Cipla Ltd. Regd. Office Cipla House,
Peninsula Business Park, Ganpatrao Kadam Marg,
Lower Parel, Mumbai - 400 013

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HCV MANAGEMENT SERIES

Cipla

Issue 3

Drug Interactions with HCV Direct-acting Antivirals

PREFACE

Direct-acting antiviral agents (DAAs) have transformed the lives of most patients with hepatitis C virus infection. Sustained virologic response (SVR) rates of >90% are consistently achievable across HCV genotypes. The accomplishment of such high cure rates, irrespective of cirrhosis or prior HCV treatment experience in these difficult-to-treat cohorts, is remarkable. Although DAAs have high efficacy and a favorable safety profile, they also have very high potential for drug–drug interactions (DDIs) that must be considered before, during, and after initiation of DAA-based therapy.

With newer drugs like ledipasvir and daclatasvir coming to the forefront, the drug interaction profiles of these drugs are becoming considerably evident. Especially with daclatasvir, drug interactions demand a reduced or an increased dose when co-administered with certain medications. Moreover, patients with hepatitis C often suffer from other concomitant illnesses such as diabetes, hypertension and hyperlipidemia, and also comorbidities like hepatitis B and HIV. Hence, the drug interactions with hepatitis C medications need thorough consideration.

This booklet summarizes the available data on the most clinically relevant DDIs of DAAs to assist in clinical decision-making.

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1. GENERAL MECHANISM OF DRUG–DRUG INTERACTIONS

The therapeutic activity of any drug depends on the exposure time to a particular target site. The exposure when suboptimal results in poor or null drug activity. On the other hand, most toxicities develop due to excessive drug exposures. The therapeutic window is defined as the range of drug concentrations within which the expected drug activity occurs with absence of or minimal associated toxicities. Drugs with a narrow therapeutic window are most likely for major clinically relevant drug interactions. The drug interactions may occur owing to many reasons.

Considering the pharmacokinetics, three major mechanisms of drug interactions exist, namely inducing or inhibiting enzymatic activities, cell transporters or protein-binding displacement. There are two major clearance mechanisms of drugs in the body that use respectively the cytochrome P450 (CYP450) isoenzyme complex and glucuronidation.

Clinically relevant drug–drug interactions (DDIs) typically occur in the absorption or the metabolism phase of the drug. Interactions in the absorption usually occur by altering the gastrointestinal pH. The liver is the major site for drug metabolism, mostly owing to the cytochrome enzymes present. The drug interaction at the metabolism state is majorly attributed to inhibition or induction of the CYP450 enzyme system, particularly 3A4 (CYP3A4), which is responsible for the oxidation of many drugs, leading to increased or decreased exposure of either of the drugs administered. This may lead to a clinically toxic or a subtherapeutic outcome of the respective drugs. Thus, administering inhibitors, inducers and substrates for these respective enzymes can lead to clinically relevant alterations in the drug concentrations.

The organic anion-transporting polypeptides, 1B1 and 1B3, are the most important influx transporters, whereas multidrug-resistant (MDR) 1, also called P-glycoprotein (P-gp), and MDR protein 2 are the major efflux transporters. Besides these cytochrome enzymes, interactions involving P-gp and breast cancer-resistant proteins (BCRP), active transport proteins have a potential to affect drug bioavailability by altering the elimination and absorption kinetics. When orally administered drugs are subjected to potential elimination by intestinal CYP450 and P-gp prior to systemic absorption, it is

termed as first-pass metabolism. Thus, inhibition of the CYP450 enzymes or P-gp with one agent may increase the concentration of the other. Drug interactions due to protein-binding displacement are particularly relevant for highly protein (albumin)-bound medications.

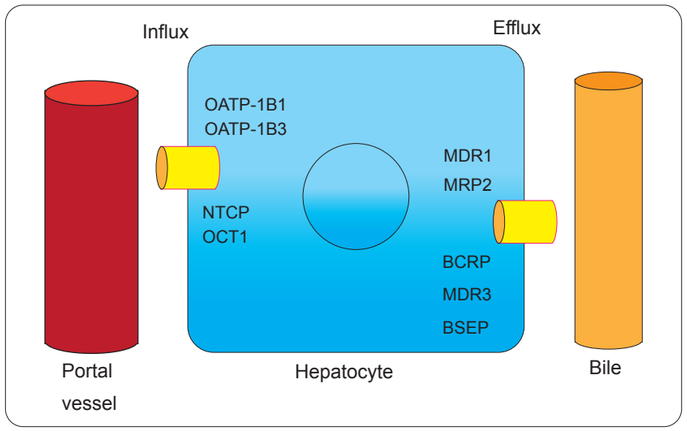

Figure 1: Main Cell Transporters in the Liver for DAAs

(Adapted from Expert Opin Drug Metab Toxicol. 2015; 11(3):333-41.)

Abbreviations: BCRP: Breast cancer resistance protein; BSEP: Bile salt export pump; NTCP: Sodium taurocholate co-transporting polypeptide; OATP: Organ anion-transporter protein; OCT: Organic cation transporter.

Besides this, some DAAs have to be taken with food, e.g., simeprevir and paritaprevir/ombitasvir/dasabuvir. On the contrary, sofosbuvir, ledipasvir and daclatasvir can be taken without any regard to meals. However, if ribavirin is added to these regimens, ribavirin is to be taken with food.

