A Structured Review of Approaches for Establishing and Evaluating Clinical Relevance of Drug Interactions in Patients with Hepatitis C Virus Genotype 1

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Abstract

Objective: Our objective was to establish and evaluate the clinical relevance of drug interactions in the treatment of patients with hepatitis C genotype 1. **Method:** We searched for articles published in English and Spanish from December 2004 to December 2014 in PubMed/MedLine. We used the following Medical Subject Headings (MESH): Hepatitis C and drug interactions OR herb-drug interactions OR food-drug interactions studies performed in humans. We conducted an additional complementary search for articles published in the same period about interactions of anti-retroviral and hepatitis C in humans using the following MESH: (Anti-retroviral agents AND Hepatitis C and drug interactions OR herb-drug interactions OR food -drug interactions). The clinical relevance of drug interactions was defined and evaluated based on the probability of occurrence and severity of interaction. **Results:** We identified 228 articles. Of these, it was possible to read the full text of 212. Of these, 62 contributed interactions which allowed us to identify 128 pairs of drug interactions, of which 120 (93.7%) were pharmacokinetic and 8 (6.3%) pharmacodynamic. Of these 128 pairs, two (1.6%) were rated Level 1: 110 (53.7%) were Level 2, 16 (7.8%) were Level 3, and 0 (0%) were Level 4. In addition, 78 pairs were identified that were grouped as interactions with evidence of absence of clinical significance. **Conclusions:** More than 90% of clinically relevant drug interactions are pharmacokinetic interactions associated with hepatic metabolism. Telaprevir has the greatest number of interactions.

Keywords

Drug Interactions, Antiretrovirals, Hepatitis C, boceprevir, telaprevir.

INTRODUCTION

The hepatitis C virus (HCV) has a minimum of six genotypes and about 100 different strains whose prevalences and responses to treatment vary geographically. Of these variants, genotype 1 is responsible for most infections in the Americas and Europe. (1) Sustained viral response (SVR), defined as the absence of any detectable HCV RNA load after 24 weeks of treatment, was used to assess the effectiveness of antiviral treatment. (2) In the past, treatment of HCV genotype was based on the combination of pegylated interferon alpha (INF) and ribavirin (RIB) which was able to reduce SVR to a range of 40% to 50%. More recently, new drugs have come into use, especially important are the protease inhibitors (PIs) such as telaprevir (TLV) and boceprevir (BOC) which achieve responses of 60% to 75% in naive patients. In addition, treatment time has been reduced from 48 weeks to a range of 24 to 28 weeks and in some cases to even 12 weeks depending on the type of polymerase or protease inhibitor used and depending on the behavior of SVR. (1)

What has happened to treatment of HCV infected patients as the result of the use of these drugs can be compared to what happened with highly active antiretroviral

therapy (HAART) for HIV patients. (1) As is known, HAART has led to a significant decrease in mortality and morbidity, but it has also been associated with the occurrence of adverse reactions, adhesion problems and drug interactions (DI).

HCV coinfections are common in HIV-infected patients, especially because of the similar modes of transmission: sexual, parenteral and vertical. (3) In addition, the existence of an HCV infection conditions the early treatment of HIV since HIV worsens and accelerates progression of hepatitis. HIV infections cause increases of two to 8 times the HCV viral load and leads to progression of the infection and the appearance of cirrhosis. (4, 5) Antiviral treatment for HCV in patients with HIV is a situation that is be common in clinical practice and which may be associated with DI related to the pharmacological treatment of the two morbidities. These interactions occur in part because of the ability of antiretrovirals to induce or inhibit hepatic metabolism and because of pharmacodynamic interactions that generate or enhance liver damage. (6) This study's objective is to deepen our understanding of how common and clinically relevant these drug interactions are in HCV patients through a structured review, based on the severity and the probability of interactions.

METHOD

A search of articles published in English and Spanish in PubMed/MedLine from December 1, 2004 until December 31, 2014 was conducted using the MESH terms: Hepatitis C and drug interactions OR herb-drug interactions OR food- drug interactions. Because of the possibility of coinfections of HCV and HIV and because in recent years some antiretroviral agents have been used for treatment of hepatitis C (e.g. ritonavir has been used to extend or enhancer some PIs), the search was supplemented with a review of articles in the same period of time about interactions of antiretroviral drugs (ARD) in humans and hepatitis C, using the following MESH terms: anti-retroviral agents AND hepatitis C and drug interactions OR herb-drug interactions OR food-drug interactions.

Inclusion criteria

Only systematic reviews, metaanalyses, multicenter studies, randomized controlled trials, quasi-experimental studies (nonrandomized), observational studies, guidelines, letters and case reports that were made in humans and in either the Spanish or English language and for which access to full text was available were selected for review. Articles about DI between medications used in the treatment of hepatitis C with other drugs were included. Some of the references used in those articles were also included in order to broaden the context or increase support for results.

Exclusion criteria

Publications of in vitro studies, animal models, experimental drugs and those which did not address interactions with drugs for the treatment of hepatitis C were excluded.

Review methods

Items included were independently selected by three researchers. They reviewed the titles and abstracts of all papers identified to determine their eligibility. The articles selected were jointly analyzed by the group which used consensus to determine whether or not an article would be included.

Measurement of results and evaluation of clinical relevance of interactions

The clinical relevance of DI was defined and evaluated using probability of occurrence and severity of interaction. (7, 8) On the basis of the type of study that documented and on whether or not the interaction had been published in indexed, peer-reviewed journals, the probability of interaction was divided into three categories: defined, probable and possible.

- **Defined**: interaction documented in metaanalyses, systematic reviews, randomized clinical trials or nonrandomized clinical trials.
- **Probable**: interaction documented in analytical studies or through description of three or more clinical cases.
- **Possible**: interactions documented by description of less than three cases or expert recommendations.

