	1 (0.7%)	1 (2.7%)	

Note 1. [†] Only *p*-values <0.05 are shown. [‡] Others (Total n) = renal insufficiency (9); brain disease (8); heart failure (8); asthma (8); peripheral arterial disease (6); malignant neoplasms (5); ischemic heart disease (4).
Note 2. BMI = body mass index; CCI = Charlson Comorbidity Index; DAA = direct-acting antivirals; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; GLE/PIB = glecaprevir/pibrentasvir; HIV = Human immunodeficiency virus; P25-P75 = 25th percentile - 75th percentile; SD = standard deviation; SOF/VEL = sofosbuvir/velpatasvir.

Table 6

Concomitant medication, number of potential interactions (DDIs) by number of comedications and therapeutic groups/subgroups involved in the antipsychotic cohort

DAA group	**Total**	**SOF/VEL**	**GLE/PIB**	
N (%)	**187 (100%)**	**150 (80.2%)**	**37 (19.8%)**	***p*-value[†]**
Concomitant medication				
Total active ingredients prescribed (%)	963	746	217	
Number of AI	337	217	120	
Active ingredients prescribed: Mean (SD)	5.1 (1.2)	5.0 (1.2)	5.9 (1.2)	**<0.001**
Patients with ≥ 2 active ingredients (%)	162 (86.6%)	130 (86.7%)	32 (86.5%)	**0.98**
Concomitant medication (% of total prescriptions and per group)				
C - Cardiovascular system[‡]	81 (8.4%)	59 (7.9%)	22 (10.1%)	**0.30**
C09 Renin-angiotensin agents	27 (33.3%)	20 (33.9%)	7 (31.8%)	
C03 Diuretics	17 (21.0%)	13 (22.0%)	4 (18.2%)	
C10 Lipid lowering agents	11 (13.6%)	9 (15.3%)	2 (9.1%)	
C07 Beta blockers	11 (13.6%)	9 (15.3%)	2 (9.1%)	
C08 Calcium channel blockers	8 (9.9%)	6 (10.2%)	2 (9.1%)	
C01 Cardiac therapy	4 (4.9%)	1 (1.7%)	3 (13.6%)	
C02 Antihypertensives	3 (3.7%)	1 (1.7%)	2 (9.1%)	
N - Nervous system[‡]	546 (56.7%)	436 (58.4%)	110 (50.7%)	**0.04**
N05 Psycholeptics	289 (52.9%)	230 (52.8%)	59 (53.6%)	
N06 Psychoanaleptics	84 (15.4%)	68 (15.6%)	16 (14.5%)	
N02 Analgesics	80 (14.7%)	59 (13.5%)	21 (19.1%)	
N03 Antiepileptics	64 (11.7%)	56 (12.8%)	8 (7.3%)	
N07 Other nervous system drugs	29 (5.3%)	23 (5.3%)	6 (5.5%)	
Main concomitant medication by the main therapeutic group, (%) [&]				
N: Nervous system drugs				
Antipsychotics				
Quetiapine	49 (9.0%)	42 (9.6%)	7 (6.4%)	
Paliperidone	33 (6.0%)	28 (6.4%)	5 (4.5%)	
Olanzapine	32 (5.9%)	26 (6.0%)	6 (5.5%)	
Aripiprazol	14 (2.6%)	11 (2.5%)	3 (2.7%)	
Risperidone	9 (1.6%)	6 (1.4%)	3 (2.7%)	
Clozapine	3 (0.5%)	3 (0.7%)	0 (0.0%)	
Potential drug interactions, n (%)				
Patients with potential DDI	92 (49.2%)	65 (43.3%)	27 (73%)	**0.001**
Total of AI prescribed with potential DDI	141 (14.6%)	95 (12.7%)	46 (21.2%)	**0.001**
Number of AI with potential DDI	40 (11.9%)	18 (8.3%)	22 (18.3%)	**<0.001**
Patients with ≥ 2 comedications with DDI potentials	32 (17.1%)	23 (15.3%)	9 (24.3%)	
DDIs by therapeutic groups (% relative to prescriptions per group and sub-group)				
N - Nervous system	70 (12.8%)	45 (10.3%)	25 (22.7%)	**<0.001**
N05 Psycholeptics	53 (18.3%)	34 (14.7%)	19 (32.2%)	**0.002**
N02 Analgesics	13 (16.2%)	8 (13.6%)	5 (23.8%)	
N03 Antiepileptics	4 (6.2%)	3 (5.4%)	1 (12.5%)	

