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Recent advances in management of the HIV/HCV coinfecting patient

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Abstract

Chronic hepatitis C virus (HCV) is a global epidemic, affecting approximately 150 million individuals throughout the world. The implications of HCV infection have been magnified in those who are infected with both HCV and the HIV as liver disease progression, liver failure and liver-related death are increased, particularly in those without well-controlled HIV disease. The development of direct-acting antiviral agents for HCV that allow shorter treatment periods with increased efficacy and decreased adverse events have greatly changed the outlook for HCV-infected individuals. With these advancements, growing treatment options for the coinfecting population have also come. This review will address pharmacotherapy issues in the HIV/HCV coinfecting population.

Keywords

direct-acting antiviral; HCV; HIV; null responder; relapse; sustained virologic response

Hepatitis C continues to be a major health issue in the USA and around the world. Current estimates are that 5.2 million individuals are living in the USA with HCV infection [1]. The WHO estimates that approximately 150 million individuals have chronic HCV infection and the yearly death-toll from HCV-related diseases is >350,000 [2].

The majority of individuals (~77%) who become infected with acute HCV go on to develop chronic hepatitis [3]. Left untreated chronic HCV infection can lead to hepatic fibrosis and ultimately cirrhosis and liver cancer [3].

About 25% of the individuals infected with HIV in the USA are also infected with HCV, with the rate approaching 100% among injection-drug users with HIV [4]. Coinfection with HIV and HCV can result in a threefold greater rate of fibrosis progression as compared with those individuals with HCV mono-infection [5], especially among those with profound immune deficiency defined as low CD4 counts with or without AIDS and high levels of HIV RNA. Development of cirrhosis and end-stage liver disease can occur in six–ten years among coinfecting patients whereas the natural history in those with HCV mono-infection ranges from 20–30 years [6]. This data substantiates the current recommendations for HCV screening among HIV-infected individuals [7]. In addition, it also underscores the importance of treating HIV infection successfully, and then proceeding to HCV treatment as soon as possible to control liver-disease progression.

Treatment for chronic HCV has made great strides over the years with particularly important developments occurring since 2011. Initially interferon monotherapy was utilized with poor-response rates, sustained virologic response (SVR) rates of 6% with 24 weeks of therapy, which increased with the combined use of ribavirin (RBV) [8,9]. In 2001 and 2002, pegylated-interferon (PEG-IFN) α -2b and α -2a were approved by the US FDA, respectively. When used in combination with RBV, PEG-IFN increased the therapeutic success and

allowed a more favorable dosage schedule. The SVR rates improved, although the regimen was complicated by drug-induced side effects [10]. Although, success rates (SVR) for HIV/HCV genotype 1 coinfecting individuals were substantially lower, 17% and 29%, as shown in the RIBAVIC and APRICOT trials, respectively [11,12], compared with approximately 39% in monoinfected individuals [13] and coinfecting populations were at increased risk of experiencing adverse events [14]. In 2011, two first-in-class direct-acting antiviral (DAA) NS3/4A protease inhibitors, telaprevir and boceprevir, were approved for HCV genotype 1 infection [15, 16], improving SVR rates to 75–80%, although treatment-related side effects, drug–drug interactions and complicated dosing continued to plague these regimens [16,17]. The addition of DAAs to PEG-IFN and RBV, closed the SVR gap between mono and coinfecting individuals [18]. This was first demonstrated in trials utilizing telaprevir or boceprevir with PEG-IFN and RBV [19, 20]. In these studies, rates of SVR ranged from 63% to 74% in patients with HCV genotype 1 infection, and the results were similar to those observed in trials of HCV monoinfected patients. In January 2014, the polymerase inhibitor, sofosbuvir and protease inhibitor, simeprevir, were approved. Similar efficacy in coinfecting individuals has been demonstrated using sofosbuvir, simeprevir and various interferon sparing regimens [21–23]. Then, in October and December of 2014, the fixed-dose combination DAA regimens of ledipasvir/sofosbuvir, and ombitasvir/paritaprevir/ritonavir plus dasabuvir were approved, respectively. These new agents have varying mechanisms of action, including NS3/4A protease inhibitors, nucleos(t)ide and non-nucleoside polymerase inhibitors and NS5A replication complex inhibitors. These agents have modernized treatment of chronic HCV by increasing SVR rates to over 90% and in the vast majority of cases, removing the need of cotreatment with PEG-IFN [24,25], however, drug interactions can still be an issue with some of these agents.

This review article will address issues in this rapidly expanding area of pharmacotherapeutics for HIV/HCV coinfecting individuals, while also addressing the risk of drug interactions when treating this patient population.

Direct acting antiviral agents

Rapid progress has been made toward all oral, interferon-free regimens with excellent SVR rates for genotype 1 HCV infection, even in prior null responders to PEG-IFN and RBV (Table 1). Some of these interferon-free regimens have proven to be highly effective even without the inclusion of RBV. Sofosbuvir, a nucleotide analog NS5B polymerase inhibitor coformulated with ledipasvir (GS-5885), an NS5A replication-complex inhibitor with potent activity against genotype 1 HCV, has recently been approved by the FDA. The addition of RBV does not appear to substantially enhance efficacy when utilizing with this combination regimen [25]. However, in a recent study, it was found that treatment experienced patients with compensated cirrhosis, who had failed sequential treatment with PEG-IFN/RBV alone and combined with a protease inhibitor, were found to have similar SVR12 rates when administered ledipasvir/sofosbuvir alone for 24 weeks, versus 12 weeks of ledipasvir/sofosbuvir combined with RBV (97% vs 96%, respectively) [26].

Simeprevir is an FDA-approved NS3/4A protease inhibitor, it is most commonly used with sofosbuvir. Treatment guidelines indicate that simeprevir combined with sofosbuvir, with or

without RBV, is an acceptable treatment for HCV genotype 1 in either treatment-naïve or PEG-IFN/RBV-experienced patients.

Another FDA-approved, interferon-free regimen consists of paritaprevir (NS3/4A protease inhibitor) boosted with ritonavir (r), ombitasvir (NS5A replication complex inhibitor), and dasabuvir (nucleoside NS5B polymerase inhibitor), known collectively as ‘3D’, given with or without RBV.

