Archives of Pharmaceutical Sciences Ain Shams University 2022; Vol. 6(2): 274-291

OPEN ACCESS

Pharmacology and Toxicology

Review Article

Direct Acting Antiviral Drugs: Pharmacokinetics and Drug-Drug Interactions

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Abstract

Hepatitis C (HCV) is a widespread health issue, which can lead to hepatic cirrhosis, liver failure, and liver cancer. Nearly 2% of the world's population or > 185 million people are chronically infected with HCV; the management of HCV and the rate of sustained virological response (SVR) were significantly assisted by direct-acting antiviral medications. Since 2014, the FDA has approved using the most potent direct-acting antiviral drug (DAA) combinations. The majority of DAAs can affect cytochrome P450 (CYP) enzymes and are extensively processed by liver enzymes. Additionally, these DAAs are both substrates and drug transporters' inhibitors, making them a potential target for drug-drug interactions (DDIs). As a result, understanding and managing DDIs with DAAs must be regarded as a crucial aspect of the treatment of HCV. Additionally, patients taking numerous medications or having various co-morbidities must be made aware of the potential consequences of DDIs, such as elevated toxicity or an absence of pharmacological efficacy, in current HCV treatments.

Keywords: *DAAs; Pharmacokinetics; pharmacodynamic; P-glycoprotein; CYP3A4; Drug interactions.*

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Citation | Barakat MH, Wahdan SA, El-Demerdash E, 2022. Direct Acting Antiviral Drugs: Pharmacokinetics and Drug-Drug Interactions. Arch Pharm Sci ASU 6(2): 274-291

DOI: 10.21608/aps.2023.189971.1106

Print ISSN: 2356-8380. **Online ISSN**: 2356-8399.

Received 27 January 2023. **Accepted** 28 February 2023.

Published by: Ain Shams University, Faculty of Pharmacy

1. Introduction

In 1989, occurred the detection of the hepatitis C virus (HCV), an enclosed virus with a single-stranded viral RNA **[1]**. Egypt has the highest global HCV prevalence (14.7%), and type 4 is the most common genotype there, with genotype 1 coming in second with 26% of the cases **[1]**. Hepatocellular carcinoma, liver cirrhosis, and liver failure can all be caused by the chronic infection of HCV, which is also linked to a significant risk of morbidity and mortality **[2]**. By diagnosing HCV early and receiving effective therapeutic care, these complications can be prevented **[2]**. The endpoint of treatment: sustained virological response (SVR), known as having no detectable serum HCV RNA twenty-four weeks following the start of treatment, is the focus of therapy **[3]**. The standard-of-care (SOC) for treating HCV was previously dependent on the administration of ribavirin (RBV) for twenty-four or forty-eight weeks along with pegylated interferon (peg-IFN) **[4]**. Treatment with peg-IFN + RBV, however, has been demonstrated to raise the rates of SVR and to be effective for various patient populations. However, this regimen has several drawbacks, including non-response, relapse, and

a lengthy course of therapy **[5]**. Direct-acting antiviral drugs (DAAs), which selectively target important sections of the HCV genome, have been developed to prevent these severe adverse events, increase acceptability with higher SVR, and shorten the length of treatment **[4]**.

2. Direct-acting antiviral agents (DAAs)

2.1. Background

With the development of DAAs, there has been a change in how hepatitis C is treated in recent years. DAAs prevent the spread of viruses by directly impairing 1 or many phases of the HCV's life cycle **[6]**. Opposite to the non-selective action of the interferon-based regimen, these new drugs target specific non-structural proteins of the HCV, interrupting viral replication, and preventing infection **[6]**. Non-structural proteins including NS3 serine protease, NS5b RNA-dependent RNA polymerase (RdRp), and NS5a are among the proteins that DAAs target**.** BILN 2061 (ciluprevir), an NS3/4A protease inhibitor that was initially made public in 2003, significantly reduced viral replication in humans while having no appreciable effects on the human liver **[7]**. By using its anti-NS3 protease activity, it can enter target cells and prevent viral RNA replication; however, clinical testing revealed certain limitations as a cardiotoxic effect **[7]**. In 2011, telaprevir (TPV) and boceprevir (BOC), the first protease inhibitors to get FDA approval, were made available as therapeutic options for severe genotype 1 HCV infection **[8]**. The treatment takes 24 to 28 weeks; monotherapy was linked to the fast development of viral resistance to the administered drugs, leading to a lack of clinical efficacy, long duration of treatment, skin rash, and anemia **[4, 8]**. Second-generation protease inhibitors, simeprevir, and paritaprevir offered several advantages over the first generation; they are distinguished by having a potentially high efficacy, minimal barriers to the development of resistance, and more manageable side-effect profiles **[5]**. In 2013, simeprevir was approved to be taken in conjunction with peg-IFN/tor to increase SVR by about 80% and reduce treatment time to twenty-four weeks **[9]**. The nonstructural (NS) protein NS5B, an RNA-dependent RNA polymerase, is a potential option for the creation of Hepatitis c therapies as nucleoside polymerase inhibitors **[10]**. The two categories of NS5B polymerase inhibitors are nucleotide inhibitors (NPIs) and non-nucleotide inhibitors (NNPIs) **[5]**. NIs, such as Sofosbuvir (SOF), directly affect the active site of the polymerase protein, bind to it, and disrupt the viral lifecycle by causing a chain termination event and stopping transcription of the viral polyprotein. As a result, they are very efficient and create a strong barrier to viral resistance **[11]**. In contrast, NNPIs target the allosteric sites on NS5B causing a change in protein conformation. As a result, NNIs as setrobuvir, Tegobuvir, and dasabuvir compared to NIs, are structurally heterogenous, have a small resistance barrier, and have moderate to medium antiviral efficacy **[12, 13]** On December 6, 2013, the US Food and Drug Administration authorized SOF as the first direct antiviral drug in its class for the management of severe hepatitis c infection when used in conjunction with a variety of other drugs, such as NS5A inhibitors: Ledipasvir (LPV), with or without peginterferon-RBV **[14, 15]**. Combination therapy aims to increase the probability of SVR in a variety of HCV patients **[15]**. NS5A inhibitors are considered to have potent antiviral activity and a low barrier to resistance. Since that time, the NS5A inhibitors daclatasvir (DCV), LDV, and ombitasvir have all been authorized **[16]**. DCV was approved to be used in conjunction with additional DAAs in the European Union (EU) in 2014 and the United States in 2015**[4]**.