Severity of interactions was assigned to three additional categories:

- **Severe:** Interaction may cause damage or injury to the patient. The consequence of negative clinical outcome of drug therapy can cause or generate a patient's death, result in a life-threatening situation or hospitalization, lead to permanent or significant disability, cause congenital anomalies or malformations at birth, or result in other effects that, in the judgment of physicians, may compromise the integrity of the patient and require surgery to prevent death, hospitalization or congenital abnormalities.
- **Moderat**e: Interaction creates the need to track the patient. The consequence of negative clinical outcome of drug therapy can cause a change or interruption in pharmacotherapy or require the use of new drugs to treat the problem related to drugs or can prolong hospitalization.

- **Mild:** Interaction does not cause harm to the patient. The consequence of the negative result of medication does not require modification, change or suspension of pharmacotherapy or the use of new drugs to treat the problem related to drugs or prolonged hospitalization.

From the possible combinations of severity and probability of occurrence, interactions can be grouped into four categories:

- **Level 1** (very high risk): Includes combinations of *severe* and *defined*, and *severe* and *probable*. The simultaneous use of these drugs is considered to be absolutely contraindicated.
- **Level 2** (high risk): Includes combinations of *severe* and *possible*, *moderate* and *definite*, and *moderate* and *probable*. The simultaneous use of these drugs requires adjustment of the dosing regimen, and assessment of signs and symptoms of effectiveness and safety of treatment. Ideally, the evaluation should be quantitative.
- **Level 3** (medium risk): Includes combinations of *moderate* and *possible*, *mild* and *definite*, *mild* and *probable*. The simultaneous use of these drugs requires adjustment of the dosing regimen, and assessment of signs and symptoms of effectiveness and safety of treatment. Ideally, the evaluation should be quantitative.
- **Level 4** (low risk): Combination of *mild* and *possible* categories. The interaction has little clinical relevance.

In addition, a list of pairs of medications for which there is no evidence of clinically relevant interactions was developed.

Data collection form

A form for recording and tabulating data on drug interactions was designed in Excel 2010 for Windows. The form had the following structure:

- Pharmacological group of drug used concomitantly with medication for treatment of HCV
- Kind of interaction (drug-drug, drug- phytotherapeutic agent, drug-food)
- Pair of interacting agents
- Level, severity and probability of interaction
- Bibliography
- Mechanism of interaction (pharmacokinetic or pharmacodynamic)
- Details of mechanism of interaction
- Comments
- Recommendation.

RESULTS

The search terms "Hepatitis C AND drug interactions OR herb-drug interactions OR food-drug interactions" yielded 193 articles, of which the full text was available for 178. Of these, 56 reported DIs. Thirty-five articles were identified with the second set of search terms. Of these, the full text was available for 34. Six of these reported HCV treatment-related DIs. In total, 228 articles were identified. The full text was available for 212 and of these 62 articles met the inclusion criteria (Figure 1). Two articles (1.6%) were Level 1, 110 articles (85.9%) were Level 2 and 16 articles (12.5%) were level 3 (Tables 2 and 3). There were 206 DI pairs of which 128 were determined to be clinically significant (Table 1). Of these 128 pairs, 120 have pharmacokinetic interaction mechanisms. These mechanisms included enzyme inhibition in 82 pairs (64.0%), enzyme induction in 35 pairs (27.3%) and change in bioavailability in three pairs (2.4%). Eight pairs had pharmacodynamic interaction mechanisms. Seventy-eight drug pairs for which there was no evidence of clinically relevant interactions were identified. Of these pairs, thirty-six included telaprevir, thirty included boceprevir, nine included sofosbuvir, one included ribavirin and two included interferon (Table 4).

Of the 8 pairs of pharmacodynamic interactions, three were due to antagonisms between ribavirin and nucleoside analog reverse-transcriptase inhibitors (NRTIs: abacavir, didanosine and stavudine) resulting from nuclear phosphorylation and associated with increased mitochondrial toxicity and especially fatal lactic acidosis. (63.71, 86-89) One was due to synergism of the antiviral effect of acyclovir and ribavirin. (21) Four were synergisms of adverse effects between zidovudine and TLV, BOC, RIB or INF which were associated with increased probability of complications related to anemia and hematological toxicity. (63-68, 70, 71- 73,75, 86, 88 , 89)

DISCUSSION

HCV is a chronic condition that can be associated with co-infections with HIV and other diseases. Coinfections may lead to therapeutic need to jointly use ARD drugs for HCV and other comorbidities, a situation that increases the probability of clinically relevant drug interactions. This structured review of interactions specific to treatment of HCV was complemented by a search of interactions between antiretrovirals and drugs for treating HCV. The review identified a total of 128 pairs of clinically relevant drug interactions: two were Level 1 (1.6 %); 110 were Level 2 (85.9%); sixteen were Level 3 (12.5%) and there were no Level 4 interactions (0.0%). The assessment of clinical relevance was based on a model proposed by the authors based on probability of occurrence and severity of interaction. (7) This method is one of the strengths of this study when it is compared to other similar studies. (1) In addition, 78 other pairs of drugs were found which had no evidence of clinically relevant interactions.