See Table 2 for guideline recommendations for the treatment of HCV genotype 1 mono-infection.

Daclatasvir is an investigational NS5A replication complex inhibitor that has been used in combination with sofosbuvir. In addition, future research in HIV/HCV coinfecting individuals will combine daclatasvir with asunaprevir, an NS3/4A, and beclabuvir (BMS-791325), a nucleoside NS5B polymerase inhibitor.

Information for HIV/HCV coinfection

The eradication of HCV in coinfecting patients has been associated with the same clinical benefits as those observed in HCV mono-infected patients, such as: reduction of liver inflammation, delayed fibrosis progression and reduced morbidity and mortality secondary to liver disease. Additionally, sustained HCV-viral suppression or clearance in coinfecting patients may reduce the risk of drug-induced liver injury associated with combination antiretroviral therapy [37]. The incidence of hepatocellular carcinoma may also be reduced with achievement of SVR as it has been demonstrated among mono-infected individuals [38].

Current guidelines suggest similar treatment regimens for patients coinfecting with HCV and HIV as those utilized to treat HCV mono-infected patients. Notably, drug interactions need to be considered before starting any treatment for HIV and HCV concurrently [25]. Overall, interferon-free regimens are exclusively preferred compared with those containing interferon as they avoid the potential toxicities of interferon [25]. However, RBV is still a requirement for many treatment regimens [25].

The decision to initiate HCV therapy in a patient with HIV must take into account a thorough understanding of drug–drug interactions between antiretroviral therapies to treat HIV and DAA medications to treat HCV. Antiretroviral agents with minimal drug–drug interactions, including integrase strand transfer inhibitors such as raltegravir or dolutegravir, or the nucleoside reverse transcriptase inhibitor, rilpivirine, tend to be favored when HCV therapy is a consideration to avoid drug–drug interactions.

Of special interest is a drug–drug interaction between ledipasvir and tenofovir containing regimens, when used with a pharmacokinetic enhancer, such as ritonavir or cobicistat. As such, caution is warranted when utilizing these agents together and coadministration may not be recommended [39].

HIV/HCV coinfection & DAA regimens of choice

Potential drug interactions and pathways (Table 3) need to be considered prior to initiation of HCV therapies with the initiation of, or switch to, a combination antiretroviral therapy regimen that avoids drug–drug interactions, or the initiation of a preferred HCV-treatment regimen that avoids these interactions (Table 4). Many agents used for the treatment of these two disease states have effects on metabolic enzymes or membrane transporters, or can be affected by alterations in these systems. In addition, ritonavir is a potent CYP3A4 inhibitor and is used with protease inhibitors in the treatment of HIV and in the treatment of HCV to boost paritaprevir. The potential for interactions has to be taken into consideration when utilizing and combining these agents.

In a recent study by Osinusi, *et al.* [61], 50 HCV/HIV coinfecting treatment-experienced patients with HCV genotype 1 were initiated on fixed-dose combination tablets of ledipasvir and sofosbuvir once daily for 12 weeks. The first arm consisted of 13 subjects who were antiretroviral (ARV) treatment naïve, whereas the second arm consisted of 37 subjects who were maintained on ARV regimens consisting of fixed-dose tenofovir plus emtricitabine plus efavirenz, rilpivirine or raltegravir with fully suppressed HIV viral loads. In the ARV treated arm, 36 of 37 (97%) achieved SVR12 and there were no changes in HIV surrogate markers or renal function reported. The individual who failed treatment relapsed 2 weeks post completion of therapy, was African–American and was infected with HCV genotype 1b. At 12 weeks post-treatment, all patients in the ARV-untreated group (100%) achieved SVR. Further, there were no serious adverse events reported related to any of the study medications, and no discontinuations were reported related to any adverse events. The authors suggested that HIV/HCV coinfection does not adversely impact outcomes in patients treated with ledipasvir/sofosbuvir therapies.

In a study by Sulkowski, *et al.* [62], 63 coinfecting patients were randomized to receive 12 versus 24 weeks of combination paritaprevir/ ritonavir/ombitasvir daily in combination with twice-daily dasabuvir plus weight-based RBV. Patients were stable on raltegravir or atazanavir-based anti-HIV regimens and were either HCV treatment naïve or PEG-IFN and RBV experienced. In the 12-week arm, 16 patients were on atazanavir-based ARV therapy and 15 were on raltegravir-based therapy. In the 24-week arm, 12 patients were on atazanavir while 20 were on raltegravir. SVR12 was achieved in 29 of 31 (93.5%) of the patients treated with 12 weeks of study drugs, while 29 of 32 (90.6%) achieved SVR12 after receiving 24 weeks of therapy [62].

The ION-4 study was a multicenter, openlabel, Phase III study [63]. Hepatitis C virus treatment naïve or treatment experienced patients who were infected with either genotype 1 or 4 were eligible for this study regardless of compensated cirrhosis status, provided that their platelets were $\geq 50,000$ cells/mm³, their hemoglobin was ≥ 10 mg/dl, and their creatinine clearance was ≥ 60 ml/min. Patients were coinfecting with HIV and had stable virologic suppression (HIV RNA <50 copies/ml) and a CD4 count ≥ 100 cells/mm³ and were on ART regimens consisting of tenofovir/emtricitabine plus either efavirenz, raltegravir or rilpivirine. In total, 331 patients with genotype 1 were initiated on ledipasvir 90 mg/sofosbuvir 400 mg daily for 12 weeks (plus four patients who were genotype 4). The SVR12

rate was 96%, comparable with results seen in HCV monoinfected populations. In multivariate analyses, there were no significant differences in SVR12 according to cirrhosis status, previous treatment for HCV, the ART regimen being utilized, baseline CD4 cell count, sex, HCV genotype or subgenotype, baseline HCV RNA or patient body mass index. However, patients of African descent had a significantly lower rate of SVR12 when compared with non-African descended patients. There were ten relapses in HCV after therapy and all of these occurred in African-American patients. Sustained virologic response rates at 12 weeks post-treatment among patients of African descent were 90%. Serious adverse events included such side effects as headache (25%), fatigue (21%), diarrhea (11%), nausea (33%), arthralgia (7%) and upper respiratory infections (5%).

