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REVIEW

Managing drug–drug interactions with new direct-acting antiviral agents in chronic hepatitis C

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Several direct-acting antiviral agents (DAAs) have marketing authorization in Europe and in the USA and have changed the landscape of hepatitis C treatment: each DAA has its own metabolism and drug–drug interactions (DDIs), and managing them is a challenge. To compile the pharmacokinetics and DDI data of the new DAA and to provide a guide for management of DDI. An indexed MEDLINE search was conducted using the keywords: DAA, hepatitis C, simeprevir, daclatasvir, ledipasvir, sofosbuvir, 3D regimen (paritaprevir/ritonavir, ombitasvir, dasabuvir), DDI and pharmacokinetics. Data were also collected from hepatology, and infectious disease and clinical pharmacology conferences abstracts. Food can play a role in the absorption of DAAs. Most of the interactions are linked to metabolism (cytochrome P450-3 A4 [CYP3A4]) or hepatic and/or intestinal transporters (organic anion-transporting polypeptide and P-glycoprotein [P-gp]). To a lesser extent other pathways can be involved such as breast cancer resistance protein transporter or UDP-glucuronosyltransferase metabolism. DDI are more likely to occur with 3D regimen, daclatasvir, simeprevir and ledipasvir, as they are all both substrates and inhibitors of P-gp and/or CYP3A4, than with sofosbuvir. They can increase concentrations of coadministered drugs and their concentrations may be influenced by P-gp or CYP3A4 inducers or inhibitors. Overdosage or low dosage can be encountered with potent inducers or inhibitors of CYP3A4 or drugs with a narrow therapeutic range. The key to interpret DDI data is a good understanding of the pharmacokinetic profiles of the drugs involved. Their ability to inhibit CYP450-3A4 and transporters (hepatic and/or intestinal) can have significant clinical consequences.

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Tables of Links

TARGETS	
Enzymes [2]	**Transporters [3]**
CYP1A2	ABCB1 (P-gp)
CYP2C8	ABCG2 (BCRP)
CYP2C9	OATP1B1
CYP2C19	
CYP2D6	
CYP3A4	

LIGANDS	
Simeprevir	Sofosbuvir
Ritonavir	Famotidine
Omeprazole	Rifampicin
Digoxin	Rosuvastatin
Pravastatin	Sulfasalazine
Lapatinib	Cyclosporine A
Tacrolimus	Methadone
Ethynylestradiol	Midazolam
Simvastatin	Atorvastatine
Everolimus	Dextromethorphan
Escitalopram	Warfarin
Theophylline	Caffeine
Duloxetine	Desipramine
Carbamazepine	Erythromycin
Ketoconazole	Gemfibrozil
Bilirubin	Norgestimate
Levonorgestel	Ribavirin

This Tables lists key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

Background

The emergence of direct-acting antiviral agents (DAAs) represents a major advance in hepatitis C virus (HCV) infection treatment. New DAAs include: new NS3 protease inhibitor simeprevir and paritaprevir boosted by ritonavir; the NS5A inhibitors daclatasvir, ledipasvir and ombitasvir; and the nucleotide NS5B polymerase inhibitors sofosbuvir and dasabuvir. They are approved in an interferon-free regimen, with or without ribavirin [4, 5] and can cure 80–90% of patients [6, 7]. Although highly effective and well tolerated, each DAA has its own metabolism and presents an important potential for drug–drug interactions (DDI). The most common metabolic pathways leading to DDI include CYP450, drug uptake transporters such as organic anion transporting polypeptide, and drug efflux transporters such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). DAAs can act as substrates, inhibitors and/or inducers of metabolic enzymes, and transporters, so they can increase toxicity or decrease effectiveness of coadministrated drugs and *vice versa* [8, 9]. Comedications can influence the choice of a DAA. In clinical practice, non-HCV medications that have the potential for interactions with HCV treatments are frequently prescribed to patients with chronic HCV infection [10, 11].

Understanding pharmacokinetic mechanisms is an essential prerequisite to manage DDI [12]. In this review we summarise pharmacokinetics and DDI with new DAA agents against hepatitis C: simeprevir, daclatasvir, ledipasvir/sofosbuvir and 3D regimen, with a view to help clinicians manage DDI issues.

Methods

Only articles, abstracts and posters in English were selected. An indexed MEDLINE search was conducted concurrently from January 2007 until December 2015 by the medical head of hepatology department and a clinical pharmacist, using the keywords: "simeprevir", "daclatasvir", "ledipasvir", "sofosbuvir", "paritaprevir", "ombitasvir", "dasabuvir", "direct-acting antiviral", "hepatitis C", "hepatitis C treatment", <AND > "drug–drug interactions" or <AND > "pharmacokinetic". Randomised clinical trials, *in vitro* studies, prospective and retrospective human studies both in HCV infected patients and in healthy subjects, literature reviews, and expert clinician opinion papers were included. We collected all reviews and articles that summarised DDI for DAA.

Articles were first reviewed based on title and abstract (n = 134) and secondly on full text (n = 61). We excluded: the first generation protease inhibitors telaprevir and boceprevir as they are no longer used; new DAA that were still in clinical trials in Europe in 2015; DAAs that were discontinued; and articles on DDI simulations.

To complete the data, the two reviewers collected abstracts from hepatology, infectious diseases and clinical pharmacology meetings. Meetings selected were the Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), the Annual Meeting of the European Association for the Study of the Liver (EASL), HEPDART, The Annual Conference on Retroviruses and Opportunistic Infections (CROI), the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), and The International Workshop on Clinical Pharmacology of HIV and

Hepatitis Therapy. Each meeting was screened to find all abstracts or posters regarding DAA and DDI and pharmacokinetics (n = 53). European summaries of product characteristics were also included (n = 5).

Results

All the factors that influence DAA pharmacokinetics are summarised in Table 1.

Table 1

Factors influencing pharmacokinetic parameters of direct-acting antiviral agents

	Sofosbuvir	**Ledipasvir**	**Simeprevir**	**Daclatasvir**	**Paritaprevir (ABT-450) Ritonavir Ombitasvir (ABT-267) Dasabuvir (ABT-333)**
Food effect	No [16]	No [16]	Take with food [13]	No [23]	Take with food [19]
Hepatic impairment	No dose adjustment for patients with mild, moderate or severe hepatic impairment [104]	No dose adjustment for patients with mild, moderate or severe hepatic impairment [105]	– Child–Pugh A, B: no dose adjustments – Child–Pugh C: no recommendation AUC 3-fold higher than HCV-compensated patients [107]	No dose adjustment for patients with mild, moderate or severe hepatic impairment [108]	– Child–Pugh A: no dose adjustment – Child–Pugh: not recommended – Child–Pugh C: contraindicated [109]
Renal impairment	– mild or moderate renal impairment: no dose adjustment – severe renal impairment: sofosbuvir 200 mg was safe and well-tolerated (but higher exposures up to 20-fold of GS-331 007 [101, 102, 110]	– mild or moderate renal impairment: no dose adjustment – severe renal impairment or ESRD: No dosage recommendation [111]	No dose adjustmentwith mild, moderate, or severe renal impairment [105, 106, 112]	No dose adjustment in renal impairment (unbound AUC of daclatasvir were increased 1.8- and 1.5-fold, respectively in subjects with severe renal impairment compared with subjects with normal renal function [113, 114]	No dose adjustmentwith mild, moderate, or severe renal impairment. (change no clinically relevant) ESRD: safe [115, 116]
Transporters	Sofosbuvir: – P-gp: substrate. – OATP 1B1/ B3: not a substrate GS 331007: – P-gp: not a substrate – OATP 1B1/ B3: not a substrate [37]	– P-gp: substrate and weak inhibitor – OATPB1/B3: substrate and weak inhibitor [21]	– P-gp: substrate and inhibitor – OATPB1: substrate and inhibitor [28]	– P-gp: substrate and inhibitor – OATP1B1: substrate and inhibitor [23]	- P-gp: substrate - OATP1B1/B3: substrate and inhibitor (paritaprevir) – BCRP: substrate and inhibitor (ritonavir, dasabuvir) [19]
Cytochromes and UGT A1	Not a substrate or inhibitor or inducer of CYP3A4 [14]	Not a substrate or inhibitor or inducer of CYP3A4 [21]	Substrate of CYP3A4, mild inhibitor of intestinal (but not hepatic) CYP3A4 and 1 A2.No clinically relevant effects on CYP2C9, 2C19 or 2D6 [22]	Substrate of CYP3A4. Not an inducer or inhibitor of CYP3A4 [23]	Substrate and inhibitor of CYP3A4 (paritaprevir + ritonavir) Substrate of CYP2C8 (dasabuvir) - UGT1A1, inhibitor [19]
QT	Avoid with amiodarone or other bradycardia treatment [37]	Avoid with amiodarone or other bradycardia treatment [37]	Avoid with amiodarone or other bradycardia treatment [22]	No clinically relevant effect with therapeutic or supra-therapeutic dose [23]	Contraindicated with CYP2C8 inhibitors [19]