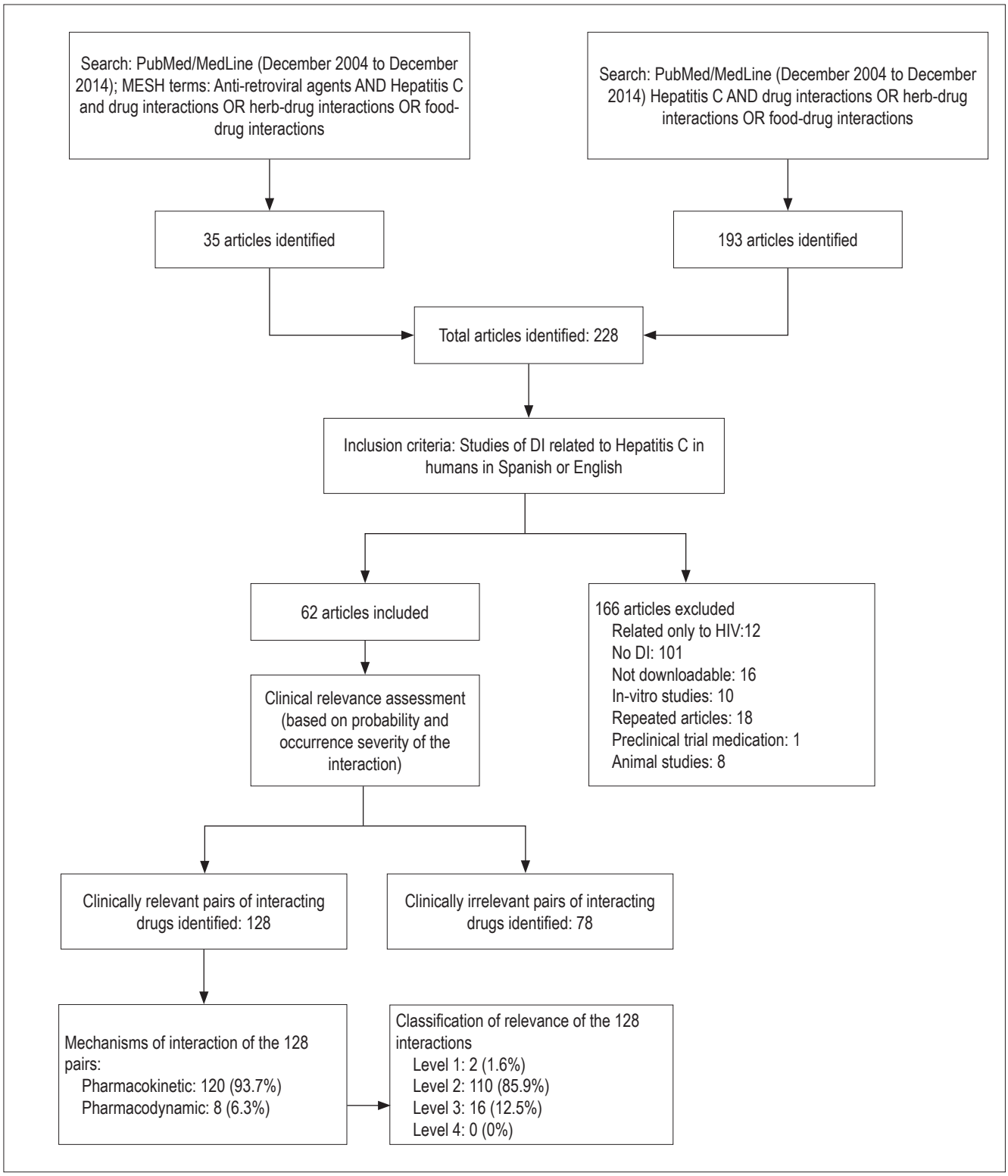

Figure 1. General scheme of the study's structured review. Clinical relevance of drug interactions in the treatment of patients infected with hepatitis C virus genotype 1

Table 1. Overall results of the 128 pairs of clinically relevant drug interactions

Interaction Mechanisms of 128 Drug Pairs	**Pharmaco-dynamic: 8 (6.3%)**	Antagonism 3 (2.4%)
		Synergism 5 (3.9%)
	Pharmaco-kinetic: 120 (93.7%)	Change in bioavailability 3 (2.4%)
		Enzyme induction 35 (27.3%)
		Enzyme inhibition 82 (64.0%)

Drug related to the 120 pairs of pharmacokinetic interactions	**Details of pharmacokinetic mechanisms**			**Clinical relevance of drug interaction**				**Total**
	Induction	**Inhibition**	**Changes in bioavailability**	**Level 1 n (%)**	**Level 2 n (%)**	**Level 3 n (%)**	**Level 4 n (%)**	
Telaprevir	**18**	**45**	**0**	2 (1.6)	56 (43.7)	5 (3.9)	0 (0.0)	**63**
Boceprevir	**17**	**36**	**1**	0 (0.0)	44 (34.4)	10 (7.8)	0 (0.0)	**54**
Ribavirin	**0**	**1**	**2**	0 (0.0)	3 (2.3)	0 (0.0)	0 (0.0)	**3**
TOTAL	35	82	3	2 (1.6)	103 (80.4)	15 (11.7)	0 (0.0)	120

Table 2. Enzyme induction drug interactions related to drugs used for treatment of hepatitis C

Pharmacological group or drugs related to interaction	**HCV drug**	**Level of Clinical Relevance**	**Commentary and Suggestions**
Methadone (9,10,22,24,25,26,28,29)	BOC/TLV	Level 3: Moderate risk	Both PIs can decrease the AUC of (R) methadone: BOC by 15% and TLV by 29%, and of (S) methadone by 22 % and 36% respectively. Dose adjustment is not required.
Contraceptives			
Ethinyl estradiol (27,28,85)	BOC/TLV	Level 2: High risk	Both PIs can decrease the AUC of Ethinyl estradiol by 25%. Monitor the effectiveness of ethinyl estradiol, the use of non-hormonal contraceptive methods is recommended.
Norethindrone (27,28,29)	BOC/TLV	Level 3: Moderate risk	Both PIs can decrease the AUC of Norethindrone: BOC by 4% and TLV by 11%. Dose adjustment is not necessary, the use of non-hormonal contraceptive methods is recommended.
Anticonvulsants			
Carbamazepine (24,27,29,30,31)	BOC/TLV	Level 2: High risk	Carbamazepine reduces the plasma concentration of both PIs. Monitor the effectiveness of boceprevir and telaprevir, a dosage adjustment may be necessary.
Phenytoin (24,27,29,30,32)	BOC/TLV	Level 2: High risk	Phenytoin decreases the plasma concentration of both PIs. Monitor the effectiveness of boceprevir and telaprevir. Monitor the effectiveness of boceprevir and telaprevir, a dosage adjustment may be necessary.
Phenobarbital (24,27,29,30)	BOC/TLV	Level 2: High risk	Phenobarbital decreases the plasma concentration of both PIs. Monitor the effectiveness of boceprevir and telaprevir. Monitor the effectiveness of boceprevir and telaprevir, a dosage adjustment may be necessary.
Antidepressants/selective serotonin reuptake inhibitors			
Escitalopram (26,27,29,31,33,34)	BOC/TLV	Level 2: High risk	Both PIs can decrease the AUC of escitalopram. BOC by 21% and TLV by 30%. Monitor effectiveness of escitalopram parameters. A dosage adjustment may be necessary.
Citalopram (30,49,45)	TLV	Level 3: Moderate risk	Telaprevir can decrease the AUC of citalopram by 35%. No dose adjustment required.
Steroidal anti-inflammatory			
Dexamethasone (27,29)	BOC/TLV	Level 2: High risk	Dexamethasone reduces levels boceprevir and telaprevir. Monitor the effectiveness of the PI. Concomitant use of these drugs is not recommended.
Antituberculosis			
Rifampicin (10,11,12,25,26,27,29,30,32)	BOC/TLV	Level 2: High risk	Rifampicin reduces plasma concentrations of boceprevir to 86% and telaprevir to 92%. Monitor the effectiveness of boceprevir and telaprevir. A dosage adjustment may be necessary.

