Review Article

Review of Clinically Relevant Drug Interactions with Next Generation Hepatitis C Direct-acting Antiviral Agents

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Abstract

In this review, we examine the pharmacokinetics and clinically relevant drug interactions of the newer generation direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C, specifically sofosbuvir/velpatasvir (Epclusa®), sofosbuvir/velpatasvir/voxilaprevir (Vosevi®), glecaprevir/pibrentasvir (Maviret®), and elbasvir/grazoprevir (Zepatier®). We searched MEDLINE (1948-January 2020), Embase (1964-January 2020), Google, and GoogleScholar using the terms pharmacokinetics, drug interaction, drug metabolism, sofosbuvir, velpatasvir, Epclusa, voxilaprevir, Vosevi, glecaprevir, pibrentasvir, Maviret, elbasvir, grazoprevir, and Zepatier, from inception to January 13, 2020. The search was limited to randomized controlled trials, *in vitro* studies, prospective and retrospective human studies, drug monographs, abstracts, and conference proceedings. All relevant published literature on pharmacokinetic and pharmacodynamic interactions involving DAAs were reviewed and the data extracted. Numerous clinically relevant drug-drug interactions (DDIs) were identified with the newer generation DAAs and commonly prescribed drugs. NS3/4A protease inhibitors are more likely to be involved in DDIs, followed by NS5A inhibitors and NS5B polymerase inhibitor. The majority of clinically relevant DDIs are predictable, according to known pharmacokinetic, pharmacodynamics, and physicochemical properties of DAAs; however, in select cases, unpredictable DDIs do occur. As expected, many drug interactions exist between newer generation DAAs and commonly prescribed medications. While the majority of clinically relevant interactions are predictable, many require therapeutic dose adjustment or careful selection of non-interacting drugs. In select cases, severe and unpredictable drug interactions can occur. Clinicians should consult hepatitis C virus pharmacotherapy experts and tertiary drug interaction resources when initiating DAA therapy in patients taking other medications.

Citation of this article: Hong J, Wright RC, Partovi N, Yoshida EM, Hussaini T. Review of clinically relevant drug interactions with next generation hepatitis C direct-acting antiviral agents. J Clin Transl Hepatol 2020;8(3):322–335. doi: 10.14218/JCTH.2020.00034.

Introduction

It is estimated that approximately 71 million people worldwide are chronically infected with hepatitis C. Chronic hepatitis C infection leads to significant morbidity and mortality, including progressive hepatic fibrosis, cirrhosis, and development of hepatocellular carcinoma. Hepatitis C virus (HCV) is associated with a global liver-related mortality rate of 399,000 people per year.[1] The introduction of direct-acting antiviral (DAA) agents has revolutionized hepatitis C therapy, offering safe and highly effective therapy with treatment success rates exceeding 95%. These agents, however, are implicated in many drug-drug interactions (DDIs); it is estimated that 30% to 60% of patients undergoing DAA treatment are at risk for clinically significant drug interactions.[2,3]

Knowledge of these pharmacokinetic and pharmacodynamic interactions is essential in optimizing therapy, avoiding drug toxicities, and ensuring adequate DAA exposure and efficacy.[2–4] This article will review the pharmacokinetic properties of the commonly used newer generation DAA regimens, namely: sofosbuvir (SOF)/velpatasvir (VEL) (Epclusa®), SOF/VEL/voxilaprevir (VOX) (Vosevi®), glecaprevir (GLE)/pibrentasvir (PIB) (Maviret®), and elbasvir (EBR)/grazoprevir (GZR) (Zepatier®). We have previously reviewed the older DAA regimens elsewhere.[5] Drug interactions with commonly prescribed therapeutic classes are discussed and management or monitoring strategies are suggested.

Methods

We searched MEDLINE, Embase, Google, and GoogleScholar using the terms pharmacokinetics, drug interaction, drug metabolism, sofosbuvir, velpatasvir, Epclusa, voxilaprevir, Vosevi, glecaprevir, pibrentasvir, Maviret, elbasvir, grazoprevir, and Zepatier, from inception to January 13, 2020. We

Keywords: Hepatitis C; Drug interactions; Pharmacokinetics; Direct-acting antiviral agents.

Abbreviations: ALT, alanine transaminase; ARA, acid reducing agent; ART, antiretroviral therapy; AST, aspartate aminotransferase; ATV, atazanavir; AUC, area under curve; BCRP, Breast Cancer Resistance Protein; c, cobicistat; CTP, Child Turcotte Pugh; DAA, direct-acting antiviral; DDI, drug-drug interaction; DRV, darunavir; EBR, elbasvir; EVG, elvitegravir; FTC, emtricitabine; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; OATP, organic-anion-transporting polypeptide; P-gp, P-glycoprotein; PI, protease inhibitor; PIB, pibrentasvir; PPI, proton pump inhibitor; r, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; UGT1A1, uridine diphosphate-glucuronosyltransferases 1A1; VEL, velpatasvir; VOX, voxilaprevir; 3TC, lamivudine.

Received: 19 April 2020; Revised: 28 June 2020; Accepted: 30 June 2020

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included randomized controlled trials, *in vitro* studies, prospective and retrospective human studies, drug monographs, abstracts, and conference proceedings. Our search excluded literature reviews, expert clinician opinion papers, and articles not available in English. After the initial search, bibliographies were hand searched for relevant articles. Relevance and severity of drug interactions were determined by synthesizing available primary and tertiary resources, in addition to consultation with clinical experts.

Pharmacokinetic characteristics

SOF/ VEL (Epclusa®)

The combination of SOF, an NS5B polymerase inhibitor and VEL, an NS5A replication complex inhibitor, is a pangenotypic DAA regimen effective against genotypes 1 through 6.[6] Designed as a single tablet regimen of 400 mg SOF and 100 mg VEL, it is dosed once daily. The absorption of both SOF and VEL is not affected by food.[6] Once absorbed, SOF, a pro-drug, enters the hepatocyte and undergoes multistep metabolism to form the active drug, GS-461203; neither SOF nor its metabolites are substrates, inhibitors, or inducers of CYP450 isoenzymes, hence they carry low potential for DDIs.[6] The main route of elimination for SOF and its primary circulating metabolite is via glomerular filtration (80%) and active tubular secretion. As a result, patients with advanced chronic kidney disease and those receiving hemodialysis have significantly higher exposure to SOF; thus, it is not recommended to use SOF in patients with severe renal dysfunction.[6] VEL undergoes hepatic biotransformation and is a substrate of CYP3A4, CYP2C8, and CYP2B6, and a substrate and an inhibitor of P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP) and organic-anion-transporting polypeptide (OATP) 1B1 and OATP1B3, hence having potential for many DDIs. VEL is primarily eliminated via biliary excretion into the feces (Table 1).[6] SOF/VEL is safe in patients with hepatic impairment, including those with decompensated (Child Turcotte Pugh (CTP) stage B and C) cirrhosis.[6,7]