AUC, area under the curve; ESRD, end-stage renal disease; HCV, hepatitis C virus; UGT, UDP-glucuronosyltransferase; P-gp, P-glycoprotein

Food effects and absorption

Food increased the area under the curve (AUC) of simeprevir by 61% after a high-fat, high-calorie breakfast, so simeprevir is best taken with food [13].

Sofosbuvir is a prodrug that is converted to GS-461 203, an active metabolite, and GS-331 007, its predominant metabolite which represents >90% of the exposure [14, 15]. As he exposure to GS-331 007 was not altered in the presence of a high-fat meal, sofosbuvir can be taken with or without food [16].

Ledipasvir exhibits pH-dependent solubility but studies showed that AUC of ledipasvir and sofosbuvir were not significantly changed by H_2-receptor antagonists (famotidine) or omeprazole 20 mg if it is taken simultaneously. However, if omeprazole 20 mg was taken 2 h before ledipasvir, exposure to ledipasvir was decreased by 50% (Table 2) [16]. As others dosages were not tested, ledipasvir should preferably not be taken with proton pump inhibitors [17]. The administration of ledipasvir/sofosbuvir with a meal did not alter ledipasvir AUC or C_{max} [16] so ledipasvir/sofosbuvir can be taken with or without food.

Daclatasvir C_{max} and AUC were reduced by 28% and 23%, respectively with a high-fat meal but this reduction was not considered clinically significant [18].

Table 2

Drug–drug interactions between digestive drugs and direct-acting antiviral agents (DAAs)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC (%)	Pharmacological effect on coadministered drug AUC (%)	Recommendations	Ref
Aluminium Magnesium hydroxide Calcium carbonate	Daclatasvir	Not tested			No data.	
	Ledipasvir/ sofosbuvir	Not tested	Expected: ledipasvir ↓ (increase in gastric pH)		It is recommended to take antacid and ledipasvir-sofosbuvir 4 hours apart.	[17]
	Simeprevir	Not tested			Not expected. No dose adjustment.	[22]
	Sofosbuvir	Not tested			No data.	
Famotidine	Daclatasvir	NA	↔	Increase in gastric pH	No dose adjustment.	[23]
	Ledipasvir/ sofosbuvir	Healthy subjects	Simultaneous ledipasvir ↔ 12 h stagger ↔	NA	H_2-receptor antagonists may be administered simultaneously with or staggered from ledipasvir/sofosbuvir at a dose that does not exceed doses comparable to famotidine at 40 mg twice daily.	[16]
	Simeprevir	Not tested			Not expected. No dose adjustment.	[22]
	Sofosbuvir	Healthy subjects	Simultaneous ↔ sofosbuvir ↔ GS-331 007: 12 h stagger ↔ sofosbuvir: ↔ GS-331 007	NA	Do not exceed doses comparable to famotidine 40 mg twice daily.	[16]
Omeprazole	Daclatasvir	NA	↔	NA	No dose adjustment.	[23]
	Ledipasvir/ sofosbuvir	NA	↓ ledipasvir	NA	Proton pump inhibitors should not be coadministrated.	[16, 17]
	Simeprevir	NA	NA	↑: +21%	Not considered clinically relevant.	[32]
	Sofosbuvir	NA	↔ sofosbuvir ↔ GS-331 007	NA	No dose adjustment.	[16, 17]
	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir		↔ ombitasvir ↔ paritaprevir ↔ dasabuvir	↓ omeprazole with dasabuvir: −38% without dasabuvir ↓ omeprazole −54% (CYP2C19 induction by ritonavir)	Use higher dose of omeprazole if needed	[33]

↔, no clinical change (< 25%); ↑, increase in AUC; ↓, decrease in AUC
AUC, area under the curve; HCV, hepatitis C virus; NA, not applicable

Paritaprevir is combined with ritonavir and ombitasvir in a tablet coat. Food increased the exposure (AUC) of 2D regimen by up to 82%, 211% and 49%, respectively relative to the fasting state, so the combination of these drugs should be taken with food [19, 20].

Food increased the AUC of dasabuvir by up to 30% compared to fasting. It is therefore recommended to take dasabuvir with food [19].

Distribution

Daclatasvir, simeprevir, ledipasvir and 3D regimen extensively bind to plasma proteins (> 98%), [19, 21–23]. Sofosbuvir is 85% bound to human plasma proteins, whereas protein binding of GS-331 007 is very low [21]. Contrary to preconceived ideas, the concentration increase linked to competitive binding to plasma proteins rarely has any clinical impact [24], as kinetic interactions initially attributed to a protein displacement are actually explained by metabolic inhibition or by renal transport inhibition [24].

Effect of transporters

P-pg. Drugs in enterocytes can be excreted back into the gut lumen by efflux transporters such as P-gp (Figure 1). P-gp can limit drug absorption [25]. In the liver, P-gp is a main transport protein on the bile canalicular membrane responsible for biliary excretion of drug metabolites [26, 27]. Sofosbuvir and ombitasvir are substrate of P-gp [14]. Paritaprevir, ritonavir, dasabuvir, ledipasvir, daclatasvir and simeprevir are substrates and inhibitors of P-gp [18, 19, 21, 28, 29] (Table 1).

Coadministration of a P-gp inhibitor (e.g. simeprevir, ledipasvir or daclatasvir) with a P-gp drug substrate will block P-gp's action and thus increases substrate absorption. Coadministration of a P-gp inducer (i.e. rifampicin) with a P-gp substrate results in a substrate concentration decrease. Thus rifampicin, when administered with ledipasvir/sofosbuvir, led to a 72% and 59% decrease in sofosbuvir and ledipasvir AUC, respectively [30, 31]. P-gp potent inducers should not be used with daclatasvir, ledipasvir/sofosbuvir or 3D regimen. In healthy subjects, administration of digoxin (a P-gp substrate) with simeprevir or daclatasvir or ledipasvir or paritaprevir/ritonavir/ombitasvir (P-gp inhibitors) led to a digoxin AUC increase of 39%, 27%, 34% and 36% AUC respectively [18, 30, 32, 33]. Digoxin should thus be initiated at a lower dosage and be monitored.

P-gp substrates are often also cytochrome P450 (CYP450) substrates, which make P-gp interactions most often negligible when compared with cytochrome interactions [25]. It should be noted, however, that a few drugs are exclusively P-gp substrates, such as digoxin, and some nucleotide and nucleoside reverse transcriptase inhibitors (NRTI) [34].

