Prevalence of drug-drug interactions with pangenotypic direct-acting antivirals for hepatitis C and real-world care management in the United States: a retrospective observational study

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What is already known about this subject

- The overall prevalence and severity of drug-drug interactions (DDIs) have been evaluated in small databases and are more common in protease-containing regimens.
- How DDIs actually impact treatment regimens is not known.
- With the expanded indications for the pangenotypic products glecaprevir-pibrentasvir and sofosbuvir-velpatasvir, and given the similar observed real-world efficacies, DDIs are a major reason that 1 regimen may be selected in comparison to another (with the exception of decompensated liver disease).

What this study adds

- Level 1 DDIs are common with all regimens, but Level 3 is clearly more prevalent in protease-containing regimens.
- Pharmacy recommendations are common for DDIs but not followed for about 40% of patients.
- This is a large, real-world comparison of DDIs in the 2 recommended regimens and includes the pharmacist database, which adds a unique component to the analysis.

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ABSTRACT

BACKGROUND: Direct-acting antiviral (DAA) regimens for hepatitis C virus (HCV) have varying potentials for drug-drug interactions (DDIs).

OBJECTIVES: To (1) identify prevalence of potential DDI with glecaprevir-pibrentasvir (GLE-PIB) and sofosbuvir-velpatasvir

(SOF-VEL) and (2) describe health care provider actions in response to pharmacist recommendations based on potential interactions with GLE-PIB or SOF-VEL, using 2 complementary data sources.

METHODS: Possible interacting drugs were identified among adult patients in a United States electronic medical record database covering 21 health care organizations and

26 million patients in 2018. DDIs were categorized as potential weak interaction (Level 1), potential interaction (Level 2), or contraindicated (Level 3). Real-world recommendations and resultant actions regarding DDIs with GLE-PIB and SOF-VEL were obtained from a specialty pharmacy database. Categorical variable comparisons were done via chi-square analysis with subsequent z-tests of column proportions.

RESULTS: DDI prevalence was higher for patients prescribed GLE-PIB (317/769 [41%]) compared with those prescribed SOF-VEL (170/633 [27%]), and the prevalence of a Level 3 (contraindicated) interaction was higher with GLE-PIB than SOF-VEL (61/769 [8%] vs 2/633 [$<1\%$]). Across all DDI levels, analgesics (139/317 [44%]), proton-pump inhibitors (129/317 [41%]), and lipid-lowering agents (59/317 [19%]) were the top drug classes for the GLE-PIB group with potential for DDI. For SOF-VEL prescribed patients, the top drug classes were proton-pump inhibitors (83/170 [49%]), histamine-2 blockers (42/170 [25%]), and lipid-lowering agents (42/170 [25%]). In real-world care management, the overall prevalence of pharmacist recommendations regarding DDIs was significantly lower for SOF-VEL (28/419 [7%]) relative to GLE-PIB (151/1,216 [12%]). Recommended guidance from pharmacists was not followed for 39% (69/179) of patients, 36% (54/151) for GLE-PIB, and 54% (15/28) for SOF-VEL.

CONCLUSIONS: The potential for DDIs with pangenotypic HCV DAAs is frequent and may be more frequent with GLE-PIB than SOF-VEL. Physician responses to pharmacist alerts regarding potential interaction can be highly variable, even in cases of contraindication.

Worldwide, approximately 71 million persons are chronically infected with hepatitis C virus (HCV),¹ which increases the risks for liver disease progression, cirrhosis, and hepatocellular carcinoma.^{2,3} Fortunately, successful treatment of HCV can halt the progression of liver disease and, in some cases, lead to improved liver histology.^{4,5} In the past decade, the introduction of direct-acting antiviral (DAA) agents has greatly improved the HCV treatment landscape. In both clinical trials and real-world studies, treating HCV with interferon-free DAA regimens results in high rates of sustained virologic response (SVR), exceeding 98%.⁶⁻⁹ Compared with the previous standard of care, peginterferon with ribavirin, all oral DAA-based regimens are easier to administer, better tolerated, and have high efficacy across a broad range of patient populations.¹⁰ The pangenotypic regimens, which are successful in previously considered difficult-to-treat patient populations, allow for treatment without prior regard for genotype, degree of liver fibrosis, gender, race or concomitant HIV infection. As a consequence, treatment of HCV has evolved from specialist gastroenterology, hepatology, and infectious disease clinics to primary care physicians, community medical centers, opioid substitution programs, and pharmacist-based clinics. However, with improvement in DAA tolerability and efficacy, patients with HCV seeking treatment have more comorbidities and take concomitant medications¹¹; it is estimated that 30%-60% of patients taking DAAs are at risk of clinically significant drug-drug interactions (DDIs).¹² Individualization