Note 1. [†] Only p-values <0.05 are shown. ǂ ATC therapeutic group and sub-group (% of total prescriptions). & Percentage relative to the number of the therapeutic group.
Note 2. AI = active ingredient; DDI = drug-drug interactions; GLE/PIB = glecaprevir/pibrentasvir; SD = standard deviation; SOF/VEL = sofosbuvir/velpatasvir.

Table 7

Strength of potential DDIs and predicted clinical outcomes in the antipsychotic cohort

Antipsychotic cohort: Patients treated with antipsychotics (AP)		
Therapeutic Group / **DAA (*n*)**	**SOF/VEL (150)**	**GLE/PIB (37)**
No Patients with AP DDIs, n (%)	**34 (23%)**	**19 (51%)***
Antipsychotics (n/N [%])	Quetiapine (42/150 [28.0%])	↑ Quetiapine (7/37 [18.9%])
	↑ Paliperidone (28/150 [18.7%])	↑ Paliperidone (5/37 [13.5%])
	Aripiprazole (11/150 [7.3%])	↑ Aripiprazole (3/37 [8.1%])
	Clotiapine (9/150 [6.0%])	↑ Clotiapine (1/37 [2.7%])
	↑ Risperidone (6/150 [4.0%])	↑ Risperidone (3/37 [8.1%])
	Clozapine (3/150 [2.0%])	↑ Clozapine (0/37 [0%])

Strength of interaction

Contraindicated	**Significant interaction**	**Weak interaction**	**No interaction**

Note 1. *p <0,001.
Note 2. (↑) = increase in comedication. (↓) = decrease in DAA. n = number of patients on treatment with the corresponding comedication within a therapeutic group (TG). (N) = total number of patients by TG. Percentages were estimated by dividing n (drug prescribed with DDI)/N (total prescribed DDI per subgroup).
Note 3. AP = antipsychotic; CV = cardiovascular; DAA = direct-acting antivirals; DDI = drug-drug interactions; GLE/PIB = glecaprevir/pibrentasvir; SOF/VEL = sofosbuvir/velpatasvir.

Table 8

Adverse events (AE) linked to comedications with potential DDIs by DAA in the antipsychotic cohort

AEs linked to antipsychotics with potential DDIs by DAA in antipsychotic cohort (n=187)		
DAA	**SOF / VEL**	**GLE / PIB**
Number of patients with AP medication, n	150	37
Number of patients with AP DDIs, n (%)	34 (23%)	19 (51%)*
Adverse Events reported, AE, n (%)	0	2 (5.4%)**
Antipsychotics associated with AE		
Quetiapine†&	0% AE (0 AE/ 42);); [No AE] *(No Action)*	14% (1AE / 7); [Extrapyramidal] *(DAA discontinued)*
Paliperidone†	0% AE (0 AE/ 28) [No AE] *(No Action)*	20% (1 AE/ 5); [Sedation] *(Dose Reduction)*

Note 1. * p <0.001; ** p = 0.038.
Note 2. † Results expressed as %AE (#AE/ patients), [AE description], (action required due to AE). ‡New treatment with DAA was required within 6 months after the end of treatment with SOF/VEL or GLE/PIB, which was considered an indirect indicator of lack of efficacy of the DAA regimen. & The dose of quetiapine was <300 mg/day.
The colours green or orange represent the strength of interaction. % = The percentage of adverse events associated with medication was calculated by dividing the number of patients with AE between the total patients treated with the corresponding medication by DAA group.
Note 3. AE = adverse events; AP = antipsychotic; CV = cardiovascular; DAA = direct-acting antivirals; DDI = drug-drug interactions GLE/PIB = glecaprevir/pibrentasvir; n = number; SOF/VEL = sofosbuvir/velpatasvir.