Organic anion-transporting polypeptide. The organic anion-transporting polypeptide 1B1 (OATP1B1) transporter at the sinusoidal pole of the hepatocyte is an influx transporter (Figure 1). This transporter is involved in the hepatic influx of some drugs such as statins (pravastatin, rosuvastatin) [35]. Simeprevir, daclatasvir, ledipasvir, paritaprevir and ritonavir are all substrates and inhibitors of the OATP1B1 transporter, whereas sofosbuvir, ombitasvir and dasabuvir

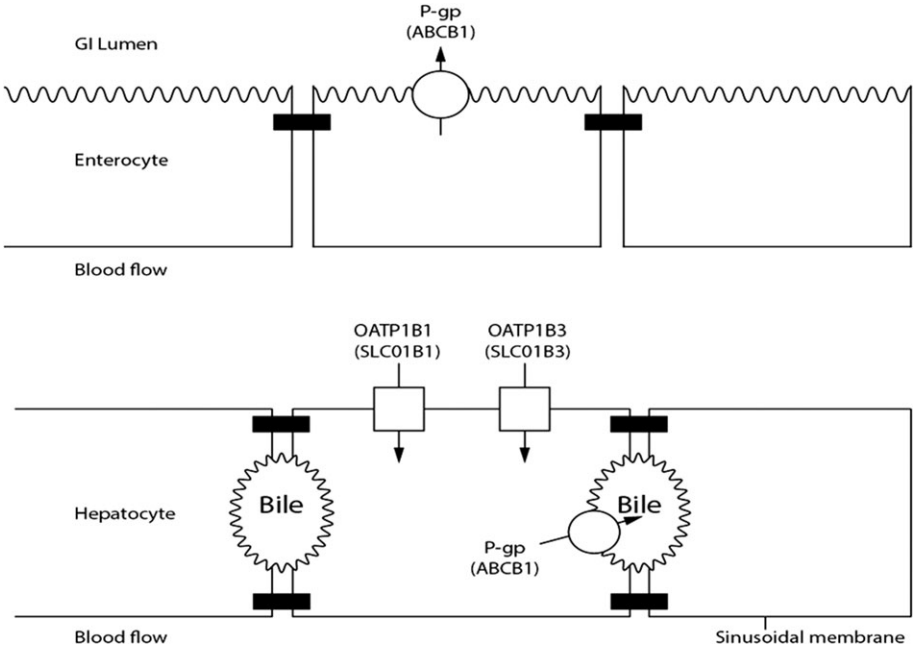

Figure 1
Transporters involved in drug–drug interaction of new DAAs

are not substrates [8–19]. In healthy subjects, administration of a single dose of rosuvastatin with simeprevir or daclatasvir at 60 mg once daily or 3D regimen results in a respectively AUC increase by 181%, 58% and 159%, by blocking their hepatic uptake [18, 28, 33]. The dose of rosuvastatin should be decreased when coadministrated with simeprevir or daclatasvir, and should not exceed 5 mg with 3D regimen. Tolerance should be monitored [19, 28, 33]. With 3D regimen pravastatin dose should be reduced by 50% [19, 33].

BCRP. BCRP (ABCG2) limits intestinal absorption of low-permeability substrate drugs and mediates biliary excretion of drugs and metabolites. Many drugs were identified as substrates (e.g. sulfasalazine, rosuvastatine) or inhibitors of BCRP (e.g. curcumin, lapatinib) *in vitro* [36], yet clinical DDIs attributed directly and specifically to BCRP are limited due to overlap with other transporters, as well as metabolic pathways. Sofosbuvir is a substrate of BCRP whereas GS-331 007 is not [37]. Ombitasvir and simeprevir are substrates of BCRP [19]. Paritaprevir, simeprevir, ritonavir, dasabuvir, ledipasvir and daclatasvir are inhibitors of BCRP [19–28]. However, sulfasalazine, curcumin, lapatinib have not been studied with any of DAAs. Only rosuvastatin was tested with daclatasvir, simeprevir and 3D regimen but the increase of rosuvastatin AUC could be also due to OATP inhibition [33].

Metabolism

Biotransformation very often involves isoenzymes of the cytochrome P450 superfamily especially the isoenzyme cytochrome P450-3 A4 (CYP3A4). A drug with a narrow therapeutic range (immunosuppressants for example) can give rise to a clinically significant interaction more readily than a drug with a wide therapeutic range [38].

Effects of DAAs on CYP3A4 substrates. Sofosbuvir and ledipasvir are not metabolised by CYP3A4 [37]. Ledipasvir is slowly metabolised via an unknown mechanism [21] (Table 1). Sofosbuvir and ledipasvir have been tested in healthy volunteers with cyclosporine, tacrolimus, methadone, ethinyl oestradiol, all substrates of CYP3A4, without clinically significant interactions as expected (Tables 3–5) [28, 39, 42]. Several studies have

Table 3

Drug–drug interactions between immunosuppressants and direct-acting antiviral agents (DAAs)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC (%)	Pharmacological effect on coadministered drug AUC (%)	Recommendations	Ref
Tacrolimus	Daclatasvir	Healthy subjects	↔	↔	No clinically relevant interactions. Monitor blood concentration of tacrolimus.	[60]
	Ledipasvir/ sofosbuvir	Not tested			Not expected. No dose adjustment.	[43, 109]
	Simeprevir	HCV transplanted patients	↑ +85%	↔	No dose adjustments.	[51, 53]
	Sofosbuvir	Healthy subjects	↔	↔	No clinically significant interactions.	[40]
	3D regimen	Healthy subjects	↔ Ombitasvir ↓ paritaprevir −34% ↔ dasabuvir	With dasabuvir ↑tacrolimus: +5610% Without dasabuvir ↑tacrolimus: +8480%	No dose adjustment of 3D regimen initiate tacrolimus at 0.5 mg every 7 days and monitore blood concentration.	[47]
Cyclosporin	Daclatasvir	Healthy subjects	↑ + 40%	↔	No clinically relevant interactions.	[60]
	Ledipasvir/ sofosbuvir	Not tested			Not expected.	[43, 109]
	Simeprevir	HCV transplanted patient	↑ + 481%	↔	Significantly increased plasma SMV concentrations.	[51, 53]
	Sofosbuvir	Healthy subjects	↑Sofosbuvir +353% ↔ GS 331007	↔	No clinically significant interactions.	[40]
	3D regimen		↔ Ombitasvir ↑ paritaprevir (with dasabuvir): +72% ↑ paritaprevir +46% (without dasabuvir) ↓ dasabuvir: −30%	With dasabuvir ↑ cyclosporin: +482% without dasabuvir ↑ cyclosporin: +328%	Give one fifth of the total daily dose of cyclosporin once daily with 3D regimen. Monitor cyclosporin levels No dose adjustment needed for 3D regimen.	[47]

↔, no clinical change (< 25%); ↑, increase in AUC; ↓, decrease in AUC
AUC, area under the curve; HCV, hepatitis C virus

Table 4

Drug–drug interactions between neuropsychiatric drugs and direct-acting antiviral agents (DAAs)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC (%)	Pharmacological effect on coadministered drug AUC (%)	Recommendations	Ref
Escitalopram	Daclatasvir	NA	↔	↔	No dose adjustment.	[23]
	Ledipasvir/ sofosbuvir	Not tested			No data.	
	Simeprevir	Healthy subjects	↓: −25%	↔	Not expected. No dose adjustment.	[99]
	Sofosbuvir	Not tested			No data.	
	3D regimen		↔ ombitasvir ↔ paritaprevir ↔ dasabuvir	↔ escitalopram ↑ S-desmethyl-citalopram (with dasabuvir) + 36% ↔ S-desmethyl-citalopram (without dasabuvir)	No dose adjustment.	[33]
Duloxetine	3d regimen		↔ ombitasvir ↔ paritaprevir ↔ dasabuvir	↓ duloxetine: −25%	No dose adjustment.	[33]
Alprazolam	3D regimen		↔ ombitasvir ↔ paritaprevir ↔ dasabuvir	↑ alprazolam: +34%	If needed, decrease the dose of alprazolam.	[33]
Midazolam	Daclatasvir	healthy subjects	NA	↔	No clinically significant interaction.	[110]
	Ledipasvir/ sofosbuvir	Not tested			No data.	
	Simeprevir	NA		↑ midazolam oral +45% ↔ midazolam i.v:	Simeprevir exhibits clinically relevant CYP3A4 inhibition in the intestine (with *per os* midazolam) but not in the liver (intravenous midazolam). Caution with midazolam oral.	[32]
	Sofosbuvir	Not tested			No data.	
Zolpidem	3D regimen		↔ ombitasvir ↓ paritaprevir: −32% ↔ dasabuvir	↔ zolpidem	No dose adjustment.	[33]
Methadone	Daclatasvir	NA	No change	↔R-methadone	No dose adjustment.	[23]
	Ledipasvir/ sofosbuvir	Not tested			Not expected.	[21]
	Simeprevir	HCV negative		↔R-methadone ↔S-methadone	No dose adjustment.	[115]
	Sofosbuvir	HCV negative patients	↑ Sofosbuvir: +30% ↔ GS-331 007	↔S-methadone ↔R-methadone	No dose adjustment.	[39]
	3D regimen		↔	↔ R-Methadone ↔ S-Methadone	No dose adjustment.	[85]
Buprenorphine/ naloxone	Daclatasvir		No change	↔Buprenorphine ↑norbuprenorphine +62%	No dose adjustment.	[23]
	Ledipasvir/ sofosbuvir	Not tested			No data.	
	Simeprevir	Not tested			Not expected. No dose adjustment.	[22]
	Sofosbuvir	Not tested			No data	
	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir		↔ paritaprevir / ombitasvir/ dasabuvir	↑ buprenorphine with dasabuvir: +107% ↑ buprenorphine (without dasabuvir): +51%	No dose adjustment.	[85]