2.2. Mechanism of Action of DAAs

Three structural proteins can be found in the

N-terminus of the HCV genome, whereas 7 NS proteins can be found in the C-terminus. HCV replication depends on the 3 non-structural proteins NS3/4A, NS5A, and NS5B, which are also potential targets for suppression **[17]**. Virus replication requires the serine protease NS3/4A. The NS3/4A inhibitors TPV, BOC, simeprevir, paritaprevir, and grazoprevir have good efficiency with minimal barriers to resistance **[17]**. HCV replication needs the RNA polymerase NS5B, which is dependent on HCV RNA. Because all HCV Genotypes (GTs) share a large portion of the same NS5B catalytic domain, Nucleotide inhibitors, such as SOF, are known for their great potency and minimal barriers to resistance and have a pan-genotypic action **[18]**. Non-nucleoside NS5B polymerase inhibitors dasabuvir and beclabuvir (BCV, formerly BMS-791325) aim NS5B's allosteric regions and have a limited field for resistance, modest potency, and minimal effect across all Hepatitis c genotypes **[18]**. NS5A is a 447 amino acid zinc-binding phosphoprotein that is essential but has not yet been identified role in the process of HCV replication. NS5A inhibitors like DCV, LDV, and ombitasvir are thought to have potent antiviral effects despite having what seems to be a low barrier to resistance **[19]**.

3. Pharmacokinetics of DAAs

For the treatment of chronic HCV infection, it is necessary to use drugs with a low frequency of dosing, few side effects, and minimum drug-drug interactions, and that was the objective of the development of the most potent HCV polymerase inhibitors known (SOF) **[20]**. It is crucial to understand that each formulation (such as Sovaldi®, Harvoni®, Epclusa®, and Vosevi®) has its unique pharmacokinetic profile when evaluating the SOF pharmacokinetic data**.** DCV is combined with SOF (Sovaldi®), LDV is combined with SOF (Harvoni®), velpatasvir (VEL) is combined with SOF (Epclusa®), velpatasvir (VEL)/voxilaprevir (VOX) are combined with SOF (Vosevi®) **[21]**.

3.1. Sofosbuvir as monotherapy

3.1.1. Absorption

Because SOF absorbs quickly, the C-max is achieved after half -two hours. GS-331007 is the main SOF circulating metabolite. After administration, GS-331007's C-max was 2–4 hours later **[22]**. Food increased SOF absorption by 1.8 times, although C-max did not change in clinically significant ways. Food did not affect GS-331007 absorption. GS-331007 and SOF both had near-dose-proportional AUCs **[21, 23]**. SOF is a substrate for the breast cancer resistance protein and P-gp transporters, as opposed to GS-331007 **[22]**.

3.1.2. Distribution

Most SOF (61–65 %) is bound to plasma proteins, whereas concentrations of 1 μg/mL to 20 μg/mL, did not affect SOF binding. A limited amount of its metabolite is linked to plasma proteins **[23]**.

3.1.3. Metabolism

The physiologically active nucleoside analog triphosphate GS-461203 is formed from SOF in the liver first **[23]**. Then, dephosphorization takes place, producing the main inactive metabolite, GS-331007. Over 90% of the systemic exposure is to GS-331007 and only 4% of systemic exposure is from SOF **[24]**.

3.1.4. Excretion

Only fourteen percent of a radioactive dose was returned in feces, which accounts for most of the excretion (80%) **[23]**. In addition, 3.5 percent of the total dose only was recovered as a parent substance, while the majority was GS-331007 (78%). The median t½ was 0.4 hours for SOF and 27 h for GS-331007**[24]**.