Paliperidone was prescribed more frequently in the SOF/VEL group, with no associated AEs. In contrast, in the GLE/PIB group, paliperidone use was associated with sedation in 20% of cases, requiring a dose reduction. Although other antipsychotics showed significant or weak interaction potential, no AEs were reported, and no clinical actions were needed.

Clinical actions reported in patients prescribed quetiapine at the prescribed dose

Clinical actions included dose adjustments, switching to an alternative antipsychotic, modifying the DAA regimen, or temporarily interrupting treatment, depending on the nature and severity of the predicted DDI. There were 49 patients treated with quetiapine, the majority with SOF/VEL (85.7% vs 14.2%). The study evaluated the need for clinical interventions for quetiapine dosages below and above 300 mg/day when combined with DAA regimens

(Figure 3). All patients on GLE/PIB taking quetiapine at doses of ≤300 mg /day or >300 mg/day required clinical actions. For SOF/VEL, no interventions were needed at quetiapine doses ≤300 mg, and interventions were necessary for only two patients at higher doses.

Discussion

To our knowledge, this is the first study to examine potential DDIs associated with pangenotypic DAAs specifically in Spanish patients with chronic HCV infection who either use drugs or receive antipsychotic treatments, using real-world data. The findings indicate that DDI risk is particularly relevant in these two vulnerable groups, and that GLE/PIB is associated with a higher frequency of potential interactions and related clinical actions than SOF/VEL.

DDIs in PWUD

Consistent with studies from Germany and Italy (Hintz et al., 2021; Nava et al., 2023) PWUD in our cohort exhibited a complex multimorbidity profile and substantial exposure to polypharmacy, particularly involving cardiovascular therapies. Hypertension and dyslipidaemia were the most frequent comorbidities, reflecting a clinically vulnerable population in which the risk of DDIs is an important therapeutic consideration (Nava et al., 2023). Use of nervous system medications was also common, with approximately 40% of PWUD receiving ATC class N agents, closely mirroring proportions reported in German cohorts (Hintz et al., 2021).

Patients treated with SOF/VEL were generally older, had more comorbidities and higher CCI scores, and were exposed to a broader range of comedications than those treated with GLE/PIB. Despite this greater polypharmacy, potential DDIs were more frequently identified among GLE/PIB recipients, consistent with the interaction profile of protease inhibitor–based regimens (Hintz et al., 2021). This pattern suggests that DDI risk in PWUD is driven primarily by the pharmacological properties of the antiviral agent rather than by the overall number of concomitant medications.

Statins were a frequent source of interaction risk. Atorvastatin and simvastatin, which are contraindicated for co-administration with GLE/PIB, were still prescribed in some patients and were associated with clinically significant DDIs. These findings highlight gaps in real-world medication optimisation and underline the need for systematic review of concomitant therapies. Consistent with previous Spanish evidence, patients on GLE/PIB showed a higher proportion of clinically relevant cardiovascular and nervous system interactions (Turnes et al., 2024).

Overall, these observations support the preferential use of regimens with fewer interaction risks, such as SOF/VEL, in PWUD with complex clinical and therapeutic profiles. They also reinforce the importance of multidisciplinary medication assessment at treatment initiation.