(*continues*)

Table 4

(Continued)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC (%)	Pharmacological effect on coadministered drug AUC (%)	Recommendations	Ref
				↑ norbuprenorphine +84% ↑ naloxone: +28%		
Dextromethorphan	Simeprevir	Healthy subjects	NA	↔	No dose adjustment.	[32]
Anticonvulsants (carbamazepine Oxcarbazepine Phenobarbital Phenytoin)	Daclatasvir	Not tested	Expected: AUC daclatasvir ↓ (strong induction of CYP3A4)		Coadministration of daclatasvir with (ox) carbamazepine, phenobarbital, phenytoin or other strong inducers of CYP3A4 is contraindicated.	[23]
	Ledipasvir/ sofosbuvir	Not tested	Expected: ledipasvir/ sofosbuvir↓ (Induction of P-gp)		Not recommended. Loss of therapeutic effect of ledipasvir.	[21]
	Simeprevir	Not tested	Expected: simeprevir↓ (strong induction of CYP3A4)		Not recommended. Loss of therapeutic effect of simeprevir.	[22]
	Sofosbuvir	Not tested	Expected: ↓ sofosbuvir AUC ↓ GS-331 007		Not recommended. Loss of therapeutic effect of ledipasvir.	[37]
	3D regimen	Healthy subjects	↓ ombitasvir −30% ↓ paritaprevir −30% ↓ dasabuvir −70%	↔Carbamazepine	Contraindicated.	[33]

↔, no clinical change (< 25%); ↑, increase in AUC; ↓, decrease in AUC
AUC, area under the curve; HCV, hepatitis C virus; NA, not applicable

Table 5

Drug–drug interactions between contraceptives and direct-acting antiviral agents (DAAs)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC (%)	Pharmacological effect on coadministered drug AUC (%)	Recommendations	Ref
Ethynilestradiol/ Norgestimate	Daclatasvir	Healthy female subjects	NA	↔: EE: ↔ norelgestromin ↔ norgestrel.	No clinically relevant effects.	[116]
	Ledipasvir/ sofosbuvir	HCV-uninfected women	NA	↔ norelgestromin ↔ norgestrel ↔ ethinylestradiol	No dose adjustment.	[42]
	Simeprevir	Healthy female volunteers		↔ EE: ↔ norethindrone	No dose adjustment.	[117]
	Sofosbuvir	HCV-uninfected women	NA	↔ norgestromin ↔ norgestrel ↔ ethinyl oestradiol	No dose adjustment.	[42]
	3D regimen		↔ ombitasvir ↓ paritaprevir: −34% ↓ dasabuvir −52%	↔ EE ↑ norgestrel: +154% ↑ norelgestromine +160%	Ethinyl oestradiol-containing oral contraceptives are contraindicated.	[33]
Norethindrone	3D regimen		↔ ombitasvir ↑ paritaprevir:+23% ↔ dasabuvir:	↔ norethindrone	No dose adjustment.	[33]

↔, no clinical change (< 25%); ↑, increase in AUC; ↓, decrease in AUC
AUC, area under the curve; HCV, hepatitis C virus; NA, not applicable

Table 6

Drug–drug interactions between cardiovascular drugs and direct-acting antrtiviral agents (DAAs)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC (%)	Pharmacological effect on coadministered drug AUC (%)	Recommendations	Ref
Atorvastatin	Daclatasvir	Not tested		Expected: ↑ (inhibition of OATPB1 by daclatasvir)	Use with caution.	[23]
	Ledipasvir/ sofosbuvir	Not tested		Expected: ↑	A reduced dose of statins should be considered.	[21]
	Simeprevir	NA		↑ +112%	Titrate the atorvastatin dose carefully and use the lowest necessary dose while monitoring for safety.	[32]
	Sofosbuvir	Not tested			No data.	
	3D regimen	Not tested			Contraindicated.	[19]
Pravastatin	Daclatasvir	Not tested		Expected: ↑ (OATP1B1 inhibition by daclatasvir)	Clinical and biochemical control. A dose adjustment may be needed.	[23]
	Ledipasvir/ sofosbuvir	NA	NA	↑ +168%	Clinical and biochemical control. A dose adjustment may be needed.	[114]
	Simeprevir	Not tested		Expected: AUC pravastatin ↑ (OATP1B1 inhibition by simeprevir)	Titrate pravastatin dose and use the lowest necessary dose while monitoring for safety.	[22]
	Sofosbuvir	Not tested			No data.	
	3D regimen		↔ ombitasvir ↔ dasabuvir ↔ paritaprevir (with dasabuvir) ↑ paritaprevir (without dasabuvir)	↑ +82%	Reduce pravastatin dose by 50%. No dose adjustment needed for 3D regimen with or without dasabuvir.	[33]
Rosuvastatin	Daclatasvir	NA	NA	↑ +58% (OATP 1B1 inhibition by daclatasvir)	Use with precaution and with a lower dose.	[23]
	Ledipasvir/ sofosbuvir	NA	NA	↑ +699%	Contraindicated.	[114]
	Simeprevir	NA	NA	↑ +181% (OATP1B1 inhibition by simeprevir)	Titrate rosuvastatin dose and use the lowest necessary dose while monitoring for safety.	[32]
	Sofosbuvir	Not tested			No data.	
	3D regimen		↔ ombitasvir ↑ paritaprevir (with dasabuvir): +52% ↔ paritaprevir (without dasabuvir) ↔ dasabuvir	With dasabuvir ↑ rosuvastatin: +159% Without dasabuvir ↑ rosuvastatin: +33%	With dasabuvir, the maximum daily dose of rosuvastatin should be 5 mg Without dasabuvir, the maximum daily dose of rosuvastatin should be 10 mg. No dose adjustment for 3D regimen.	[33]
Simvastatin	Daclatasvir	Not tested		OATP inhibition by daclatasvir is expected	A reduced dose of statins should be considered careful monitoring for statin adverse reactions.	[23]
	Ledipasvir/ sofosbuvir	Not tested		Expected: ↑ possible OATP inhibition by ledipasvir	A reduced dose of statins should be considered and careful monitoring for statin adverse reactions.	[21]

(*continues*)