SOF/VEL/VOX (Vosevi®)

VOX is a potent pangenotypic NS3/4A protease inhibitor (PI). The fixed-dose combination containing 400 mg SOF, 100 mg VEL and 100 mg VOX administered once daily is indicated for patients with previous DAA treatment failures.[8] VOX exposure is increased by 435% when administered with high fat meals, as such it is recommended to take SOF/VEL/VOX with food. VOX is primarily metabolized in the liver by CYP3A4 and to a lesser extent by CYP1A2, CYP2C8 (Table 1). It is both a substrate and an inhibitor of the drug transporters P-gp, BCRP, OATP1B1 and OATP1B3.[8] VOX is primarily eliminated by biliary secretion (Table 1). VOX exposure increased by 299% and 500% in patients with CTP B and CTP C cirrhosis, respectively, relative to patients with normal hepatic function.[8] As a result, SOF/VEL/VOX is not recommended in patients with moderate to severe hepatic impairment (CTP-B or CTP-C).

GLE/PIB (Maviret®)

The combination of GLE, a pangenotypic NS3/4A PI and PIB, an NS5A replication complex inhibitor is indicated for the treatment of HCV genotypes 1-6 in both treatment-naïve and DAA-experienced patients.[9] The recommended dosage is GLE (300 mg)/PIB (120 mg) once daily, administered as three tablets of GLE/PIB 100 mg/40 mg. It is recommended to take GLE/PIB with food, as moderate to high fat meals have been shown to increase the exposure of both GLE and PIB (Table 1).[9]

GLE is a minor substrate of CYP3A4, although this pathway is not believed to be clinically relevant.[9] PIB is not subject to biotransformation. Both GLE and PIB are substrates and inhibitors of multiple transport proteins.[9] GLE and PIB are predominantly cleared via biliary excretion with minimal renal elimination.[10,11] While safe in patients with renal dysfunction, GLE/PIB plasma concentrations may increase several fold in those with decompensated cirrhosis. In a phase 1 study, GLE exposure increased by 2- and 11-fold in patients with CTP B and CTP C cirrhosis, respectively.[9,12] Retrospective analysis of multiple phase 2 and 3 trials has demonstrated that GLE/PIB is safe and efficacious when administered to patients with compensated cirrhosis (CTP A).[13] As such, GLE/PIB is contraindicated in patients with CPT C and not recommended in those with CTP B cirrhosis.[9]

EBR/GZR (Zepatier®)

The combination of EBR, an NS5A replication complex inhibitor, and GZR, a NS3/4A PI, is available as a once daily fixed-dose tablet containing 50 mg EBR and 100 mg GZR. EBR/GZR is indicated for the treatment of HCV genotypes 1 and 4 as monotherapy, as well as genotype 3 when combined with SOF.[14] Both EBR and GZR exhibit low oral bioavailability. Administration with a high fat meal is known to increase GZR exposure by 50%; however, EBR exposure is not affected by food. As a result, EBR/GZR can be administered without regard to meals. Both EBR and GZR undergo hepatic biotransformation and can inhibit transporter proteins (Table 1).[14] As such, renal impairment will not affect the exposure of EBR/GZR and in fact the efficacy and safety of standard dose EBR/GZR has been demonstrated in a phase 3 study of patients with end-stage renal disease.[15] EBR/GZR is considered safe in patients with CTP A; however, in patients with decompensated liver disease (CTP B and C), the GZR area under the plasma drug concentration-time curve (AUC) has been shown to increase by 5- and 12-fold, respectively.[16] Therefore, similar to other PI containing regimens, EBR/GZR is not recommended in patients with moderate or severe hepatic impairment.[14]

DDIs

As described above, many DAAs undergo hepatic biotransformation and are substrates or inhibitors of CYP450 isoenzymes and/or transporter proteins (Table 1). As such, many are implicated in clinically significant DDIs; the extent and severity of such interactions vary significantly depending on the class of DAAs. Fortunately, newer generation DAAs, especially NS3/4A PI containing regimens, have much improved interaction profiles as compared to their earlier predecessors. Table 2 summarizes most relevant DDIs with DAA regimens.

Acid reducing agents

Acid reducing agents (ARAs), such as H2 blockers or proton pump inhibitors (PPIs), are widely available without a

Table 1. Summary of DAA clinical pharmacokinetics

Drug	Epclusa®		Vosevi®	Maviret®		Zepatier®	
	sofosbuvir	velpatasvir	voxilaprevir	glecaprevir	pibrentasvir	elbasvir	grazoprevir
Food considerations	Administer with or without food		Administer with food	Administer with food		Administer with or without food	
T_{max} in h	0.5-2	3-4	4	3-5	5	3-6	0.5-3
Plasma protein binding	61-65%	>99.5%	>99%	97.5%	99.9%	>99.8%	>99.8%
Half Life $T_{1/2}$ in h	0.5 metabolite: 25-29	15-17	33	6	13	31	24
CYP450 metabolism: substrate	-	CYP2B6/2C8/ 3A4	CYP3A4	CYP3A4	-	CYP3A4	CYP3A4
Transporter proteins: substrate	Cathepsin A, CES1, HINT1 P-gp, BCPR	P-gp, BCRP, OATP1B1/3	P-gp, BCRP, OATP1B1/B3	P-gp, BCRP, OATP1B1/B3	P-gp, BCRP	P-gp, BCRP, OATP1B1	P-gp
Inhibitor of CYP isoenzyme or transporter	-	P-gp, BCRP, OATP1B1/B3	P-gp, BCRP, OATP1B1/B3	P-gp, BCRP, OATP1B1/B3	P-gp, BCRP, OATP1B1	CYP3A4 (weak), BCRP, P-gp (weak)	BCRP
Major route of elimination	Renal	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic

prescription and are commonly used by patients with hepatitis C infection.[17] The solubility and hence absorption of some DAAs, specifically VEL and GLE, are pH-dependent, with decreased bioavailability at higher gastric pH.[6,8,9] VEL is the most significantly affected by this interaction. In phase I clinical trials the combination of SOF/VEL and omeprazole 20 mg, under fasting conditions, lead to 56% reduction in VEL exposure.[18] Ideally, VEL-containing DAAs should not be administered with PPIs. If the co-administration of VEL with PPIs is unavoidable, it is recommended not to exceed PPI dosages equivalent to omeprazole 20 mg daily. SOF/VEL should be taken with food 4 h prior to taking omeprazole, at a maximum dose of 20 mg daily, and SOF/VEL/VOX should be taken with food at the same time as low dose PPI.[6,8] Recommendations for antacid (e.g., calcium carbonate) administration are extrapolated from these studies and it is recommended to separate them by 4 h.[6,8]