of treatment remains important for minimizing the risk of clinically relevant DDIs and optimizing efficacy.

Currently available pangenotypic HCV regimens include glecaprevir-pibrentasvir (GLE-PIB) and sofosbuvir-velpatasvir (SOF-VEL). Glecaprevir is a NS3/4A serine protease inhibitor. Sofosbuvir is an NS5B nucleotide analogue inhibitor of the NS5B polymerase. Pibrentasvir and velpatasvir are NS5A inhibitors. Although both regimens have favorable safety profiles, the presence of NS3/4A protease inhibitors has been associated with higher rates of DDIs.^{11,13}

In this study, we assessed (1) prevalence of potential DDIs and (2) care management for patients prescribed GLE-PIB or SOF-VEL for HCV. Because a single data source was insufficient to address both objectives, we used 2 sources: a large electronic medical record (EMR) database as well as a national specialty pharmacy database.

Methods

DATA COLLECTION

For this retrospective observation study, data were obtained from the TriNetX global federated research network (EMR database) and from a national specialty pharmacy (pharmacy data).

The analytics subset available from the EMR database at time of data obtainment covered 26 million patients in care at 21 health care organizations in the United States. From this sample, we selected data for 1,402 adult patients (aged ≥ 18 years) with HCV who initiated GLE-PIB or SOF-VEL in 2018 and for whom more than 90 days of follow-up and more than 60 days of history relative to DAA initiation were available. For patients with multiple DAA prescriptions, only the first qualifying date (index date) was considered. Concomitant drug prescriptions were considered for DDI assessment if they were generated between 60 days before to 56 days after the index date. Comorbid conditions were considered if indicated any time before or up to 56 days after the index date.

Pharmacy data were collected electronically through Trio Health's disease management platform. Included were 1,635 adult patients (aged ≥ 18 years) with HCV who were prescribed GLE-PIB or SOF-VEL in 2018, independent of whether the prescription was per label. Patients resided in 24 US states and were under care of 382 providers. Upon receipt of the prescription from the provider, pharmacists used 1 or more resources including Micromedex, Facts and Comparisons, UpToDate, Lexicomp, and Package Insert (Daily Med) to search for potential DDIs. Potential DDIs that resulted in pharmacist recommendations to physicians

were captured in the database, as were subsequent physician and/or patient actions.

The overlap between the databases was unknown as data were deidentified prior to receipt, and demographic information was insufficient for matching.

ASSESSMENTS AND ENDPOINTS

From the EMR database, we determined the prevalence of potential DDIs with stratification by severity, the most common drug classes with DDIs, and the comorbid burden. Using the pharmacy database, we determined the frequency of pharmacist DDI recommendations, classified the potential DDI drugs by severity, described the recommendations made to the provider and patient, and described the resultant action taken by the provider and patient.

In the EMR database, lab measures, race, HCV genotype, and geographic location were often lacking or insufficiently detailed. Comorbidities were identified using *International Classification of Diseases, Tenth Revision, Clinical Modification* codes. In the pharmacy database, select comorbidities were prompted as Y/N fields and completed by the provider or pharmacy using patient chart notes. Concurrent medications were not available in the pharmacy database aside from those triggering pharmacist action.