Table 2. Enzyme induction drug interactions related to drugs used for treatment of hepatitis C. *Continued*

Pharmacological group or drugs related to interaction	HCV drug	Level of Clinical Relevance	Commentary and Suggestions
ARD/PI			
Atazanavir (10,11,13-18, 24,25,28,35-39,79,84)	BOC	Level 2: High risk	Combination produces decreased plasma concentrations of both drugs. Monitor the effectiveness of atazanavir and boceprevir. Dose adjustment may be necessary.
Atazanavir (10,11,19,16,24,25, 27,28,35,37,38,39,40,42,43,48, 79,84,85)	TLV	Level 3: Moderate risk	Atazanavir decreases the AUC of telaprevir by 20% while the AUC of atazanavir increases by 17%. No dose adjustment is required.
Darunavir (10,11,16,18,19,20, 24,27,28,35,37,38,39, 40,41,42,43,79,84,85)	TLV	Level 2: High risk	Combination produces decreased plasma concentrations of both drugs: 40% for darunavir 35% for telaprevir. Monitor the effectiveness of atazanavir and boceprevir. Dose adjustment may be necessary.
Darunavir (10,11,13,14,16,17,20, 24,28,35,36,37,38,39,79,84)	BOC	Level 2: High risk	Combination causes a decrease in plasma concentrations of both drugs: 44% for darunavir and 32% for boceprevir. Monitor the effectiveness of darunavir and boceprevir. Dose adjustment may be necessary.
Fosamprenavir (10,17,18,24, 28,35,38,79)	BOC	Level 3: Moderate risk	Insignificant decreases in levels of both drugs. No dose adjustment required.
Fosamprenavir (10,11,15,16, 18,19,24,27,28,35,38,39,40, 41,42,43,79,84,85)	TLV	Level 2: High risk	Fosamprenavir decreases the AUC of telaprevir by 32 %. The AUC of fosamprenavir decreases by 47% due to the action of telaprevir. Monitor effectiveness of both drugs. Dose adjustment may be required.
Lopinavir (10,11,13,14,16,17, 18,25,28,36,37,38,39,79,84)	BOC	Level 2: High risk	Combination produces decreased plasma concentrations of both drugs (34% and 45%). Monitor the effectiveness of atazanavir and boceprevir. Dose adjustment may be necessary.
Lopinavir (10,11,16,18,24,25, 27,28,35,37-40,42,43, 79,84,85)	TLV	Level 2: High risk	Combination produces decreased plasma concentrations of both drugs (54% for telaprevir). Monitor the effectiveness of atazanavir and boceprevir. Dose adjustment may be necessary.
ARD/NRTI			
Efavirenz (10-12,19,18,24,27,28,35, 37-41,43,79,84,85)	TLV	Level 2: High risk	TLV may cause clinically insignificant decreases of efavirenz concentrations. Efavirenz decreases the AUC of telaprevir by 20%. Adjust dose of telaprevir to 1125 mg every 8 hours.
Efavirenz (10,11,16,18,19,24,28,35,36,38-42,44,79,84,85)	BOC	Level 2: High risk	Boceprevir may cause clinically insignificant decreases of efavirenz. Efavirenz decreases the AUC of boceprevir by 40%. No dose adjustment is not required.
Etravirine (11,15,16,24,28, 35,38,39,79)	BOC	Level 3: Moderate risk	Boceprevir may decrease concentrations of etravirine by 23% but causes no clinically important changes. The combination increases the AUC of boceprevir by 10%. No dose adjustment is required.
Nevirapine (11,79)	TLV	Level 3: Moderate risk	Telaprevir may decrease concentrations of nevirapine, but causes no clinically important changes. No dose adjustment is required.
Nevirapine (11,15,79)	BOC	Level 3: Moderate risk	Boceprevir may decrease concentrations of nevirapine, but causes no clinically important changes. No dose adjustment is required.
Hypnotics			
Zolpidem (24,26,27,29,30,45)	TLV	Level 2: High risk	Telaprevir decreases the AUC of zolpidem by 47%. Monitor the effectiveness of zolpidem. A dosage adjustment may be necessary.
Natural product			
St. John's wort (11,25,29, 30,32,47)	BOC/TLV	Level 2: High risk	St. John's wort may induce CYP3A4 and increase ARD metabolism which can cause a decrease in plasma concentrations and virological response. Monitor effectiveness of ARD and continuously monitor viral load.

AUC: area under the curve; ARD: antiretroviral agent; BOC: boceprevir; PI: protease inhibitor; PI: protease inhibitor NNRTI: non-nucleoside reverse transcriptase inhibitors; TLV: telaprevir.