An alternative regimen that held promise based on studies involving HCV monoinfected patients utilizes simeprevir plus sofosbuvir given with or without RBV for 12 weeks provided that the patient's combination ARV regimen is compatible with simeprevir. This regimen, however, has not been directly assessed in HIV/HCV coinfecting patients [36]. Data from OPTIMIST-2, a study in HIV-negative, HCV genotype 1 individuals with cirrhosis, administered simeprevir with sofosbuvir without RBV for 12 weeks, obtained a combined SVR12 rate of 83% [64]. Showing that this combination, as administered in the study, may not be widely utilized while going forward.

Study A1444-040 was a randomized, openlabel, parallel group, Phase II trial that studied the use of sofosbuvir and daclatasvir with or without RBV in treatment of naive patients with HCV infection with genotypes 1, 2 or 3 [30]. Patients were included if they had hepatitis C viral RNA levels of >100,000 IU/ml and were noncirrhotic. Patients were enrolled and randomized in two stages, the first of which consisted of all 24-week arms, and the second of which consisted of 12-week arms. Treatment naive, noncirrhotic patients with genotype 1 HCV were randomized into five arms. The first group (n = 15) received a lead-in week of sofosbuvir, followed by treatment with the combination of sofosbuvir plus daclatasvir for a total of 24 weeks. The second group (n = 14) received sofosbuvir plus daclatasvir for a total of 24 weeks, with no lead in period of sofosbuvir. The third group (n = 15) received sofosbuvir plus daclatasvir plus RBV for 24 weeks. Group four (n = 41) received sofosbuvir plus daclatasvir for 12 weeks, and group five (n = 41) received sofosbuvir plus daclatasvir plus RBV for 12 weeks. All patients were followed for 48 weeks post-treatment. Following a protocol adjustment, 41 patients who experienced virologic failure on previous treatment with boceprevir or telaprevir-based therapies were also included in the study arms, 21 patients receiving sofosbuvir and daclatasvir for 24 weeks, and 20 patients receiving sofosbuvir plus daclatasvir plus RBV for 24 weeks.

The combination of daclatasvir and sofosbuvir appears well tolerated and the most common adverse events were fatigue, nausea and headache. Low hemoglobin levels only occurred in patients who were placed in the study arms containing RBV. Of patients with genotype 1 who were enrolled in the study, 98% of patients achieved SVR12, regardless of whether they were treatment naive or treatment experienced. Similarly, SVR12 rates were similar between patients with genotype 1a (98%) and 1b (100%).

In the ALLY-2 study, daclatasvir was combined with sofosbuvir in HIV/HCV coinfecting individuals. Patients were either treatment naïve or experienced, and received sofosbuvir and daclatasvir (dose adjusted for drug–drug interactions with ARVs) daily for eight or 12 weeks (naïve) or 12 weeks (experienced). Eighty-three percent of patients were genotype 1, and 14% were cirrhotic. The SVR12 for all genotype 1 patients (naïve and experienced/white and black) that received treatment for 12 weeks was approximately 97 and 91% for cirrhotics. The SVR12 was much lower in the 8-week treatment arm [65].

Management of adverse reactions to HCV pharmacotherapies

Based on clinical experience at our practice site, before starting anti-HCV therapies, patients, both mono- and co-infected, should discuss readiness to start treatment. Common reasons for patients avoiding HCV treatment include an inability to be adherent to the treatment regimen, a lack of social support throughout therapy or fears of past failures or adverse effects from past regimens. There are many ways that patients can alleviate or prevent the adverse effects of therapies related to the treatment of HCV, but they must first feel comfortable in bringing these adverse events to the attention of their healthcare providers, and be educated by a provider proficient in the management of these adverse events. Adverse effects of older HCV regimens were typically caused by the use of PEG-IFN, and it is important that patients know that it is no longer prescribed. Simeprevir is rarely associated with adverse effects, but it may lead to rash or pruritus and photosensitivity reactions. While most of these symptoms occur within the first four weeks of therapy, they may occur at any point throughout therapy. Other rare symptoms include dyspnea, nausea or myalgias, although these symptoms are more commonly associated with RBV therapies.

Sofosbuvir has a clinically insignificant adverse event profile when compared with other anti-HCV therapies such as PEG-IFN and RBV. It is important to note, however, that no anti-HCV agent is given alone, and as such, adverse events are common for any patient being treated with these agents in combination. The most common adverse reactions associated with the combination of ledipasvir and sofosbuvir are fatigue and headache [24].

In the TURQUOISE-I study, which enrolled HIV/HCV coinfecting patients who were administered paritaprevir/ritonavir/ombitasvir daily, and twice-daily dasabuvir, plus weight-based RBV for 12 or 24 weeks and were on a stable raltegravir or atazanavir-based anti-HIV regimen, the authors concluded that the following adverse events were related to the use of study medications: fatigue (48%), insomnia (19%), headache (16%) and irritability (10%) [62]. Adverse events in HCV monoinfected patients using dasabuvir, ombitasvir, paritaprevir and ritonavir, include fatigue (13–34%), asthenia (4–14%) and insomnia (5–14%) [41].

Key adverse effects of DAAs include fatigue or insomnia, headache and nausea. Patients with nausea or other forms of gastrointestinal upset should be counseled to take the medication with a moderate to high-fiber food, which eases some of the stomach upset. Taking medication at night before bed also allows for the patient to sleep through any adverse gastrointestinal events that might occur, which might impact the quality of the patient's day. In the event of severe nausea, a prescription strength antiemetic may be

considered as adjuvant therapy, along with antidiarrheals or simethicone as needed. Headache may be treated after consultation with a physician or pharmacist utilizing over-the-counter pain medications such as acetaminophen (in doses of less than 2 g/day) or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or naproxen. Gentle massages or ice applied to the area of pain have also been noted to help patients in our clinical population. Appropriate timing of the dose of medication has been noted to assist with adverse events of fatigue or insomnia.