Patients receiving antipsychotic treatment

Patients on antipsychotics were typically receiving more than five concomitant active ingredients, and approximately half of them presented potential DDIs, which is consistent with previous evidence showing high levels of polypharmacy and frequent psychotropic DDIs in psychiatric populations (Pinkoh et al., 2023). SOF/VEL was more frequently prescribed in these patients, which is consistent with its favourable interaction profile and its suitability for individuals with multiple comorbidities (Fagiuoli et al., 2023; Hintz et al., 2021). In contrast, GLE/PIB was associated with a higher proportion of clinically significant interactions that required therapeutic actions, particularly in patients treated with quetiapine or paliperidone. These observations align with the expected DDI profile of protease inhibitor-based regimens and underline the importance of selecting antiviral therapy according to the patient's psychiatric and comedication burden.

Overall, these findings highlight the need for close coordination between hepatology, psychiatry, and pharmacy services when treating HCV in patients receiving antipsychotics. A careful review of psychotropic medication at the time of DAA initiation may help anticipate interactions and reduce the risk of avoidable adverse events. These findings may also inform future updates of clinical practice guidelines and contribute to public health strategies aimed at enhancing HCV micro-elimination in vulnerable populations.

Limitations

This study has several limitations. First, the clinical overlap between antipsychotic use and drug use makes it difficult to separate the contribution of each factor to the observed DDIs. Second, the Liverpool interaction checker does not consider the cumulative effects of multidrug regimens or combinations with overlapping toxicity profiles, which are common in patients receiving psychotropic medication or opioid substitution therapies (Andersen et al., 2021; Davidson et al., 2022). Third, the retrospective design may lead to incomplete recording of diagnoses, prescriptions, or adverse events, and documentation practices may differ between healthcare centres (Gonzalez-Colominas et al., 2023). These limitations are unlikely to have affected the comparison between DAA groups, but they should be considered when interpreting the results. Additionally, a potential prescription bias should also be acknowledged, as patients receiving SOF/VEL presented a higher burden of comorbidities and polypharmacy, which may have influenced clinicians' preference for this regimen and partially contributed to the differences observed between treatment groups. On the other hand, the BIG-

PAC database only includes information from the Spanish National Health System; therefore, treatments prescribed in private healthcare were not captured. Finally, the interaction assessment was based on the November 2022 version of the Liverpool tool, and subsequent updates may modify the predicted relevance of some DDIs.

Despite the limitations in this study, our findings suggest that, in real clinical practice in Spain, HCV patients treated with antipsychotics and those addicted to substances have a high risk of potential DDIs, particularly if treated with GLE/PIB. Potential interactions between DAAs and comedications require a comprehensive approach to their clinical follow-up to optimise their treatment and improve their safety by choosing the available DAA with less potential DDIs.

Conclusion

Our findings indicate that HCV patients who use drugs or antipsychotic treatment face a high risk of potential DDIs, particularly with GLE/PIB. These interactions may compromise treatment safety, requiring close clinical monitoring and therapy adjustments. Given the high prevalence of comorbidities and polypharmacy in these patients, optimising DAA selection is crucial. SOF/VEL appears to have a more favourable safety profile in this context. A multidisciplinary approach, integrating pharmacists and clinicians, is essential to minimise risks and ensure effective treatment. Future prospective studies should validate these findings and explore strategies to mitigate DDIs, including AI-driven tools for early detection and personalised treatment optimisation. Given the high level of polypharmacy observed in both cohorts, the participation of clinical pharmacists is crucial for optimising treatment, identifying potential DDIs at baseline, and reducing avoidable adverse events during antiviral therapy.

Institutional Review Board Statement

The study was approved by the Research Ethics Committee of Consorci Sanitari de Terrassa, Barcelona, Spain.

Informed Consent Statement

Patient consent was not necessary, according to Article 5 of Royal Decree 957/2020, of November 3rd, which regulates observational studies with medicines for human use (MINISTERIO DE SANIDAD, 2020).

Data Availability Statement

The data supporting this study are based on patient records, and no link is available; the info is aggregated upon study request. The data supporting this study's findings is not available due to the nature of the data (from patients belonging to the National Health System).

Funding

This study was funded by Gilead Sciences, Spain.