The DAAs used for the treatment of hepatitis C virus (HCV) are metabolized through these pathways, thus, predisposing them to DDIs. Figure 1 depicts the common metabolic pathways for potential DDIs for DAAs.

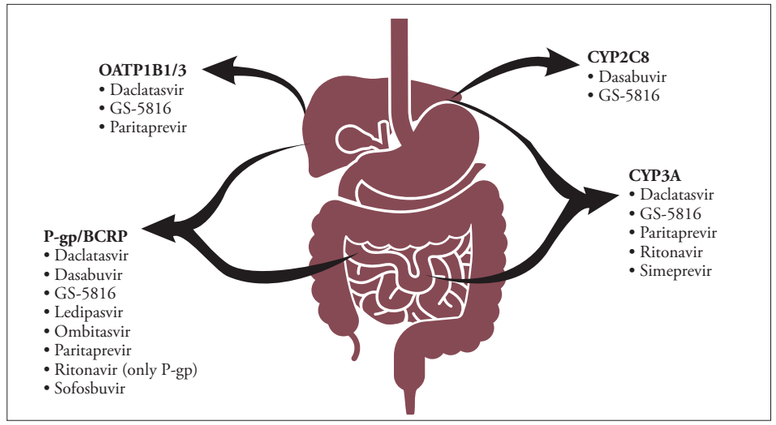

Figure 2: Metabolic Pathways for Potential DDIs

(Adapted from Hepatology. 2016; 63(2): 634-43.)

Knowing about the drug interactions of new hepatitis C drugs has become an important issue. There is further concern regarding patients with HIV co-infection who are on multiple antiretroviral (ARV) regimens and those who are on immunosuppressants post-transplant. The clinically significant drug interactions are discussed in the forthcoming chapters. The currently approved DAAs and their properties with respect to some parameters are presented in Table 1.

Table 1: Few of the Currently Approved HCV Drugs with Pharmacological Properties

Class/Drug	Clinical Potency	Clinical Genotype Coverage	Clinical Resistance Barrier	DDI Risk
Protease inhibitors				
Simeprevir	High	All but G3	Low	High
Paritaprevir/ritonavir	High	All but G3	Low	Very high
Polymerase inhibitors				
Sofosbuvir	High	All	Very high	Low
Dasabuvir	High	G1	Low	High
NS5A inhibitors				
Daclatasvir	Very high	All but G1a	Low	Moderate
Ledipasvir	High	All	Low	Low
Ombitasvir	Very high	All but G1a	Low	High

2. DRUG INTERACTIONS WITH DAA FAMILIES

HCV Polymerase Inhibitors

Sofosbuvir

Currently, sofosbuvir, a uridine analog, is the backbone of HCV therapy and is the only nucelos(t)ide analog approved so far for treating chronic HCV. Hence, the drug interactions with sofosbuvir are of major relevance. Sofosbuvir is a prodrug that undergoes intracellular metabolism within human hepatocytes to a pharmacologically active uridine triphosphate form (GS-461203). GS-461203 is incorporated into the HCV RNA by NS5B polymerase, which leads to termination of HCV replication.

However, this active metabolite, GS-461203, contributes only about 4% of the administered sofosbuvir. The remnant circulates as an inactive metabolite, viz., GS-331007, which accounts for more than 90% of the systemic exposure of the administered sofosbuvir. GS331007 is excreted through the renal route and, hence, its exposure increases in patients with renal impairment, viz., patients with chronic kidney disease and end-stage renal disease. So, in such patients, dose adjustments of sofosbuvir should be considered.

Sofosbuvir can be administered without any regard to food.

In addition, sofosbuvir is a substrate of drug transporter P-gp and BCRP while GS-331007 is not. Hence, potent intestinal P-gp inducer drugs (e.g., rifampin or St. John's wort) may decrease sofosbuvir plasma concentration, leading to a reduced therapeutic effect of sofosbuvir; hence, co-administration should be avoided. Co-administration of sofosbuvir with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration. Accordingly, sofosbuvir may be co-administered with P-gp and/or BCRP inhibitors. Sofosbuvir and GS-331007 are not inhibitors of P-gp and BCRP and, thus, are not expected to increase exposures of drugs that are substrates of these transporters.

However, sofosbuvir does have clinically relevant interactions with the following category of drugs as listed in Table 1.

Table 1: Interaction of Sofosbuvir with Other Drugs[a]

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiarrhythmics: Amiodarone	Effect on amiodarone and sofosbuvir concentrations is unknown	Coadministration of amiodarone with sofosbuvir in combination with another DAA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with sofosbuvir in combination with another DAA is not recommended; if coadministration is required, cardiac monitoring is recommended.
Anticonvulsants: Carbamazepine Phenytoin Phenobarbital Oxcarbazepine	↓ sofosbuvir ↓ GS-331007	Co-administration of sofosbuvir with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Co-administration is not recommended.
Antimycobacterials: Rifabutin Rifampin Rifapentine	↓sofosbuvir ↓ GS-331007	Co-administration of sofosbuvir with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Co-administration is not recommended. sofosbuvir should not be used with rifampin, a potent intestinal P-gp inducer.
Herbal Supplements: St. John's wort (Hypericum perforatum)	↓ sofosbuvir ↓ GS-331007	Sofosbuvir should not be used with St. John's wort, a potent intestinal P-gp inducer.
HIV Protease Inhibitors: Tipranavir/ritonavir	↓ sofosbuvir ↓ GS-331007	Co-administration of sofosbuvir with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Co-administration is not recommended.

[a] This table is not all inclusive. [b] ↓ = decrease.