Dry skin or itchiness, from treatment or disease, and rash are common complaints of patients undergoing treatment for HCV. Patients should be counseled to discuss skin problems with their providers immediately. Cutaneous reactions that involve blisters (including oral lesions) or conjunctivitis, or are associated with any systemic symptoms should promptly be evaluated by a physician. As RBV is still included in many regimens, it is important to note some significant adverse events related to this medication. The major toxicity of oral RBV is hemolytic anemia, which is observed in approximately 10–15% of patients utilizing this medication in combination with PEG-IFN, and typically occurs within 1–2 weeks of initiation of therapy [66]. This anemia may require an RBV-dose reduction, erythropoiesis-stimulating agents or a blood transfusion [41]. Other adverse effects include, fatigue (60–70%), gastrointestinal event including nausea (25–47%) and diarrhea (10–22%), arthralgias (21–34%) and myalgias (22–64%). In addition to rest, relaxation and giving oneself time to become accustomed to the adverse effects of RBV, it has been noted that over-the-counter pain medications such as NSAIDs often assist with muscle or joint pains [66].

It is also significant to recognize that RBV causes teratogenesis and embryocidal effects and is listed as a pregnancy category X drug. It can be detected in human blood up to four weeks after discontinuation of therapy. The drug is known to accumulate inside the cell and it is cleared slowly. Because it is not known whether RBV contained in sperm will exert a potential teratogenic effect upon fertilization of the ova, appropriate methods of contraception are required for both males and females utilizing this agent [66].

Adherence pharmacology & complexity considerations in HIV/HCV coinfecting patients

Many HIV/HCV coinfecting patients may be on complex HIV regimens prior to starting HCV treatment. Research on medication adherence has shown that as medication regimens become more complex, overall medication adherence decreases [67]. In coinfecting patients, this has been one of the primary barriers to HCV treatment. Complexity of the medication regimen is not only a concern for adherence to HCV treatment, but also a concern for continued adherence to the ARV regimen. If the two treatment regimens become too complex with multiple medications, dosing schedules and individual medication requirements, it is likely that patient will become less adherent to both regimens. With the introduction of the next generation DAAs, the pill burden and complexity of medication regimens for HCV have been dramatically reduced in many cases. Patients now have an option of interferon-free regimens, as well as therapies as simple as a pill once daily such as the ledipasvir/sofosbuvir fixed-dose combination. These improvements have greatly assisted

patients with adherence; however, not all of the next generation DAA regimens are as simple. The FDA approved combination of ombitasvir, paritaprevir, ritonavir and dasabuvir requires a higher pill burden and increased regimen complexity. Patients are required to take two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily plus a dasabuvir 250 mg tablet twice daily and RBV for all genotype 1a and 1b with cirrhosis [41]. Regardless of the pill burden and complexity of HIV and HCV treatment regimens, all patients should be counseled on the importance of adherence.

Side effects have also been shown to be a predictor of nonadherence [68]. With the next generation DAAs, the severity of side effects have been lessened. Previously with the use of PEG-IFN and RBV, patients commonly experienced depression, flu-like symptoms, gastrointestinal upset, insomnia and other side effects. These side effects are no longer common and tolerability of therapy is much improved.

Pharmacogenetics in the treatment of HCV infection

The importance of pharmacogenetics in the treatment of HCV infection has been demonstrated in a number of clinical trials and summarized in recent review articles [69,70]. The American Association for the Study of Liver Diseases guideline for testing, managing and treating chronic HCV infection recommends HCV genotyping for selecting appropriate antiviral regimen, determining treatment duration and predicting response [71]. In addition, a strong association between human genetic variation in the *interleukin 28B (IL28B)* gene and treatment outcomes of the previous mainstay of HCV treatment, PEG-IFN and RBV therapy, has been identified through genome-wide association studies and confirmed in different clinical trials, which made it a good candidate as a biomarker for PEG-IFN/RBV HCV treatment outcomes [71–73]. While the evolving standard of care for HCV infection incorporates new DAAs, the relationship between *IL28B* genotype and virologic response to DAAs and its clinical utility as an outcome predictor for treatment individualization is currently being evaluated [74,75]. Preliminary results in regimens without interferon suggest limited clinical relevance.

The pharmacogenetic data on *IL28B* genotype and new DAAs are summarized in Table 5. Two major polymorphisms, rs12979860 (C>T) [76,77] and rs8099917 (T>G) [72,73], in strong linkage disequilibrium are associated with responses to PEG-IFN and RBV [71,78]. The mechanism might be related to the regulation of innate immune responses by the *IL28B* gene product, IFN- λ 3 [79]. The association appears relatively weaker between *IL28B* genotype and simeprevir with PEG-IFN and RBV. No associations were observed between *IL28B* genotype and newer DAAs, suggesting other mechanisms of action rather than IFN- λ 3 mediated antiviral responses (Table 5).

The significant impact of the main RBV transporter gene, the solute carrier (*SLC*) 29A1 for the equilibrative nucleoside transporter 1 (ENT1), has been demonstrated by the rapid virologic response to PEG-IFN/RBV therapy among 109 HIV/HCV coinfecting patients [83]. Patients with the variant genotype (GG, *SLC29A1* rs760370 A>G) more frequently achieved rapid virologic response than AA/AG carriers (50% vs 17%), likely due to lack of ENT1 function and resultant high RBV exposure within hepatocytes. Such a strong association

between *SLC29A1* (rs6932345), SVR and rapid virologic response was confirmed in 529 patients with HCV genotype 1b mono-infection from East Asia [84]. More recent studies have also identified an important association between *SLC28A2* (rs11854484, C>T) and higher RBV serum concentrations among Swiss and Italian patients, reinforcing the importance of *SLC* gene polymorphisms and RBV pharmacokinetics. These pharmacogenetic findings should be interpreted with caution considering the small sample size in most of studies, and therefore, their clinical implications warrant further investigation in a larger patient population as long as RBV remains part of the treatment regimen.