Table 6

(Continued)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC (%)	Pharmacological effect on coadministered drug AUC (%)	Recommendations	Ref
	Simeprevir		NA	↑ +51% (OATP inhibition and CYP3A4 by simeprevir)	Titrate simvastatin dose carefully and use the lowest necessary dose while monitoring for safety.	[32]
	Sofosbuvir	Not tested			No data.	
	3D regimen	Not tested			Contraindicated.	[23]
Gemfibrozil	3d regimen		↑ paritaprevir +38% OATP inhibition by gemfibrozil ↑ dasabuvir + 1025% (CYP2C8 inhibition by gemfibrozil)	NA	Contraindicated.	[33]
Calcium channel blockers	Daclatasvir	Not tested	Expected: ↑daclatasvir (moderate inhibition of CYP3A4 by verapamil, diltiazem, mild inhibition by amlodipine)		Use with caution.	[23]
	Ledipasvir/ sofosbuvir	Not tested			Not expected.	[21]
	Simeprevir	Not tested	Expected: ↑simeprevir (moderate inhibition of CYP3A4 by verapamil, diltiazem, mild inhibition by amlodipine)		Use with caution.	[22]
	Sofosbuvir	Not tested			No data.	
	3D regimen		↔ ombitasvir ↓ paritaprevir: −22% ↔ dasabuvir	↑amlodipine: +157%	Decrease the dose of amlodipine by 50%.	[33]
Valsartan	3d regimen	Not tested		Expected: ↑ (OATP1B inhibition by paritaprevir.)	Clinical monitoring and dose reduction is recommended.	[19]
Furosemide	3D regimen		↔ ombitasvir ↔ paritaprevir ↔ dasabuvir	↑ furosemide possibly due to UGT1A1 inhibition by paritaprevir, ombitasvir and dasabuvir.	A decrease in furosemide dose of up to 50% may be required. No dose adjustment needed for Viekirax with or without dasabuvir.	[33]
Alfuzosine	3d regimen	Not tested		Expected: ↑ (CYP3A4 inhibition by ritonavir)	Contraindicated.	[33]
Dabigatran	Daclatasvir	Not tested		Expected: ↑ dabigatran (inhibition of P-gp)	Safety monitoring is advised when initiating.	[23]
	Ledipasvir/ sofosbuvir	Not tested	Expected: ↔ ledipasvir	Expected ↑ dabigatran (inhibition of P-gp)	Clinical monitoring is recommended.	[21]
	Simeprevir	Not tested		Expected ↑ dabigatran (inhibition of P-gp)	Safety monitoring is advised when initiating.	[22]
	Sofosbuvir	Not tested	Expected: ↔sofosbuvir ↔ GS-331 007		Not expected.	
	3D regimen	Not tested		Expected: AUC↑ (inhibition of P-gp by paritaprevir and ritonavir	Use with caution.	[19]
Digoxine	Daclatasvir		NA	↑ + 27% (P-gp inhibition by daclatasvir)	The lowest dose of digoxin should be initially prescribed. Serum digoxin concentrations should be monitored.	[23]

(*continues*)

Table 6

(Continued)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC (%)	Pharmacological effect on coadministered drug AUC (%)	Recommendations	Ref
	Ledipasvir/ sofosbuvir	NA	NA	↑ +34%	Monitor for serum digoxin.	[114]
	Simeprevir	Healthy subjects	NA	↑ +39% (P-gp inhibition by simeprevir)	AUC increase of digoxin. Monitor for digoxin blood concentration.	[32]
	Sofosbuvir	Not tested			No data.	
	3D regimen		No change	With dasabuvir ↔ Without dasabuvir↑	With dasabuvir; no dose adjustment. Without dasabuvir decrease digoxin dose by 30–50%. Monitor for digoxin blood concentration.	[33]
Amiodarone/ quinidine	Daclatasvir	Not tested	Expected: ↑ (inhibition of CYP3A4 by amiodarone.)		Use only if no other alternative is available. Close monitoring is recommended.	[23]
	Ledipasvir/ sofosbuvir	Not tested		Case of severe bradycardia	Use only if no other alternative is available. Close monitoring is recommended.	[21]
	Simeprevir	Not tested	Expected: ↑ (due to inhibition of CYP3A4 by amiodarone)	Expected: ↑ amiodarone (intestinal CYP3A4 enzyme inhibition)	Use only if no other alternative is available. Close monitoring is recommended.	[22]
	Sofosbuvir	Not tested		Case of severe bradycardia	Use only if no other alternative is available. Close monitoring is recommended.	[37, 115]
	3D regimen	Not tested		Expected: ↑ amiodarone (intestinal CYP3A4 enzyme inhibition)	Contraindicated.	[19]
Warfarin	Daclatasvir	Not tested			No dose adjustment but monitor for INR.	[23]
	Ledipasvir/ sofosbuvir	Not tested			No data, monitor for INR.	
	Simeprevir	Healthy volunteers	NA	↔	Not considered clinically significant. Monitor for INR.	[22]
	Sofosbuvir	Not tested			No data, monitor for INR.	
	3D regimen		↔ ombitasvir ↔ paritaprevir ↔ dasabuvir	↔	No dose adjustment, monitore for INR.	[23]

↔, no clinical change (< 25%); ↑, increase in AUC; ↓, decrease in AUC
AUC, area under the curve; INR, International Normalised Ratio; NA, not applicable; OATP, organic anion-transporting polypeptide

tested sofosbuvir and ledipasvir in post-transplant patients and no interaction with any concomitant immunosuppressive agent was reported [43, 44]. German *et al*. suggest that sofosbuvir with ledipasvir could be administered with cyclosporine or tacrolimus [30, 45].

Paritaprevir, ombitasvir and dasabuvir are substrates of CYP3A4 [19]. Paritaprevir is an inhibitor of CYP3A4 and ritonavir is used as a booster in 3D regimen because it is a strong inhibitor of CYP3A4 that leads to increased bioavailability of paritaprevir [20]. Ritonavir of the 3D regimen increases human immunodeficiency virus (HIV) protease inhibitors exposure, which is why the recommended dose of darunavir is 800 mg once daily and the recommended dose of atazanavir is 300 mg once daily, without ritonavir, when administered with 3D regimen [46].

3D regimen with substrates of CYP3A4 could increase coadministered drug exposition. A phase 1 study

Table 7

Drug–drug interactions between anti-infective drugs and direct-acting antiviral agents (DAAs)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC (%)	Pharmacological effect on coadministered drug AUC (%)	Recommendations	Ref
Rifampicin	Daclatasvir	NA	↓ −79% CYP3A4 induction by rifampicin	NA	Coadministration with rifampicin, rifabutin, rifapentine or other strong inducers of CYP3A4 is contraindicated.	[23]
	Ledipasvir/ sofosbuvir	NA	↓ C_{max} −35% ↓ AUC −59%	NA	Not recommended.	[30]
	Simeprevir	Healthy volunteers	↓: −48%	↔	Not recommended loss of ther apeutic effect of simeprevir.	[50]
	Sofosbuvir	Healthy volunteers	Sofosbuvir ↓ −72% GS-331 007: ↔	*NA*	Decrease in sofosbuvir exposure is clinically significant and is likely to alter therapeutic effect; sofosbuvir should not be used with potent inducers of intestinal P-gp.	[30, 31]
	3D regimen	Not tested			Contraindicated.	[19]
Rifabutin	Daclatasvir	Not tested	Expected: ↓simeprevir (induction of CYP3A4 by rifabutin)		Coadministration of daclatasvir with rifampicin, rifabutin, rifapentine or other strong inducers of CYP3A4 is contraindicated.	[23]
	Ledipasvir/ sofosbuvir	Not tested	Expected: ↓ ledipasvir		Not recommended. May result in loss of therapeutic effect of ledipasvir.	[21]
	Simeprevir	Not tested	Expected: ↓simeprevir (induction of CYP3A4 by rifabutin)		Not recommended. May result in loss of therapeutic effect of simeprevir.	[22]
	Sofosbuvir	Not tested	Expected: ↓ sofosbuvir ↔ GS-331 007 (Induction of P-gp)		Not recommended. May result in loss of therapeutic effect of sofosbuvir.	[37]
Ketoconazole	Daclatasvir	NA	AUC ↑: +200% (strong inhibition of CYP3A4 by krtoconazole)	NA	The dose of daclatasvir should be reduced to 30 mg once daily when coadministered with ketoconazole or other strong inhibitors of CYP3A4.	[23]
	Ledipasvir/ sofosbuvir	Not tested			No data.	
	Simeprevir	Not tested	Expected: ↑ simeprevir (strong CYP3A4 inhibition)	NA	Not recommended.	[22]
	Sofosbuvir	Not tested			No data.	
	3D regimen		↔ ombitasvir ↑ paritaprevir (with dasabuvir): +98% ↑ paritaprevir (without dasabuvir): +116 ↑ dasabuvir: +42/%	↑ +117%	Contraindicated.	[33]
Erythromycin	Daclatasvir	Not tested	Expected AUC ↑ (strong CYP3A4 inhibition by erythromycin)		Not recommended. Prefer azithromycin without dose adjustment.	[23]
	Ledipasvir/ sofosbuvir	Not tested			No data.	