Author Contributions

Ignacio Hernández, Cándido Hernández and Marinela Méndez conceived the study. Ignacio Hernández, Cándido Hernández and Marinela Méndez participated in and contributed to its design. Ignacio Hernández collected data and performed statistical analysis. Alfonsina Trento wrote the first draft. Juan Turnes, Antonio García-Herola, Marinela Méndez, Cándido Hernández, Alfonsina Trento, Ramón Morillo-Verdugo, Francisco Pascual and Ignacio Hernandez interpreted the results and critically reviewed and approved the final version of the manuscript.

Acknowledgements

The authors would like to thank Dr Antoni Sicras and Dr Elena Rebollo-Gómez for their support with data analysis and drafting of the manuscript.

Conflicts of Interest

Authors have received funding not conditional on results for their participation as Speaker/consultant/research: Juan Turnes (AbbVie, Gilead Sciences, MSD), Antonio García-Herola (AbbVie, Gilead Sciences), Ramón Morillo-Verdugo (AbbVie, Gilead Sciences, Janssen, MSD, ViiV Healthcare), Francisco Pascual (Gilead). Cándido Hernández and Marinela Méndez are employees of Gilead Sciences, Spain. Ignacio Hernández and Alfonsina Trento are employees of Atrys Health, a contract research organisation that received funds from Gilead to conduct this study. The sponsor, including both the pharmaceutical company and its local affiliate, had no role in the data analysis or interpretation. The authors retained full editorial control and responsibility for the final content.

References

AASLD. (2022). *IDSA (Infectious Disease Society of America): HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C.* Retrieved from https://www.hcv-guidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_October_24_2022.pdf

Andersen, F. D., Simonsen, U., & Andersen, C. U. (2021). Quetiapine and other antipsychotics combined with opioids in legal autopsy cases: A random finding or cause of fatal outcome? *Basic & Clinical Pharmacology*

& Toxicology, *128*(1), 66-79. https://doi.org/10.1111/bcpt.13480

Bhattacharya, D., Aronsohn, A., Price, J., Lo Re, V., & Panel, A.-I. H. G. (2023). Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Clinical Infectious Diseases*, *ciad319*. https://doi.org/10.1093/cid/ciad319

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases*, *40*(5), 373-383. https://doi.org/10.1016/0021-9681(87)90171-8

Davidson, K., Boyle, A., Barclay, S., Boxall, E., Fleming, C., Gossman, P., McAvennie, J., Reilly, E., Sheridan, E., Sommerville, A., & Marra, F. (2022). *THU-424. The quetiapine question: management strategies for drug-drug interactions with antipsychotics and direct acting antivirals; a multi-centre review* EASL 2022, London. https://doi.org/10.1016/S0168-8278(20)31196-X

Degenhardt, L., Peacock, A., Colledge, S., Leung, J., Grebely, J., Vickerman, P., Stone, J., Cunningham, E. B., Trickey, A., Dumchev, K., Lynskey, M., Griffiths, P., Mattick, R. P., Hickman, M., & Larney, S. (2017). Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *Lancet Glob Health*, *5*(12), e1192-e1207. https://doi.org/10.1016/S2214-109X(17)30375-3

Di Marco, L., La Mantia, C., & Di Marco, V. (2022). Hepatitis C: Standard of Treatment and What to Do for Global Elimination. *Viruses*, *14*(3). https://doi.org/10.3390/v14030505

Dick, T. B., Lindberg, L. S., Ramirez, D. D., & Charlton, M. R. (2016). A clinician's guide to drug-drug interactions with direct-acting antiviral agents for the treatment of hepatitis C viral infection. *Hepatology*, *63*(2), 634-643. https://doi.org/10.1002/hep.27920

European Association for the Study of the, L., Clinical Practice Guidelines Panel, C., representative, E. G. B., & Panel, m. (2020). EASL recommendations on treatment of hepatitis C: Final update of the series(□). *Journal of Hepatology*, *73*(5), 1170-1218. https://doi.org/10.1016/j.jhep.2020.08.018