The protective effects of inosine triphosphatase (ITPA) genotype against RBV-induced anemia have been well documented, particularly with rs1127354 and rs7270101 [85–89]. Inosine triphosphatase deficiency, resulting from ITPA genetic variation, protects against RBV-induced anemia [86,88]. The ITPA genotype has been associated with RBV dose reduction [85] and SVR [86,89]. However, the clinical utility of ITPA deficiency to predict early anemia has been recently questioned; in that, no association between ITPA deficiency with hemoglobin decline, RBV dose reduction, erythropoietin support or blood transfusions was identified among 69 HCV-1 infected patients with advanced fibrosis receiving telaprevir treatment, suggesting the need for further investigation with regimens that contain RBV [90].

Although no direct evidence has emerged, DAAs as substrates for drug transporters, such as P-glycoprotein (P-gp), MRP2 and OATP1B1/3, as well as the cytochrome P450 (CYP) enzymes, such as 3A4/5, are subject to the impact of genetic variants on pharmacokinetics and treatment outcomes [43–44,48]. The interactions between DAAs and transporters have been investigated with a particular focus on P-gp, OATP1B1/3 and BCRP. While paritaprevir exhibits a significant inhibitory effect on OATP1B1/BCRP by increasing its substrate rosuvastatin exposure 159% and C_{max} 613%, asunaprevir has moderate effects with 41 and 95% increases in exposure and C_{max} , respectively. Both paritaprevir and asunaprevir are substrates for P-gp and asunaprevir is also a substrate of OATP1B1 since an OATP1B1 inhibitor, rifampin, increases asunaprevir exposure and C_{max} by 1381 and 2011%, respectively [91]. The potential impact of polymorphisms in liver uptake transporters, OATP1B1 and 2B1, on asunaprevir pharmacokinetics has been recently reported among 74 HCV-infected patients with different ethnic background, 40 Japanese and 34 Caucasians [92]. While a significantly higher asunaprevir exposure (~ twofold) was observed among Japanese patients in comparison to that observed among Caucasians, neither OATP1B1 nor OATP2B1 genetic variations were associated with such ethnic differences. OATP1B1 haplotypes were not a significant covariate for asunaprevir clearance and no association was observed between OATP2B1 polymorphisms (rs12422149 and rs2306168) and exposure in an integrated population pharmacokinetic analyses suggesting that more complex factors rather than genetic variations were involved in the modification of ethnic differences in drug clearance.

In summary, since new DAAs are significant substrates for CYP enzymes and membrane transporters, genetic variations in these enzymes and transporters could potentially have a significant impact on drug interactions, mediated either by CYP, efflux transporters, for

example, P-gp and BCRP, or uptake transporters, for example, OATP1B1/1B3. Therefore, these issues warrant further investigation.

Conclusion

Recently, new DAA containing regimens that target HCV and that provide all-oral treatments with SVR rates >90% in most cases, have been approved. These regimens offer tremendous advantages for HIV/HCV coinfecting individuals since they have comparable SVR rates and adverse event profiles to those observed in HCV mono-infection populations.

Drug interactions play a large role in the majority of the new treatment regimens, and this is magnified when treating HIV/HCV coinfecting individuals. To improve patient safety and treatment outcomes, healthcare providers should understand the clinical pharmacology, including metabolism and transporter effects of these new regimens, while taking into account potential drug–drug interactions. They should also always be cognizant of the effect of underlying disease on these processes.

Pharmacogenetics plays an important role when deciding treatment regimens, durations and expected response. Notably, *IL28B* polymorphisms were a strong predictor of response in PEG-IFN and RBV-containing regimens. While data generated to date suggest that newer HCV agents do not have this strong association, additional polymorphisms in the human host including metabolic and transporter polymorphisms could affect responses to HCV treatment. Depending on the type of mechanism affected, drugs could have increased or decreased exposures potentially resulting in an increased chance of adverse effects, or possibly a decrease in efficacy.

Treating the HIV/HCV coinfecting subject is best achieved in a multidisciplinary setting to ensure that all aspects of medication therapy are considered, including minimizing drug interactions, maximizing adherence and successfully managing adverse events.

Future perspective

Currently, many drug–drug interaction studies are completed in healthy volunteers. It is difficult to extrapolate these results to coinfecting patients since these disease states affect organs such as the gut and liver where drug metabolism and transport take place. These viral infections can also result in chronic inflammation which can have a profound effect on many processes, including drug metabolism. In the future, new methods of analysis will be applied to incorporate pathophysiologic changes when considering *de novo* drug interactions during the drug development process.

Future DAA drug development will hopefully progress to a point where RBV is no longer required for the treatment of HCV, treatment duration will continue to decline and drug interactions will be minimized. HCV therapy has made great strides in increasing SVR rates for all patient groups, shortening treatment duration and decreasing adverse events.

In addition to improvements in the previously mentioned areas, a true accomplishment would be to allow access and availability of HCV treatment for everyone, regardless of

disease severity, socioeconomic standing or geographical location. In addition, cost will not make treatment prohibitive for the individuals, and all individuals who are infected with HCV will be properly diagnosed and treated with the current standards of care.

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EXECUTIVE SUMMARY

Chronic hepatitis C virus infection is a global epidemic

- The WHO estimates that approximately 150 million individuals have chronic hepatitis C virus (HCV).
- The yearly death toll globally from HCV-related diseases is >350,000 individuals.

HIV/HCV coinfection

- Chances of HIV/HCV coinfection are increased greatly with HIV acquisition via injection drug use.
- The HIV/HCV coinfecting population can experience an increased risk of fibrosis progression and increased rate of development of cirrhosis and end-stage liver disease.

Rapid emergence of new direct-acting antivirals

- Next generation direct-acting antivirals (DAAs) offer an increase in efficacy, interferon-free treatment, shorter treatment duration and improved adverse event profiles.
- Multiple first-line, interferon-free treatment options have recently been approved.
- The new HCV treatment regimens have equivalent sustained virologic response (SVR) rates for HIV/HCV coinfecting as they do for HCV mono-infected individuals.