(*continues*)

Table 7
(Continued)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC (%)	Pharmacological effect on coadministered drug AUC (%)	Recommendations	Ref
	Simeprevir	Healthy volunteers	↑ + 647% (strong CYP3A4 inhibition)	↑ +90%	Not recommended. Prefer azithromycin without dose adjustment.	[32]
	Sofosbuvir	Not tested			No data.	
	3D regimen	Not tested	Expected: ↑paritaprevir ↑ dasabuvir (strong CYP3A4 inhibition by erythromycin)	Expected ↑ (CYP3A4 and P-gp inhibition by paritaprevir, ritonavir, dasabuvir)	Caution is advised.	[32]

↔, no clinical change (< 25%); ↑, increase in AUC; ↓, decrease in AUC
AUC, area under the curve; NA, not applicable; P-gp, P-glycoprotein

demonstrated a three-fold increase in cyclosporine half-life and seven-fold increase in tacrolimus half-life when administered concomitantly with 3D regimen [47]. Therefore, in liver transplant recipients with recurrent HCV genotype 1 infection on stable cyclosporine or tacrolimus therapy, cyclosporine was reduced to 20% of the usual daily dose given once daily, while tacrolimus was reduced to either 0.5 mg once weekly or 0.2 mg every 3 days [48]. Dick *et al*. recommend empirically close monitoring, 2–3 times a week when 3D regimen is used with immunosuppressive agents [49].

Simeprevir is a substrate and mild inhibitor of CYP3A4 in the intestine by increasing midazolam AUC by 45% when administered orally and C_{max} by 31%, [32] (Table 4) [50]. In healthy volunteers, administration of single atorvastatin dose at 40 mg or simvastatin at 40 mg with simeprevir increases atorvastatin AUC by 110% and simvastatin AUC by 50%, probably via inhibition of CYP3A and OATP by simeprevir [32] (Table 6).

Sometimes, interactions are not as expected. For example, simeprevir with single-dose tacrolimus at 2 mg resulted in a 17% decrease in tacrolimus AUC compared with tacrolimus administered alone [51]. With cyclosporine, simeprevir increased cyclosporine AUC by 19%, which was not considered clinically relevant [51]. However, therapeutic drug monitoring is recommended [52]. These results were confirmed in the SATURN study [28, 53] but cyclosporine increased simeprevir exposure AUC by 481% so the coadministration is now contraindicated (Table 3). Apart from this result, new DAAs in liver transplanted patients have a good safety profile [54–58].

Daclatasvir is a CYP3A4 substrate [19, 23]. Tacrolimus and cyclosporin were unaffected by concomitant administration of multiple doses of daclatasvir [59, 60]. Studies conducted in liver-transplanted patients treated with tacrolimus or everolimus or cyclosporine confirms that the coadministration of sofosbuvir and daclatasvir is safe and efficient in these patients. [61–63].

Effects of DAAs on other CYP substrates. Simeprevir and daclatasvir have no clinically relevant effects on CYP2C9, 2C19 and 2D6 [50] as confirmed by their nonsignificant effect when coadministrated with escitalopram, dextrometorphan (substrates of CYP2D6) [32, 64], omeprazole (substrate of CYP2C19) and warfarin (substrate of CYP2C9) [32].

Ritonavir could induce CYP2C19 [65]. When omeprazole 40 mg once daily was coadministered with the 3D regimen in healthy volunteers, omeprazole AUC decreased by 38% due to ritonavir induction on CYP2C19, so it is recommended to monitor patients for decreased efficacy of all proton pump inhibitors [33] (Table 2). However, with sulfamethoxazole (substrate of CYP2C19) and trimethoprim, no dose adjustment is required [66].

The 3D regimen did not affect the exposures of the CYP2C9 substrates (such as warfarin) or the CYP1A2 substrates (such as theophylline and caffeine) or CYP2D6 substrates (such as duloxetine, desipramine). Therefore, these drugs are not expected to require dose adjustments [67].

Table 8

Drug–drug interactions between direct-acting antiviral agents (DAAs) and antiretrovirals

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC	Pharmacological effect on coadministered drug AUC	Recommendations	Ref
Efavirenz	Daclatasvir	Healthy subjects	AUC ↓ –32%	↔	An extrapolated daclatasvir dose of 90 mg with efavirenz is estimated to provide exposures similar to daclatasvir at 60 mg daily alone.	[116]
	Ledipasvir/ sofosbuvir	Not tested	Expected: ↔	Expected: ↔	No dose adjustment.	[29]
	Simeprevir	Healthy subjects	AUC ↓ –71%	↔	Avoid coadministration of simeprevir and efavirenz.	[69]
	Sofosbuvir	Not tested			No data.	
	3 Regimen	Not tested			Contraindicated (adverse effect with efavirenz/emtricitabine/tenofovir).	[46]
Raltegravir	Daclatasvir	HIV/HCV coinfected patient			No clinically relevant drug interaction.	[93]
	Ledipasvir/ sofosbuvir	Healthy subjects	↔	↔	No dose adjustment of raltegravir or ledispavir is required.	[29]
	Simeprevir	Healthy subjects	↔	↔	No dose adjustments.	[69]
	Sofosbuvir	Healthy subjects	↔ sofosbuvir ↔ GS-33 100	↔	No dose adjustment of sofosbuvir or raltegravir.	[73]
	3D regimen			With dasabuvir ↑raltegravir: +134% Without dasabuvir ↑raltegravir: + 20%	No dose adjustment.	[46]
Rilpivirin	Daclatasvir	Not tested			Not expected. No dose adjustment.	[23]
	Ledipasvir/ sofosbuvir	Not tested	Expected: ↔	Expected: ↔	Not expected.	[21]
	Simeprevir	Healthy subjects	↔	↔	Not considered clinically significant. No dose adjustments.	[69]
	Sofosbuvir	Healthy subjects	↔ sofosbuvir ↔ GS-331 007	↔	Not considered clinically significant. No dose adjustments.	[73]
	3D regimen		↔ ombitasvir ↑ Paritaprevir +23% ↔ dasabuvir	↑ +225%	Not recommended. If the combination is used, repeated ECG-monitoring should be done.	[46]
Ritonavir	Daclatasvir	Not tested	Expected: daclatasvir ↑ Inhibition of CYP3A4 by ritonavir		Dose of daclatasvir should be reduced to 30 mg with strong inhibitors of CYP3A4.	[23]
	Ledipasvir/ sofosbuvir	Not tested			Not expected.	[21]

(*continues*)