Where possible, Fibrosis-4 Index for Liver Fibrosis (FIB4) scores were calculated per Sterling et al,¹⁴ estimated glomerular filtration rates (eGFR) were calculated using the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation,¹⁵ and comorbidity burden was calculated based on Charlson's methodology.¹⁶

Potential DDIs were identified using the Hepatitis Drug Interaction Database from the University of Liverpool (www.hep-druginteractions.org) accessed May 2019 and classified as Level 1 (potential weak interaction), Level 2 (potential interaction), or Level 3 (contraindicated). For classification of patients by DDI level, the most severe DDI level was assigned to a patient if the patient had multiple concomitant drugs across more than 1 level.

For classification of pharmacist recommendations, the order of assignment was the following: (1) guidance to not coadminister, (2) guidance to switch interacting drug, (3) guidance to dose modify interacting drug, and (4) proceed as prescribed. Guidance to not coadminister was defined by the pharmacists as holding interacting drug or DAA or switching to another DAA.

Baseline measures were those closest to, but between 6 months before and up to 1 month after, the index date. For all analyses, sample sizes less than the starting group size are provided.

The studies performed with both data sources met the criteria for institutional review board (IRB) exemption under 45 CFR 46.101(b)(4) as determined by WCG IRB.

STATISTICAL ANALYSES

Categorical variable comparisons were done via chi-square analysis with subsequent z-tests of column proportions. Bonferroni correction was applied for repeated measures. For continuous variables, comparisons were made by using the Mann-Whitney U test for independent samples.

Results

STUDY POPULATION CHARACTERISTICS

GLE-PIB was prescribed to 769 patients in the EMR database and 1,216 in the pharmacy database, and SOF-VEL was prescribed to 633 in the EMR database and 419 in the pharmacy database. In both databases, the populations prescribed GLE-PIB were on average younger, had fewer patients with FIB4 > 3.25, and had fewer patients with hypertension (Table 1). In the EMR database, the GLE-PIB group had a higher prevalence of anxiety (230/769 [30%] vs 143/633 [23%] SOF-VEL) and lower mean Charlson Comorbidity Index (2.7 vs 3.0 SOF-VEL), and the SOF-VEL group had more patients with dyslipidemia (53/633 [8%] vs 19/769 [2%] GLE-PIB). In the pharmacy database, there were fewer patients with genotype 1 HCV in the SOF-VEL group (199/410 [49%] vs 848/1,181 [72%] GLE-PIB), and Medicaid as primary coverage was more common among GLE-PIB prescribed patients (577/1,216 [47%] vs 126/419 [30%] SOF-VEL).

PREVALENCE OF POTENTIAL DDIs

Among GLE-PIB prescribed patients, 73/769 (9%) were prescribed drugs with a potential weak interaction (Level 1), 183/769 (24%) with a potential interaction (Level 2), and 61/769 (8%) with a contraindication (Level 3; Figure 1A). The most common DDI drug classes for GLE-PIB prescribed patients were analgesics (139/317 [44%]), proton-pump inhibitors (129/317 [41%]), and lipid-lowering agents (59/317 [19%]; Table 2). Specific drugs with a potential for a DDI in more than 10% of patients prescribed GLE-PIB were fentanyl (25%), oxycodone (24%), omeprazole (23%), pantoprazole (17%), atorvastatin (12%), esomeprazole (12%), and hydrocodone (12%; [Supplementary Table 1](#), available in online article). Eleven drugs were prescribed that were contraindicated with GLE-PIB, most frequent among them were atorvastatin, simvastatin, ethinyl estradiol, and oxcarbazepine (Figure 1; [Supplementary Table 2](#), available in online article).