Fagiuoli, S., Toniutto, P., Coppola, N., Ancona, D. D., Andretta, M., Bartolini, F., Ferrante, F., Lupi, A., Palcic, S., Rizzi, F. V., Re, D., Alvarez Nieto, G., Hernandez, C., Frigerio, F., Perrone, V., Degli Esposti, L., & Mangia, A. (2023). Italian Real-World Analysis of the Impact of Polypharmacy and Aging on the Risk of Multiple Drug-Drug Interactions (DDIs) in HCV Patients Treated with Pangenotypic Direct-Acting Antivirals (pDAA). *Therapeutics and Clinical Risk Management*, *19*, 57-65. https://doi.org/10.2147/TCRM.S394467

Fiore, V., Manca, V., Colpani, A., De Vito, A., Maida, I., Madeddu, G., & Babudieri, S. (2023). Facing HCV as a Major Public Healthcare Threat in Italy: Epidemiology and Micro-Elimination Pathways among Underserved Populations. *Healthcare (Basel)*, *11*(14). https://doi.org/10.3390/healthcare11142109

Gao, L. H., Nie, Q. H., & Zhao, X. T. (2021). Drug-Drug Interactions of Newly Approved Direct-Acting Antiviral Agents in Patients with Hepatitis C. *International Journal of General Medicine*, *14*, 289-301. https://doi.org/10.2147/IJGM.S283910

Gonzalez-Colominas, E., Lopez-Mula, C., Martinez-Casanova, J., Luque, S., Conde-Estevez, D., Monge-Escartin, I., & Ferrandez, O. (2023). Primary care electronic medication record discrepancies in patients starting treatment at a hospital-based ambulatory care pharmacy and impact on prevalence of potential drug-drug interactions. *Eur J Hosp Pharm*, *30*(6), 333-339. https://doi.org/10.1136/ejhpharm-2021-002963

Gutierrez-Rojas, L., de la Gandara Martin, J. J., Garcia Buey, L., Uriz Otano, J. I., Mena, A., & Roncero, C. (2023). Patients with severe mental illness and hepatitis C virus infection benefit from new pangenotypic direct-acting antivirals: Results of a literature review. *Gastroenterología y Hepatologia*, *46*(5), 382-396. https://doi.org/10.1016/j.gastrohep.2022.06.001

Hintz, A., Umland, T., Niess, G., Guendogdu, M., Moerner, A., & Tacke, F. (2021). Pharmacotherapy Profiles in People with Opioid Use Disorders: Considerations for Relevant Drug-Drug Interactions with Antiviral Treatments for Hepatitis C. *Pathogens*, *10*(6). https://doi.org/10.3390/pathogens10060648

MINISTERIO DE SANIDAD, C. Y. B. S. (2020). *Clasificación Internacional de Enfermedades. 10a revisión. Modificación clínica. 3a edición*. Retrieved from https://www.mscbs.gob.es/estadEstudios/estadisticas/normalizacion/CIE10/Clasif_Inter_Enfer_CIE_10_rev_3_ed.diag.pdf

Moore, K. J., Gauri, A., & Koru-Sengul, T. (2019). Prevalence and sociodemographic disparities of Hepatitis C in Baby Boomers and the US adult population. *J Infect Public Health*, *12*(1), 32-36. https://doi.org/10.1016/j.jiph.2018.08.003

Nava, F. A., Mangia, A., Riglietta, M., Somaini, L., Foschi, F. G., Claar, E., Maida, I., Ucciferri, C., Frigerio, F., Hernandez, C., Dovizio, M., Perrone, V., Degli Esposti, L., & Puoti, M. (2023). Analysis of Patients' Characteristics and Treatment Profile of People Who Use Drugs (PWUDs) with and without a Co-Diagnosis of Viral Hepatitis C: A Real-World Retrospective Italian Analysis. *Therapeutics and Clinical Risk Management*, *19*, 645-656. https://doi.org/10.2147/TCRM.S409134