Serious Symptomatic Bradycardia Occurs When Sofosbuvir is administered with Amiodarone

Co-administration is not recommended, since this interaction is reported to be fatal. Patients taking amiodarone, who have no other alternative, viable treatment options and who will be co-administered sofosbuvir-based therapies, should be counselled about the risk of serious symptomatic bradycardia. Additionally, cardiac monitoring in an in-patient setting for the first 48 hours of co-administration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Drugs without Clinically Significant Interactions with Sofosbuvir

In addition to the drugs included in Table 1, the interactions between sofosbuvir and the following drugs were evaluated in clinical trials and no dose adjustment is needed for either drug:

Cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, raltegravir, rilpivirine, tacrolimus, or tenofovir disoproxil fumarate.

Dasabuvir

It is the first approved non-nucleoside HCV polymerase inhibitor administered twice daily with activity against HCV genotype 1. Dasabuvir has neither inhibitory nor inducing effects on CYP450 and, therefore, no major drug interactions are expected. It follows a primary oxidative pathway in the liver by conjugation as a glucuronide, being eliminated mainly by biliary excretion. Food has no impact on dasabuvir bioavailability. Resistance mutations like the C316Y mutation emerge very rapidly when dasabuvir is not used properly and viral replication is not completely suppressed using combination therapy.

HCV NS5A Inhibitors

HCV NS5A inhibitors form a significant component of sofosbuvir-based all-oral therapies. Ledipasvir-sofosbuvir fixed-dose combination (FDC) and daclatasvir (with sofosbuvir) are currently approved NS5A regimens in India. These drugs have to be taken either with NS5B inhibitors or (NS3/4A) protease inhibitors.

The recently approved regimen by the USFDA, sofosbuvir –velpatasvir FDC, is the first pan-genotypic regimen approved for treating HCV.

Daclatasvir

Daclatasvir is administered as one pill of 60 mg once daily, irrespective of food. It is to be taken concomitantly with sofosbuvir and should not be administered alone. Daclatasvir-sofosbuvir regimen with or without ribavirin is recommended by US FDA for use in HCV genotype 1 and 3 infection.Daclatasvir is a substrate of CYP3A as well as P-gp. Daclatasvir has a high potential for drug interactions needing dose modification. In addition, as it is administered with sofosbuvir, the drug interactions applicable to sofosbuvir apply to the combination regimen as well. The dosage modification as recommended by the US FDA is as given below. The full prescribing information should be referred to for details regarding drug interactions.

Additionally, some interactions which are specific to daclatasvir are·stated below.

Table 2: Daclatasvir Dosage Modifications with Concomitant Drugs

Concomitant Drugs	Daclatasvir Dosage
Strong CYP3A inhibitors and certain HIV antivirals	30 mg once daily
Moderate CYP3A inducers and nevirapine	90 mg once daily
Strong CYP3A inducers	Contraindicated

Drugs that strongly induce CYP3A such as anticonvulsants, e.g., phenytoin and carbamazepine, antimycobacterials such as rifampin, and herbal products such as St. John's wort reduce the virologic response produced by daclatasvir. Hence, they are strongly contraindicated for use with daclatasvir.

The drug interactions seen are listed in Table 3.

Table 3: Established and Other Potentially Significant Drug Interactions with Daclatasvir

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Strong CYP3A inhibitors		
Atazanavir/ritonavir,[b] clarithromycin, indinavir, itraconazole, ketoconazole,[b] nefazodone, nelfinavir, posaconazole, saquinavir, telithromycin, voriconazole	↑ Daclatasvir	Decrease daclatasvir dose to 30 mg once daily when co-administered with strong inhibitors of CYP3A.
Moderate CYP3A inhibitors		
Atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil	↑ Daclatasvir	Monitor for daclatasvir adverse events.
Moderate CYP3A inducers		
Bosentan, dexamethasone, efavirenz,[b] etravirine, modafinil, nafcillin, rifapentine	↓ Daclatasvir	Increase daclatasvir dose to 90 mg once daily when co-administered with moderate inducers of CYP3A.

Anticoagulants		
Dabigatran etexilate mesylate	↑ Dabigatran	Use of daclatasvir with dabigatran etexilate is not recommended in specific renal impairment groups, depending on the indication. Please see the dabigatran prescribing information for specific recommendations.
Cardiovascular agents		
Antiarrhythmic: Amiodarone	Amiodarone: effects unknown	Co-administration of amiodarone with daclatasvir in combination with sofosbuvir is not recommended because it may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. If co-administration is required, cardiac monitoring is recommended.
Antiarrhythmic: Digoxin[b]	↑ Digoxin	**Patients already receiving daclatasvir initiating digoxin:** Initiate treatment using the lowest appropriate digoxin dosage. Monitor digoxin concentrations; adjust digoxin doses if necessary and continue monitoring. **Patients already receiving digoxin prior to initiating daclatasvir:** Measure serum digoxin concentrations before initiating daclatasvir. Reduce digoxin concentrations by decreasing digoxin dosage by approximately 30–50% or by modifying the dosing frequency and continue monitoring.

Lipid-lowering agents		
HMG-CoA reductase inhibitors:		Monitor for HMG-CoA reductase inhibitor associated adverse events such as myopathy.
Atorvastatin	↑Atorvastatin	
Fluvastatin	↑ Fluvastatin	
Pitavastatin	↑ Pitavastatin	
Pravastatin	↑ Pravastatin	
Rosuvastatin[b]	↑ Rosuvastatin	
Simvastatin	↑ Simvastatin	

[a] The direction of the arrow (↑ = increase, ↓= decrease) indicates the direction of the change in pharmacokinetic parameters.