Table 3. Drug Interactions due to inhibitions related to drugs used for treatment of hepatitis C

Pharmacological group or drugs related to interaction	HCV drug	Level of Clinical Relevance	Commentary and Suggestions
Nonsteroidal analgesic			
Celecoxib (30)	BOC/TLV	Level 2: High risk	Both PIs inhibit CYP3A4 and increase levels of celecoxib. Monitor the safety of celecoxib. A dosage adjustment may be necessary.
Opioid analgesic			
Buprenorphine (9,10,24,26)	BOC	Level 3: Moderate risk	Boceprevir can increase the AUC of buprenorphine by 19%. No dose adjustment is required.
Anesthetic/benzodiazepine			
Midazolam (10,11,24,27,26, 30,32)	BOC	Level 2: High risk	Boceprevir increases AUC of oral midazolam by 430%. Monitor the safety of midazolam. Concomitant use is not recommended.
Midazolam (11,24,27,26,29,30, 32)	TLV	Level 2: High risk	Telaprevir increases AUC of oral midazolam by 796%. Monitor the safety of midazolam. Concomitant use is not recommended.
Midazolam IV (27,29)	TLV	Level 1: very high risk	Telaprevir can increase the AUC of midazolam IV by 240%. Concomitant use is not recommended.
Anxiolytic			
Alprazolam (10,24,27,29,30)	TLV	Level 2: High risk	Telaprevir increases the AUC of alprazolam by 35%. Monitor the safety of alprazolam. A dosage adjustment may be necessary.
Antianginal/anti-arrhythmic			
Sotalol (30)	TLV	Level 2: High risk	Telaprevir inhibits CYP3A4 which can increase levels of Sotalol. Monitor for safety. Concomitant use of these drugs is not recommended.
Antiarrhythmic			
Amiodarone (26,29,30)	TLV	Level 2: High risk	Telaprevir inhibits CYP3A4 which can increase levels of amiodarone. Monitor for safety. Concomitant use of these drugs is not recommended.
Quinidine (30)	TLV	Level 2: High risk	Telaprevir inhibits CYP3A4 which can increase levels of quinidine. Monitor for safety. Concomitant use of these drugs is not recommended.
Anti-arrhythmic/inotropic			
Digoxin (26)	BOC	Level 2: High risk	Boceprevir increases the AUC of digoxin by 19%. Monitor digoxin safety parameters. Consider dosage adjustment.
Digoxin (24,26,27,29,30)	TLV	Level 1: very high risk	Telaprevir increases the AUC of digoxin 85%. This combination is not recommended.
Anti-asthma			
Budesonide (30)	BOC/TLV	Level 2: High risk	Both PIs inhibit CYP3A4 which can increase levels of budesonide. Monitor safety of budesonide. Concomitant use of these drugs is not recommended.
Salmeterol (29)	TLV	Level 2: High risk	Telaprevir inhibits CYP3A4 which can increase levels of salmeterol. Monitor safety of salmeterol, especially watch for increases in the QT interval. Concomitant use of these drugs is not recommended.
Antibiotic/macrolide			
Clarithromycin (27,29,30)	TLV	Level 2: High risk	Telaprevir inhibits CYP3A4 which increases the AUC of the both drugs. Monitor the safety of PIs and macrolide. A dosage adjustment may be necessary. Consider use of azithromycin.
Clarithromycin (26,27,30,42)	BOC	Level 3: Moderate risk	Clarithromycin (26,27,30,42) BOC 3: medium risk Clarithromycin increases the AUC of boceprevir by 21%. No dose adjustment required.
Erythromycin (29,30)	BOC/TLV	Level 2: High risk	Both PIs inhibit CYP3A4 which increases the AUC of both drugs. Monitor the safety of PIs and macrolide. A dosage adjustment may be necessary. Consider use of azithromycin.

Table 3. Drug Interactions due to inhibitions related to drugs used for treatment of hepatitis C. *Continued*

Pharmacological group or drugs related to interaction	HCV drug	Level of Clinical Relevance	Commentary and Suggestions
Contraceptives			
Drospirenone (27,30,32,85)	BOC	Level 2: High risk	Drospirenone (27,30,32,85) BOC 2: Boceprevir increases AUC of drospirenone by 99%. Monitor safety of drospirenone. Concomitant use of these drugs is not recommended.
Atypical antidepressants			
Bupropion (30)	BOC/TLV	Level 2: High risk	Both PIs inhibit CYP3A4 and increase plasma levels of bupropion. Monitor the safety of bupropion. Dosage adjustment may be necessary.
Trazodone (29)	TLV	Level 2: High risk	Telaprevir inhibits CYP3A4 and increases the levels of trazodone. Monitor the safety of trazodone. Dosage adjustment may be necessary.
Antiemetics			
Domperidone (27,29,30)	TLV	Level 2: High risk	Telaprevir inhibits CYP3A4 and increases the levels of domperidone. Monitor safety of domperidone. Dosage adjustment may be necessary. Consider the use of metoclopramide.
Pulmonary hypertension drugs			
Bosentan (30,50)	TLV	Level 2: High risk	Telaprevir inhibits CYP3A4 and P-glycoprotein and can increase the level of bosentan 400%. Monitor the safety of bosentan. A dosage adjustment may be necessary. Consider the use of Ambrisentan.
Calcium channel blockers used to lower high blood pressure			
Amlodipine (10,21,24,26,27,29, 30,85)	TLV	Level 2: High risk	Telaprevir increases the AUC of amlodipine by 179%. Monitor the safety of amlodipine. Start with low doses and adjust dosage according to response.
Bepridil (26,29,30)	BOC/TLV	Level 2: High risk	Both PIs inhibit CYP3A4 and increase the levels of bepridil. Monitor safety of bepridil. Concomitant use of these drugs is not recommended.
Diltiazem (29,30)	TLV	Level 2: High risk	Telaprevir inhibits CYP3A4 and increases the levels of diltiazem. Monitor safety of diltiazem. Dosage adjustment may be necessary. Consider the use of amlodipine at low dosages.
Anti-inflammatory Steroids			
Prednisolone (28)	BOC	Level 3: Moderate risk	Boceprevir increases the AUC of prednisolone by 37%. No dosage adjustment required.
Prednisone (28)	BOC	Level 3: Moderate risk	Boceprevir increases the AUC of prednisone by 22%. No dosage adjustment required.
Antimitotic			
Itraconazole (29)	TLV	Level 2: High risk	This combination increases the AUC of itraconazole by 225%. Monitor the safety of both drugs, A dosage adjustment may be necessary. The dosage of itraconazole should not exceed 200 mg/day.
Ketoconazole (10,12,26,27,29)	TLV	Level 2: High risk	This combination can increase the plasma concentrations of telaprevir by 62% and ketoconazole by 46% to 125%. Monitor the safety of both drugs. A dosage adjustment may be necessary. The dosage of ketoconazole should not exceed 200 mg/day.
Ketoconazole (26,27,42)	BOC	Level 2: High risk	This combination increases the AUC of boceprevir by 131%. Monitor the safety of both drugs. A dosage adjustment may be necessary. The dosage of ketoconazole should not exceed 200 mg/day.
Voriconazole (30)	BOC/TLV	Level 2: High risk	Voriconazole inhibits CYP3A4 and increases levels of boceprevir y telaprevir. Monitor safety of los IPs, Dosage adjustment may be necessary. Consider the use of fluconazole.