Pineda, J. A., Climent, B., Garcia, F., Garcia Deltoro, M., Granados, R., Gomez, F., Macias, J., Mena, A., Merchante, N., Ochoa, E., Roncero, C., Ruiz, J. J., Tellez,

F., & Morano, L. (2020). Executive summary: Consensus document of GEHEP of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), along with SOCIDROGALCOHOL, SEPD and SOMAPA on hepatitis C virus infection management in drug users. *Enferm Infecc Microbiol Clin (Engl Ed)*, *38*(3), 127-131. https://doi.org/10.1016/j.eimc.2018.09.006

Pinkoh, R., Rodsiri, R., & Wainipitapong, S. (2023). Retrospective cohort observation on psychotropic drug-drug interaction and identification utility from 3 databases: Drugs.com(R), Lexicomp(R), and Epocrates(R). *PloS One*, *18*(6), e0287575. https://doi.org/10.1371/journal.pone.0287575

POLARIS. (2024). *Polaris Observatory - Historical Data* Retrieved from https://cdafound.org/polaris-regions-dashboard/

Rifai, M. A., Gleason, O. C., & Sabouni, D. (2010). Psychiatric care of the patient with hepatitis C: a review of the literature. *Primary Care Companion to the Journal of Clinical Psychiatry*, *12*(6), PCC.09r00877. https://doi.org/10.4088/PCC.09r00877whi

Schulte, B., Wubbolding, M., Marra, F., Port, K., Manns, M. P., Back, D., Cornberg, M., Stichtenoth, D. O., Honer Zu Siederdissen, C., & Maasoumy, B. (2020). Frequency of Potential Drug-Drug Interactions in the Changing Field of HCV Therapy. *Open Forum Infect Dis*, *7*(2), ofaa040. https://doi.org/10.1093/ofid/ofaa040

Sicras-Mainar, A., Enriquez, J. L., Hernández, I., Sicras-Navarro, A., Aymerich, T., & Leon, M. (2019). Pmu146 Validation and Representativeness of the Spanish Big-Pac Database: Integrated Computerized Medical Records for Research into Epidemiology, Medicines and Health Resource Use (Real Word Evidence). *Value in Health*, *22*, S734. https://doi.org/10.1016/j.jval.2019.09.1764

The University of Liverpool. (2024). *HEP Drug Interactions*. Retrieved from https://www.hep-druginteractions.org/checker

Turnes, J., Garcia-Herola, A., Morillo-Verdugo, R., Mendez, M., Hernandez, C., & Sicras-Mainar, A. (2024). Impact of potential multiple drug-drug interactions on the adverse event profile of patients with hepatitis C treated with pangenotypic direct-acting antivirals in Spain. *Rev Esp Sanid Penit*, *26*(3), 98-112. https://doi.org/10.18176/resp.00095

Voeller, A., Razavi-Shearer, D., Gamkrelidze, I., Razavi-Shearer, K., Blach, S., & Razavi, H. (2023). *Total HCV patients treated with direct acting antivirals since 2014* AASLD 2023, Boston, US. https://www.natap.org/2023/AASLD/AASLD_42.htm

Winter, R. J., Sheehan, Y., Papaluca, T., Macdonald, G. A., Rowland, J., Colman, A., Stoove, M., Lloyd, A. R., & Thompson, A. J. (2023). Consensus recommendations on the management of hepatitis C in Australia's prisons. *Medical Journal of Australia*, *218*(5), 231-237. https://doi.org/10.5694/mja2.51854

World Health Organisation. (2023). *Hepatitis C* Retrieved from https://www.who.int/news-room/fact-sheets/detail/hepatitis-c

World Health Organization. (2022). *The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD). Published 2022.* . Retrieved from https://www.who.int/standards/classifications/other-classifications/the-anatomical-therapeutic-chemical-classification-system-with-defined-daily-doses