3.2. Sofosbuvir (SOF)/Ledipasvir (LDV)

Recent research has shown that DAA combination therapy is highly potent and has the potential to produce SVR in 85–95 percent of patients **[25]**. This combination medicine was authorized for the management of genotype 1 in October 2014. The SOF and LDV combination, for treatment genotypes 1 to 6, was authorized by FDA in April 2017 **[26]**.

3.2.1. Absorption

LDV attains its C-max after 4 to 4.5 hours. The SOF t-max occurred about one hour after drug consumption. GS-331007 had a t-max of 4 h. Moderate calorie and high-fat meals have no impact on LDV and GS-331007absorption **[21]**. However, when taken with meals, SOF's AUC from zero to infinity increased by almost 2 times, but its C-max was unaffected **[27]**. Additionally, as the pH rises, LDV's solubility declines. Finally, LDV also as SOF is a substrate for both P-gp and BCRP **[28]**.

3.2.2. Distribution

Plasma protein is bound to LDV (61-65%). LDV inhibits OATP1B1/2 and the bile salt export pump **[27]**.

3.2.3. Metabolism

Since the parent drug accounts for more than 98 percent of the total systemic exposure, it is predicted that LDV's metabolism will be minimal. **[28]**.

3.2.4. Excretion

87 percent of the parent medication was found in urine and feces after receiving a radioactive dosage of LDV, with feces accounting for 86 percent of the total **[27]**.

3.3. SOF/Velpatasvir (VEL)/Voxilaprevir (VOX)

A fixed-dose combination (FDC) tablet involving SOF, velpatasvir (the HCV NS5A inhibitor), and voxilaprevir (the novel HCV NS3/4A protease inhibitor) is the first triple-DAA to be accepted for use in the USA and European Union to treat adult patients with persistent HCV genotype 1-6 infection, including those who have previously undergone DAA therapy **[29, 30]**.

3.3.1. Absorption

After being administered, VOX, VEL, and GS-331007 achieve C-max after around four hours, and SOF after two hours **[31]**. SOF C-max rose from 9 to 76% and AUC increased from 64 to 114%, **[32]**. The AUC and C-max for VEL were raised, with increases of 40 to 166% and 37 to 187%, respectively **[21]**. When given food, the VOX AUC and C-max both rose, from 112 to 435% and 147 to 680%, respectively. In light of this, this combination should be taken with a meal **[21]**.

3.3.2. Distribution

Both VEL and VOX have significant plasma protein binding levels (> 99%) **[29]**. This was concentration independent for SOF and VEL in the concentration ranges of 1-20 and 0.09-1.8 g/mL, respectively. P-gp and BCRP are substrates for VEL and VOX [**29, 21]**.

3.3.3. Metabolism

The enzymes CYP2B6, CYP2C8, and CYP3A4 metabolized VEL. But after a single dose, it was discovered that > 98 percent of the original medication was still in the blood **[21, 31]**. BCRP, OATP1B1/3, and P-gp are all inhibited by both VOX and VEL **[21, 31]**. Although VOX is a CYP3A4 substrate, over 91 percent of the drug in circulation was the original compound after a single administration **[32]**.

3.3.4. Excretion

The majority of VEL is cleared by the liver since > 94% of it was found in stools and only

0.4% in urine. Feces were found to contain 77% of the parent drug, VEL **[21, 31]**. The t½ of VEL is nearly 17 h. The SOF's t½ was 0.5 h, while GS-331007's was 29 h **[32, 31]**. The primary route of elimination of VOX is a biliary system. Nearly 40% of the original medication and 22% percent of the metabolite des-[methylcyclopropylsulfonamide]-voxilaprevir, together with 3 additional intermediates (less than 10%), were detected after a single dose **[31, 32]**.

3.4. Sofosbuvir (SOF)/ Daclatasvir (DCV)

Of all chronic Hepatitis C cases worldwide, 12%–15% (15–18 million) are associated with severe hepatitis C GT-4 infections. Its earlier geographic range was just Egypt, where GT- four and subtype 4a in particular dominate the severe hepatitis C infection **[33]**. Adults with chronic HCV GT- four infections should use a SOF and DCV combination, according to EASL **[33]**.

3.4.1. Absorption

DCV is quickly absorbed and takes 1-2 h to reach its t-max. Exposure was the same after a dose of 60 mg in both HCV-infected patients and healthy subjects **[34]**. Following a high-fat meal, the C-max and AUC both dropped by twenty-eight percent and twenty -three percent, respectively, indicating decreased absorption **[21]**. Eating a limited-fat meal does not appear to affect absorption. Data from in vitro tests have shown that DCV has an absolute bioavailability of 67% and is P-gp a substrate. DCV is combined with SOF, and C-max was determined after 2.5 h, indicating that SOF is rapidly absorbed **[21]**.

3.4.2. Distribution

DCV was closely bound to plasma proteins (nearly 98 percent of the total) **[34]**. The apparent volume of distribution (Vd/L) is 47.1 L. DCV is delivered into hepatocytes both passively and actively **[35]**.