For the SOF-VEL prescribed group, 12/633 (2%) were prescribed Level 1 drugs, 156/633 (25%) Level 2 drugs,

TABLE 1 Study Population Characteristics

	EMR database			Pharmacy database		
	GLE-PIB ^a (n=769)	SOF-VEL ^a (n=633)	P value ^b	GLE-PIB ^a (n=1,216)	SOF-VEL ^a (n=419)	P value ^b
Sex, n (%)			0.047			0.684
Female	324/765 (42)	235 (37)	z	523 (43)	185 (44)	
Male	441/765 (58)	398 (63)	z	693 (57)	234 (56)	
Age, mean (SD), years	51.3 (13.1)	55.3 (11.5)	<0.001	54.3 (13.1)	58.4 (11.9)	<0.001
Age group, years, n (%)			<0.001			<0.001
18-35	127 (17)	53 (8)	z	147 (12)	30 (7)	z
36-49	159 (21)	100 (16)	z	220 (18)	42 (10)	z
50-64	383 (50)	369 (58)	z	570 (47)	205 (49)	
65+	100 (13)	110 (17)	z	279 (23)	142 (34)	z
Treatment naive, n/n (%)	*	*		1,130/1,210 (93)	378/416 (91)	0.087
HCV genotype, n/n (%)						<0.001
1	*	*		848/1,181 (72)	199/410 (49)	z
2	*	*		184/1,181 (16)	94/410 (23)	z
3	*	*		124/1,181 (10)	101/410 (25)	z
4-6	*	*		25/1,181 (2)	16/410 (4)	z
Baseline platelets <100 cells/μL, n/n (%)	51/597 (9)	64/437 (15)	0.002	57/1,136 (5)	42/392 (11)	<0.001
Baseline FIB4 >3.25, n/n (%)	51/399 (13)	116/360 (32)	<0.001	174/1,212 (14)	117/417 (28)	<0.001
Baseline eGFR <60 mL/min/1.73m², n/n (%)	*	*		96/1,130 (8)	22/390 (6)	0.191
Baseline viral load, n/n (%)						0.945
<800K IU/L	*	*		392/1,189 (33%)	133/412 (32%)	
800K-6MM IU/L	*	*		554/1,189 (47%)	192/412 (47%)	
>6MM IU/L	*	*		243/1,189 (20%)	87/412 (21%)	
Comorbidities, n (%)						
Anxiety	230 (30)	143 (23)	0.002	200 (16)	85 (20)	0.074
Diabetes	111 (14)	114 (18)	0.070	179 (15)	56 (13)	0.495
Dyslipidemia	19 (2)	53 (8)	<0.001	66 (5)	31 (7)	0.141
Hypertension	288 (37)	278 (44)	<0.001	411 (34)	174 (42)	0.004
Comorbidity index, mean (SD)	2.7 (2.6)	3.0 (2.5)	0.003	*	*	
Academic site of care, n (%)	*	*		148 (12)	51 (12)	1.000
Primary payer, n (%)	*	*				<0.001
Commercial	*	*		246 (20)	112 (27)	z
Medicaid	*	*		577 (47)	126 (30)	z
Medicare (including dual)	*	*		389 (32)	178 (42)	z
Other	*	*		4 (0)	3 (1)	

Note: Denominator indicated if less than starting sample.

^aData missing or insufficient for assessment are indicated by asterisk.^bz indicates column proportions that are significantly different by z-test for variables with more than 2 levels.

eGFR=estimated glomerular filtration rates; EMR=electronic medical record; FIB4=Fibrosis-4 Index for Liver Fibrosis; GLE-PIB=glecaprevir-pibrentasvir; SOF-VEL=sofosbuvir-velpatasvir.

FIGURE 1 Prevalence of Potential Drug-Drug Interactions and Prevalence Pharmacist Guidance**A. EMR database: prevalence of potential DDI** **B. Pharmacy database: prevalence of DDI guidance**

^aEMR database potential Level 3 DDIs (contraindicated) with GLE-PIB: atorvastatin n=39, simvastatin n=9, ethinyl estradiol n=4, levonorgestrel n=2, oxcarbazepine n=2, carbamazepine n=1, eltrombopag n=1, etonogestrel n=1, phenobarbital n=1, phenytoin n=1, rifampicin n=1.

^b2/633 (<1%) of SOF-VEL prescribed patients had potential Level 3 DDI.

^cEMR database potential Level 3 DDIs (contraindicated) with SOF-VEL: phenobarbital n=1, rifampicin n=1.