Similarly, GLE absorption is improved in an acidic environment. In a pooled analysis of nine phase 2 and 3 clinical trials, while patients taking GLE/PIB with either high or low dose PPIs had 41% lower GLE exposure, the sustained virologic response (SVR) at week 12 rates were similar to patients not receiving ARAs.[19,20] Therefore, despite the modest pharmacokinetic interaction, given the lack of any significant clinical impact, GLE/PIB can be used in combination with ARAs.[9]

Although the solubility of both EBR and GZR appears to be pH-independent, phase 1 trials reported no difference in the plasma exposure of EBR and GZR with concomitant administration of either famotidine 20 mg or pantoprazole 40 mg.[21] In a pooled analysis of 1322 patients from phase 3 studies, no difference was found in the SVR rates achieved in patients receiving EBR/GZR and ARAs versus those who did not receive ARAs.[22] Manufacturer labelling does not recommend any dosage adjustment for EBR/GRZ when used in combination with ARAs.[14]

Anti-arrhythmics

Several case reports have documented symptomatic bradycardia in patients receiving concurrent amiodarone and SOF-containing DAA regimens.[23] Of these cases, there was one death and two cases of a patient requiring placement of a permanent pacemaker.[23,24] Bradycardia has been reported after a single dose of a SOF-containing regimen.[25] Although the exact mechanism of the interaction is unknown, several hypotheses have been postulated, including increased free amiodarone levels due to serum protein displacement caused by SOF, increased SOF concentration due to P-gp inhibition by amiodarone, or potential additive effects of SOF and amiodarone on disrupting cardiac myocytes calcium handling with resultant changes in cellular electrophysiology.[23–26] Regardless of the proposed mechanism, the concomitant administration of SOF-containing DAAs with amiodarone should be avoided. There are no reports of EBR/ GZR- or GLE/PIB-induced bradycardia with amiodarone; however, theoretically, GLE/PIB and EBR can increase amiodarone exposure via CYP3A4 and P-gp inhibition.[9,14] Monitoring for amiodarone adverse effects is required when administered concurrently with EBR/ GZR or GLE/PIB.

Digoxin is a cardiac glycoside with a narrow therapeutic index, digoxin is a P-gp substrate and is susceptible to interaction with most DAAs.[27] When digoxin is co-administrated with VEL, the AUC of digoxin can increase by as much as 35%.[18,28] Therefore, it is recommended to monitor serum

Table 2. Summary of drug interactions

Interacting drug class, drug name	Effect on drug exposure	Recommended management			
		Epclusa (SOF/VEL)	*Vosevi* (SOF/VEL/ VOX)	*Maviret* (GLE/PIB)	*Zepatier* (EBR/ GZR)
		Acid suppression agents			
Antacids	↓ VEL – potential clinically significant interaction	Take SOF/VEL 4 h before antacid administration	Take SOF/VEL/VOX 4 h before antacid administration	No dose adjustment required	No dose adjustment required
H2-receptor antagonists	↓ VEL – clinically significant interaction ↓ GLE - weak interaction, not clinically significant	Max dose of famotidine 40 mg twice daily or equivalent Administer simultaneously with, or 12 h apart from H_2-receptor antagonists	Max dose of famotidine 40 mg twice daily or equivalent Administer simultaneously with, or 12 h apart from H_2-receptors antagonists	No dose adjustment required	No dose adjustment required
Proton pump inhibitors	↓ VEL – potential clinically significant interaction ↓ GLE – weak interaction, not clinically significant	Avoid if possible, Administer SOF/VEL with food and 4 h prior to PPI Max dose of omeprazole 20 mg daily	Avoid if possible, Administer SOF/VEL/VOX with food and 4 h prior to PPI Max dose of omeprazole 20 mg daily	No dose adjustment required	No dose adjustment required
		Anti-arrhythmics			
Amiodarone	↑ Amiodarone – potential clinically significant interaction	Co-administration is not recommended	Co-administration is not recommended	Monitor for amiodarone adverse effects required	Monitor for amiodarone adverse effects required
Digoxin	↑ Digoxin – potential clinically significant interaction	Monitor digoxin level	Monitor digoxin level	Reduce digoxin dose by 50%	No dose adjustment required
		Anticoagulants			
Dabigatran etexilate	↑ Dabigatran – potential clinically significant interaction	Monitoring of dabigatran adverse effects required	Co-administration is contraindicated	Co-administration is contraindicated	Monitoring of dabigatran adverse effects required
Apixaban	↑ Apixaban – potential clinically significant interaction	Monitoring of apixaban adverse effects required	Monitoring of apixaban adverse effects required	Monitoring of apixaban adverse effects required	Monitoring of apixaban adverse effects required
Rivaroxaban	↑ Rivaroxaban – potential clinically significant interaction	Monitoring of rivaroxaban adverse effects required	Monitoring of rivaroxaban adverse effects required	Monitoring of rivaroxaban adverse effects required	Monitoring of apixaban adverse effects required
Edoxaban	↑ Edoxaban – potential clinically significant interaction	Monitoring of edoxaban adverse effects required	Co-administration is not recommended	Monitoring of edoxaban adverse effects required	Monitoring of apixaban adverse effects required
Vitamin K antagonist	↑ Warfarin – potential clinically significant interaction	INR monitoring is required	INR monitoring is required	INR monitoring is required	INR monitoring is required

(*continued*)

Table 2. (*continued*)

Interacting drug class, drug name	Effect on drug exposure	Recommended management			
		Epclusa (SOF/VEL)	*Vosevi* (SOF/VEL/ VOX)	*Maviret* (GLE/PIB)	*Zepatier* (EBR/ GZR)
		Aromatic anticonvulsants			
Carbamazepine	↓ VEL, VOX, GLE, PIB, EBR, GZR – potential clinically significant interaction	Co-administration is contraindicated	Co-administration is contraindicated	Co-administration is contraindicated	Co-administration is contraindicated
Phenytoin	↓ VEL, VOX, GLE, PIB, EBR, GZR - potential clinically significant interaction	Co-administration is contraindicated	Co-administration is contraindicated	Co-administration is contraindicated	Co-administration is contraindicated
Phenobarbital	↓ VEL, VOX, GLE, PIB, EBR, GZR – potential clinically significant interaction	Co-administration is contraindicated	Co-administration is contraindicated	Co-administration is contraindicated	Co-administration is contraindicated
		Anti-infective			
Ketoconazole	↑ GLE, PIB, EBR, GZR – potential clinically significant interaction ↑ Ketoconazole - potential clinically significant interaction ↑ VEL, VOX - weak interaction, not clinically significant	No dose adjustment required	No dose adjustment required	Monitor for GLE/PIB and ketoconazole adverse effects required. LFT monitoring required	Co-administration is not recommended
Voriconazole	↑ VOX - weak interaction/ clinically insignificant	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Posaconazole	↑ Posaconazole – potential clinically significant interaction	No dose adjustment required	No dose adjustment required	Monitoring of posaconazole adverse effects required	No dose adjustment required
Fluconazole	No interaction expected	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Rifampin	↓ SOF, VEL, VOX, GLE, PIB, GZR – potential clinically significant interaction	Co-administration is not recommended	Co-administration is contraindicated	Co-administration is contraindicated	Co-administration is contraindicated
		Anti-retroviral			
Abacavir	No interaction expected	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Tenofovir disoproxil fumarate	↑ Tenofovir – potential clinically significant interaction	Monitor for nephrotoxicity	Monitor for nephrotoxicity	No dose adjustment required	No dose adjustment required