3.4.3. Metabolism

A significant number of metabolites, mostly byproducts of oxidation, were produced during the biotransformation of DCV, however, only 5% of the parent drug and 97% of the circulating drug are metabolites, in plasma. DCV is a substrate of CYP3A4 **[36]**.

3.4.4. Elimination

DCV is predominantly removed through the liver, as 88% of a radioactive test dosage, of which 53% was the parent substance, was recovered in the stool **[35]**. Urinary excretion of the parent medication was just 6.6%. $T_{1/2}$ ranges between 12 and 15 hours, while the clearance is 4.24 L/h. **[36]**.

4. Efficacy and Toxicity

4.1. SOF/DCV

SOF/DCV combination therapy is authorized to cure patients with HCV 1 -6 genotypes **[37]**. The SOF/DCV combination was most frequently associated with the side effects of weariness, headaches, and GIT disturbance as nausea and vomiting **[38]**. Combined therapy with RBV caused anemia and leukopenia in several studies. Only 7% of patients continued SOF/DCV therapy after experiencing an adverse event, except in cases where the patient's mortality rate was < twelve months due to liver fibrosis or Hepatitis relapse after hepatic transplantation, where 10% and 18% of patients, respectively, stopped treatment because of an adverse event (AE) **[39]**.

4.2. SOF/LDV

Treatment with SOF/LDV at a dose of 90 mg/400 mg each day is efficient. people with HCV genotypes 1, 4, 5, and 6 can be administered the treatment (12 weeks) **[40]**. Fatigue, headaches, and nausea were the mild side effects that were noted in investigations using SOF/LDV **[41]**. In numerous researches, less than 10% of the study population reported

any negative effects. In all investigations, fewer than 5% of patients stopped receiving treatment because of an AE **[42]**.

4.3. SOF/VEL/VOX

This pan-genotypic combination (SOF/ VEL/VOX) is approved to treat people with liver cirrhosis or without, and patients who did not respond to combination therapy of peg-IFN/RBV and DAAs [**43]**. This combination regimen is also very effective and has a low toxicity profile. Headache, diarrhea, exhaustion, fatigue, vomiting, and constipation were AEs that were most often reported across all of the trials. In addition, all trials had modest (3%) discontinuation rates due to AEs **[44]**. SOF/ VEL/VOX mustn't be utilized for individuals with CP-B/C cirrhosis since VOX is a PI and exposure could rise **[45]**.

5. The Possible Drug-Drug Interactions of Directly acting antiviral drugs (DAAs)

5.1. DAAs/ CNS Drugs

Due to the high incidence of psychiatric conditions, in HCV-infected persons, DAAs and psychotropic drugs are frequently given together **[46]**. Most DAAs are largely degraded by liver enzymes and may have an impact on cytochrome P450 enzymes. Additionally, due to their dual roles as drug transporter substrates and inhibitors, these DAAs can either be the victims or the cause of drug-drug interactions (DDI) **[46]**.

5.1.1. Protease Inhibitors

One of the most effective inhibitors of CYP3A4 is BOC. Due to the greatly raised midazolam AUC and C-max, taking midazolam and BOC together is not recommended **[47]**. This significant rise was not observed with other DAAs, indicating significant CYP3A4 suppression activity of BOC. On the other hand, when escitalopram is given along with BOC, there isn't a need to change the dose **[47]**. Additionally, BOC is a P-gp inhibitor. Although this suppression theoretically may affect P-gp substrates, BOC only moderately inhibits P-gp, therefore it doesn't seem to have much of a clinical impact **[48]**. Additionally, BOC concentration in plasma did not change in response to St. John's wort, showing the safety of this combination **[48]**. Finally, clinicians should use caution when administering BOC along with medications that may cause the QT interval to lengthen and medications that are metabolized by CYP3A4. Psychoactive drugs can be taken with simeprevir without worry **[46]**. Simeprevir inhibits intestinal CYP3A4, hence only interactions with drugs taken by oral have clinical significance. As a result, simeprevir and midazolam I.V. can be used without risk, however using it orally requires caution because the AUC and max of midazolam are elevated by 45 and 31 percent, respectively **[49]**. When used with simeprevir, escitalopram can be administered without risk. OATP1B1 and P-gp are inhibited by simeprevir. In comparison to BOC, simeprevir has a stronger impact on P-gp transport activity. Simeprevir's P-gp inhibition may consequently cause a slight increase in the concentration of P-gp substrates such as risperidone and nortriptyline in the brain. Even yet, it appears that the clinical importance is only limited **[49]**. St John's wort may result in a reduction in the concentration of simeprevir since it is a CYP3A4 inducer and simeprevir is metabolized by CYP3A4. However, this modification might not have clinical significance **[50]**.