^dPharmacy database potential Level 3 DDIs with GLE-PIB: atorvastatin n=91, simvastatin n=16, ethinyl estradiol n=8, oxcarbazepine n=5, carbamazepine n=4, phenytoin n=3, phenobarbital n=1.

^ePharmacy database potential Level 3 DDIs with SOF-VEL: phenobarbital n=2. DDI=drug-drug interaction; EMR=electronic medical record; GLE-PIB=glecaprevir-pibrentasvir; SOF-VEL=sofosbuvir-velpatasvir.

and 2/633 (<1%) Level 3 (Figure 1A). The top DDI drug classes for SOF-VEL prescribed patients were proton-pump inhibitors (83/170, 49%), histamine-2 receptor antagonists (42/170, 25%), and lipid-lowering agents (42/170, 25%; Table 2). Specific drugs with a potential for a DDI in 10% or more of patients prescribed SOF-VEL were pantoprazole (26%), omeprazole (25%), atorvastatin (21%), famotidine (15%), buprenorphine (11%), esomeprazole (10%), and ranitidine (10%). Two drugs prescribed were contraindicated

with SOF-VEL: phenobarbital and rifampicin (Figure 1; [Supplementary Table 2](#), available in online article).

Prevalence of a potential DDI was greater among patients prescribed GLE-PIB (317/769 [41%]) than SOF-VEL (170/633 [27%], $P<0.001$; Table 2; [Supplementary Table 1](#), available in online article). Possible Level 3 (contraindicated) interaction was also more frequent with GLE-PIB than SOF-VEL (61/769 [8%] vs. 2/633 [<1%], $P<0.001$; Figure 1A).

PREVALENCE OF PHARMACIST GUIDANCE FOR POTENTIAL DDIs

In the pharmacy database, the overall prevalence of pharmacist recommendations was significantly lower for SOF-VEL (7%, 28/419) relative to GLE-PIB (12%, 151/1,216, $P<0.001$; Figure 1B). Among GLE-PIB prescribed patients, none had a pharmacist recommendation for a potential weak interaction (Level 1), 18/1,216 (1%) had a recommendation for a potential interaction (Level 2), and 133/1,216 (11%) had a recommendation for contraindicated potential interactions (Level 3; Figure 1B). Among SOF-VEL prescribed patients; 1/419 (<1%) had a pharmacist recommendation for a potential weak interaction (Level 1), 18/419 (4%) had a recommendation for a potential interaction (Level 2), and 9/419 (2%) had a recommendation for contraindicated potential interactions (Level 3).

In the pharmacy database, the most common drug classes triggering a pharmacist recommendation for a potential DDI with GLE-PIB were lipid-lowering agents (125/151, 83%) and anticonvulsants (7/151, 5%). For SOF-VEL, top classes were lipid-lowering agents (10/28, 36%), proton-pump inhibitors (8/28, 29%), and anticonvulsants (7/28, 25%).

CHARACTERISTICS OF PATIENTS RECEIVING PHARMACIST RECOMMENDATIONS

Patients receiving DDI recommendations differed significantly from those without recommendations (Table 3). In the GLE-PIB prescribed population, relative to patients without a pharmacist recommendation, the group with DDI recommendations was older (mean age 60 vs 54 years; $P<0.001$) and had a significantly higher prevalence of baseline eGFR < 60 mL/min/1.73m² (29/140 [21%] vs 67/990 [7%]; $P<0.001$), diabetes (53/151 [35%] vs 126/1,065 [12%]; $P<0.001$), dyslipidemia (32/151 [21%] vs 34/1,065 [3%]; $P<0.001$), and hypertension (90/151 [60%] vs 321/1,065 [30%]; $P<0.001$). A larger fraction of the GLE-PIB prescribed group receiving pharmacist guidance was treated in academic centers (35/151 [23%] vs 113/1,065 [11%]; $P<0.001$) relative to those without guidance. Moreover, a larger fraction of the GLE-PIB prescribed group receiving pharmacist guidance had

TABLE 2 Prevalence of Potential Drug-Drug Interactions and Pharmacist Recommendations Based on Drug Class