(*continued*)

Table 2. (*continued*)

Interacting drug class, drug name	Effect on drug exposure	Recommended management			
		Epclusa (SOF/VEL)	*Vosevi* (SOF/VEL/ VOX)	*Maviret* (GLE/PIB)	*Zepatier* (EBR/ GZR)
Tenofovir alafenamide	↑ Tenofovir – weak interaction, not clinically significant	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Emtricitabine	No interaction expected	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Lamivudine	No interaction expected	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Entecavir	No interaction expected	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Efavirenz	↓ VEL, VOX, GLE, PIB, EBR, GZR – potential clinically significant interaction	Co-administration is not recommended	Co-administration is not recommended	Co-administration is not recommended	Co-administration is contraindicated
Rilpivirine	No interaction expected	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Atazanavir/ ritonavir	↑ VOX, GLE, EBR, GZR – potential clinically significant interaction	No dose adjustment required	Co-administration is not recommended	Co-administration is contraindicated	Co-administration is contraindicated
Darunavir/ ritonavir	↑ GLE, EBR, GZR – potential clinically significant interaction ↑ VOX – potential clinically significant interaction	No dose adjustment required	Max darunavir/ritonavir 800 mg/100 mg once daily	Co-administration is not recommended	Co-administration is contraindicated
Dolutegravir	No interaction expected	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Elvitegravir/cobicistat in combination with tenofovir and emtricitabine	↑ EBR, GZR, potential clinically significant interaction ↑ VOX, GLE, PIB, weak interaction, not clinically significant	No dose adjustment required	No dose adjustment required	No dose adjustment required, LFT monitoring required	Co-administration is not recommended
Raltegravir	↑ Raltegravir - weak interaction, not clinically significant	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
		HMG-CoA inhibitor			
Atorvastatin	↑ Atorvastatin – potential clinically significant interaction	Monitor for myopathy / rhabdomyolysis	Max dose of atorvastatin 10 mg	Co-administration is contraindicated	Max dose of atorvastatin 20 mg

(*continued*)

Table 2. (*continued*)

Interacting drug class, drug name	Effect on drug exposure	Recommended management			
		Epclusa (SOF/VEL)	*Vosevi* (SOF/VEL/ VOX)	*Maviret* (GLE/PIB)	*Zepatier* (EBR/ GZR)
Lovastatin	↑ Lovastatin – potential clinically significant interaction	Monitor for myopathy / rhabdomyolysis	Use lowest dose possible	Co-administration is not recommended	Use lowest dose possible
Simvastatin	↑ Simvastatin – potential clinically significant interaction	Monitor for myopathy / rhabdomyolysis	Use lowest dose possible	Co-administration is contraindicated	Use lowest dose possible
Pravastatin	↑ Pravastatin – potential clinically significant interaction	No dose adjustment required	Max dose of pravastatin 40 mg	Reduce dose of pravastatin by 50%	No dose adjustment required
Rosuvastatin	↑ Rosuvastatin – potential clinically significant interaction	Max dose of rosuvastatin 10 mg	Co-administration is contraindicated	Max dose of rosuvastatin 5 mg	Max dose of rosuvastatin 10 mg
		Immunosuppression			
Cyclosporine	↑ VOX, GLE, GZR – potential clinically significant interaction ↑ SOF, VEL – weak interaction, not clinically significant	No dose adjustment required	Co-administration is not recommended	Max dose of cyclosporine 100 mg daily	Co-administration is contraindicated
Tacrolimus	↑ Tacrolimus – potential clinically significant interaction	Monitor tacrolimus level	Monitor tacrolimus level	Monitor tacrolimus level	Monitor tacrolimus level
Sirolimus	Sirolimus – potential clinically significant interaction	Monitor sirolimus level	Monitor sirolimus level	Monitor sirolimus level	Monitor sirolimus level
Prednisone	No interaction expected	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Mycophenolate	No interaction expected	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
		Oral contraceptive			
Ethinyl estradiol containing contraceptives	Increased risk of ALT elevation	No dose adjustment required	Co-administration is contraindicated	Co-administration is contraindicated	No dose adjustment required
Norethindrone	No interaction expected	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
		Opioid agonists and antagonist			
Methadone	↑ Methadone – weak interaction, potentially clinically significant	Monitor for decrease in level of consciousness and respiratory depression	Monitor for decrease in level of consciousness and respiratory depression	Monitor for decrease in level of consciousness and respiratory depression	Monitor for decrease in level of consciousness and respiratory depression

(*continued*)

Table 2. (*continued*)

Interacting drug class, drug name	Effect on drug exposure	Recommended management			
		Epclusa (SOF/VEL)	*Vosevi* (SOF/VEL/ VOX)	*Maviret* (GLE/PIB)	*Zepatier* (EBR/ GZR)
Buprenorphine	↑ Buprenorphine – weak interaction, potentially clinically significant	Monitor for decrease in level of consciousness and respiratory depression	Monitor for decrease in level of consciousness and respiratory depression	Monitor for decrease in level of consciousness and respiratory depression	Monitor for decrease in level of consciousness and respiratory depression
Naloxone	No interaction expected	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Fentanyl	↑ Fentanyl – weak interaction, potentially clinically significant	No dose adjustment required	No dose adjustment required	Monitor for decrease in level of consciousness and respiratory depression	Monitor for decrease in level of consciousness and respiratory depression

Color	Description
	No action required
	Administer with caution, specific monitoring required
	Administration is not recommended or contraindicated

↓, decrease;

↑, increase;

Abbreviations: ALT, alanine transaminase; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; INR, international normalized ratio; LFT, liver function tests; PIB, pibrentasvir; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

digoxin concentrations closely when co-administered with VEL-containing regimens. Similarly, the combination of GLE/PIB with digoxin has been shown to increase digoxin exposure by approximately 50% and as a result, it is recommended to decrease digoxin dosage by half when combined with GLE/PIB.[29] EBR/GZR does not result in clinically important changes in digoxin exposure.[14]