Table 3. Drug Interactions due to inhibitions related to drugs used for treatment of hepatitis C. *Continued*

Pharmacological group or drugs related to interaction	HCV drug	Level of Clinical Relevance	Commentary and Suggestions
Antimigraine/ergot alkaloids			
Dihydroergotamine (11,29,30,32)	BOC/TLV	Level 2: High risk	Both PIs increase the serum concentrations of dihydroergotamine. Monitor safety of dihydroergotamine. Dosage adjustment may be necessary.
Ergonovine (11,29,30)	BOC/TLV	Level 2: High risk	Both PIs increase the serum concentrations of ergonovine. Monitor safety of ergonovine. Dosage adjustment may be necessary.
Ergotamine (11,29,30)	BOC/TLV	Level 2: High risk	Both PIs increase the serum concentrations of ergotamine. Monitor safety of ergotamine. Dosage adjustment may be necessary.
Methylergonovine (11,29,30)	BOC/TLV	Level 2: High risk	Both PIs increase the serum concentrations of methylergonovine. Monitor safety of methylergonovine. Dosage adjustment may be necessary.
Antimalarial			
Halofantrine (30)	BOC/TLV	Level 2: High risk	Both PIs inhibit CYP3A4 and increases the levels of halofantrine. Monitor safety of halofantrine. Concomitant use of these drugs is not recommended.
Lumefantrine (30)	BOC/TLV	Level 2: High risk	Both PIs inhibit CYP3A4 and increases the levels of lumefantrine. Monitor safety of lumefantrine. Concomitant use of these drugs is not recommended.
Typical Antipsychotics			
Pimozide (11,30,32)	BOC/TLV	Level 2: High risk	Both PIs increase the serum concentrations of pimozide. Monitor safety of la pimozide. Dosage adjustment may be necessary.
ARD/fusion inhibitors			
Maraviroc (28,39,79)	BOC/TLV	Level 2: High risk	Boceprevir levels of maraviroc 300 % and telaprevir increases them 950 %. Monitor the safety of maraviroc. A dosage adjustment may be necessary. A dosage of 150 mg of maraviroc two times a day is recommended.
ARD/NNRTI			
Rilpivirine (11,15,28,35,38,39)	TLV	Level 2: High risk	Telaprevir increases the AUC of rilpivirine by 78%. Monitor safety of rilpivirine. Dosage adjustment may be necessary.
Rilpivirine (11,28,35,38,39,51)	BOC	Level 3: Moderate risk	Boceprevir increases the AUC of rilpivirine but without clinical significance. Levels of boceprevir do not vary. No dosage adjustment required.
Cytostatic			
Imatinib (30)	BOC/TLV	Level 2: High risk	Both PIs inhibit CYP3A4 and increase the levels of imatinib. Monitor safety of imatinib. Concomitant use of these drugs is not recommended.
Sunitinib (30)	BOC/TLV	Level 2: High risk	Both PIs inhibit CYP3A4 and increase levels of sunitinib. Monitor safety of sunitinib. Concomitant use of these drugs is not recommended.
Adjuvant treatment of gout			
Colchicine (29)	TLV	Level 2: High risk	Telaprevir inhibits CYP3A4 and increases levels of colchicine. Because colchicine has a narrow therapeutic margin. Concomitant use of these drugs is not recommended.
Hypnotic drugs/Benzodiazepine			
Triazolam (11,27,29,30)	BOC/TLV	Level 2: High risk	Both PIs increase serum concentrations of triazolam. Monitor safety of triazolam. Dosage adjustment may be necessary.
Hypolipidemic drugs/Statins			
Atorvastatin (11,24,26,27, 29,30,32,33,41,52,85)	BOC/TLV	Level 2: High risk	Boceprevir increases the AUC of atorvastatin by 270% and telaprevir increases it by 688%. Monitor safety of atorvastatin. Dosage adjustment may be necessary.
Lovastatin (10,11,30,32)	BOC/TLV	Level 2: High risk	Both PIs increase serum concentrations of lovastatin. Monitor safety of lovastatin. Dosage adjustment may be necessary.
Simvastatin (10,11,30,32,34)	BOC/TLV	Level 2: High risk	Both PIs increase serum concentrations of simvastatin. Monitor safety of simvastatin. Dosage adjustment may be necessary.