Drug class, ^a n (%)	EMR database: patients with potential DDI		Pharmacy database: patients with pharmacist recommendation regarding DDI	
	GLE-PIB (n=317)	SOF-VEL (n=170)	GLE-PIB (n=151)	SOF-VEL (n=28)
PPI	129 (41)	83 (49)	–	8 (29)
Analgesics	139 (44)	18 (11)	–	–
Lipid-lowering agents	59 (19)	42 (25)	125 (83)	10 (36)
H2 blockers	39 (12)	42 (25)	–	–
Beta-blockers	20 (6)	12 (7)	–	–
Anticoagulant, antiplatelet, and fibrinolytic	19 (6)	8 (5)	1 (1)	–
Antipsychotics/neuroleptics	35 (11)	–	–	–
Steroids	29 (9)	–	–	–
Other GI drugs	10 (3)	10 (6)	–	–
Calcium channel blockers	12 (4)	4 (2)	–	–
Immunosuppressants	19 (6)	–	–	–
Other	17 (5)	2 (1)	–	–
Antibacterials	13 (4)	1 (1)	–	–
Hypertension/heart failure agents	8 (3)	4 (2)	–	–
Cancer therapies	7 (2)	3 (2)	–	–
Contraceptives and hormone replacement	9 (3)	2 (1)	7 (5)	–
Antiarrhythmics	7 (2)	2 (1)	6 (4)	3 (11)
Anticonvulsants	5 (2)	1 (1)	13 (9)	7 (25)
Antidiabetics	4 (1)	2 (1)	–	–
HIV entry/integrase inhibitors	1 (0)	2 (1)	–	–
HIV NNRTIs	–	–	1 (1)	–
HIV NRTIs	–	1 (1)	–	–
HIV protease inhibitors	2 (1)	–	2 (1)	–
Antihistamines	1 (0)	–	–	–
Bronchodilators	1 (0)	–	–	–
Urological agents	1 (0)	–	–	–

^aPatients may have received more than 1 drug class.

DDI = drug-drug interaction; GI = gastrointestinal; GLE-PIB = glecaprevir-pibrentasvir; H2 blocker = histamine H2-receptor antagonists; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PPI = proton-pump inhibitor; SOF-VEL = sofosbuvir-velpatasvir.

PROVIDER/PATIENT ACTION AFTER RECEIVING A PHARMACIST RECOMMENDATION

The predominant pharmacist-recommended action regarding DDIs in GLE-PIB and SOF-VEL prescribed groups was to switch the interacting drug to another drug or, if not possible, hold the interacting drug while receiving DAA treatment (Figure 2). Recommended guidance was not followed for 39% (69/179) patients overall, 36% (54/151) of GLE-PIB patients, and 54% (15/28) of SOF-VEL patients (Supplementary Table 3, available in online article). When the recommended guidance was not followed, it was predominantly expressed as “proceed with therapy as prescribed”: 96% (66/69) in the overall population, 96% (52/54) with GLE-PIB, and 93% [14/15] SOF-VEL patients.

Discussion

The changing landscape of HCV treatment over the past 2 decades has resulted in significant improvement in tolerability and efficacy and an increase in the number of patients seeking treatment. Patients who once were thought to have contraindications for treatment such as elderly patients and/or those with comorbid disease can now be effectively treated with all-oral DAA regimens. Earlier DAA regimens had the propensity for significant DDIs because of inhibition of the cytochrome P450 (CYP) 3A4 pathways. More recent DAA regimens do not cause significant inhibition of CYP 3A4; however, because patients increasingly have more comorbid diseases and concomitant medications, there continues to be a concern for DDIs.¹⁷

In this analysis of potential DDIs among HCV patients prescribed the pangenotypic regimens GLE-PIB or SOF-VEL, GLE-PIB was associated

Medicare as the primary payer (63/151 [42%] vs 326/1,065 [31%]; $P=0.002$).

For SOF-VEL, significant differences between patients with pharmacist DDI recommendations vs

patients without were limited to dyslipidemia (6/28 [21%] vs 25/391 [6%]; $P=0.003$) and hypertension (19/28 [68%] vs 155/391 [40%]; $P=0.003$).