Drug–drug interactions

- Complex drug–drug interactions can arise from new DAA treatment regimens when used in HIV/HCV coinfection.
- Many new DAA agents affect or are affected by metabolizing enzymes and membrane transporters.
- Many antiretrovirals are substrates, inhibitors and inducers of metabolizing enzymes and substrates and/or inhibitors of membrane transporters.

Pharmacogenomics is a changing area in the treatment of HCV

- Simeprevir, when administered with pegylated-interferon/ribavirin (PEG-IFN/ribavirin) shows a slightly weaker association between *IL28B* and SVR than when PEG-IFN/ribavirin are administered alone. There appears to be no association between SVR for new DAA agents and the *IL28B* polymorphism, compared with PEG-IFN and ribavirin therapy alone.
- Since DAAs are substrates of drug transporters and CYP450 enzymes, pharmacokinetics and treatment outcomes could be influenced by the impact of genetic variants.

Future perspective

- We will likely have a greater understanding of the effect of inflammation and chronic disease on human pharmacokinetics. New approaches such as physiologically based pharmacokinetic modeling will likely be used to simulate the pharmacokinetic/pharmacodynamic effects in these patient populations.
- All infected patients will be properly identified and the standard of care for HCV treatment will become available to all individuals regardless of disease severity, socioeconomic standing and geographical location.

Table 1

Clinical trials on treatment of HCV genotype 1 mono-infection.

				Ref.
ION-1	Ledipasvir plus sofosbuvir with or without weight-based RBV for 12 or 24 weeks.	865 treatment-naïve, genotype 1 with or without cirrhosis	SVR12 ranged from 97–99% across all four groups, and SVR rates were similarly high among subgroups that have been considered ‘difficult to treat’, including cirrhotic and African-American patients, with rates of 94–100% and 91–100%, respectively.	[27]
ION-2	Ledipasvir plus sofosbuvir, with or without weight-based RBV for 12 or 24 weeks.	440 treatment-experienced, genotype 1, with or without cirrhosis	SVR12 percentages ranged from 94–96% with 12 weeks of therapy (with or without RBV) and were 99% in patients without RBV for 24 weeks. The SVR12 among treatment-experienced cirrhotics treated for 24 weeks was 100% (n = 22), the treatment of cirrhotics with only 12 weeks of combination therapy resulted in higher relapse rates (14%) as compared with 24 weeks (0%).	[28]
ION-3	Ledipasvir plus sofosbuvir for 8 or 12 weeks or ledipasvir plus sofosbuvir with RBV for eight weeks.	647 naïve, noncirrhotic genotype 1	SVR12 ranged from 93–95%. Higher rates of relapse in the eight-week groups, regardless of RBV use. It was found that those individuals with baseline HCV RNA levels smaller than six million IU/ml achieved SVR12 rates of 97% with sofosbuvir and ledipasvir for an eight-week duration. This group was found to have relapse rates equivalent to 12-week treatment duration. This was found in a post-hoc, noncontrolled analysis.	[24,29]
Sofosbuvir + daclatasvir	Sofosbuvir and daclatasvir with or without RBV for 12 or 24 weeks in different populations.	211 naïve, genotype 1, 2 and 3, and genotype 1 experienced, without cirrhosis	SVR12 rates were 98% among genotype 1 patients treated for 12 or 24 weeks and 91% among those with genotypes 2 and 3 who were treated for 24 weeks.	[30]
Daclatasvir + asunaprevir + beclabuvir	Daclatasvir, asunaprevir, beclabuvir (75 vs 150 mg) × 12 weeks.	166 naïve, genotype 1 (n = 133) 9% cirrhotics.	SVR12 of 92% in the 150 mg beclabuvir arm 71% of cirrhotics achieved SVR12 (n = 7) versus 100% in the 75 mg group (n = 8).	[31]
SAPPHIRE-I	12 weeks of paritaprevir/ritonavir/ombitasvir and dasabuvir, plus weight-based RBV (n = 473) or placebo (n = 158).	631 treatment-naïve patients with genotype 1 infection without cirrhosis	Overall SVR12 rate of 96%.	[32]
SAPPHIRE-II	12 weeks of paritaprevir/ritonavir/ombitasvir, and dasabuvir, plus weight-based RBV or placebo.	297 prior treatment-experienced patients	SVR12 96% response rates were 95, 100 and 95% among those with prior relapse, prior partial response, and prior null response to therapy, respectively.	[33]
TURQUOISE-II	Received 12 or 24 weeks of paritaprevir/	380 genotype 1 treatment-naïve and -experienced patients with cirrhosis	Rates of SVR12 and 24 were 92 and 96%, respectively.	[34]

				Ref.
	ritonavir, ombitasvir, dasabuvir plus weight-based RBV.			
PEARL-III	12 weeks of paritaprevir/ritonavir, ombitasvir, dasabuvir with or without RBV.	419 treatment-naïve, noncirrhotic, genotype 1b infected patients	SVR12 rates of 99% regardless of whether or not RBV was used with 3D in treatment.	[35]
PEARL-IV	12 weeks of paritaprevir/ritonavir, ombitasvir, dasabuvir with or without RBV.	305 treatment-naïve, noncirrhotic, genotype 1a infected patients	SVR12 rates that were notably higher when RBV were included (97% vs 90% without RBV).	35:
COSMOS	150 mg simeprevir and 400 mg sofosbuvir daily for 24 weeks with or without RBV or for 12 weeks with or without RBV, in two cohorts divided by previous treatment experience and METAVIR score.	167 HCV treatment naïve and experienced, genotype 1	SVR12 achieved in 92% of patients overall.	[36]

SVR: Undetectable HCV RNA at a defined number of weeks after the end of treatment, usually 12 weeks after treatment cessation.

PEG-IFN: Pegylated interferon; RBV: Ribavirin; SVR: Sustained virologic response; 3D: paritaprevir/ritonavir, ombitasvir, dasabuvir.

Table 2Guideline recommendations for the treatment of HCV genotype 1[†].