5.1.2. NS5A Inhibitors

When DCV was evaluated in combination with midazolam, no dose modifications were necessary because it had a minor impact on the activity of CYP3A4 and other CYP enzymes **[46, 51]**. According to this knowledge, it is acceptable to combine DCV with the majority of diazepam,

antidepressants, and antipsychotics **[46, 51]** Because CYP3A4 is involved in the degradation of DCV, CYP3A4 inducers, and inhibitors have the potential to influence DCV plasma levels, it isn't advised to provide St. John's wort along with DCV **[46, 51]**. P-gp and BCRP are both inhibited by LDV, which may also interact with their substrates (e.g., risperidone, and nortriptyline). LDV and St. John's wort must not be taken at the same time **[46, 52]**.

5.1.3. NS5B Polymerase Inhibitor

Because SOF does not affect drug transporters or CYP enzymes, it has no impact on the concentrations of psychotropic drugs in the blood **[46]**. SOF interacts with inducers and inhibitors of P-gp since SOF is a P-gp substrate **[53]**. St. John's wort and other P-gp inducers may lower both plasma levels and pharmacological effects of SOF **[53]**. Therefore, giving the two medications at the same time is not advised. Trazodone is another potential P-gp inducer and may have an impact on SOF plasma levels **[54]**. Drug-Drug interaction between DAAs and CNS Drugs was summarized in **Table 1**.

Table 1. Summary of Drug interactions between DAAs and CNS drugs

DAAs	CNS Drug	Drug-Drug Interaction Results
BOC	Midazolam	Raised midazolam AUC and C-max
DCV	St. John's wort	CYP3A4 inducers have the potential to influence DCV plasma levels
SOF	St. John's wort	Decreased both plasma levels and pharmacological effects of SOF
SOF	Trazodone	Decreased SOF plasma level

5.2. DAAs / Anticonvulsant Drugs

Carbamazepine, phenytoin, and phenobarbital are examples of first-generation anticonvulsant medications that strongly induce both p-gp and CYP3A4. These drugs greatly lessen DAA exposure after coadministration, which may lessen their virological effectiveness **[55]**. Consequently, with all HCV treatments, these drugs are either not recommended or inappropriate **[55]**. If no other antiepileptic drug is available, SOF with a higher dose of DCV appears to be the optimum anti-HCV therapy **[56]**. Using oxycodone, tramadol, and fentanyl along with BOC or telaprevir may necessitate a dose reduction because CYP3A is primarily involved in their metabolism. telaprevir, BOC, faldaprevir, simeprevir, SOF, and DCV minimize the risk of interactions with other opioids **[57]** Drugs that affect CYP enzymes can affect methadone and buprenorphine's pharmacokinetics and pharmacodynamics even if these medications don't inhibit or stimulate CYP enzymes **[58]**. Telaprevir pushes methadone out from methadone's plasma binding protein sites, reducing total drug concentrations while leaving drug concentrations in the free state unaffected. Therefore, the addition of telaprevir probably does not require a change in methadone dosage **[58]**. R -methadone's AUC is decreased by BOC by 15%, whereas buprenorphine's AUC is increased by 19%. Since the changes are minor, adjusting the dose of an opioid replacement would be improbable. Both simeprevir and SOF do not affect the pharmacokinetics of methadone **[58].** Drug-Drug interaction between DAAs and Anticonvulsant Drugs was summarized in **Table 2**.

5.3. DAAs / Human Immunodeficiency Virus (HIV) and Antimicrobial Drugs

The possibility of drug interactions is important to take into consideration in patients with HIV and HCV co-infection. Due to the activation or suppression of CYP3A and p-gp, antiretroviral medications have a significant danger of DDIs **[57]**. NNRTIs are largely CYP3A enzyme inducers **[21]**. VEL, BOC, and telaprevir AUC were reduced almost by 50% after co-administration with efavirenz (the much more potent inducer of the class). The preferred NNRTIs for coadministration with SOF/VEL and SOF/VEL/VOX are doravirine and rilpivirine **[59, 60]**. Due to decreasing DCV exposure, when used along with efavirenz, the daily dose of DCV must be elevated from 60 mg to 90 mg daily **[61]**. On the other hand, PIs are CYP3A, OATP, and P-gp inhibitors. Therefore, the recommended DCV dose must be lowered to 30 mg when CYP3A4 inhibitors, such as atazanavir/ritonavir, are used concurrently because decreased CYP3A4 metabolism increases DCV plasma levels **[62]**. Since there were no clinically significant variations in the pharmacokinetics of SOF/VEL, it can be taken with any antiretroviral therapy, even those that include PI supplements (such as atazanavir, darunavir, and lopinavir) **[63]**. Darunavir/ritonavir and atazanavir/ritonavir both with SOF /VEL/VOX combination caused a 2.4- and 4.3-fold rise, respectively in the VOX AUC as a consequence of inhibiting CYP3A, P-gp, and OATP1B and is not advised **[21]**. Because SOF/LDV inhibits P-gp, it enhances the exposure to tenofovir. The integrase inhibitors raltegravir, dolutegravir, and bictegravir can be safely taken with DAAs Due to their favorable interaction profiles **[64]**. Ketoconazole and telaprevir both are CYP3A inhibitor**.** It has been demonstrated that levels of both telaprevir and Ketoconazole were increased by 62% and 46–125%, respectively when taken together **[65]**. to prevent the development of toxicity; it is advised that 200 mg/day of ketoconazole is the maximum recommended dosage while the telaprevir dosage can be administered as normally. Itraconazole has also been added to this recommendation **[65]**. The effects of BOC and ketoconazole are comparable. Therefore, the product label for BOC similarly lists maximum daily doses of 200 mg for itraconazole and ketoconazole **[66]**. Macrolide clarithromycin can be co-administration safely without dose adjustments with both BOC and telaprevir **[66]**. Since rifampin is a potent enzyme inducer and can be hard to combine with CYP substrates, as a result, DAAs (CYP substrates) are contraindicated when using this medication **[58]**. Drug-Drug interaction between DAAs and HIV Drugs was summarized in **Table 3**.