Anticoagulants

Dabigatran is a P-gp substrate with a narrow therapeutic index.[2] While no clinical studies have examined the potential DDIs between dabigatran and EBR/GZR or SOF/VEL, an increase in dabigatran exposure is expected since both EBR and VEL are weak P-gp inhibitors.[30] In isolation, interactions between EBR or VEL with dabigatran are unlikely to be clinically significant; however, it is prudent to monitor patients for signs of bleeding. When combined with SOF/VEL/VOX, dabigatran AUC increases by up to 161%, due to the P-gp inhibition by VOX.[30–32] Similarly, the administration of dabigatran with GLE/PIB has been shown to increase dabigatran AUC by 138%.[33] Given the increased exposure to dabigatran and lack of clinical studies, concurrent administration with SOF/VEL/VOX or GLE/PIB is contraindicated.[8,9,34]

There are no pharmacokinetic studies conducted with DAAs and the direct factor Xa inhibitors apixaban or rivaroxaban. However, since they are both CYP3A4, P-gp and BCRP substrates, it is recommended to monitor for bleeding when apixaban or rivaroxaban are combined with DAA regimens, as their plasma concentration can theoretically increase.[6,8,9,14]

Edoxaban, another direct factor Xa inhibitor, is a P-gp substrate with an active metabolite (M4), which is an OATP1B1 substrate.[35,36] The European summary of product characteristics for SOF/VEL/VOX recommends that rivaroxaban or apixaban should be preferred over edoxaban due to potential additive OATP1B1 inhibition by both VEL and VOX; however, given that M4 accounts for <10% of edoxaban exposure, the significance of this interaction is unknown.[8,35,37] It is possible that co-administration with DAAs would lead to increased edoxaban. Although no clinical studies have been conducted to assess the magnitude of this interaction, monitoring for signs of bleeding is highly recommended.

Vitamin K antagonists, such as warfarin, have not been studied with newer generation DAAs. As a substrate of CYP1A2 and CYP2C9, warfarin may theoretically interact with GLE/PIB, although this interaction is not likely to be clinically significant.[9]

Aromatic anticonvulsants

The aromatic anticonvulsants carbamazepine, phenobarbital and phenytoin are considered strong CYP450 enzyme inducers, and can reduce the exposure of many DAAs.[38] There are no direct studies analyzing the effect of concomitant administration of anticonvulsants on the plasma concentration of EBR/GZR. The likelihood of interactions was derived from pharmacokinetic studies with efavirenz, a moderate CYP3A4 inducer, and rifampin, another strong CYP3A4 inducer. The concomitant use of EBR/GZA, SOF/VEL and SOF/VEL/VOX with carbamazepine, phenytoin, and phenobarbital is contraindicated.[6,8,14,18,32] Glecaprevir and pibrentasvir exposure are both affected by carbamazepine, with a decrease of 50-80% in GLE AUC and 31-42% in PIB AUC.[9] These results were also used to extrapolate recommendations for co-administration of phenobarbital and phenytoin, which are both deemed contraindicated.[9]

Anti-infectives

Triazole antifungals inhibit the cytochrome P450 isoenzymes to a varying extent. Most pharmacokinetic studies addressing DDIs with DAAs have included ketoconazole, which is a strong inhibitor of CYP3A4, CYP2C8, and P-gp.[38] The combination of EBR/GZR with a single dose of ketoconazole at 400 mg resulted in a 1.8-fold increase in EBR AUC and a 3-fold increase in GZR AUC.[14] Therefore, ketoconazole should not be co-administered with EBR/GZR. No pharmacokinetic studies have been reported with EBR/GZR and voriconazole; however, their co-administration is unlikely to result in a clinically significant interaction, as EBR/GZR is only partially metabolized by the CYP3A system.[14]

When VEL was co-administered with ketoconazole, the VEL Cmax and AUC increased modestly by 29% and 71%, respectively.[18] Similarly, co-administration of voriconazole and voxilaprevir increased voxilaprevir AUC by 84% but had no effect on Cmax.[28,31,32] Therefore, both SOF/VEL and SOF/VEL/VOX can be concurrently administered with ketoconazole or voriconazole.[6,8]

There are no pharmacokinetic studies conducted with the combination of GLE/PIB with ketoconazole or voriconazole; however, since GLE/PIB is a substrate of CYP3A4 and an inhibitor of P-gp and BCRP, the AUC of both GLE/PIB, and ketoconazole are expected to increase. More frequent monitoring of GLE/PIB and ketoconazole adverse events, such as hepatotoxicity, is required when this combination is used.

Neither posaconazole nor fluconazole co-administration with DAAs has been formally studied. The results from voriconazole and ketoconazole pharmacokinetic studies can be used to predict their potential interaction with the newer DAAs. Posaconazole is a potent inhibitor of CYP3A4 but to a lesser extent than ketoconazole.[38,39] Posaconazole can increase EBR/GZR, SOF/VEL, SOF/VEL/VOX, and GLE/PIB AUC; therefore, close monitoring for hepatotoxicity is required during their concurrent administration. Posaconazole concentration could also be increased by EBR/GZR via P-gp inhibition, and monitoring for posaconazole adverse events or serum trough levels are recommended when co-administered together. Fluconazole, a moderate inhibitor of CYP3A4, is unlikely to cause any clinically significant drug interactions with SOF, VEL, VOX, GLE, PIB, EBR, and GZR and is therefore likely safe for concurrent administration.[38]

Rifampin is a strong CYP450 enzyme inducer, with a peak effect when multiple doses are given.[38] A pharmacokinetic study of GZR and rifampin in healthy volunteers found a significant decrease in C_{24h} of GZR after multiple oral rifampin doses, likely due to CYP3A4/P-gp induction by rifampin.[40]

Combination of multiple doses of rifampin and SOF/VEL also led to a significant decrease in both SOF and VEL AUC by 72% and 82%, respectively.[18] Likewise, VOX AUC decreased by 73% when given with multiple doses of rifampin.[31,32] Multiple dose administration of rifampin with GLE/PIB resulted in a decrease in GLE AUC by 88% and PIB by 87%.[9] Co-administration of rifampin with EBR/GZR, SOF/VEL, SOF/VEL/VOX and GLE/PIB is contraindicated due to significant decreases in DAA exposure which could lead to loss of virologic response.[6,8,9,14]

Anti-retrovirals

Patients on antiretroviral therapy (ART) are at a high risk of DDIs. PIs, and non-nucleoside reverse transcriptase inhibitors are substrates, inhibitors, and/or inducers of the CYP450 system, making them prone to drug interactions.[41] On the other hand, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and integrase strand transfer inhibitors are less reliant on the CYP450 system and thus are less susceptible to drug interactions.