Treatment	Genotype	Previous treatment
Harvoni × 12 weeks [‡]	1a 1b	Naive (including cirrhosis)
Viekira Pak and weight-based RBV [§] × 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)	1a	Naive
Viekira Pak × 12 weeks (no cirrhosis) + weight-based RBV [§] (cirrhosis)	1b	Naive
Sofosbuvir + simeprevir w/ or w/o weight-based RBV [§] × 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)	1a	Naive
Sofosbuvir + simeprevir × 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)	1b	Naive
Harvoni × 12 weeks [‡]	1a 1b	PEG-IFN/RBV/PI experienced (no cirrhosis)
Harvoni × 24 weeks	1a 1b	PEG-IFN/RBV/PI experienced (with compensated cirrhosis)
Harvoni and weight-based RBV [§] × 12 weeks	1a 1b	PEG-IFN/RBV/PI experienced (with compensated cirrhosis)
Viekira Pak × 12 weeks	1b	PEG-IFN/RBV experienced (no cirrhosis)
Viekira Pak and weight-based RBV [§] × 12 weeks	1a	PEG-IFN/RBV experienced (no cirrhosis)
Viekira Pak and weight-based RBV [§] × 12 weeks (1b)	1a	PEG-IFN/RBV experienced (with compensated cirrhosis)
× 24 weeks (1a)	1b	
Sofosbuvir + simeprevir w/ or w/o weight-based RBV [§] × 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)	1a	PEG-IFN/RBV experienced
Sofosbuvir + simeprevir w/ or w/o weight-based RBV [§] × 12 weeks	1b	PEG-IFN/RBV experienced (no cirrhosis)
Sofosbuvir + simeprevir w/ or w/o weight-based RBV [§] × 24 weeks	1b	Peg-IFN/RBV experienced (with compensated cirrhosis)

[†] See guidelines for recommendations when patients have failed agents besides PEG-IFN/RBV.[‡] Harvoni for 8 weeks in treatment-naïve patients (without cirrhosis) with baseline HCV RNA <6 million IU/ml should be done with caution and performed at the discretion of the practitioner.[§] (1000 [<75 kg] to 1200 mg [>75 kg]).

Harvoni: ledipasvir/sofosbuvir (90mg/400mg); PEG-IFN: Pegylated interferon; PI: Protease inhibitor; w/: With; w/o: Without; RBV: Ribavirin; Viekira Pak: paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) daily, plus twice-daily dosed dasabuvir (250 mg).

Reproduced from [25].

Table 3

Metabolism and transport pathways of HCV DAA.

	Mechanism of action	Metabolism	Transporters	Ref.
Paritaprevir	HCV NS3 protease inhibitor	Substrate: CYP3A4. Inhibitor: CYP2C8, UGT1A1	Substrate: P-gp, OATP1B1, OATP1B3, BCRP. Inhibitor: OATP1B1, OATP1B3, BCRP.	[40,41]
Ombitasvir	HCV NS5A inhibitor	Substrate: CYP3A4 (minor role). Inhibitor: CYP2C8, UGT1A1	Substrate: P-gp, BCRP	[40,41]
Dasabuvir	HCV NS5B nonnucleoside polymerase inhibitor	Substrate: CYP2C, CYP3A, CYP2D6. Inhibitor: UGT1A1	Substrate: P-gp, BCRP. Inhibitor: OATP1B1, BCRP	[40,41]
Sofosbuvir	HCV NS5B nucleotide polymerase inhibitor		Substrate: P-gp, BCRP	[42]
Ledipasvir	HCV NS5A inhibitor		Substrate: P-gp, BCRP. Inhibitor: OATP1B1, OATP1B3, BCRP, P-gp (intestinal)	[42]
Simeprevir	HCV NS3/4A protease inhibitor	Substrate: CYP3A. Inhibitor: CYP1A2 (mild), CYP3A4 (intestinal)	Substrate: P-gp, OATP1B1, OATP1B3. Inhibitor: OATP1B1, OATP1B3, MRP2	[43,44]
Asunaprevir	HCV NS3 protease inhibitor	Substrate: CYP3A. Inhibitor: CYP2D6. InducerL CYP3A4 (weak)	Substrate: P-gp, OATP1B1, OATP2B1. Inhibitor: P-gp, OATP1B1 (weak), OATP1B3 (weak)	[45–47]
Daclatasvir	HCV NS5A inhibitor	Substrate: CYP3A4	Substrate: P-gp. Inhibitor: P-gp, OATP1B1, OCT1, BCRP	[48]
Beclabuvir	HCV NS5B nonnucleoside polymerase inhibitor	Substrate: CYP3A4. Inducer: CYP3A4 (weak to moderate)	Substrate: P-gp. Inhibitor: P-gp, BCRP, OATP1B1, OATP1B3	[46,49]

DAA: Direct-acting antiviral; P-gp: P-glycoprotein; BCRP: Breast cancer resistance protein.

Table 4

Pharmacokinetic interactions with HCV DAAs.

Drug	Simeprevir [†]	Daclatasvir [‡]	Asunaprevir [§]	Beclabuvir [¶]	Sofosbuvir ± ledipasvir [#]	Paritaprevir/ritonavir ombitasvir and dasabuvir ^{††}
<i>Antiretrovirals</i>						
ABC					↔ ^{‡‡‡}	
ATR	Not recommended ^{‡‡}				LDV ↓ 34% SOF ↓ 6% TDF ↑ 98% ^{§§} Monitor for tenofovir-associated adverse reactions	
ATV/r	Not recommended ^{‡‡}	DCV ↑ 110% ^{¶¶} Reduce dose to 30 mg			↔ ^{‡‡‡##}	ABT-450 ↑ 94% ^{†††‡‡‡} Give ATV 300 mg without ritonavir in am
CPA					LDV ↑ 8% SOF ↑ 10% TDF ↑ 40% Monitor for tenofovir-associated adverse reactions	Not recommended
DRV/r	SPV ↑ 159% DRV ↑ 18% RTV ↑ 32% Not recommended ^{§§§}				SOF ↑ 37% Not clinically relevant ^{##}	Not recommended ^{‡‡‡}
DTG					↔ ^{‡‡‡}	
EFV	SPV ↓ 71% Not recommended	DCV ↓ 32% ^{¶¶¶} Increase dose to 90 mg				EFV ↓ 10% ^{##} (See ATR)
ENF	↔ ^{###}					
ETR	Not recommended ^{‡‡}					
FTC	↔ ^{###}				FTC ↑ 5% Not clinically relevant ^{##}	↔ ^{†††}
LPV/r	Not recommended ^{‡‡}					ABT-450 ↑ 87% (LPV C _{min} ↑ >200%) Not recommended
MVC	↔ ^{###}					