Table 2. Drug-Drug interactions between DAAs and Anticonvulsant drugs

DAAs	Anticonvulsant Drugs	Drug-Drug Interaction
DCV	Carbamazepine,Phenytoin, and Ph	Greatly decreased the virological effectiveness of DCV
BOC	Oxycodone, Tramadol, and Fentanyl	BOC decreased there effect of them by increasing their metabolism
Telaprevir	Methadone	Telaprevir reduces the total drug concentrations of methadone
BOC	Methadone	Methadone's AUC is decreased by BOC by 15%

Table 3. Drug-Drug interactions between DAAs and HIV Drugs

DAAs	HIV Drugs	Drug-Drug Interaction
VEL, BOC, and telaprevir	Efavirenz	AUC of DDAs was reduced almost by 50%
DCV	Atazanavir/Ritonavir	Increase in DCV plasma levels
Darunavir/ritonavir	SOF /VEL/VOX Combination	Increase in VOX AUC as a consequence of inhibiting CYP3A, P-gp, and OATP1B
Atazanavir/ritonavir	SOF /VEL/VOX Combination	Increase in the VOX AUC as a consequence of inhibiting CYP3A, P-gp, and OATP1B
DAAs (CYP substrates)	Rifampin	Increase in Plasma level of DAAs(CYP substrates) since rifampin is a potent enzyme inducer

5.4. DAAs /Immunosuppressive Drugs

Because HCV is the principal reason for liver fibrosis, which may necessitate hepatic transplantation, people with HCV infection frequently take immunosuppressant drugs **[21]**. Therefore, while administering both DAAs and immunosuppressive medications to these patients, potential DDIs should be taken into account **[21]**. Due to the suppression effects of BOC and telaprevir on CYP3A and P-gp and the fact that Immunosuppressive medications like tacrolimus and ciclosporin are both CYP3A and P-gp substrates, it was predicted that the immunosuppressant's plasma concentrations might be significantly raised **[67]**. The tacrolimus is a CYP3A4 substrate, and the tacrolimus AUC is elevated to 70.3-old when administered with telaprevir and this combination would be fatal if doses are not changed. Tacrolimus has a limited therapeutic window, therefore monitoring or dose adjustments may be required **[58]**. To avoid potential DDIs and since tacrolimus plasma concentration can change in individuals healing from an HCV due to altered CYP3A4 metabolism, it is possible to avoid this DDI by monitoring Tacrolimus plasma levels during therapy of HCV-infected individuals **[68]**. When cyclosporine was added to VOX, the AUC, and C-max multiplied by nineteen and nine times, respectively. As a result, SOF/VEL/VOX is not advised for patients who are taking cyclosporine. However, when no other DAA treatment choices are available, therapeutic drug monitoring of the DAA may be employed to avoid this medication interaction **[21]**. Drug-Drug interaction between DAAs and Immunosuppressive Drugs was summarized in **Table 4**.

5.5. DAAs /Cardiovascular Drugs

Patients who have HCV infections and are being treated with DAAs frequently use medications for cardiovascular risk management**.** DDIs between cardiovascular medicines (CVDs) and DAAs are crucial to understanding a result. HMG-CoA reductase inhibitors are substrates for several drug transporters, including P-gp, BCRP,