Abacavir, an NRTI, is not metabolized by the CYP450 system; although no pharmacokinetic studies have investigated the co-administration of abacavir alone with EBR/GZR, SOF/VEL, SOF/VEL/VOX, or GLE/PIB, no clinically significant DDIs are expected.[42,43]

Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are two NRTI pro-drugs that are converted by intracellular hydrolysis to the active form tenofovir.[44,45] In phase 1 studies of TDF and EBR/GZR, no significant changes in the plasma exposure of EBR and GZR were reported.[46] Another phase 1 study found that no clinically significant DDIs exist between SOF/VEL and TDF or TAF.[47] A phase 3 trial of SOF/VEL enrolled patients taking TDF and did not identify any safety or efficacy concerns.[48] When administered with SOF/VEL/VOX, tenofovir exposure increases by nearly 40%.[8] Given the increased exposure of tenofovir, monitoring for adverse effects, such as nephrotoxicity, is recommended when combining with TDF-containing regimens. When combined with GLE/PIB, TDF exposure increases by 30%; as a result, no dose adjustments are required.[9,43]

Emtricitabine (FTC) is not metabolized by CYP enzymes and is therefore not anticipated to interact with any of the HCV drug combinations.[49] FTC, commonly used as part of fixed anti-retroviral combinations, has been studied in multiple phase 1 trials of co-administrations with DAAs. Studies with EBR/GZR, GLE/PIB, SOF/VEL and SOF/VEL/VOX indicated no change in exposure of FTC, EBR, GZR, GLE, PIB, SOF, VEL, or VOX.[32,46,47] Pharmacokinetic data from FTC can be extrapolated and applied to patients taking lamivudine (3TC) due to physicochemical similarities.[50]

Entecavir, an NRTI with weak activity against human immunodeficiency virus (commonly referred to as HIV) and potent activity against hepatitis B virus, is indicated solely for the treatment of hepatitis B virus in non-HIV patients or in HIV patients on fully active ART. Entecavir is not a substrate, inhibitor, nor inducer of any CYP enzymes, and is primarily eliminated unchanged in the urine; as such, entecavir is not anticipated to interact with any of the HCV combinations.[14,51]

Efavirenz is a potent inducer of CYP3A4 and CYP2B6, which could decrease the concentration of EBR, GZR, VEL, VOX, GLE, and PIB.[38] Results of a pharmacokinetic study demonstrated an 83% decrease in GZR AUC and a 54% decrease in EBR AUC.[46] Concurrent administration of SOF/VEL and efavirenz resulted in similar SOF plasma exposure but a 57% decrease in VEL AUC.[47] VOX exposure also decreased by 53% with efavirenz co-administration.[32] In a phase one study of healthy volunteers, administration of GLE/PIB with efavirenz resulted in a 69% to 71% decrease in plasma exposure of GLE and PIB, respectively.[9] It is not recommended to co-administer any newer generation DAAs with efavirenz due to decreased DAA exposure and the potential loss of antiviral efficacy.

Rilpivirine is metabolized extensively by CYP3A; however, its administration with EBR/GZR did not significantly change the plasma exposure of either EBR/GZR or rilpivirine.[46] Co-administration of rilpivirine with either SOF/VEL or SOF/VEL/VOX is not associated with clinically significant changes in AUC of any of the drugs involved.[32,46] When co-administered with GLE/PIB, rilpivirine exposure is increased by 84%; however, this interaction is not believed to be clinically significant and no dosage adjustment is required.[9,52]

Co-administration of atazanavir (ATV)/ritonavir (r) with EBR/GZR resulted in a 4.8-fold increase in EBR AUC and a 10.6-fold increase in GZR AUC.[14] This significant increase in GZR plasma concentrations caused by ATV-mediated OATP1B1/3 inhibition can lead to significant alanine transaminase (ALT) elevations and hepatotoxicity.[14] As such the co-administration of ATV/r with EBR/GZR is contraindicated. A phase 1 study of SOF/VEL with ATV/r demonstrated a 142% increase in SOF plasma exposure, with no changes in VEL or ATV/r AUC.[47] The interaction was not considered to be clinically significant and concurrent administration of ATV/r was allowed in the phase 3 clinical trial, ASTRAL-5, where no safety concerns were reported.[48] On the other hand, the administration of SOF/VEL/VOX with ATV/r is not recommended, as the combination led to a clinically significant increase in VOX AUC by 331%.[32] Similarly, the concurrent use of GLE/PIB with ATV/r is not recommended.[9] In a phase 1 study involving 24 healthy subjects, the administration of GLE/PIB lead to five treatment discontinuations due to asymptomatic elevations of aspartate transaminase (AST)/ALT. The cause of the elevation in liver enzymes is likely due to the significant increase in GLE AUC (6.35-fold) as a result of ritonavir-mediated P-gp inhibition.[43]

The administration of EBR/GZR and darunavir (DRV)/r is contraindicated, as co-administration resulted in increased EBR AUC by 1.7-fold and GZR AUC by 7.5-fold.[14] Administration of SOF/VEL/VOX with DRV/r resulted in a decrease of SOF AUC by 28%, no effect on VEL AUC, and a modest increase in VOX plasma exposure by 57%.[32,47] No dosage adjustments are recommended when administrating DRV/r once daily with either SOF/VEL or SOF/VEL/VOX, as the pharmacokinetic interactions resulting in drug exposure fluctuations are not deemed clinically relevant. Twice daily dosing of DRV/r with either SOF/VEL or SOF/VEL/VOX has not been studied and is not recommended.[6,8]

In a phase 1 study where GLE/PIB was combined with DRV/r, GLE AUC increased by 4.38-fold.[43] Given the significant increase in GLE concentration and the potential for ALT elevations, their co-administration is not recommended.[9]

Dolutegravir undergoes UDP-glucuronosyltransferase metabolism and is not expected to have any DDIs with newer generation DAAs.[53] When EBR/GZR, SOF/VEL, SOF/VEL/VOX, and GLE/PIB were co-administrated with dolutegravir, no differences were found in EBR, GZR, SOF, VEL, VOX, GLE, PIB, or dolutegravir plasma exposures.[43,46,47]

Elvitegravir (EVG) is an integrase strand transfer inhibitor that is only available as a combination product combined with the pharmacokinetic booster cobicistat (c) as well as either TAF/FTC or TDF/FTC. EVG inhibits OATP1B, while c inhibits P-gp, BCRP, and OATP1B1/3.[38] Co-administration of EVG/c/FTC/TDF with EBR/GZR led to a 436% increase in plasma exposure of GZR and a 118% increase in EBR AUC; as such, EBR/GZR is not recommended for patients taking EVG/c-containing regimens.[14] Studies of EVG/c in combination with SOF/VEL/VOX did not identify any significant differences in plasma exposure of SOF or VEL but did demonstrate a 171% increase in VOX AUC.[32,47] Despite the increase in

VOX exposure, the manufacturer does not recommend dose adjustment with either SOF/VEL or SOF/VEL/VOX when combined with EVG/c-containing regimens.[8] The administration of EVG/c-containing regimens with GLE/PIB, resulted in a modest increase in plasma exposure of GLE and PIB by 47% and 42%, respectively.[43] As such, no dosage adjustment is required when GLE/PIB is combined with EVG/c-containing regimens.