[b] These interactions have been studied.

Ledipasvir

Ledipasvir is another NS5A inhibitor and available as a single-tablet FDC with sofosbuvir. The recommended dose of ledipasvir-sofosbuvir FDC is 90 mg and 400 mg, respectively. It is approved by US FDA for use in HCV genotype 1 ,4, 5 and 6 with or without ribavirin. As ledipasvir is administered with sofosbuvir as a FDC, any interactions that have been identified with these agents individually may occur with the combination, as well.

Ledipasvir is an inhibitor of the drug transporters P-gp and BCRP, and may increase intestinal absorption of the co-administered substrates for these transporters.

Ledipasvir and sofosbuvir are substrates of the drug transporters P-gp and BCRP, whereas GS-331007 is not. P-gp inducers (e.g., rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir plasma concentrations, leading to a reduced therapeutic effect of the combination and, hence, use with P-gp inducers is not recommended.

Table 4: Established and Other Potentially Significant Drug Interactions with Ledipasvir-Sofosbuvir FDC

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Acid-reducing Agents: Antacids (e.g., aluminum and magnesium hydroxide)	↓ ledipasvir	Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
		It is recommended to separate antacid and ledipasvir-sofosbuvir FDC administration by 4 hours.
H2-receptor antagonists[c] (e.g., famotidine)		H2-receptor antagonists may be administered simultaneously with or 12 hours apart from ledipasvir-sofosbuvir FDC at a dose that does not exceed doses comparable with famotidine 40 mg twice daily.
Proton-pump inhibitors[c] (e.g., omeprazole)		Proton-pump inhibitor doses comparable with omeprazole 20 mg or lower can be administered simultaneously with ledipasvir-sofosbuvir FDC under fasted conditions.
Antiarrhythmic: Amiodarone	Effect on amiodarone, ledipasvir, and sofosbuvir concentrations unknown	Co-administration of amiodarone with ledipasvir-sofosbuvir FDC may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Co-administration of amiodarone with ledipasvir-sofosbuvir FDC is not recommended; if co-administration is required, cardiac monitoring is recommended.
Digoxin	↑ digoxin	Co-administration of ledipasvir-sofosbuvir FDC with digoxin may increase the concentration of digoxin. Therapeutic concentration monitoring of digoxin is recommended.
Anticonvulsants: Carbamazepine Phenytoin Phenobarbital Oxcarbazepine	↓ ledipasvir ↓ sofosbuvir	Co-administration is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of ledipasvir-sofosbuvir FDC. **Co-administration is not recommended.**
Antimycobacterials: Rifabutin Rifampin[c] Rifapentine	↓ ledipasvir ↓ sofosbuvir	Co-administration expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of ledipasvir-sofosbuvir FDC. **Co-administration is not recommended. Co-administration of ledipasvir-sofosbuvir FDC with rifampin, a P-gp inducer, is not recommended**

[a] The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters.

[b] These interactions have been studied.

Velpatasvir

Velpatasvir is a recently approved pan-genotypic NS5A inhibitor, with high potency across all the HCV genotypes, available as a FDC tablet with sofosbuvir. The recommended dosage of sofosbuvir-velpatasvir (400 mg/100 mg) FDC is one tablet once daily.

Velpatasvir is an inhibitor of drug transporters P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1. Co-administration of sofosbuvir-velpatasvir FDC with drugs that are substrates of these transporters may increase the exposure of such drugs. Drug interactions with sofosbuvir are applicable to the combination regimen as well.

Table 5: Established and Other Potentially Significant Drug Interactions with Sofosbuvir-Velpatasvir FDC[a]

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Acid-reducing Agents:	↓ Velpatasvir	Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		Separate antacid and sofosbuvir-velpatasvir FDC administration by 4 hours.
H2-receptor antagonists[c] (e.g., famotidine)		H2-receptor antagonists may be administered simultaneously with or 12 hours apart from at a dose that does not exceed doses comparable with famotidine 40 mg twice daily.
Proton-pump inhibitors[c] (e.g., omeprazole)		Co-administration of omeprazole or other proton-pump inhibitors is not recommended. If it is considered medically necessary to co-administer, sofosbuvir-velpatasvir FDC should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton-pump inhibitors has not been studied.
Antiarrhythmics: Amiodarone	Effect on amiodarone, velpatasvir, and sofosbuvir concentrations unknown	Co-administration may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. **Co-administration of amiodarone with sofosbuvir-velpatasvir FDC is not recommended;** if co-administration is required, cardiac monitoring is recommended.
Digoxin	↑digoxin	Therapeutic concentration monitoring of digoxin is recommended when co-administered with sofosbuvir-velpatasvir FDC. Refer to digoxin prescribing information for monitoring and dose modification recommendations for concentration increases of less than 50%.
Anticancer: Topotecan	↑ topotecan	Co-administration is not recommended.
Anticonvulsants: Carbamazepine Phenytoin Phenobarbital Oxcarbazepine	↓sofosbuvir ↓ velpatasvir	Co-administration is not recommended.
Antimycobacterials: Rifabutin Rifampin[c] Rifapentine	↓ sofosbuvir ↓ velpatasvir	Co-administration is not recommended.
HIV ARVs: Efavirenz[c]	↓ velpatasvir	Co-administration of sofosbuvir-velpatasvir FDC with efavirenz-containing regimens is not recommended.
Regimens containing tenofovir DF	↓ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving sofosbuvir-velpatasvir FDC concomitantly with a regimen containing tenofovir DF. Refer to the prescribing information of the tenofovir DF-containing product for recommendations on renal monitoring.
Tipranavir/ritonavir	↓ sofosbuvir ↓ velpatasvir	Co-administration is not recommended.
Herbal Supplements: St. John's wort (Hypericum perforatum)	↓ sofosbuvir ↓ velpatasvir	Co-administration is not recommended.