OATP1B1, and CYP enzymes **[69]**. The risk of toxicities such as myopathies is often increased when statins and DAAs are co-administered **[70]**. Digoxin has been investigated with telaprevir and BOC as a model P-gp substrate. Telaprevir is a moderate P-gp inhibitor because it caused digoxin levels to rise by 85%. With telaprevir use, patients should begin taking digoxin at a modest dose. Digoxin's AUC and C-max were both increased by BOC by 19% and 18%, respectively **[71]**. These data suggest that BOC may be a minor P-gp inhibitor. Some anti-arrhythmic are CYP3A substrates and have a narrow therapeutic window (e.g., amiodarone and bepridil). With the potent CYP3A inhibitor as telaprevir, they are contraindicated, and with the mild CYP3A inhibitor as BOC, caution is advised **[21]**. Events of severe bradycardia happened when amiodarone and SOF were used together. Since all new oral anticoagulants, including apixaban and rivaroxaban, are substrates for P-gp and BCRP, there may be raised incidence of harmful effects when these medications are taken with DAAs (SOF/VEL/VOX) **[72]**. This may also include bleeding as a result; it is advised to either avoid using these medications with DAAs or to use them carefully **[72]**. β-Blocking Agents as carvedilol is a substrate of CYP2C19, CYP2D6, and P-gp. A DDI is therefore predicted with all DAAs, except SOF alone. SOF is a P-gp substrate and inhibits P-gp, however, it is quickly broken down, and its main metabolite, GS-331007, is not a P-gp substrate **[69]**. Therefore, we anticipate that the P-gp inhibition caused by carvedilol will not affect the SOF and its derivatives' toxicity profile. However, when taken with carvedilol, the level of DCV, simeprevir, and LDV in plasma may increase. This necessitates monitoring DAA toxicity, particularly for protease inhibitors, as skin responses, for example, may happen **[69]**. Verapamil, a calcium antagonist, Verapamil inhibits P-gp, making it a DDI with P-gp substrates that are approximately exclusively DAAs. When taking verapamil and DAAs together, it is advisable to keep an eye out for any negative effects **[58]**. The majority of DAAs have broad therapeutic uses and good safety profiles, so it should be underlined that interaction likely has no therapeutic significance **[58]**. Furthermore, calcium channel blockers have DDIs with DAAs that inhibit CYP3A4 since they are CYP3A4 substrates. Therefore, it is suggested that those using DAAs and calcium channel blockers also have their blood pressure and heart rate measured **[69]**. Drug-Drug interaction between DAAs and CVS Drugs was summarized in **Table 5**.

Table 4. Drug-Drug interactions between DAAs and Immunosuppressive Drugs

DAAs	Immunosuppressive Drugs	Drug-Drug Interaction
Telaprevir	Tacrolimus	Increase in tacrolimus AUC
SOF /VEL/VOX	Cyclosporine	AUC and C-max of VOX were multiplied
BOC	Tacrolimus or Cyclosporine	Increase in the immunosuppressant˝s plasma concentrations might be due to the suppression effects on CYP3A and P-gp.

Table 5. Drug-Drug interactions between DAAs and CVS Drugs

DAAs	CVS Drugs	Drug-Drug Interaction
All DAAs	Statins	Increased risk of statins toxicity
SOF	Amiodarone	Events of severe bradycardia
SOF/VEL/VOX	Oral anticoagulants	Raised incidence of bleeding
LDV OR DCV	Carvedilol (B blockers)	Increased plasma levels of LDV and DCV
DAAs (CYP3A4 substrates)	Calcium channel blockers	Unexpected effects on blood pressure and heart rate

5.6. DAAs / Tuberculosis Drugs

Combination therapy can be used to treat tuberculosis (TB) disease; however, because of issues with resistance, compliance to therapy is essential. The first-line treatments for TB include ethambutol, pyrazinamide, isoniazid, rifampicin (rifampin), rifabutin, and rifapentine **[73]**. Given that rifampicin, rifabutin, and rifapentine are all potent inducers of CYP3A4, all DAA is not recommended with these drugs**.** For example, when coupled with rifampicin 600 mg once daily, SOF and VEL AUC of both dropped by seventy-two percent and eighty -two percent respectively, and the C-max by 77% and 71% respectively **[74]**. Therefore, it is not recommended for patients that take DAAs with rifampicin, rifabutin, or rifapentine **[74]**. Since the metabolic pathways are not interfering with one another, there will be no substantial clinically relevant medication interactions between that isoniazid, ethambutol, or pyrazinamide and the DAAs **[21, 74]**.

5.7. DAAs / Acid-Reducing Agents

Drugs that affect gastric pH include acid-reducing substances like proton pump inhibitors and histamine H 2 -receptor blockers. Absorption of LDV and VEL is pH-dependent. Since VEL is weakly basic, it is not soluble in water and becomes more soluble at higher pH levels **[75]**. The AUC and C-max of VEL were reduced (36 percent and 37 percent) when omeprazole (20 mg) was taken with SOF/VEL in fasting individuals. Omeprazole 20 mg once daily was administered 12 h before SOF/VEL administration, and this caused even greater reductions in VEL AUC and C-max (55% and 57%) **[74]**. AUC and C-max values were reduced by 38 percent and 48 percent when the same dose of omeprazole was given with food and 2 h before SOF/VEL **[76]**. When omeprazole 20 mg was taken 4 h after SOF/VEL was taken with meals, the highest beneficial effects were observed; the AUC and C-max only decreased by twenty-six percent% and thirty-three percent. It is recommended that SOF/VEL and H2-receptor antagonists (famotidine 40 mg twice daily) be given separately or at least twelve hours **[21]**. LDV solubility is also pH-dependent; at pH 2.3, it is just weakly soluble, but at pH 4-7.5, it is highly insoluble. The AUC and C-max were reduced by four percent and eleven percent when SOF/LDV and omeprazole 20 mg once daily were given together. The LDV AUC and C-max fell by forty-two percent and forty-eight percent when given separated by 2 hours. If used together with SOF/LDV, it can optionally be paired with

omeprazole 20 mg once a day or famotidine 40 mg twice daily **[76]**. It's essential to remember that these suggestions depend on pharmacokinetic changes made to the DAAs rather than effectiveness **[76]**.