Raltegravir is a uridine diphosphate-glucuronosyltransferases 1A1 (known as UGT1A1) substrate and co-administration with GLE/PIB, a mild UGT1A1 inhibitor, can modestly increase exposure of raltegravir by approximately 50%.[52] Concurrent administration with EBR/GZR, resulted in increased raltegravir AUC by 43%, whereas the EBR AUC decreased by 19% and GZR AUC decreased by 11%.[46] When combined with SOF/VEL, there were no changes in exposure of SOF/VEL or raltegravir.[47] Raltegravir has not been studied with VOX; however, no DDI is expected. Overall, given the modest changes in DAA exposures, none of the manufacturers recommend dose adjustment with raltegravir co-administration.[6,8,9,14]

HMG-CoA inhibitors

Atorvastatin, lovastatin, and simvastatin are substrates of CYP3A4, OATP, P-gp and BCRP transporter proteins; therefore, significant potential exists for clinically relevant DDI with most DAA regimens.[54–56] While some combinations are contraindicated, others require a substantial decrease in statin dosage, often to the lowest recommended daily dosage. All patients who require concomitant administration of statin therapy while receiving DAA regimens should be closely monitored for signs of statin toxicity, such as myopathy and rhabdomyolysis.

The co-administration of atorvastatin and EBR/GZR has been shown to increase atorvastatin exposure by 5.7-fold; thus, it is recommended to decrease atorvastatin dosage to a maximum of 20 mg per day in patients receiving EBR/GZR.[14] By extrapolation, lovastatin and simvastatin should also be used at the lowest possible dosage.[14] When a single dose of atorvastatin was administered with SOF/VEL, atorvastatin AUC increased by 54%.[57] As a result, no dose adjustment is required but patients should be monitored for clinical signs of myopathy and rhabdomyolysis. Similarly, simvastatin and lovastatin are likely safe for concurrent administration with SOF/VEL but monitoring is required. No clinical studies have been conducted on the interaction between atorvastatin, lovastatin, and simvastatin with SOF/VEL/VOX but it is speculated that both VEL and VOX can cause inhibition of statin metabolism. The product monograph recommends limiting the dose of atorvastatin at 10 mg per day and to use the lowest dose of lovastatin and simvastatin when co-administrating with SOF/VEL/VOX.[8] The administration of GLE/PIB with atorvastatin, simvastatin, and lovastatin, increased the AUC of the statins by 8.27-, 2.23- and 1.7-fold, respectively.[9] The co-administration of atorvastatin and simvastatin with GLE/PIB is contraindicated, and the co-administration of lovastatin with GLE/PIB is not recommended.[9]

Pravastatin is a substrate of OATP1B1/1B3 alone, while rosuvastatin is a substrate of OATP1B1/1B3 and BCRP.[58,59] When administered in combination, EBR/GZR increased pravastatin AUC by 33% and increased rosuvastatin AUC by 2.3-fold; as a result, rosuvastatin is limited to a maximum dose of 10 mg daily with concurrent EBR/GZR administration, while no dose change is required for pravastatin.[14] When administered with SOF/VEL, pravastatin AUC increased by 35% and rosuvastatin AUC increased by 169%.[6] The manufacturer recommends no dose adjustments with pravastatin but a maximum of 10 mg per day of rosuvastatin when co-administered with SOF/VEL.[6] VEL and VOX in combination were found to increase rosuvastatin AUC by 639% via both BCRP and OATP1B inhibition.[18,32] Therefore, the co-administration of rosuvastatin with SOF/VEL/VOX is contraindicated. Pravastatin exposure was increased by 116% with SOF/VEL/VOX, limiting the dose to a maximum of 40 mg per day is recommended.[31,32] A single study of GLE/PIB demonstrated moderate increases in AUC of both pravastatin and rosuvastatin; moreover, in this study, AUC increased by 130% and 115%, respectively.[33] The manufacturer recommends decreasing pravastatin dose by 50%, and a maximum dose of 5 mg per day of rosuvastatin when co-administered with GLE/PIB.[9]

Immunosuppressive medications

The calcineurin inhibitors cyclosporine and tacrolimus are effective immunosuppressants that are commonly used in solid organ transplantation, bone marrow transplantation, and other immune-mediated pathologies. Tacrolimus is a substrate of CYP3A4, while cyclosporine, also a substrate of CYP3A4, inhibits P-gp, BCRP, and OATPB1/1B3.[60,61]

EBR/GZR has been shown to increase tacrolimus AUC by 43%; therefore, increased frequency of tacrolimus monitoring is recommended when a patient is initiated on EBR/GZR.[62] The administration of cyclosporine with EBR/GZR is contraindicated due to a 10-fold increase in GZR AUC.[62]

No clinically relevant interactions were found with tacrolimus, SOF/VEL or SOF/VEL/VOX.[18,32] No dosage adjustments are required when co-administrating cyclosporine with SOF/VEL, as the co-administration resulted in similar exposures for cyclosporine and an modest increase in VEL AUC of 56%.[18] The co-administration of SOF/VEL/VOX with cyclosporine is not recommended because of the 9.4-fold increase in VOX AUC, likely due to OATP inhibition by cyclosporine.[31,32] Patients on cyclosporine who require SOF/VEL/VOX should be switched to tacrolimus if possible. When combined with GLE/PIB, tacrolimus AUC has been shown to increase by 53%, with no impact on GLE or PIB exposure. As such, tacrolimus therapeutic drug monitoring is recommended when this combination is used.[63] Cyclosporine-mediated inhibition of P-gp, BCRP, and OATP1B1/3 is dose-dependent. The administration of cyclosporine 100 mg increased GLE exposure by 37%, while a 400 mg dose increased GLE AUC by 5-fold.[63] The manufacturer recommends not to co-administer cyclosporine in doses greater than 100 mg per day with GLE/PIB.[9] In summary, the inhibition of transporter proteins by cyclosporine can lead to a significant increase in PI concentrations, which can in turn lead to elevations in liver biochemistries and hepatotoxicity. As such, PI-containing DAA regimens are generally not recommended in combination with cyclosporine.

Sirolimus is a P-gp substrate and its plasma exposure can be increased when combined with P-gp inhibitors like VOX, GLE, PIB, or GZR.[64] The extent of this interaction is unknown and, therefore, sirolimus therapeutic drug monitoring is recommended.

No drug interactions are expected between prednisone or mycophenolate and any of the DAAs.