Table 8

(Continued)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC	Pharmacological effect on coadministered drug AUC	Recommendations	Ref
	Simeprevir	Healthy subjects	↑ +618%	↑ +32%	It is not recommended to coadminister simeprevir with ritonavir, boosted or unboosted HIV protease inhibitors.	[50]
	Sofosbuvir	Not tested		↔	Not expected.	[37]
Tenofovir	Daclatasvir	Healthy subjects	↔	↔	No dose adjustment is required with coadministration.	[115]
	Simeprevir	Healthy subjects	↔	↔	No dose adjustments are required.	[69]
	Sofosbuvir	Not tested			No data.	[37]
Tenofovir/ emtricitabine	3d regimen		↔ ombitasvir ↔ paritaprevir with dasabuvir: ↔ paritaprevir without dasabuvir: ↔ dasabuvir	↔ emtricitabine ↔ tenofovir	No dose adjustment.	[46]
Abacavir/ lamivudine	Daclatasvir	Not tested			Not expected.No dose adjustment.	[23]
	Simeprevir	Not tested			Not expected.No dose adjustment.	[22]
	Ledipasvir/ sofosbuvir	Healthy subjects	↔ ledipasvir ↔ sofosbuvir ↔ GS-331 007	↔ abacavir ↔ lamivudine	No dose adjustment is required.	[21]
	Ombitasvir/ paritaprevir/ ritonavir / dasabuvir	Healthy subjects	↔ ombitasvir ↔ paritaprevir with dasabuvir ↔ paritaprevir without dasabuvir ↔ dasabuvir	↔ abacavir ↔ lamivudine	No dose adjustment.	[117]
Darunavir/ ritonavir	Daclatasvir	HIV/HCV	↔ daclatasvir	↔ darunavir	No dose adjustment.	[90, 118]
	Ledipasvir/ sofosbuvir	Healthy subjects	↑ledipasvir: +39%	↔ darunavir	No dose adjustment of ledipasvir/ sofosbuvir or darunavir (ritonavir boosted).	[21]
	Simeprevir	Healthy subjects	↑ +159%	↔ darunavir ↑ritonavir +32%	It is not recommended to coadminister simeprevir with ritonavir, boosted or unboosted HIV protease inhibitors.	[119]
	Sofosbuvir	Healthy subjects	↑ sofosbuvir + 34% ↔ GS-331 007	↔ darunavir ↔ ritonavir:	These changes are not considered clinically significant and dose adjustments are not warranted.	[73]
Darunavir alone	3D regimen	Healthy subjects	↓ombitasvir: – 27% ↓paritaprevir: – 41% ↓dasabuvir: –27%	↔ darunavir	Not considered clinically significant. No dose adjustment.	[19, 46]
Lopinavir/ritonavir	Daclatasvir	Healthy subjects	NS	Not studied	No dose adjustment.	[97]

(*continues*)

Table 8

(Continued)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC	Pharmacological effect on coadministered drug AUC	Recommendations	Ref
	Ledipasvir/ sofosbuvir		Expected: AUC ↑ (P-gp inhibition by lopinavir)		No data.	[21]
	Sofosbuvir	Not tested	Expected: AUC ↑ (P-gp inhibition by lopinavir)		No data.	[37]
	Simeprevir	Not tested	Expected: AUC ↑		Not recommended.	[22]
	3D regimen		↔ ombitasvir ↑ paritaprevir with dasabuvir: +117% ↑ paritaprevir (without dasabuvir): ↑ +510% ↔ dasabuvir	↔ lopinavir	Contraindicated.	[46]
Atazanavir/ ritonavir	Daclatasvir	Healthy subjects	↑ + 110%	↔	An extrapolated daclatasvir dose of 30 mg with atazanavir/ ritonavir is estimated to provide exposures similar to daclatasvir at 60 mg daily alone.	[116]
	Ledipasvir/ sofosbuvir	Healthy subjects	↑ ledipasvir +113% ↔ sofosbuvir ↔ GS-331 007	↔ atazanavir	No dose adjustment of ledipasvir/ sofosbuvir or atazanavir (ritonavir boosted) is required.	[21]
	Simeprevir	Not tested	Expected: ↑ AUC simeprevir (CYP3A4 enzyme inhibition by ritonavir)		It is not recommended to coadminister simeprevir with any HIV PI, with or without ritonavir.	[22]
Atazanavir alone	3D regimen	Healthy subjects	↔ ombitasvir ↑ paritaprevir with dasabuvir: + 94% ↑paritaprevir without dasabuvir +187% ↔ dasabuvir	↔ atazanavir	No dose adjustment needed for ombitasvir/ paritaprevir/ ritonavir with dasabuvir and atazanavir alone.Treatment with atazanavir + Ombitasvir/ paritaprevir/ ritonavir without dasabuvir is not recommended.	[46]
Atazanavir ritonavir + emtricitabine/ tenofovir disoproxil fumarate /	Daclatasvir	Not tested	Expected AUC daclatasvir ↑ (CYP3A4 enzyme inhibition by ritonavir)		Not recommended.	[23]
	Ledipasvir/ sofosbuvir	Healthy subjects	↑ ledipasvir: +96% ↔ sofosbuvir ↔ GS-331 007	↔ AUC atazanavir ↑ C_{min} + 63% ↔ AUC ritonavir ↑ C_{min} + 45% ↔Emtricitabine ↑ tenofovir +35%	Ledipasvir–sofosbuvir increased the concentration of tenofovir. The combination should be used with caution with frequent renal monitoring. Atazanavir concentrations are also	[120]

(*continues*)

Table 8

(Continued)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC	Pharmacological effect on coadministered drug AUC	Recommendations	Ref
				C_{min+} 47%	increased, with a risk for an increase in bilirubin levels/icterus.	
	Simeprevir	Not tested	Expected: AUC simeprevir↑ (CYP3A4 enzyme inhibition)		It is not recommended to coadminister simeprevir with any HIV PI, with or without ritonavir.	[22]
	3D regimen	Discontinued due to adverse effect			Contraindicated (alanine amino transferase elevation).	[19, 46]
Darunavir / ritonavir + emtricitabine/ tenofovir disoproxil fumarate	Daclatasvir	Not tested	Expected AUC daclatasvir ↑ (CYP3A4 enzyme inhibition by ritonavir)		Not recommended.	[23]
	Ledipasvir/ sofosbuvir	Healthy subjects	↔ ledipasvir ↔ sofosbuvir ↔ GS-331 007	↔ darunavir ↔ ritonavir ↔ emtricitabine ↑ tenofovir +50%	Ledipasvir-sofosbuvir is expected to increase the concentration of tenofovir. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available.	[21]
	Simeprevir	Not tested	Expected: simeprevir ↑ (CYP3A4 enzyme inhibition)		It is not recommended to coadminister simeprevir with any HIV PI, with or without ritonavir.	[22]
	3D regimen	Not tested			Not recommanded with association with ritonavir.	[19]
Efavirenz, tenofovir, emtricitabine	Daclatasvir	Not tested	Expected: AUC daclatasvir ↓ (CYP3A4 induction by efavirenz)		Increase the dose of daclatasvir to 90 mg.	[23]
	Ledipasvir/ sofosbuvir	Healthy subjects	↓ledipasvir: −34% ↔ sofosbuvir ↔ GS-331 007	↔ efavirenz ↔ emtricitabine ↑ tenofovir: +98%	No dose adjustment of ledipasvir-sofosbuvir or emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate is required.	[29]
	Simeprevir	Not tested	Expected: AUC simeprevir ↓ CYP3A4 induction by efavirenz		Not recommended.	[22]
	Sofosbuvir	Healthy subjects	↔ sofosbuvir ↔ GS-331 007	↔ tenofovir ↔ emtricitabine ↔ efavirenz	No dose adjustments.	[73]
	Ombitasvir/ paritaprevir/ ritonavir / dasabuvir	Discontinuated due to adverse effect			Contraindicated.	[19]

(*continues*)

Table 8

(Continued)

Drug	DAA	Type of patients	Pharmacological effect on DAA AUC	Pharmacological effect on coadministered drug AUC	Recommendations	Ref
Emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate	Daclatasvir	Not tested			Not expected. No dose adjustment.	[23]
	Ledipasvir/ sofosbuvir	Healthy subjects	↔ ledipasvir ↔ sofosbuvir ↔ GS-331 007	↔ emtricitabine ↔ rilpivirine ↑ tenofovir +40%	No dose adjustment of ledapasvir-sofosbuvir or emtricitabine/rilpivirine/ tenofovir disoproxil fumarate is required.	[29]
	Simeprevir	Not tested			Not expected. No dose adjustment.	[22]
	Ombitasvir/ paritaprevir/ ritonavir / dasabuvir	Not tested		Expected: ↑ rilpivirin ↔ tenofovir ↔ emtricitabine	Not recommended. Monitore ECG.	[19]
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate	Daclatasvir	Not tested	Expected: daclatasvir ↑ (CYP3A4 inhibition by cobicistat)		The dose of daclatasvir should be reduced to 0 mg once daily when coadministered with cobicistat or other strong inhibitors of CYP3A4.	[18]
	Ledipasvir/ sofosbuvir	Healthy subjects	↑ ledipasvir +78% ↑ sofosbuvir + 36% ↑ GS-331 007 + 44%	↔ elvitegravir ↑ cobicistat: +59% tenofovir not studied	Ledapasvir-sofosbuvir is expected to increase tenofovir exposure. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available.	[121]
	Simeprevir	Not tested	Expected AUC simeprevir ↑ (CYP3A4 inhibition by cobicistat)		Not recommended.	[22]
	3D regimen	Not tested	Expected: ↑ ombitasvir ↑ paritaprevir ↑ dasabuvir		Contraindicated.	[19]

↔, no clinical change (< 25%); ↑, increase in AUC; ↓, decrease in AUC.