HMG-CoA Reductase Inhibitors: Rosuvastatin[c]	↑ rosuvastatin	Co-administration may significantly increase the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with sofosbuvir-velpatasvir FDC at a dose that does not exceed 10 mg.
Atorvastatin	↑ atorvastatin	Co-administration is expected to increase the concentrations of atorvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis.

DF = disoproxil fumarate.

[a] This table is not all inclusive. [b] ↓ = decrease, ↑ = increase. [c]These interactions have been studied in healthy adults.

Drugs without Clinically Significant Interactions with Sofosbuvir-Velpatasvir FDC

Based on drug interaction studies conducted with the components of (sofosbuvir or velpatasvir) or sofosbuvir-velpatasvir FDC, no clinically significant drug interactions have been observed with the following drugs:

- Sofosbuvir-velpatasvir FDC: atazanavir/ritonavir, cyclosporine, daruna vir/ritonavir, dolutegravir, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, raltegravir or rilpivirine
- Sofosbuvir: ethinyl estradiol/norgestimate, methadone, or tacrolimus
- Velpatasvir: ethinyl estradiol/norgestimate, ketoconazole, or pravastatin

Other NS5A Inhibitors

Ombitasvir

Ombitasvir is a substrate of CYP3A4 and P-gp and inhibits CYP2C8 and UGT1A1. In patients with moderate-to-severe hepatic insufficiency, ombitasvir exposure increases up to 55%. It contributes to hyperbilirubinemia when taken with other UGT1A1 substrates. The ombitasvir-based regimen has to be taken with meals.

Elbasvir

Elbasvir (present as a FDC with the NS3/4A protease inhibitor, grazoprevir) is a substrate of CYP3A and P-gp. Co-administration of moderate or strong inducers of CYP3A may decrease elbasvir and grazoprevir plasma concentrations, leading to a reduced therapeutic effect. Co-administration with strong CYP3A inducers or efavirenz is contraindicated. Co-administration with strong CYP3A inhibitors may increase elbasvir and grazoprevir concentrations and, hence, is not recommended. The full prescribing information should be referred to for details of drug interactions with these regimens.

HCV Protease Inhibitors

Currently, three HCV protease inhibitors are approved, viz., simeprevir, paritaprevir and grazoprevir. Simeprevir moderately inhibits CYP3A4 and P-gp in the gut and OATO1B1 and MDR protein 2 in the hepatocyte. However, co-administration of simeprevir with HIV protease inhibitors and HIV non-nucleoside analog inhibitors (except rilpivirine) is not recommended. The interactions related to HIV antivirals are discussed in detail in the next chapter.

Simeprevir is an intestinal CYP3A4 inhibitor and also inhibits OAT-P1B1 and P-gp. Moderate or severe inducers or inhibitors of CYP3A4 may reduce or increase simeprevir concentrations. It is recommended at a dose of 150 mg, to be taken orally with food. It has specific drug interactions with digoxin, antiarrhythmics, antimycobacterials, antifungals and calcium channel blockers. It significantly interacts with HIV protease inhibitors irrespective whether they are boosted or unboosted with ritonavir. Hence, co-administration is not recommended. Simeprevir interacts significantly with statins and, hence, dose reduction of statins is recommended when co-administered.

Paritaprevir is a component of the Abbvie triple-drug regimen (3D), which consists of ritonavir-boosted paritaprevir, ombitasvir FDC and dasabuvir. Paritaprevir has a very short half-life and, hence, needs administration with a pharmacoenhancer like ritonavir. It is co-formulated with ritonavir and an NS5A inhibitor, ombitasvir, Ritonavir is one of the potent inhibitors of CYP450, and high exposure to medication metabolized by this complex is a major concern. Zolpidem, alprazolam, duloxetine, methadone, escitalopram, buprenorphine, naloxone and norethidrone may be co-administered without dose modification. For warfarin, digoxin and furosemide, no dose adjustment

is needed; however, clinical monitoring is advisable. Omeprazole may be administered with 3D but a higher dose may be required. The dose of ketoconazole should not exceed 200 mg/day. Pravastatin, if used, needs a 50% dose reduction and the dose of rosuvastatin should be limited to 10 mg/day. Additionally, amlodipine, if co-administered, needs a 50% dose reduction.

Grazoprevir is a substrate of OATP1B1/3 transporters. Co-administration of elbasvir and grazoprevir FDC with drugs that inhibit OATP1B1/3 transporters may result in a significant increase in the plasma concentrations of grazoprevir. As such, co-administration of elbasvir and grazoprevir FDC with OATP1B1/3 inhibitors is contraindicated. Elbasvir and grazoprevir are substrates of CYP3A and P-gp, but the role of intestinal P-gp in the absorption of elbasvir and grazoprevir appears to be minimal. Co-administration of moderate or strong inducers of CYP3A with elbasvir and grazoprevir FDC may decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of elbasvir and grazoprevir FDC. Co-administration of elbasvir and grazoprevir FDC with strong CYP3A inducers or efavirenz is contraindicated. Co-administration of elbasvir and grazoprevir FDC with moderate CYP3A inducers is not recommended. Co-administration of elbasvir and grazoprevir FDC with strong CYP3A inhibitors may increase elbasvir and grazoprevir concentrations. Co-administration of elbasvir and grazoprevir FDC with certain strong CYP3A inhibitors is not recommended. For details, the full prescribing information should be referred to.