TABLE 3 Characteristics of Patients Receiving vs Not Receiving Pharmacist Guidance for a Potential Drug-Drug Interaction

	GLE-PIB (n = 1,216)			SOF-VEL (n = 419)		
	Guidance (n = 151)	No guidance (n = 1,065)	P value ^a	Guidance (n = 28)	No guidance (n = 391)	P value ^a
Sex, n (%)			0.385			0.591
Female	60/151 (40)	463/1,065 (43)		11/28 (39)	174/391 (45)	
Male	91/151 (60)	602/1,065 (57)		17/28 (61)	217/391 (55)	
Age, mean (SD), years	59.7 (9.5)	53.6 (13.4)	<0.001	61.7 (6.7)	58.2 (12.2)	0.087
Age group, years, n (%)			<0.001			0.254
18-35	6 (4)	141 (13)	z	0 (0)	30 (8)	
36-49	11 (7)	209 (20)	z	1 (4)	41 (10)	
50-64	84 (56)	486 (46)	z	16 (57)	189 (48)	
65+	50 (33)	229 (22)	z	11 (39)	131 (34)	
Treatment naive, n/n (%)	139/149 (93)	991/1,061 (93)	0.958	23/27 (85)	355/389 (91)	0.289
HCV genotype, n (%)			0.051			0.353
1	106/143 (74)	742/1,038 (71)		17/27 (63)	182/383 (48)	
2	27/143 (19)	157/1,038 (15)		4/27 (15)	90/383 (23)	
3	6/143 (4)	118/1,038 (11)		6/27 (22)	95/383 (25)	
4-6	4/143 (3)	21/1,038 (2)		0/27 (0)	95/383 (25)	
Baseline platelets <100 cells/μL, n/n (%)	10/140 (7)	47/996 (5)	0.219	2/25 (8)	40/367 (11)	0.650
Baseline FIB4 > 3.25, n (%)	28/151 (19)	146/1,061 (14)	0.117	6/28 (21)	111/389 (29)	0.419
Baseline eGFR < 60 mL/min/1.73m², n/n (%)	29/140 (21)	67/990 (7)	<0.001	3/25 (12)	19/365 (5)	0.159
Baseline viral load, n/n (%)			0.998			0.391
<800K IU/L	49/148 (33)	343/1,041 (33)		9/27 (33)	124/385 (32)	
800K-6MM IU/L	69/148 (47)	485/1,041 (47)		15/27 (56)	177/385 (46)	
>6MM IU/L	30/148 (20)	213/1,041 (20)		3/27 (11)	84/385 (22)	
Comorbidities, n (%)						
Anxiety	20 (13)	180 (17)	0.257	8 (29)	77 (20)	0.259
Diabetes	53 (35)	126 (12)	<0.001	6 (21)	50 (13)	0.194
Dyslipidemia	32 (21)	34 (3)	<0.001	6 (21)	25 (6)	0.003
Hypertension	90 (60)	321 (30)	<0.001	19 (68)	155 (40)	0.003
Academic site of care, n (%)	35 (23)	113 (11)	<0.001	4 (14)	47 (12)	0.723
Primary payer, n (%)			0.002			0.437
Commercial	38 (25)	208 (20)		10 (36)	102 (26)	
Medicaid	50 (33)	527 (49)	z	5 (18)	121 (31)	
Medicare (including dual)	63 (42)	326 (31)	z	13 (46)	165 (42)	
Other or unknown	0	4 (0)		0	3 (1%)	

^az indicates column proportions that are significantly different by z-test for variables with more than 2 levels.

eGFR = estimated glomerular filtration rate; GLE-PIB = glecaprevir-pibrentasvir; HCV = hepatitis C virus; FIB4 = Fibrosis-4 Index for Liver Fibrosis;

SOF-VEL = sofosbuvir-velpatasvir.