Table 3. Drug Interactions due to inhibitions related to drugs used for treatment of hepatitis C. *Continued*

Pharmacological group or drugs related to interaction	HCV drug	Level of Clinical Relevance	Commentary and Suggestions
Immunosuppressive drug			
Azathioprine (46)	RIB	Level 2: High risk	Ribavirin inhibits inosine 5'-monophosphate dehydrogenase, an enzyme on the metabolic pathways of azathioprine leading to the accumulation of a metabolite responsible for myelosuppression and thence to pancytopenia. Suspend azathioprine and consider the use of a different immunosuppressive drug.
Cyclosporine (10,23,24,26-30,41,44,53,54, 55,56,57,85)	BOC/TLV	Level 2: High risk	Both PIs increase serum concentrations of cyclosporine. Boceprevir increases the AUC by 2,200 % and telaprevir increases the AUC by 364%. Monitor safety of cyclosporine. Dosage adjustment may be necessary.
Sirolimus (10,27,28,29,49,55,85)	BOC/TLV	Level 2: High risk	Both PIs increase levels of sirolimus. Telaprevir increases the AUC of sirolimus 2610 %. Monitor the safety of sirolimus A dosage adjustment may be necessary.
Tacrolimus (10,24,27,28,29, 44,53,54,55,56,85)	BOC/TLV	Level 2: High risk	Both PIs increase the AUC of tacrolimus. Telaprevir increases it by 6900% and boceprevir by 1600%. Monitor the safety of tacrolimus. A dosage adjustment may be necessary.
Prokinetics			
Cisapride (10,29,30,32)	BOC/TLV	Level 2: High risk	Both PIs increase serum concentrations of cisapride. Monitor safety of cisapride. Concomitant use of these drugs is not recommended.
Treatment of benign prostatic hyperplasia			
Alfuzosin (11,27,29,30,32)	BOC/TLV	Level 2: High risk	Both PIs increase serum concentrations of alfuzosin. Monitor safety of alfuzosin. Dosage adjustment may be necessary.
Erectile dysfunction treatment/phosphodiesterase-5 inhibitor			
Sildenafil (11,25,27,29,30,32)	BOC/TLV	Level 2: High risk	Both PIs increase serum concentrations of sildenafil. Dosage adjustment of sildenafil to 25 mg/48 hours should be considered.
Tadalafil (11,27,29,30)	BOC/TLV	Level 2: High risk	Both PIs increase serum concentrations of tadalafil. Dosage adjustment of tadalafil to 10 mg/72 hours should be considered.

AUC: area under the curve; ARD: antiretroviral agent; BOC: boceprevir; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; TLV: telaprevir.

This reviews findings were similar to those of other structured reviews about interactions in patients infected with HIV and dyslipidemia. (8, 80) Clinically relevant DIs are those with pharmacokinetic mechanisms, especially inhibition or enzyme induction. This indicates that physicians in clinical practice need to evaluate concomitant drug therapy in cases in which drugs that have the ability to affect CYP450 enzyme complex are used.

In general, a CYP450 inducer generates increased enzyme activity and a resulting decrease in plasma levels of substrates. An inhibitor decreases the activity of the enzyme and thereby increases plasma concentrations of substrates. However, boceprevir and telaprevir do not always behave in this manner. One example was found in a study conducted among healthy volunteers. Rather than increasing their levels as would be expected because of the strong inhibiting effect of ritonavir on CYP3A4, TLV levels decreased when it was administered with ritonavir-boosted protease inhibitors. (81, 82) The importance of structured reviews like this one which aim at identifying articles with results from human studies surpasses that of theoretical projections of drug interactions based on similarities or differences of metabolic pathways of related drugs that may possibly interact.

Antiarrhythmic drugs, immunosuppressants, statins and ergot derivatives are the drugs that most commonly interact. They account for 26 of the 128 pairs of relevant drug interactions. This is due to the ability of protease inhibitors, in this case boceprevir and telaprevir, to inhibit CYP3A4 and P-glycoprotein (TLV). Pegylated interferon alpha and ribavirin have lower frequencies of pharmacokinetic interactions because they are primarily eliminated by the kidneys. D. Back et al. have established that pharmacological groups such as diuretics, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers are not significantly metabolized by CYP3A4. For this reason, it would be expected that they would not generate drug interactions with telaprevir. (29) This hypothesis is supported by the results of

Table 4. Drugs without evidence of clinically relevant interactions

Pharmacological group or drugs related to interaction	HCV drug	Commentary and Suggestions
Opioid analgesics		
Buprenorphine (9,10,24,29)	TLV	Telaprevir decreases the AUC of buprenorphine by 4% but is without clinical relevance.
Buprenorphine (9)	Sofosbuvir	Sofosbuvir has no affinity, and does not interact, with any cytochrome of CYP450. Metabolic pathways do not converge.
Methadone (9,26,58,59,60)	INF	Interaction without clinical relevance
Methadone (61)	Sofosbuvir	Sofosbuvir has no affinity, and does not interact, with any cytochrome of CYP450. Metabolic pathways do not converge.
Methadone (60)	RIB	Interaction without clinical relevance
Anesthetic		
Propofol (26)	BOC/TLV	Propofol is metabolized by CYP2B6 and has an extrahepatic metabolism and extra renal excretion.
Antibiotics		
IV Aminoglycosides (33)	BOC/TLV	Interaction without clinical relevance
Amoxicillin (33)	BOC/TLV	Interaction without clinical relevance
Azithromycin (33)	BOC/TLV	Interaction without clinical relevance
Third generation cephalosporins (33)	BOC/TLV	Interaction without clinical relevance
Ciprofloxacin (33)	BOC/TLV	Interaction without clinical relevance
Anticonvulsive drugs		
Valproic acid (29,31,33)	BOC/TLV	Interaction without clinical relevance
Gabapentin (24,31)	BOC/TLV	Metabolic pathways do not converge.
Lamotrigine (29,31)	BOC/TLV	Metabolic pathways do not converge.
Levetiracetam (29)	TLV	Interaction without clinical relevance
Pregabalin (24,31)	BOC/TLV	Metabolic pathways do not converge.
Antidepressants/selective serotonin reuptake inhibitors		
Fluoxetine (24,31)		Fluoxetine is metabolized by CYP2D6. Metabolic pathways do not converge.
Paroxetine (24,31)	BOC/TLV	Paroxetine is metabolized by CYP2D6. Metabolic pathways do not converge.
Antidiabetic agents		
Metformin (11,26,29,30,32)	BOC/TLV	Interaction without clinical relevance
Repaglinide (29)	TLV	Repaglinide is partially metabolized by CYP3A4 but has an escape metabolism due to CYP2C8. Interactions are without clinical relevance.
Antihypertensives		
Atenolol (26,33)	BOC/TLV	Interaction without clinical relevance
Propranolol (33)	BOC/TLV	Interaction without clinical relevance
Enalapril (33)	BOC/TLV	Interaction without clinical relevance
Ramipril (33)	BOC/TLV	Interaction without clinical relevance
Antihistamines		
Desloratadine (33)	BOC/TLV	Interaction without clinical relevance
Diphenhydramine (30)	BOC/TLV	Interaction without clinical relevance
Levocetirizine (33)	BOC/TLV	Interaction without clinical relevance
Atypical antipsychotic drugs		
Olanzapine (24,31)	BOC/TLV	Olanzapine is metabolized by el CYP1A2. Metabolic pathways do not converge.
Antiulcer drugs/Proton pump inhibitors		
Esomeprazole (29)	TLV	Interaction without clinical relevance
Omeprazole (29,33)	BOC/TLV	Interaction without clinical relevance
Pantoprazole (33)	BOC/TLV	Interaction without clinical relevance