3. DAA INTERACTION WITH HIV ARVs

HIV-infected persons under antiviral therapy as well as those at high risk for HIV and receiving ARVs for pre- as well as post-exposure prophylaxis should be assessed if they are to be recommended for hepatitis C treatment. Drug interactions resulting because of inhibition or induction of the cytochrome enzymes are the most troublesome, but there are also other interactions caused by interference with glucuronidation or cell transporters.

Interaction with HIV Protease Inhibitors

In general, protease inhibitors are known to inhibit CYP3A iso-enzymes. However, the potency of HIV and HCV protease inhibitors varies. If comparing the inhibitory potential of simeprevir and ritonavir, the latter is much more potent. When both are given in combination, the exposure of simeprevir increases by 6-fold. Hence, the combination of both these agents is not recommended. Apart from ritonavir, other HIV agents such as atazanavir, fosamprenavir, lopinavir, indinavir, nelfinavir, saquinavir and tipranavir can also result in altered plasma concentration of simeprevir. Hence, co-administration of simeprevir with any HIV protease inhibitor is not recommended.

Tipranavir can reduce the plasma concentrations of sofosbuvir and, hence, co-administration is not recommended.

The effect of selective anti-HIV agents on the kinetics of DAAs is presented below.

Table 1: Effect of Select HIV Antiviral agents on Daclatasvir, Ledipasvir, Sofosbuvir, Simeprevir and Ribavirin

Medication	Daclatasvir		Ledipasvir		Sofosbuvir		Simeprevir	
	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
Darunavir/ritonavir	Expected to ↑ but ND to date*	Expected to ↑ but ND to date*	↑45%	↑39%	↑45%	↑34%	↑79%†	↑159%†
Efavirenz	↓17%*	↓32%*	↓34%‡	↓34%‡	↓19%‡	↓6%‡	↓51%*	↓71%*
Raltegravir	ND	ND	↔	↔	↔	↔	↔ ↓7%	↔ ↓11%
Rilpivirine	ND	ND	↔	↔	↑21%	↑9%	↔ ↑10%	↔ ↑6%
Ritonavir	ND	ND	ND	ND	↔	↔	↑370	↑618%†
Tenofovir	↑6%	↑10%	↔	↔	↔	↔	↔ ↑15%	↔ ↑14%

†Denotes a potentially dangerous combination of medications and that the concomitant administration of the agent(s) should be avoided.
*Denotes using caution and/or additional monitoring may be necessary when administering the respective medications together.
‡Administered as efavirenz, emtricitabine, tenofovir DF FDC with ledipasvir 90 mg and sofosbuvir 400 mg.
Abbreviations: AUC, area under the concentration curve; C_{max}, maximal concentration; ND, no data; ↑, increase; ↓, decrease; ↔, negligible change.

Non-Nucleoside Reverse Transcriptase Inhibitors

The combination of ritonavir-¬boosted paritaprevir, ombitasvir and dasabuvir, collectively referred to as a 3D regimen, is not recommended for concomitant use with rilpivirine. Efavirenz is also not recommended as the combination results in elevation of the liver enzymes. Efavirenz can also reduce the simeprevir exposure, leading to a reduced therapeutic effect of the latter. Delavirdine can increase exposure to simeprevir, while efavirenz and nevirapine can reduce exposure to the same. Efavirenz can decrease both the extent and exposure of daclatasvir as well as velpatasvir. Increase in the dose of daclatasvir to 90 mg is recommended when co-administered with efavirenz. However, co-administration of velpatasvir is contraindicated with efavirenz.

Nucleotide Reverse Transcriptase Inhibitors: Tenofovir

Few but significant drug interactions between nucleotide reverse transcriptase inhibitors such as tenofovir and DAAs have been noted. Ledipasvir, which is co-administered in a FDC with sofosbuvir, can increase the exposure of tenofovir, but co-administration is not contraindicated. When ledipasvir-sofosbuvir was given in combination with tenofovir, elevated levels exceeding the suprath-erapeutic doses of tenofovir were only assessed when administered with ritona-vir-boosted protease inhibitors such as atazanavir and darunavir. Based on the limited available data, the interaction does not appear clinically relevant but special consideration has to be given when the combination is prescribed in patients predisposed to the risk of renal toxicity of tenofovir, such as those with hypertension or diabetes. The influence of individual drugs such as sofosbuvir, ledipasvir, daclatasvir or velpatasvir has been presented in the respective tables in the previous chapters.

Various trials with DAAs such as sofosbuvir, ledipasvir and daclatasvir have been conducted in HIV-HCV co-infected patients. The overall SVR rates have been around 90% in these trials. Additionally, there were no negative effects on the HIV viral suppression by ARTs resulting from reduced exposure. Drug interaction profile was found to be favorable between HIV and HCV drugs. Similar experiences have been reported with the trials of recently approved drugs grazoprevir-elbasvir FDC (C-EDGE trial), and velpatasvir-sofosbuvir FDC (ASTRAL-5 trial).