Drug	Simeprevir [†]	Daclatasvir [‡]	Asunaprevir [§]	Beclabuvir [¶]	Sofosbuvir ± ledipasvir [#]	Paritaprevir/ritonavir ombitasvir and dasabuvir ^{††}
NVP	Not recommended ^{‡‡}					
RAL	SPV ↓ 11% RAL ↑ 8% Not clinically relevant ^{###}				SOF ↓ 8.5% RAL ↓ 16% ^{†††} Not clinically relevant ^{##}	↔ ^{†††} No adjustments necessary ^{†††}
RPV	SPV ↑ 6% RPV ↑ 12% Not clinically relevant ^{###}				RPV ↑ 6% ^{##,††} Not clinically relevant (warning with tenofovir)	RPV ↑ 150–243% Not recommended
TDF	SPV ↓ 14% TDF ↑ 18% Not clinically relevant ^{###}	DCV ↑ 10% TDF ↑ 10% Not clinically relevant			TDF ↑ (see ATR, CPA; caution with boosted regimens-see prescribing information)	TDF ↑ 13% ^{†††} No adjustments necessary ^{†††}
TPV/r	Not recommended ^{‡‡}				SOF ↓ Not recommended ^{‡‡}	
3TC	↔ ^{###}				↔ ^{‡‡}	
Non-ARVs						
Digoxin		Digoxin ↑ 27% ^{§§§§} Use with caution	Digoxin ↑ 30% ^{§§§§} Use with caution			
Midazolam				Midazolam ↓ 46– 50% ^{¶¶¶¶}		

Arrows indicate increased, decreased or unaffected plasma area under the curve (AUC).

^{‡‡} Not explicitly studied.

^{§§} Monitor for tenofovir-associated adverse reactions in patients receiving ledipasvir/sofosbuvir concomitantly with the combination of efavirenz, emtricitabine and TDF [24].

^{¶¶} DCV 20 mg once a day (q.d.); showed less than the threefold elevation in systemic exposure predicted by prior studies with potent CYP3A inhibitors [52].

^{##} Results from PHOTON-2 show that coinfecting patients on these ARVs and SOF plus RBV achieved SVR12 rates of 84–89%. These SVR12 rates were similar to those observed in HCV mono-infection with no subject requiring ARV changes [56].

^{†††} Initial data from pharmacokinetic studies in the coinfecting population reported no significant interactions between the '3D' regimen and these agents. SVR rates for both evaluated arms were high (94% in 12-week arm and 91% in 24-week arm) and consistent with those observed in HCV mono-infecting patients. No subject had a confirmed HIV-1 RNA of >400 copies/ml and none required a switch of their antiretroviral therapy regimen due to loss of HIV-1 virologic suppression [19,60].

^{†††} Based on data from healthy subjects [57,58].

SPV 50 mg q.d. compared with intake of SPV 150 mg alone [51].

DCV 120 mg q.d.; showed less than the twofold reduction in systemic exposure predicted by prior interaction studies with potent CYP3A inducers [52].

These antiretrovirals (ARVs) were utilized in clinical studies with SPV in coinfecting patients without any clinically significant interactions [50].

With LDV alone [42].

With SOF alone [54].

The lowest dose of digoxin should be initially prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect. Effects of DCV and ASV inhibition of P-gp do not appear to be additive when given concomitantly [45].

Beclabuvir 150 or 300 mg; resulted in dose-dependent decrease in midazolam exposure and increase in 1'-hydroxymidazolam exposure by 10–22% [49].

ABC: Abacavir; ATR: Atripla (efavirenz/emtricitabine/tenofovir); ATV/r: Atazanavir/ritonavir; CPA: Complera (rilpivirine/emtricitabine/tenofovir); DAA: Direct-acting antiviral; DCV: Daclatasvir; DRV/r: Darunavir/ritonavir; DTG: Dolutegravir; EFV: Efavirenz; ENF: Enfuvirtide; ETR: Etravirine; FTC: Emtricitabine; HCV: Hepatitis C virus; LPV/r: lopinavir/ritonavir; MVC: Maraviroc; NVP: Nevirapine; RAL: Raltegravir; RPV: Rilpivirine; SOF: Sofosbuvir; SPV: Simeprevir; TDF: Tenofovir; TPV/r: Tipranavir/ritonavir; 3TC: Lamivudine; ABT-450/r: Paritaprevir/ritonavir; ABT-267: Ombitasvir; ABT-333: Dasabuvir; 3D: Paritaprevir/ritonavir; ombitasvir, dasabuvir.

Data taken from [50,51].

Data taken from [45,52–53].

Data taken from [45].

Data taken from [49].

Data taken from [42,54–56].

Data taken from [57–60].

Table 5
IL28B polymorphisms and treatment responses (SVR12) in patients receiving new DAAs for HCV -1 infection.

Agent	Study cohort	IL28B genotypes (rs12979860)			Ref.
		CC	CT	TT	
Simeprevir + PEG-IFN + RBV	264 white (86%), black or African-American (10%)	94%	76%	65%	[80]
Simeprevir + PEG-IFN + RBV	257 white (92%), black or African-American (6%)	96%	80%	58%	[81]
Sofosbuvir + Ledipasvir	865 treatment naive, white (~85%), black (~12%)	100%	99.2–100%	9 7.7–10 0 %	[27]
daclatasvir + asunaprevir	645, white (~70%), black (~5%), Asian (~24%)	76–89%	81–88%	86–96%	[82]
Pariaprevir/r, ombitasvir, dasabuvir	380 primarily whites (~95%)	94–97%	91–96%		[34]

DAA: Direct-acting antiviral; HCV: Hepatitis C virus; PEG-IFN: Pegylated interferon; RBV: Ribavirin; r: Ritonavir.