AUC, area under the curve; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NA, not applicable

Effect of CYP inducers or inhibitors on DAAs. The US Food and Drug Administration classification states that a drug is a powerful inhibitor (or inducer) of CYP if it increases (or decreases) substrate exposure by a factor of at least five [68]. Strong inducers of CYP3A4 (e.g. rifampicin, carbamazepine) may decrease therapeutic effect of daclatasvir, simeprevir and 3D regimen. Thus in healthy subjects, administration of rifampin with simeprevir or with daclatasvir at 60 mg once daily led to a 48% decrease in simeprevir AUC [50] and a 79% decrease in daclatasvir AUC [18]. 3D regimen was tested with carbamazepine, it resulted in paritaprevir AUC decrease by 70%, dasabuvir AUC by 70% and ombitasvir AUC by 30% respectively [33]. Coadministration of daclatasvir or simeprevir or 3D regimen with a strong inducer is therefore not recommended. Likewise, the concomitant use of efavirenz with simeprevir or daclatasvir 60 mg induced a reduction of simeprevir AUC by 71% and of daclatasvir AUC by 22% [69, 70]. An extrapolated daclatasvir dose of 90 mg with efavirenz is estimated to provide exposure similar to daclatasvir at 60 mg daily alone [71] and simeprevir and efavirenz should not be associated.

Efavirenz with 3D regimen resulted in alanine aminotransferase elevations and early discontinuation of the study. The association is contraindicated [72].

As expected, coadministration of sofosbuvir/ledipasvir and efavirenz did not induce a clinically significant effect on ledipasvir and sofosbuvir AUC [29, 73].

Strong inhibitors of CYP3A4 may increase the plasma levels of daclatasvir, simeprevir and 3D regimen. In healthy volunteers, erythromycin and simeprevir association increased AUC simeprevir by 647% and AUC erythromycin by 90%. [32]. Ritonavir with simeprevir increases simeprevir AUC by 618% respectively [47, 70]. Thus coadministration of simeprevir with any protease inhibitor is not recommended. Ketoconazole at 400 mg once a day with daclatasvir or 3D regimen increases daclatasvir AUC by 200% [18], paritaprevir AUC by 100%, ritonavir AUC by 57%, and dasabuvir AUC by 42% [74]. The dose of daclatasvir should be decreased to 30 mg once daily if coadministered with ketoconazole and 3D regimen is contraindicated with all antifungal azoles (Table 7).

Daclatasvir, simeprevir or paritaprevir coadministration with cyclosporine (a CYP3A4 inhibitor) resulted in daclatasvir, simeprevir and paritaprevir AUC increase (40%, 481% and 72%) [19, 53, 59]. No dose adjustment of antiviral is required except for simeprevir, coadministration of which is contraindicated [45, 49, 75].

Dasabuvir is a substrate of CYP2C8: in the presence of gemfibrozil (CYP2C8 inhibitor), dasabuvir AUC increased by 1030%, so gemfibrozil is contraindicated with 3D regimen [19].

Other drugs were tested with simeprevir, sofosbuvir, ledipasvir, daclatasvir and 3D regimen [76–82]: data available are appended in supporting information (Tables S1, S2, S3, S4, S5 published online). Treatment with daclatasvir, simeprevir, sofosbuvir/ledipasvir is associated with a low potential for serious DDI. However, moderate DDI are frequent and have to be considered [73, 83]. Polepally *et al*. have studied the effects of more than 120 comedications with the 3D regimen. Despite of an apparent effect on paritaprevir exposure, no dose adjustment of 3D regimen was necessary [80, 81]. In HIV-coinfected patients, addition of sofosbuvir-containing therapy is associated with a lower DDI prevalence than a simeprevir-containing therapy [86, 87] (Table 8). Sofosbuvir and daclatasvir are ideally suited for HCV/HIV-coinfected patients, whereas simeprevir with sofosbuvir is recommended for HCV-monoinfected patients [88–91]. 3D regimen has a highest potential of DDI and comedication should be analysed carefully before initiating HCV treatment [87, 92].

Other factors influencing the metabolism of DAAs: UGTA1 enzyme. UDP-glucuronosyltransferase (UGT) enzymes catalyse the conjugation of endogenous substances such as bilirubin and exogenous drugs. Sofosbuvir, ledipasvir, simeprevir and daclatasvir were tested with raltegravir, whose metabolism depends on UGTA1 enzyme: no clinically significant pharmacokinetic changes were observed, and no dose adjustments are needed [42, 69, 73, 93]. Paritaprevir, ombitasvir and dasabuvir are inhibitors of UGT1A1 so coadministration with raltegravir increase raltegravir AUC by 134%. 3D regimen is contraindicated with norgestimate/ethynylestradiol because of an increase of norgestrel and norgestromine by 164 and 160% respectively [33].

Elimination

Only competition in the urinary excretion of a drug causes a risk of clinically significant DDI. Elimination of simeprevir, ledipasvir daclatasvir and 3D regimen occurs mainly via biliary excretion. Sofosbuvir is eliminated at the rate of approximately 80%, 14% and 2.5% in urine, faeces and expired air, respectively [37]. Most of the sofosbuvir dose recovered in urine was GS-331 007 (78%). As GS-331 007 is an inactive metabolite, a competition with another drug mainly eliminated by the kidneys could lead to an overdosage of sofosbuvir [94]. A small study in HCV patients with severe renal impairment showed that low dose of sofosbuvir (200 mg) with ribavirin at 200 mg once daily resulted in comparable sofosbuvir and approximately four-fold higher GS-331 007 exposures compared with sofosbuvir at 400 mg. The treatment was safe and well-tolerated [95, 96].

Conclusion

DDIs can occur at several steps during drug metabolism. Food can play a role in the absorption of DAAs. Transporters and cytochromes are mainly responsible for clinically significant interactions. Sofosbuvir is less prone to DDIs, because its metabolism does not depend on cytochromes. Online tools can be helpful, but clinicians should also run a checklist of key questions before beginning a HCV treatment, such as:

- Does the liver metabolise the coadministered drug? If so, are they substrates inhibitors or inducers of P-gp, OATP or CYP3A4 or other transporters?
- Is the patient taking drugs with a narrow therapeutic range? Is it possible to monitor the drug?
- Should a substitution be considered? How?

The selected treatment will need to be regularly re-assessed jointly with the pharmacist in an effort to minimise potential interactions and provide therapeutic alternatives.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work. A. Abergel has received speaking and teaching fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, and Merck Sharp & Dohme (MSD); grant and research support from Abbvie, Bristol-Myers Squibb, Gilead Sciences, and MSD; and he has served on advisory boards for Abbvie, Bristol-Myers Squibb, Gilead Sciences, and MSD in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Contributors

F.T.C. collected the data; S.T.P. and A.A. contributed to literature searching, reviewing, and writing the paper; A.B., V. S., P.C. and G.L. corrected the paper; A.A. supervised the topic. All authors approved the final version of the manuscript.

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Supporting Information

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Table S1 Drug–drug interactions with sofosbuvir.
Table S2 Drug–drug interactions with simeprevir.
Table S3 Drug–drug interactions with daclatasvir.
Table S4 Drug–drug interactions with ledipasvir/sofosbuvir.
Table S5 Drug–drug interactions with 3D regimen.