Overview of DDIs between ARVs and DAAs

DDIs between ARVs and DAAs require special attention and are summarized in Table 2.

Table 2: DDIs between ARVs and DAAs

	3D	2D	Sofosbuvir	Sofosbuvir-Ledipasvir	Daclatasvir	Simeprevir
NRTIs						
Emtricitabine						
Tenofovir						
Lamivudine						
Abacavir						
NNRTIs						
Efavirenz						
Rilpivirine						
Etravirine						
Protease Inhibitors						
Atazanavir/r						
Darunavir/r						
Lopinavir/r						
Entry/IntegraseInhibitors						
Raltegravir						
Dolutegravir						
Elvitegravir/cobicistat						
Maraviroc						

Red: Co-administration is not recommended or contraindicated.
Orange: Potential interaction – close monitoring or dose adjustment required.
Green: No clinically significant interaction.

Abbreviations: 3D, paritaprevir/ritonavir, ombitasvir, dasabuvir; 2D, paritaprevir/ritonavir, ombitasvir; DAA, direct-acting antiviral; HCV, hepatitis C virus; r, ritonavir.

4. DAA INTERACTION IN POST ORGAN TRANSPLANT PATIENTS AND PATIENTS WITH IMPAIRED ORGAN FUNCTION

Post-Transplant: Immunosuppressants

Hepatitis C is one of the major causes of liver transplantation. Additionally, due to renal manifestations of the disease, treating hepatitis C is common in patients after renal transplant. Treatment of hepatitis C in post-transplant brings into considerations the drug interactions between DAAs and immunosuppressants. During the peg-interferon (IFN)era, physicians were reluctant to use IFNs in treating patients after transplant due to the apprehension of graft rejections. However, such considerations may not be relevant in today's era of DAAs. However, the risk of drug interactions remains an issue of significant relevance. Calcineurin inhibitors (tacrolimus, sirolimus, everolimus, and cyclosporin) are the frequently employed immunosuppressants post-transplant.

Simeprevir and daclatasvir only slightly increase cyclosporine or tacrolimus exposure. Sofosbuvir does not modify the exposure to either cyclosporine or tacrolimus. On the other hand, cyclosporine elevates sofosbuvir exposure to more than 4.5-fold, but the clinical effects or apparent toxicities, however, are not significantly seen. Tacrolimus only slightly increases sofosbuvir exposure and does not modify daclatasvir concentrations. Concomitant administration of sofosbuvir, ledipasvir or daclatasvir with either calcineurin inhibitors is considered safe. In combination with the 3D regimen, tacrolimus exposure is increased 57-fold, whereas cyclosporine exposure is increased approximately 6-fold, necessitating empiric dose adjustments of both calcineurin inhibitors. The drug interaction of immunosuppressive agents with simeprevir, sofosbuvir and daclatasvir are given in the table below. Limited data exist for concomitant use of sirolimus or everolimus with new DAAs. It is recommended to avoid these drugs with all DAAs if possible. However, if they have to be used, everolimus may be the preferred agent, despite being labeled as contraindicated, because it has a shorter half-life than sirolimus and dose adjustments may be more readily noticed on laboratory evaluation.

Table 1: Effect of Immunosuppressive Agents on DAAs

Medication	Daclatasvir		Ledipasvir		Sofosbuvir		Simeprevir	
	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
Cyclosporine	↑4%	↑40%	ND	ND	↑154%	↑353%	↑374%*	↑481%*
Tacrolimus	↑7%	↑5%	ND	ND	↓3%	↓13%	↑79%	↑85%

*Denotes a potentially dangerous combination of medications and that the concomitant administration of the agent(s) should be avoided.
Abbreviations: AUC, area under the concentration curve; C_{max}, maximal concentration; ND, no data; ↑ increase; ↓, decrease.

Drug Interactions in Patients with Impaired Liver and Kidney Functions

Individuals with significant liver impairment may present reduced elimination of drugs that are metabolized by the hepatic route. Sofosbuvir exposure increases 130% in this population, as sofosbuvir is a liver-metabolized prodrug. Daclatasvir exposure reduces in patients with hepatic insufficiency, mostly owing to hypoalbuminemia. However, the free concentration remains unchanged and, therefore, no dose adjustment is recommended.

Sofosbuvir is found to be safe and effective in patients with decompensated cirrhosis. However, if ribavirin is administered, the dose should be appropriately titrated based on patient tolerability. In patients with advanced cirrhosis/or decompensated cirrhosis, hepatotoxicity produced by ritonavir is of a particular concern with the Abbvie 3D regimen and low response rates have also been observed in this population. In patients with advanced cirrhosis/or decompensated cirrhosis, the hepatotoxicity produced by ritonavir is of particular concern with the Abbvie 3D regimen. It is contraindicated in patients with moderate and severe hepatic impairment. In case of grazoprevir-elbasvir FDC, it is contraindicated in patients with moderate hepatic impairment (Child-Pugh B) due to the lack of clinical safety and efficacy experience in HCV-infected Child-Pugh B patients, and in patients with severe hepatic impairment (Child-Pugh C) due to a 12-fold increase in grazoprevir exposure in non-HCV-infected Child-Pugh C.