FIGURE 2 Pharmacist Guidance (Bars) and Subsequent Physician or Patient Action (Areas)**A. Guidance and response for GLE-PIB prescribed patients**

GLE-PIB (n = 151)

B. Guidance and response for SOF-VEL prescribed patients

SOF-VEL (n = 28)

GLE-PIB = glecaprevir-pibrentasvir; SOF-VEL = sofosbuvir-velpatasvir.

with a significantly greater likelihood of potential DDIs than SOF-VEL. GLE-PIB was also prescribed in spite of being contraindicated more frequently than SOF-VEL, with the most frequent contraindications for GLE-PIB being lipid-lowering agents and anticonvulsants. DDIs with lipid-lowering agents have previously been reported to be most frequent with regimens containing NS3/4A serine protease inhibitors.¹⁷

EMR and pharmacy data suggest that population characteristics are

different between the 2 prescribed drugs, with GLE-PIB patients being younger and potentially with less severe disease and comorbid burden relative to those prescribed SOF-VEL. This is consistent with a previous analysis in which patients receiving a SOF-based regimen had more advanced disease with a greater frequency of having low platelets and high FIB-4 scores.¹⁸

In this analysis, physicians or patients did not accept

recommendations from a pharmacist to avoid potential DDIs in a significant percentage of cases. Rationale for accepting or not accepting recommendations was not captured in the databases. Although it is not possible to compare recommendations to avoid DDIs across studies, failure to follow recommendations to avoid DDIs was also seen in a significant proportion of patients (40%) in a large real-world study.¹⁷ In the future, it will be important to collect specific reasons for not accepting recommendations to explore potential avenues for reducing potential DDIs. Awareness of DDIs is of paramount importance, and care could also be improved by inclusion of the Hepatitis Drug Interaction Database as a resource for pharmacists along with currently used sources (Micromedex, Facts and Comparisons, UpToDate, Lexicomp, and package inserts).

Our data suggest that for patients prescribed GLE-PIB, pharmacist recommendations regarding potential DDIs were more frequent in the setting of academic centers. It warrants further investigation whether potential GLE-PIB DDIs are being underreported in community settings and, by extension, whether academic centers are a more appropriate setting for prescribing GLE-PIB than community ones. It is also possible that community practices do not have the resources of a pharmacist to advise on DDIs.

With the availability of all-oral DAAs offering a short duration of treatment and high likelihood of cure, the World Health Organization (WHO) has a goal of reducing new viral infections by 90% and mortality by 65% by 2030 with the ultimate aim of eliminating HCV.¹⁹ Countries such as Egypt and Georgia have elimination programs in progress.^{20,21} Efforts to eliminate HCV will be aided by availability of therapies that can be applied broadly

to large populations of patients, especially with a small likelihood of DDIs. Yet even with large-scale efforts, treatment individualization based on comorbidities and concurrent medications is paramount.

LIMITATIONS

Large size and population diversity are strengths of this study, but there are limitations to consider. The available demographic, lab, and treatment information available within the received EMR data were sparse, and limited comorbid conditions and concomitant medications were available in the pharmacy database. Although both sources contain data for patients that reside in every US state and the District of Columbia, the selected sample may not have represented patients in the United States as a whole. Populations that may have been underrepresented in the study were those receiving care in drug addiction treatment centers and correctional institutions and patients with HIV. In both data sources, the prevalence of DDIs was likely underrepresented due to incomplete or inaccurate prescription data (EMR) or due to data limited to pharmacist action (pharmacy database). Finally, we lacked safety, adherence, and virologic response data and thus could not ascertain if the DDIs resulted in any adverse event or change in the duration or efficacy of the treatment regimen chosen by the provider.

Conclusions

In this analysis of EMR and pharmacy databases in the United States, the potential for DDIs with the HCV DAAs GLE-PIB and SOF-VEL were frequent, especially with GLE-PIB. Physician responses to pharmacist alerts regarding potential interaction were highly variable, even in cases of contraindication. These results

highlight the importance of safety considerations and individualized therapies even for pangenotypic DAA regimens for chronic HCV, especially as treatment is expanded to high-risk populations to meet the WHO goal of HCV elimination.

DISCLOSURES

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