Oral contraceptives

The co-administration of ethinyl estradiol and levonorgestrel with EBR/GZR resulted in no clinically significant alteration in plasma concentrations of ethinyl estradiol and levonorgestrel.[9] In a study of healthy volunteers, the administration of norgestimate/ethinyl resulted in no clinically relevant effects on the exposure of SOF/VEL, norgestimate, norgestrel, or ethinyl estradiol.[18] In all phase 3 studies of SOF/VEL, oral contraceptives use was allowed, and there was no signal of loss of contraceptive efficacy.[7,48,65,66] The administration of SOF/VEL/VOX or GLE/PIB with oral contraceptives in healthy subjects did not result in any significant pharmacokinetic or pharmacodynamic alterations, but resulted in elevated liver enzymes in some participants.[9,32,67] In the phase 1 study of SOF/VEL/VOX with ethinyl estradiol, 13 out of 15 patients reported elevated liver enzymes. Two of the patients had grade 3 evaluation classification (greater than 5 but less than 10 times the upper limit of normal in ALT/AST).[68] Likewise, in combined analysis of phase 2 and 3 studies of GLE/PIB with ethinyl estradiol, six patients had reported abnormal liver biochemistries.[9,69] The cause of the increased liver enzyme is unknown. It is not recommended to co-administer SOF/VEL/VOX or GLE/PIB with any ethinyl estradiol-containing contraceptives, including intravaginal products.[9]

Norethindrone, the only available progestin-only oral contraceptive, has not been studied in combination with any DAAs; however, as it is metabolized solely via CYP3A4, no clinically significant interactions are expected.[70]

Opioid agonists

Methadone is metabolized via CYP3A4, CYP2B6 and CYP2C19.[71] In a pharmacokinetic study, methadone AUC was increased by 14% and 16% when combined with EBR or GZR, respectively.[72] The administration of SOF alone with methadone resulted in 30% increase in SOF AUC.[6] No studies were conducted between methadone and VEL or VOX; however, in post-hoc analysis of phase 3 trials, SVR12 rates were not different in those who received methadone and those who did not.[73] Methadone co-administration did not increase the exposure of GLE/PIB.[74] Despite modest changes in methadone exposure, no dose adjustments are required with concurrent administration of methadone and EBR/GZR, SOF/VEL, SOF/VEL/VOX, or GLE/PIB but increased monitoring is recommended.

Buprenorphine/naloxone (Suboxone®) is a fixed-dose combination tablet, commonly used for treatment of opioid-use disorder. Buprenorphine is a substrate of CYP3A4 and P-gp, while naloxone is minimally absorbed when taken enterally.[75] Administration of EBR/GZR and buprenorphine/naloxone did not result in any clinically significant changes in EBR/GZR exposure.[14,76] No pharmacokinetic studies have been conducted with SOF/VEL or SOF/VEL/VOX but post-hoc analysis of phase 3 trials found no efficacy or safety signals of either drug in patients who received buprenorphine/naloxone compared to those who did not.[73] However, there is a theoretical risk of increased buprenorphine AUC mediated through P-gp inhibition by VEL and VOX. In patients who are receiving concomitant SOF/VEL/VOX and buprenorphine/naloxone, close monitoring for signs of buprenorphine/naloxone overexposure, such as decreased level of consciousness and respiratory depression, is recommended. The administration of GLE/PIB with buprenorphine can increase buprenorphine AUC modestly by 17%.[73] Based on these studies, no dosage adjustments are required when co-administering buprenorphine/naloxone with EBR/GZR, SOF/VEL, SOF/VEL/VOX, or GLE/PIB; as with methadone, increased monitoring is recommended.

There are no pharmacokinetic studies on the co-administration of fentanyl with EBR/GZR, SOF/VEL, SOF/VEL/VOX, or GLE/PIB. No DDIs are expected between SOF/VEL and SOF/VEL/VOX. Since fentanyl is a CYP3A4 substrate, co-administration with PI-containing regimens, EBR/GZR or GLE/PIB may lead to increased exposure to fentanyl.[9,14,77]

Summary and conclusions

The newer generation DAA regimens have simplified the treatment of hepatitis C with pangenotypic once daily regimens that are effective and well tolerated. However, DDIs remain common with these agents and should be assessed prior to any DAA therapy initiation. DAA regimens containing NS3/4A PIs, such as, SOF/VEL/VOX, EBR/GZR, and GLE/PIB are most susceptible to drug interactions with strong CYP3A4, P-gp, and OATP inhibitors. Regimens that contain VEL are most susceptible to interactions with ubiquitously used acid-reducing agents, leading to decreased VEL absorption and carrying potential for treatment failures.

The major limitation of this review is the reliance on pharmacokinetic studies conducted in healthy volunteers. Chronic infection with hepatitis C will affect drug disposition and metabolism, such as reduced hepatic microsomal enzyme activity. The results of PK studies in healthy populations may not be applicable to those with HCV infection.[78] In addition, due to a lack of experimental data for all possible drug interaction scenarios, we made inferences from limited PK studies to derive recommendations for DDIs where no data were available. These studies may not reflect the actual interaction nor predict adverse effects that may result. An example of this is the unpredictable interaction between SOF and amiodarone. No prior pharmacokinetic/pharmacodynamic studies were able to predict the excessive bradycardia caused by the co-administration of the combination.

Prior to starting any HCV therapy, clinicians should assess for any potential DDIs to avoid adverse events or therapeutic failure. Given the number of safe and effective DAA regimens available, in most cases, DDIs can be avoided altogether through careful selection of DAA therapy. In cases where only specific DAA regimens can be used and DDIs become unavoidable, clinicians must make every effort to appropriately modify the patient's non-HCV medication regimen to avoid potentially harmful DDIs. As we move forward with the goal of HCV elimination by 2030, more patients will be initiated on HCV DAA regimens and clinicians are encouraged to consult with colleagues with expertise in DAA pharmacotherapy or tertiary drug interaction resources prior to treatment initiation.

Funding

None to declare.

Conflict of interest

Dr. Eric M. Yoshida has been an investigator in clinical trials sponsored by Hoffman LaRoche, Merck Inc, Vertex Inc, Pfizer

Inc, Boehringer Ingelheim Inc, Janssen Inc, Novartis Inc, Gilead Sciences, and AbbVie. He has received honoraria from Hoffman LaRoche Canada, Schering Canada, Vertex Inc, Merck Canada Inc, Gilead Sciences Canada, Boehringer Ingelheim Canada, and AbbVie for CME lectures, to attend or to speak at board meetings. Dr. Yoshida has also received unrestricted research grants from Hoffman LaRoche Canada, Gilead Sciences Canada, and Astellas Canada Inc. Dr. Yoshida has no financial interest in the submitted article. The other authors have no conflict of interests related to this publication.

Author contributions

Contributed to review concept and design (EMY, TH), acquisition and interpretation of data (JH, RCW, TH), drafting of manuscript (JH, RCW, TH), critical revision of the manuscript (RCW, NP, EMY, TH), supervision (TH).

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