Drugs and their metabolites that are eliminated renally may be subject to accumulation owing to impaired kidney function. Since sofosbuvir-based therapy currently forms the backbone, special precaution needs to be taken in patients with severe renal impairment, since the major metabolite of sofosbuvir, GS-331007, excretes through the renal route. However, a few studies have reported full-dose sofosbuvir to be safe in these patients and no significant adverse effects attributed to sofosbuvir have been reported. Even so, data is limited and judicious monitoring is warranted in these patients. The pharmacokinetics of sofosbuvir in renally impaired patients is presented in Table 2.

Table 2: Comparative Pharmacokinetics of Sofosbuvir and GS-331007 in Healthy and Renally Impaired Patients

$AUC_{0-\infty}$ (as percentage in comparison with healthy volunteers with normal renal function)	Sofosbuvir	GS-331007
Mild	61% higher	55% higher
Moderate	107% higher	88% higher
Severe	171% higher	451% higher
End-Stage Renal Disease (in patients on hemodialysis)		
Sofosbuvir administered 1 h before hemodialysis	28% higher	1,280% higher
Sofosbuvir administered 1 h after hemodialysis	60% higher	2,070% higher

Dosing recommendations: No dose adjustment of sofosbuvir is required for patients with mild or moderate renal impairment. The safety and efficacy of sofosbuvir have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or ESRD requiring hemodialysis. No dose recommendation can be given for patients with severe renal impairment or ESRD. Refer also to RBV and peg-IFN alfa prescribing information for patients with CrCl <50 mL/min.

Clinically significant toxicities due to increased drug exposure are mainly seen in patients with moderate (31–60 mL/min creatinine clearance) to severe (<30 mL/min creatinine clearance), end-stage renal disease and rarely in patient with mild kidney insufficiency (61–90 mL/min creatinine clearance). Accordingly, caution has to be exercised and/or dose reduction is recommended for sofosbuvir, ribavirin, paritaprevir, and dasabuvir. In contrast, ledipasvir, daclatasvir and velpatasvir are eliminated in the feces, and may not pose a problem in patients with impaired renal function. However, since these regimens are to be administered with sofosbuvir, the contraindications for sofosbuvir apply to these combination regimens as well.

Other Relevant Interactions

Summarized below are some recommendations to avoid known DDIs of HCV DAAs (available in India) with commonly used medications:

- ***Acid Suppressants:*** Co-administration with proton-pump inhibitors is not recommended, and avoiding anti-acids within 4 hours of ledipasvir administration is important as the solubility of ledipasvir decreases as pH increases. The same pH dependence is expected for the next-generation NS5A inhibitor, velpatasvir. Other DAAs for HCV, including NS5A, NS5B and protease inhibitors, are not dependent upon the pH for drug absorption. It is recommended to not give doses greater than 20 mg by mouth twice daily. Also, separating administration of ledipasvir and famotidine by 4 hours and giving ledipasvir with orange or tomato juice to increase the likelihood of absorption. and exposure to the anti-HCV agents through induction of the CYP3A system

- ***Anti-epileptics:*** Co-administration of phenytoin, carbamazepine, or phenobarbital with any of the DAAs is expected to decrease the concentrations. The concomitant use of any of these inducing agents is not recommended. However, if HCV treatment with any of the DAAs is necessary, it is recommended to use levetiracetam in consultation with a neurologist. For any patient switched to levetiracetam, all other anti-seizure medications should be discontinued at least 1 week prior to starting a DAA.

- ***Lipid-lowering Agents:*** Concurrent administration with lovastatin and simvastatin is discouraged by the manufacturer; however, if monitoring for myopathy, the concurrent administration of any DAA with 3-hydroxy-3-methylglutaryl- coenzyme A reductase inhibitors is likely safe. Rosuvastatin concentrations may also be increased if given with sofosbuvir-ledipasvir, and its co-administration is discouraged. In case of patient concern or if statin therapy can be temporarily withheld while undergoing HCV treatment, the statin can be resumed upon completing therapy.

- ***Cardiovascular Agents:*** Clinical monitoring for hypotension and bradycardia are warranted, depending upon the calcium channel blocker used. Postmarketing data show that sofosbuvir and ledipasvir or sofosbuvir in combination with another DAA when co-administered with amiodarone can lead to symptomatic bradycardia or a fatal cardiac arrest. In reported cases, bradycardia has occurred within hours and up to 2 weeks after starting the sofosbuvir-containing regimen. It is recommended that amiodarone be stopped for a minimum of 4–8 weeks prior to initiating sofosbuvir and in the absence of an alternative to amiodarone, cardiac monitoring in an inpatient setting for at least 48 hours is needed.

- ***Azole Antifungal Agents:*** Daclatasvir concentrations are expected to increase when given with azole antifungals, but the magnitude of the interaction and clinical significance are not yet known.

- It is recommended to stop herbals and dietary supplements at least 1 week prior to starting HCV therapy.

CONCLUSION

The advent of several all-oral DAA-based therapies for treating HCV has brought about safe and effective regimens across the HCV population. Although treatment has become simpler, other considerations such as drug interactions have become more relevant. Critical interactions exist between the DAAs and many commonly prescribed over-the-counter medications, as well as with HIV drugs and immunosuppressants. The most common route for influencing drug metabolism is by inducing or inhibiting CYP450 or P-gp, which can lead to attainment of subtherapeutic or toxic concentrations of drugs. Thus, DAAs can both cause as well as can be affected by drug interactions. Hence, detailed and thorough monitoring of potential is needed prior to, during, and after DAA therapy. However, most of the drug interaction data is based on hypothesis and literature reviews. Further research in DAAs may help provide valuable data about the clinical significance of these drug interactions.

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NOTES