5.8. DAAs / Antidiabetic agents

To prevent the development of severe hypogl ycemia, in individuals with hepatic encephalopathy, the usage of antidiabetic medications should be carefully observed. One of only a few available oral diabetes medications, repaglinide, is mainly metabolized by CYP3A and may interact with the CYP3A inhibitors **[58, 77]**. However, CYP2C8 is the enzyme that metabolizes repaglinide most effectively; as a result, no reaction with DAAs via this pathway is anticipated. Repaglinide can interact with DAAs through a mechanism other than CYP since it is a substrate for OATP transporters **[58, 77]**. Several additional oral diabetes medicines are likewise metabolized by the liver, but not by the CYP3A isoenzyme. When taken with DAAs, metformin is not likely to have any negative effects **[77]**.

5.9. Foods, dietary and herbal supplements

Furanocoumarins and flavonoids, two components of grapefruit juice, have both been associated with the inhibition of drug transporters and intestinal CYP3A, respectively **[57]**. Because BOC, telaprevir, and numerous experimental DAA are substrates for CYP3A, P-gp, and organic anionic transporter polypeptides, theoretically, reactions with grapefruit juice are possible **[78]**. The bioavailability of the DAA, the intrinsic level of CYP3A4 or transporter expression in the stomach, as well as the amount and features of the grapefruit juice taken, would all have an impact on how severe interaction with the DAA would be **[79]**. It would be advised to stop ingesting grapefruit juice while taking DAA without formal interaction research. The usage of herbal products is widespread among HCV patients. According to study results published in 2012, 64% of medication interactions involving telaprevir or BOC patients involved herbal supplements **[79]**. In vitro studies have shown that Echinacea, garlic, ginseng, ginkgo biloba, silymarin, and St. John's wort can all suppress or activate the transporters and enzymes required for the metabolism or excretion of DAAs. In vivo, Echinacea and silymarin have little effect on HIV protease inhibitor exposures while Garlic and ginseng lower CYP3A substrates by 44-51% [**80]**. Use of supplements containing garlic and ginseng shouldn’t be used since reductions of a similar size could lead to exposures to BOC or telaprevir that are below therapeutic levels. St. John's wort is a strong enzyme and transporter inducer, and as a result, several DAAs medicines have failed to treat HCV patients **[80]**.

Conclusion

For the management of HCV infection, several very efficient direct-acting antiviral combinations have been accepted. The possibility of pharmacokinetic interactions is increased when the recently approved DAA regimens are taken concurrently with other medications. As a result, understanding and managing DDIs with DAAs must be regarded as a crucial aspect of the treatment of HCV. Additionally, patients taking numerous medications or having various co-morbidities must be made aware of the potential drawbacks of drug-drug interactions (for example, elevated toxicity or an absence of pharmacological efficacy) in current HCV treatments.

List of Abbreviations

AHC, Acute Hepatitis C; VEL, Velpatasvir; VOX, Voxilaprevir; RAVs, resistance-associated variations; AUC ,Area under the concentration-time curve; BAV, Bioavailability; BCRP, Breast Cancer Resistance Protein; BCV, beclabuvir;

BOC, boceprevir; C max, Peak plasma Concentration; CYP, Cytochrome P450 enzymes; DAA, Direct acting antiviral drug; DCV, Daclatasvir; DDI, Drug-Drug Interactions; EASL, European Association of the Study of the Liver; EDHS, Egyptian Demographic Health Survey; GT, Genotype; HCC, Hepatocellular Carcinoma; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; IDU, Intravenous drug use; LT, Liver transplantation; NS Proteins, Non Structural proteins; OATP, organic transporting polypeptides; OCT, organic cation transporter; PAT, parenteral anti schistose miasiscampaigns; PEG-IFN, pegylated interferon; P-gp, P-glycoprotein; PK, Pharmacokinetics; PXR , Pregnant X receptor; QD, Once daily; QOL, Quality of life; RBV, Ribavirin; SOF, sofosbuvir; SVR, Sustained Virological response; TPV, telaprevir; T1/2, Half-life; AEs , adverse event ; PI, Protease inhibitors; TB, tuberculosis; Non-nucleoside reverse transcriptase inhibitors; LDV, Ledipasvir;NPIs, the nucleotide inhibitors; NNPIs, the non-nucleotide inhibitors; RdRp, RNA dependent RNA polymerase; SOC, standard-of-care.

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing interests

No competing interests were declared by the authors

Funding statement

No funding source was received

Authors' contributions

Marina H. Barakat: collecting literature, and writing the first draft of the review.

Sara A. Wahdan, Azza Awad & Ebtehal El-Demerdash: organizing, editing, and reviewing the manuscript.

All authors read and approved the final manuscript.

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