Table 4. Drugs without evidence of clinically relevant interactions. *Continued*

Pharmacological group or drugs related to interaction	HCV drug	Commentary and Suggestions
ARDs		
Abacavir (83)	INF	Interaction without clinical relevance
Darunavir (61)	SOFOSBUVIR	Sofosbuvir has no affinity, and does not interact, with any cytochrome of CYP450. Metabolic pathways do not converge.
Dolutegravir (39,77,78)	BOC/TLV	Interaction without clinical relevance
Efavirenz (61)	SOFOSBUVIR	Sofosbuvir has no affinity, and does not interact, with any cytochrome of CYP450. Metabolic pathways do not converge.
Emtricitabine (15,38,40)	BOC/TLV	Interaction without clinical relevance
Etravirine (11,24,28,35,38,39)	TLV	Etravirine decreases the AUC of telaprevir by 29% but is without clinical relevance.
Lamivudine (38,40)	BOC/TLV	Interaction without clinical relevance
Raltegravir (61)	SOFOSBUVIR	Sofosbuvir has no affinity, and does not interact, with any cytochrome of CYP450. Metabolic pathways do not converge.
Raltegravir (16,11,24,28,37,38,39,51,84)	BOC/TLV	Interaction without clinical relevance
Rilpivirine (61)	SOFOSBUVIR	Sofosbuvir has no affinity, and does not interact, with any cytochrome of CYP450. Metabolic pathways do not converge.
Ritonavir (10,11,16,19,40)	BOC/TLV	Interaction without clinical relevance
Tenofovir (61)	SOFOSBUVIR	Sofosbuvir has no affinity, and does not interact, with any cytochrome of CYP450. Metabolic pathways do not converge.
Tenofovir (10,15,16,19,24,28,62,37,38, 39,42,74,84,85)	BOC/TLV	Interaction without clinical relevance
Hypolipidemic/Statins		
Fluvastatin (52)	BOC/TLV	Fluvastatin is metabolized by CYP2C9. Metabolic pathways do not converge.
Pravastatin (26,52)	BOC	Boceprevir increases the AUC of pravastatin 70% but is without clinical relevance.
Immunosuppressive drugs		
Cyclosporine (61)	SOFOSBUVIR	Sofosbuvir has no affinity, and does not interact, with any cytochrome of CYP450. Metabolic pathways do not converge.
Tacrolimus (61)	SOFOSBUVIR	Sofosbuvir has no affinity, and does not interact, with any cytochrome of CYP450. Metabolic pathways do not converge.
Sedatives		
Ketamine (26)	TLV	Metabolic pathways do not converge.

ARD: antiretroviral agent; BOC: boceprevir; INF: pegylated interferon alpha; IV: intravenous; RIB: ribavirin; TLV: telaprevir.

our review. However, absence of interactions were only evident with enalapril and ramipril. Back et al. also established that β-blockers have problems when used with PIs because some of them such as atenolol and sotalol are primarily eliminated by the kidneys and others such as metoprolol and carvedilol are metabolised by CYP2D6. (29) This generally coincides with the absence of clinically relevant interactions of telaprevir and boceprevir with atenolol identified in our study, but it departs from the finding of increased plasma levels of sotalol when combined with TLV. This effect may be because sotalol is a substrate for P-glycoprotein and this glycoprotein inhibits TLV. (76)

Our review has documented information about the absence of interactions of clinical relevance for sofosbuvir (61), a polymerase inhibitor recently approved by the Food and Drug Administration and available in the market. This drug is apparently not a substrate, inhibitor and inducer of some isoenzymes of CYP450 which limits the possibility of relevant interactions with drugs such as tacrolimus, cyclosporine, rilpivirine and efavirenz. This could be clinically beneficial for patients with HCV and other comorbidities. The main limitation of this study is that the search was restricted to the databases of PubMed/Medline. Nevertheless, this limitation was minimized by the com-

plementary search for references to DIs in HIV-infected patients on antiretroviral therapy.

CONCLUSIONS

More than 90% of clinically relevant drug interactions in patients infected with HCV who receive drug therapy are pharmacokinetic. They are associated with induction or inhibition of hepatic metabolism. When antiviral drugs such as boceprevir and telaprevir are used to treat patients infected with HCV and other associated diseases, clinically relevant interactions are likely to occur. The largest number of drug interaction pairs identified include telaprevir. There were sixty-three pairs including telaprevir in total: two in Level 1 (1.6%), 56 in Level 2 (43.7%), and five in Level 3 (3.9 %). There were fifty-four pairs that included boceprevir: 44 in Level 2 (34.4%) and 10 in Level 3 (7.8%). Clearly, HCV patients who have other associated diseases and who are being treated with three drugs may have altered plasma concentrations of concomitant medications. This is more probable in cases in which TLV or BOC are used concomitantly with antiarrhythmic drugs, immunosuppressants, statins and ergot derivatives. When INF, RIB or sofosbuvir are used, the probability of relevant interactions is lower. This is primarily due to the fact that CYP450 isoenzymes are not involved in their elimination. This feature enhances their choice for the treatment of HCV in patients who have other associated diseases, especially HIV-infected patients and patients who have solid organ transplants.

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